MASARYKOVA UNIVERZITA

LÉKAŘSKÁ FAKULTA

Léčba pacientů s akutním infarktem myokardu s elevacemi ST-úseku (STEMI): Primární koronární intervence

Habilitační práce

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Obsah

Abstract

Acute myocardial infarction (AMI) remains one of the most life-threatening diseases. In this thesis, consisted of 21 articles, the applicant tried to discover not only the current and up-to-date technique of primary coronary intervention (primary PCI) but also the unanswered questions and future perspectives.

By using the best available combination of potent antiplatelet drugs and special interventional instruments, we are able to decrease the risk of dying of the patients together with improving the quality of surviving.

Special attention desire the patients with AMI at higher age, patients with multi-vessel coronary artery disease or right ventricle involvement, with presence of new or presumably new right bundle-brunch block, high-risk acute myocardial infarction without ST-segment elevation and after the out-of-hospital cardiac arrest.

Though the current therapy especially of patients with ST-elevation AMI (STEMI) is relatively safe and very effective, there is a profound need for further research requiring close multi-disciplinary collaboration.

In near future, the concept of functional revascularization of the non-culprit coronary lesions and precise morphologic assessment of the culprit ones, seems to be very promising and has been studied intensively.

Primary coronary intervention (primary PCI) should be taken into consideration in all suspicious acute coronary syndrome patients and requires a highly trained and experienced team working in non-stop (24/7) high-volume catheterization laboratory.

The fast track to the catheterization laboratory should be simplified and probably based on the presence or absence of ongoing myocardial ischemia.

Předmluva

Tato habilitační práce je sestavena jako soubor 21 prací publikovaných a odeslaných k publikaci jejichž je uchazeč autorem nebo spoluautorem. Publikované práce jsou vloženy v PDF formátu se zachováním původní grafické podoby a jazyka odpovídajícím příslušnému časopis, u prací odeslaných k publikaci je využit standardní formát Wordu. Po úvodu do problematiky jsou jednotlivé články doplněny krátkými shrnujícími komentáři (je zmíněna případná hodnota impakt faktoru a počet citací ve Web of Science).

Poděkování

Děkuji všem spolupracovníkům i přátelům, se kterými jsem měl a mám v rámci Interní kardiologické kliniky Lékařské fakulty Masarykovy university a Fakultní nemocnice Brno, České republiky i zahraničí možnost dlouhodobě spolupracovat na četných výzkumných a edukačních projektech.

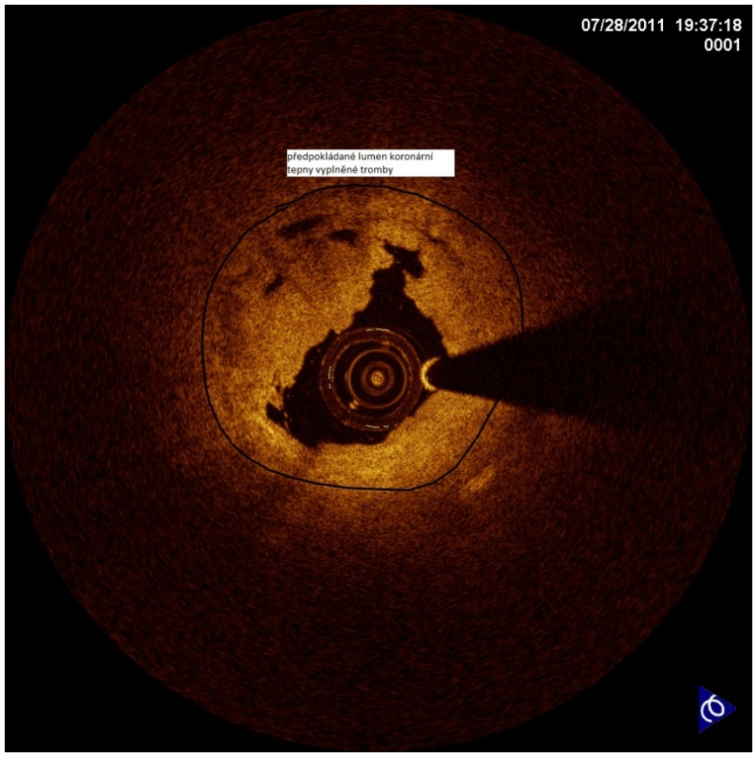
Práci věnuji svému otci, MUDr. Antoninu Kalovi, a celé rodině.

1. Úvod

Kardiovaskulární onemocnění jsou nejčastější příčinou úmrtí ve vyspělých zemích. Nejvíce ohroženi jsou pacienti s akutními formami ischemické choroby srdce (ICHS), kam patří akutní infarkt myokardu s/bez elevací ST-úseku (STEMI/NSTEMI), nestabilní angina pectoris a náhlá srdeční smrt. Především u pacientů se STEMI nabízí současná medicína velmi rychlou a efektivní léčbu formou reperfuze, tzn. zprůchodnění infarktové tepny. Ta může být farmakologická podáním fibrinolytické léčby, která, co se týče počtu léčených pacientů celosvětově, zatím dominuje, nebo celkově bezpečnější a efektivnější reperfuze mechanická pomocí primární perkutánní koronární intervence (pPCI). Ve všech případech je reperfuzní léčba indikována v průběhu prvních 12 hod od vzniku prvních příznaků s výjimkou pacientů v kardiogenním šoku, kde tento časový interval je prodloužen na 18 – 48 hod (1).

Patofyziologickým podkladem STEMI je ve více než 90 % případů ruptura (2/3) nebo eroze (1/3) aterosklerotického plátu v koronární tepně (2) s rychle nasedajícími krevními destičkami a nepříznivou aktivací koagulační kaskády. Teprve nedávno bylo zjištěno, že ačkoli se jedná o velmi akutní a život ohrožující příhodu vyžadující léčbu v průběhu několika hodin, stáří přítomných trombů v infarktové lézi může dosahovat až 5 – 7 dnů (3) (obr. 1).

Obr. 1: Infarktová koronární tepna s akutní trombózou na příčném řezu získaném z optické koherentní tomografie



Vedle důležitého, převážně 12-ti hodinového časového intervalu od vzniku obtíží je s výjimkou kardiogenního šoku primární PCI indikována u všech pacientů se STEMI v případě, že transport pacienta do katetrizační laboratoře netrvá déle než 120 min. Cílem je však dosažení ještě kratších časů od prvního medicínského kontaktu nebo stanovení diagnózy do zavedení vodiče do infarktové tepny. Za optimálních podmínek by tento časový interval měl činit maximálně 90 min u všech pacientů a 60 min u vysoce rizikových pacientů s rozsáhlým infarktem přední stěny a časnou diagnózou v průběhu prvních 2 hod. V případě delších transportních časů, je indikováno podání trombolytika. Česká republika se svým systémem péče o pacienty se STEMI řadí mezi nejlépe fungující státy a je považována za jednu ze vzorových zemí pro ostatní. Více než 90% pacientů se STEMI je léčeno pomocí pPCI a trombolytická léčba je aktuálně použita v méně než 1% případů. Samozřejmě i v současnosti se setkáváme s pacienty přicházejícími s velkým časovým odstupem, u kterých není indikován ani jeden z reperfuzních postupů. Ihned po stanovení diagnózy STEMI je indikováno podání kombinace základních farmak s antikoagulačním a protidestičkovým účinkem (heparin nebo lépe enoxaparine (4) respektive kyselina acetylosalicylová a některý z blokátorů receptorů destiček pro adenosindifostát). Především v katetrizační laboratoři je možné podání blokátorů glykoproteinových receptorů destiček IIb/IIIa. Přímý inhibitor trombinu je v České republice v současnosti komerčně nedostupný.
V regionech či zemích, ve kterých chybí nebo není dostatečně rozvinutá spolupráce zdravotnické záchranné služby, non-stop katetrizačních center pro léčbu akutního infarktu myokardu nebo tam, kde jsou nepříznivé geografické podmínky s dlouhými transportními časy, je možné uplatnit tzv. farmako-invazivní strategii. Ta kombinuje akutní podání přednostně fibrin-specifického trombolytika s následným transportem do katetrizačního centra a bezpečným provedením invazivního koronárního vyšetření (koronarografii) v průběhu 3 – 24 hod od jeho aplikace. Koncept tzv. facilitované PCI založené na podání trombolytika nebo kombinace trombolytika a blokátorů destiček IIb/IIIa před primární PCI se klinicky neosvědčil a není součástí doporučených postupů.

V roce 2008 byla s cílem zlepšení péče o pacienty s akutním koronárním syndromem a především STEMI založena zajímavá a velmi úspěšná iniciativa Stent for Life (www.stentforlife.com). Ta byla iniciována Evropskou asociací perkutánních kardiovaskulárních intervencí (EAPCI) jako součástí Evropské kardiologické společnosti a EuroPCR, organizující výroční kongres EAPCI. V současné době se k této iniciativě přidalo

celkem 18 zemí nebo kardiologických organizací nejen z Evropy, ale z celého světa. I přes výrazná zlepšení v péči o pacienty se STEMI v průběhu 4 – 5 let však nadále existují velké rozdíly v jejich léčbě (5).

Tato práce je zaměřena především na výsledky léčby pacientů se STEMI pomocí primární PCI a na některé důležité podskupiny pacientů. Další důležité otázky, jako je optimálně vedená sekundární prevence, prevence a léčba závažných arytmií a další nejsou v této práci rozebírány.

Výhody primární PCI oproti trombolytické léčbě byly jasně prokázány v mnoha studiích, ze kterých je třeba zdůraznit čtyři přelomové – studii PAMI v rámci prosté primární PCI (6), STENT-PAMI s využitím implantace koronárních stentů (7) a poté pak studie PRAGUE (8,9) a DANAMI-2 (10), které ukázaly vyšší efektivitu i bezpečnost primární PCI oproti trombolytické léčbě i při delším transportu do katetrizační laboratoře. Oproti trombolytické léčbě je primární PCI spojena s významně lepšími výsledky ve všech sledovaných ukazatelích, kterými jsou úmrtí (9,3% vs 7,0%), reinfarkt (6,8% vs 2,5%) i mozkové příhody (2,0% vs 1%) (11). Rizikem mozkového krvácení, které se vyskytuje až v 1,1% jsou zatíženi pouze nemocní léčeni trombolytikem. Primární PCI je tedy v současnosti nejefektivnější a nejrychlejší reperfuzní léčbou. U nemocných v kardiogenním šoku je PCI indikována až do 48 hod od jeho vzniku a jedná se o jediný stav, při kterém je v průběhu STEMI doporučeno provést primární PCI nejen na infarktové tepně, ale v případě trvající hemodynamické nestability i na tepnách dalších s kritickým nálezem. Ve všech případech je časový faktor ten nejdůležitější a každá minuta zdržení může nemocného se STEMI ohrozit na životě.
V optimálním případě vypadá organizace péče o nemocného následovně: 1. volání nemocného na linku zdravotnické záchranné služby (telefonní číslo 155), 2. do 15-20 min příjezd zkušeného týmu rychlé lékařské pomoci vybaveného 12-svodovým EKG, defibrilátorem, plicním ventilátorem, monitorem vitálních funkcí a zevní kardiostimulací, 3. stanovení diagnózy v terénu a podání první medikamentózní léčby (prasugrel 60 mg, ticagrelor 180 mg eventuálně clopidogrel 600 mg, aspirin 125 - 250 mg, nefrakcionovaný heparin 70 – 100 IU/kg eventuálně lépe enoxaparin), 4. kontaktování nejbližšího katetrizačního centra s non-stop (24/7) PCI provozem, 5. přímý transport na katetrizační sál a provedení primární PCI.

1.1 Akutní protidestičková léčba v průběhu STEMI

Blokátory receptorů destiček pro adenosindifostát (ADP)

Nejdéle známým blokátorem $P2Y_{12}$ ADP- receptoru je **tiklopidin**, jehož podání v kombinaci s kyselinou acetylosalicylovou (ASA) dramaticky snížilo riziko akutních trombóz po implantaci koronárních stentů (12). Následně byl tento preparát nahrazen účinnějším a bezpečnějším lékem, kterým je **klopidogrel**. Indikace jeho podání vychází z příznivých výsledků studií COMMIT a CLARITY, které testovaly přidání klopidogrelu k ASA (13,14). Po úvodní sytící dávce klopigorelu (dříve 300mg a nyní 600mg) je doporučena udržovací dávka 75mg denně po dobu 12 měsíců. Léčba klopidogrelem však má své limitace, kterými je nedostatečné snížení reaktivity destiček u 20 – 40 % pacientů. Tento fakt byl jedním z hlavních důvodů pro hledání dalších a účinnějších molekul, kterými jsou prasugrel, ticagrelor a další preparáty ve fázi výzkumu. Prvním novým a komerčně dostupným protidestičkovým lékem je **prasugrel**. Jedná se o „prodrug", tzn. látku, jejíž ireverzibilní efekt se dostavuje po rychlé jednostupňové metabolické přeměně a tento efekt je výraznější oproti klopidogrelu. Ve studii TRITON TIMI-38 bylo podání prasugrelu porovnáno s podáním klopidogrelu před pPCI. Prasugrel významně snížil riziko hlavních kardiovaskulárních komplikací o 32% resp. 21% v průběhu 30 dnů resp. 15 měsíců. Zároveň byl pozorován významně nižší výskyt infarktu myokardu a trombózy stentu, a to bez zvýšení rizika velkých nebo život ohročujících krvácivých příhod. S výjimkou pacientů s předchozí cévní mozkovou příhodou nebo transitorní ischemickou atakou, je podání prasugrelu u STEMI plně indikováno (15). Reverzibilním, ale ještě vyšším účinkem blokády ADP receptorů destiček, disponuje druhý nový lék, **ticagrelor** (16)**.** Jeho podání u pacientů se STEMI, a to bez ohledu na eventuální předléčení klopidogrelem, bylo ve studii PLATO spojeno s významným snížením rizika infarktu myokardu, trombózy ve stentu a celkové úmrtnosti (o 20%; 34% resp. 13%) v průběhu 12-ti měsíčního sledování a zvýšením rizika cévní mozkové příhody. Významného snížení hlavních kardiovaskulárních příhod jako primárního ukazatele studie, nebylo dosaženo. Podání ticagreloru nezvýšilo riziko výskytu závažných krvácení.

Podání prasugrelu nebo ticagreloru nebo klopidogrelu je indikováno co nedříve po stanovení diagnózy STEMI, tzn. ve většině případů před provedením invazivního vyšetření a pPCI. V případě pochybností o správnosti základní diagnózy a při výraznému riziku krvácivých komplikací u pacientů indikovaných ke kardiochirurgické operaci po prasugrelu, je vhodné

podání ticagreloru nebo klopidogrelu. Stejný postup by měl být zvolen i u pacientů s klinicky vysokým rizikem krvácení.

Blokátory glykoproteinových receptorů destiček IIb/IIIa (GPI)

Různorodou skupinu GPI látek tvoří monoklonální protilátka abciximab s ireverzibilním a širokým spektrem dlouhodobého účinku až 72 hod a malé reverzibilně účinné molekuly, tirofiban a eptifibatide s krátkodobým efektem do 4 hod. Společnou pro všechny látky je blokáda cílových receptorů agregace destiček a vazby fibrinogenu na aktivovanou destičku a tedy zamezení tvorby bílého trombu. Především u pacientů přicházejících časně v prvních 4 hod a s premorbidně postiženou mikrocirkulací, tzn. u diabetiků, zlepšuje podání GPI výsledky pPCI.

Abciximab (i.v. bolus + infuze) v kombinaci s heparinem snížil o 30% riziko ischemických příhod u STEMI (17,18). Podobného účinku jako podání abciximabu bylo dosaženo podáním dvojího i.v. bolusu eptifibatidu a následné infuse (19). O něco nižší se jeví účinek tirofibanu. Z praktického hlediska je důležité posuzovat různé dávkovací režimy.

Podání GPI není vzhledem k riziku krvácení indikováno rutinně, ale jako tzv. bail-out léčba, tzn. v případě trombotických nebo potenciálně trombotických komplikací (např. tzv. no-reflow fenomén) anebo iniciálně přítomné rozsáhlé intrakoronární trombózy.

Vedle standardních dávkovacích schémat se zkouší i nové režimy podání GPI s cílem zvýšení intrakoronární koncentrace léků a jejich vyššího účinku. Zajímavé jsou výsledky Gu et al. (20), kteří aplikovali intrakoronárně pouze bolus abciximabu bez následné infuze. Tato forma podání speciálním katetrem byla spojena se zlepšením myokardiální perfuze a menším rozsahem myokardiální nekrózy (21).

1.2 Technika primární PCI

Podobně jako při jakémkoliv invazívním zákroku či vyšetření se využívá atraumatické techniky popsané Sven-Ivar Seldingerem již v roce 1953 (22). Vlastní techniku primární PCI je možné rozdělit na **základní“** zahrnující prostou balónkovou dilataci (POBA = Plain Old Balloon Angioplasty) a implantaci koronárních stentů „holých“ (BMS = Bare Metal Stent) i „lékových“ (DES = Drug-Eluting Stent), ke které nyní řadíme i katetry pro manuální aspiraci sloužící k extrakci aterotrombotického materiálu.

Po přidání invazívních zobrazovacích metod, speciálních typů instrumentária a adjuvantní farmakoterapie je zřejmé, že technika PCI vyžaduje při řešení komplexní koronární problematiky nejen dobře vybavenou katetrizační laboratoř pracující v non-stop provozu, ale i velmi zkušený tým sestávající z intervenčních kardiologů, specializovaných sester a zdravotnických techniků.

Balónková dilatace

Jedná se o techniku nejstarší, která ale doznala velkého zlepšení v použitém materiálu vlastního balónku i těla katetru. V současnosti rozlišujeme tzv. **semi-compliant katétry** využívané pro predilataci léze a jako nosič koronárních stentů a tzv. **non-compliant katétry (NC katétry)** pro vysokotlakou postdilataci. Při řešení běžných infarktových lézí se využívají insuflační tlaky 12 – 16 atmosfér.

Prostá balónková dilatace se v současnosti samostatně využívá ve velmi malé míře a ve více než 90% úspěšných primárních PCI je doplněna o implantaci koronárních stentů.

Implantace koronárních stentů

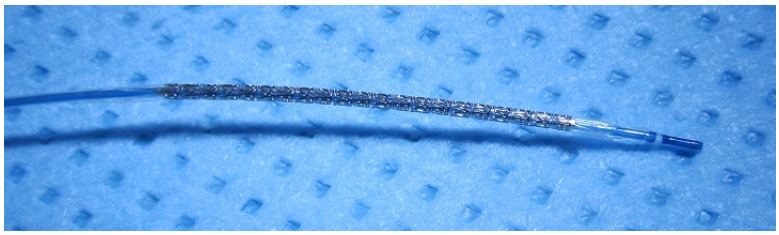
Ačkoliv se koronární stenty (**BMS**) začaly implantovat do koronárních tepen již v roce 1986 (23), teprve v roce 1994 byl prokázán jejich přesvědčivý efekt oproti balónkové dilataci. (24,25) Přesto se jednalo o techniku, která byla ve svých počátcích zatížena riziky. Jedním z nich byla akutní (do 24 hod) a subakutní (>1den – 30 dnů) trombóza stentu, která byla určitou daní za cizorodý materiál ponechaný v koronární tepně. K jejímu dramatickému snížení přispěly především dva faktory: 1) nutnost vysokotlaké postdilatace (≥12 atmosfér) a tím i dosažení optimální apozice stentu v koronární tepně, který vycházel z velmi přesných morfologických nálezů na intrakoronárním ultrazvuku (26) *a* 2) klinický průkaz aditivního účinku kombinované antiagregační léčby přidáním tiklopidinu ke kyselině acetylosalicylové (ASA) (27). Při této kombinaci bylo minimalizováno riziko subakutní trombózy stentu – komplikace, které se všichni intervenční kardiologové obávali, a která vznikala až v 15 % při léčbě kumariny (28).

Další kapitola intervenční kardiologie se začala psát od roku 2001, kdy byly prezentovány první příznivé výsledky implantace lékových stentů (**DES**) ze studie RAVEL (29). Od první generace DES kryté sirolimem a paclitaxelem se přešlo k implantaci DES druhé nebo dokonce třetí generace vylučující většinou deriváty rapamycinu (sirolimu). Těmi jsou everolimus, biolimus, zotarolimus, tacrolimus a další. Zajímavou koncepci s prvními

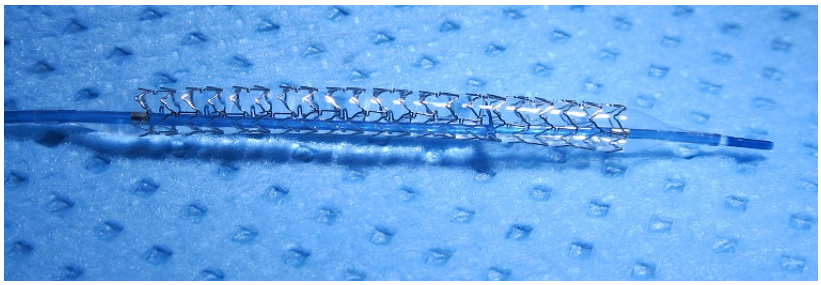
příznivými výsledky pak představuje plně resorbovatelný stent s everolimovým pokrytím již druhé generace (30,31).

Éra DES však otevřela i relativně opomíjenou otázku pozdní (>30 dnů – 1 rok) a dokonce i velmi pozdní (>1 rok) **trombózy stentů**, a to vzhledem k tomu, že endotelizace implantovaného stentu a jejich „vhojení“ do cévní stěny bylo antiproliferativně účinnými látkami výrazně potlačeno (obr. 2 - 4).

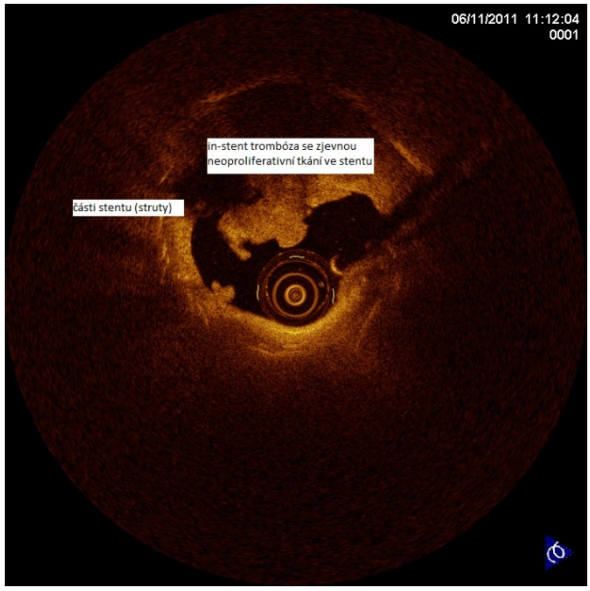
Obr. 2: In-vitro balonkový katetr se stentem připravený k zavedení do koronární tepny



Obr. 3: In-vitro roztažený balonkový katetr se stentem



Obr. 4: In-stent akutní trombóza v příčném řezu získaném z optické koherentní tomografie



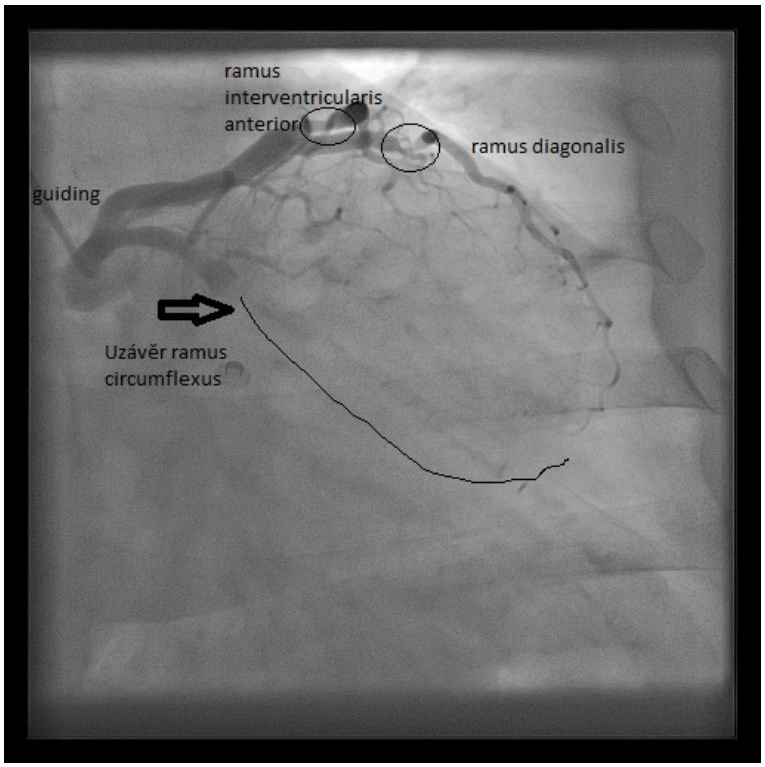
V případě DES první i druhé generace se jedná o riziko přibližně 1% v průběhu prvního roku od implantace a toto riziko trvá pouze v případě DES první generace i v následujících letech (přibližně v 0,6% ročně). Zároveň se zjistilo, že i po implantaci BMS toto riziko existuje, ale dlouhodobě se neliší od DES druhé generace (přibližně 0,2% ročně). To, co je ale společným efektem DES obou generací, je výrazné snížení rizika ISR i nutnosti následné revaskularizace oproti BMS, které vedlo k doporučení implantace DES ve všech případech, kde to je klinicky možné (32,33). Při rozhodování o volbě stentu je vzhledem k nutnosti déletrvajícího podávání kombinované antiagregačně účinné léčby nutné vzít v potaz následující **relativní kontraindikace implantace DES**: nedostatečné anamnestické údaje nebo nedostatečná spolupráce, zvýšené riziko krvácení, přítomnost alergie ke kyselině acetylsalicylové nebo clopigorelu/prasugrelu/ticagrelolu, nutnost časného neplánovaného chirurgického zákroku nebo absolutní indikace pro dlouhodobou antikoagulační léčbu (34).

Protekce myokardu pomocí aspiračních technik

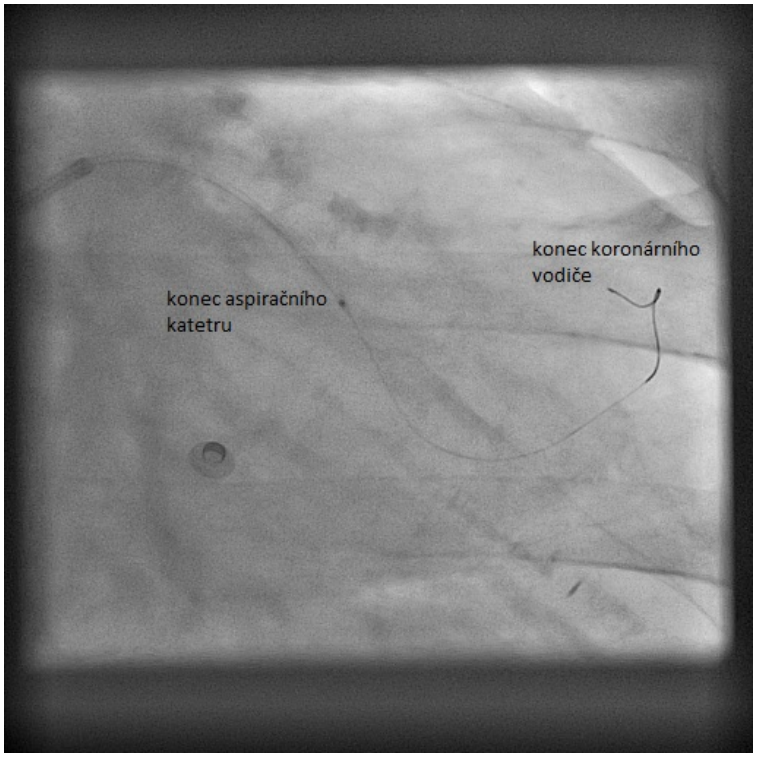
Aspirační techniky se především při primární PCI využívají již dlouhodobě s cílem odstranění trombu a snížení rizika distální embolizace. Teprve v roce 2008 však byl ve studii TAPAS vedle lepších „laboratorních“ ukazatelů myokardiální reperfůze (35) doložen i efekt klinický spojený s manuální tromboaspirací před implantací stentu oproti konvenčnímu přístupu balónek + stent (36,37). Následně bylo zjištěno, že úspěšnost této techniky je vázána pouze na jednoduchou **manuální tromboaspiraci** pomocí speciálních tromboaspiračních katétrů a naopak bez úspěchu jsou techniky složitější. Na základě výsledků studie TASTE (38) však rutinní manuální aspirace nemá klinický přínos a tato technika by měla být minimálně do výsledků studie TOTAL (39) užívána individuálně, a to především v případě přítomnosti rozsáhlé koronární trombózy.

Optimálně vedená primární PCI radiálním přístupem je znázorněna na obr. 5 – 11.

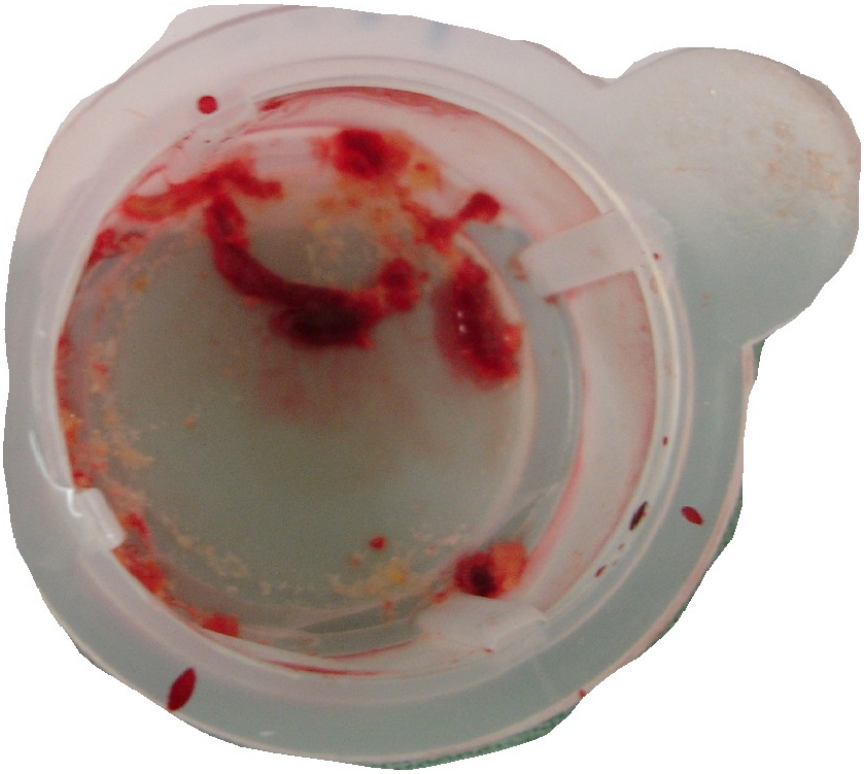
Obr. 5: Uzavřená infarktová tepna ramus circumflexus (šipka) a angiograficky hraniční až významné postižení ramus interventricularis anterior a ramus diagnonalis (kruh)



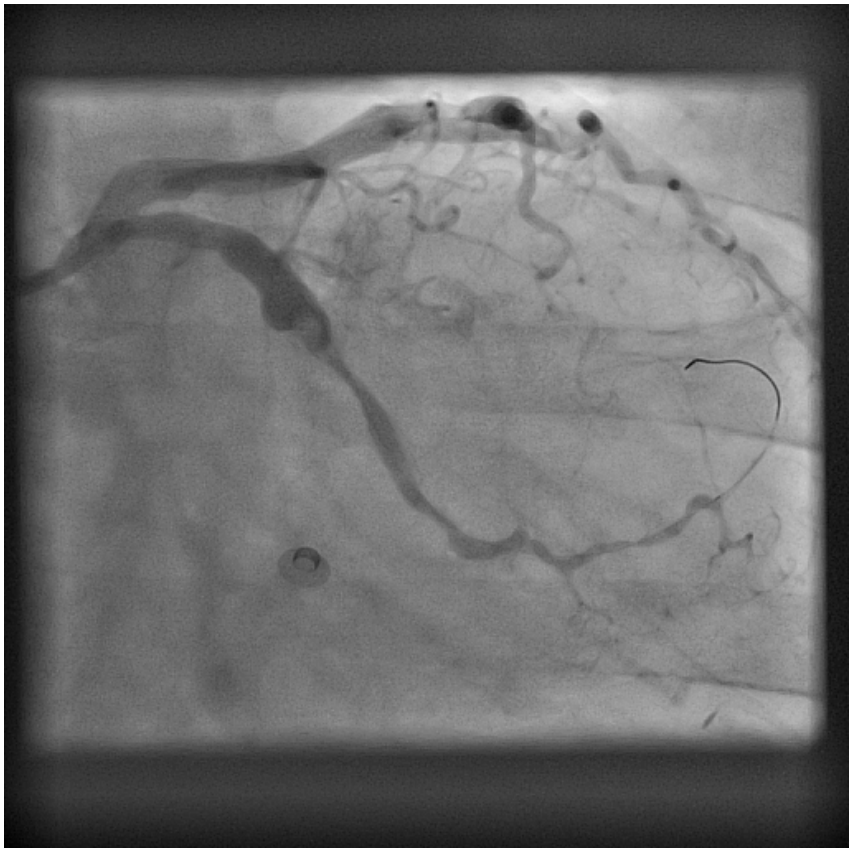
Obr. 6: Koronární vodič a konec tromboaspiračního katetru



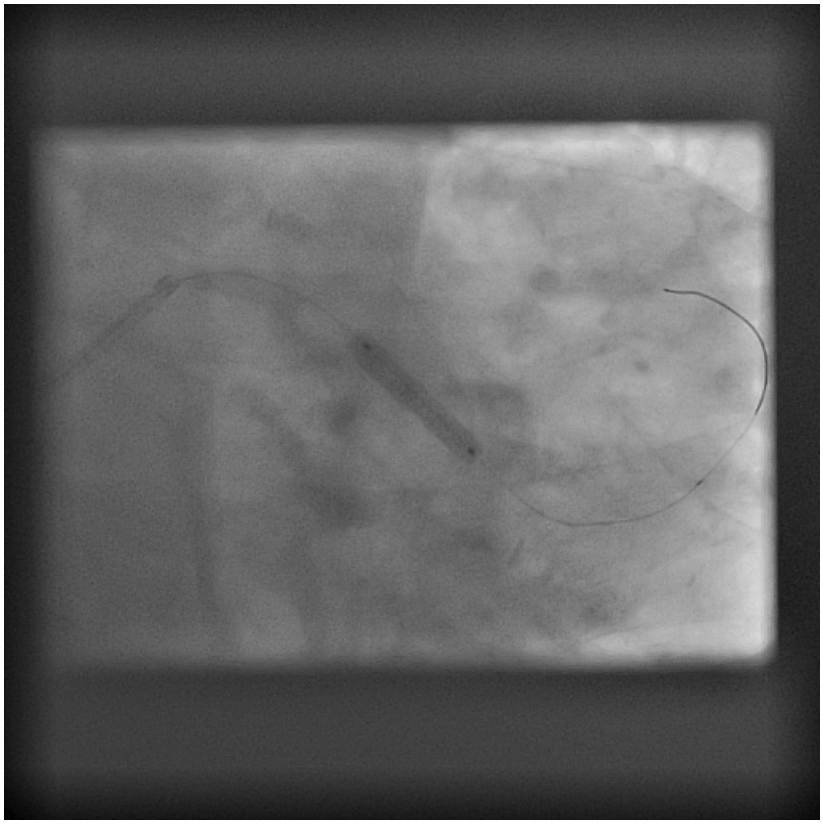
Obr. 7: Aspirát z infarktové tepny



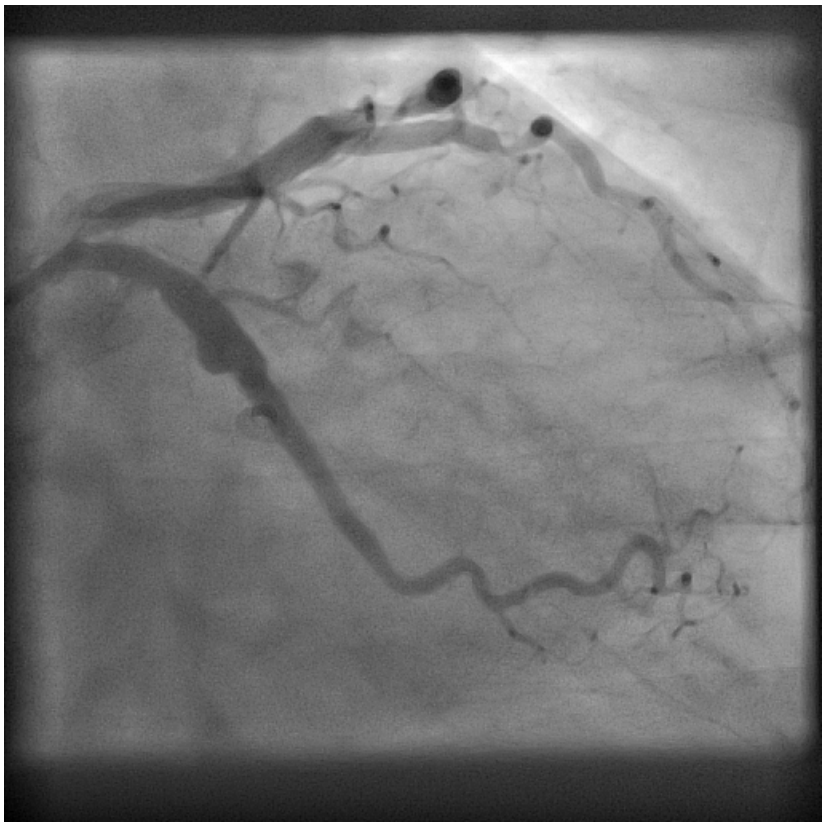
Obr. 8: Angiografický obraz po opakované aspiraci



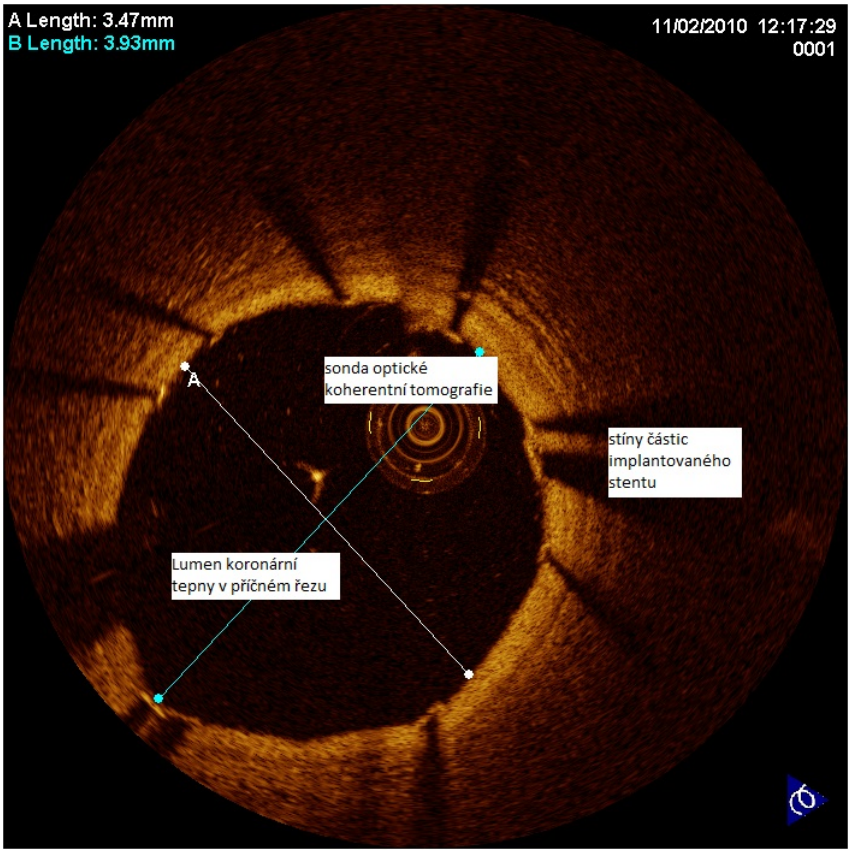
Obr. 9: Implantace lékového stentu



Obr. 10: Optimální výsledek po primární PCI



Obr. 11: Demonstrační obrázek optimálně implantovaného stentu na příčném řezu koronární tepnou získaný z optické koherentní tomografie



2. Současné možnosti a perspektivy léčby pacientů se STEMI (doprovodný komentář k publikacím)

2.1 Perspektivy doporučených postupů Evropské kardiologické společnosti

Současné doporučené postupy Evropské a Americké kardiologické společnosti (1,40) v léčbě STEMI představují optimálně vedenou léčbu pacientů, která však musí být modifikována na základě rizikového profilu pacientů, zkušenosti jednotlivých týmů a take dostupnosti doporučených technik a technologií. Vedle známých indikací reperfuzní léčby zaměřené na primární PCI zmiňuji v publikaci i možné perspektivy zjednošující praktické rozhodování o transportu pacientů do katetrizační laboratoře. Je zde též zdůrazněna role záchranné služby, která by měla v optimálním případě sloužit jako první kontakt pacienta se zdravotním systémem. Pouze tak je možné zabránit často zbytečným úmrtím v průběhu iniciální faze STEMI. Samozřejmostí je pak doporučení optimálního vybavení vozů záchranné služby ke stanovení diagnózy v terénu a zajištění vitálních funkcí pacienta. Probírány jsou i nové poznatky týkající se vlastního intervenčního zákroku ve světle nedávno publikovaných studií.

Celý text níže uvedené publikace v mezinárodním recenzovaném časopise je uveden v příloze 3.1.

Kala, P. *European society of cardiology st-segment elevation myocardial infarction guidelines in perspective - focused on primary percutaneous coronary intervention (2014) Interventional Cardiology Review, 9(1): 7-10.*

2.2 Problematika antitrombotické léčby z pohledu farmako-mechanického přístupu

Práce popisuje aktuální poznatky týkající se strategie ovlivnění koronární trombózy, a to jak z pohledu farmakoterapie, tak techniky primární PCI. Zároveň je zde přehledně graficky popsán algoritmus péče doporučené Evropskou kardiologickou společností, který je porovnán s lokálním postupem v centru s rozsáhlými, 15-ti letými zkušenostmi s intervenční léčbou pacientů se STEMI. V práci je zdůrazněna nutnost individuálně vedené léčby v závislosti na posouzení aterotrombotického a krvácivého rizika, koronární anatomii a zkušenosti léčebných týmů.

Celý text níže uvedené publikace je uveden v příloze 3.2.

Kala, P (Kala, Petr)*; Miklik, R (Miklik, Roman). Title: Pharmaco-mechanic Antithrombotic Strategies to Reperfusion of the Infarct-Related Artery in Patients with ST-Elevation Acute Myocardial Infarctions. Source: JOURNAL OF CARDIOVASCULAR TRANSLATIONAL RESEARCH. Volume: 6, Issue: 3,Special Issue: SI, Pages: 378-387*

2.3 Dlouhodobé výsledky léčby STEMI u pacientů ve vysokém věku

S rostoucím věkem populace minimálně ve vyspělých zemích, je stale aktuálnější otázka léčby pacientů s akutním infarktem myokardu (AIM) i ve vyšším – vysokém věku. Z výsledků naší multicentrické práce na souboru 3814 konsekutivních pacientů pak vyplývá, že i v České republice, která patří mezi nejlépe fungující systémy péče o pacienty s AIM na světě, bylo významně méně starších pacientů (>65 let) indikováno ke koronagrafii v průběhu akutní hospitalizace oproti pacientům mladším (95,9% vs 92,4%; p<0,0001) podobně jako k PCI (74,7% vs 85,6%; p<0,001). Nejhorší krátko- i dlouhodobou životní prognózu měli pacienti, kteří nepodstoupili PCI a měli oběhové známky těžkého srdečního selhání nebo kardiogenního šoku. Věk se tedy jeví jako samostatný diskriminační faktor, který by však i ve světle současných doporučených postupů měl být eliminován.

Celý text níže uvedené publikace je uveden v příloze 3.3.

Kala, P (Kala, Petr); *Kanovsky, J (Kanovsky, Jan); Rokyta, R (Rokyta, Richard); Smid, M (Smid, Michal); Pospisil, J (Pospisil, Jan); Knot, J (Knot, Jiri); Rohac, F (Rohac, Filip); Poloczek, M (Poloczek, Martin); Ondrus, T (Ondrus, Tomas); Holicka, M (Holicka, Maria); Spinar, J (Spinar, Jindrich); Jarkovsky, J (Jarkovsky, Jiri); Dusek, L (Dusek, Ladislav. Age - related treatment strategy and long-term outcome in acute myocardial infarction patients in the PCI era. BMC CARDIOVASCULAR DISORDERS, Volume: 12, Article Number: 31 DOI: 10.1186/1471-2261-12-31.* (Příloha 3.3)

2.4 Problematika STEMI s postižením pravé komory srdeční

Postižení pravé srdeční komory v průběhu STEMI je relativně častou komplikací postihující především, ale ne výlučně, pacienty s významným postižením pravé koronární tepny a tedy ischemií spodní stěny levé komory. Klinické konsekvence se mohou pohybovat od zcela němých až po obraz kardiogenního šoku a mohou vyžadovat velmi odlišný terapeutický přístup. Jako jednoduchý a poměrně specifický diagnostický test může posloužit EKG doplněné o pravostranné hrudní svody, které mohou pomoci při stanovení optimální léčby včetně agresivnějších přístupů. V případě překonání akutní faze onemocnění, mají pacienti s postižením pravé komory příznivou prognózu. Nadále se řeší otázka rizika závažných srdečních arytmií. V přehledné práci je celá problematika od patofyziologie po terapii a prognózu podrobně probrána, výsledky vlastního výzkumu jsou uvedeny v práci další.

Celé texty níže uvedených publikací je uveden v přílohách 3.4 a 3.5.

Ondrus T, Kanovsky J, Novotny T, Andrsova I, Spinar J, ***Kala P.***
Right ventricular myocardial infarction: From pathophysiology to prognosis. Exp Clin Cardiol. 2013 Winter;18(1):27-30.

Kanovsky J, ***Kala P,*** *Novotny T, Benesova K, Holicka M, Jarkovsky J, Koc L, Mikolaskova M, Ondrus T, Malik M. Association of the right ventricle impairment with electrocardiographic localization and related artery in patients with ST-elevation myocardial infarction. J Electrocardiol. 2016 Aug 5. pii: S0022-0736(16)30156-X. doi: 10.1016/j.jelectrocard.2016.08.001. [Epub ahead of print]*

2.5 Výskyt deprese u pacientů po STEMI léčeném primární PCI

V éře před primární PCI byla deprese po akutním infarktu myokardu identifikována u 20% pacientů, tzn. výrazně vice než v běžné populaci a spolu s anxietou se může podílet na vyšší dlouhodobé kardiální úmrtnosti. V naší prospektivní práci jsme se zaměřili na zhodnocení výskytu symptomů deprese a anxiety u 79 pacientů po STEMI léčeném primární PCI za 24 hod, před propuštěním a s odstupem 3, 6 a 12měsíců. Celkově jsme zjistili relativně nižší výskyt symptomů deprese a anxiety, který byl nejvyšší v akutní fázi STEMI, poklesl za hospitalizace, ale znovu se postupně navyšoval v průběhu jednoho roku.

Celý text níže uvedené publikace je uveden v příloze 3.6

***Kala P**, Hudakova N, Jurajda M, Kasparek T, Ustohal L, Parenica J, Sebo M, Holicka M, Kanovsky J. Depression and Anxiety after Acute Myocardial Infarction Treated by Primary PCI. PLoS One. 2016 Apr 13;11(4):e0152367. doi: 10.1371/journal.pone.0152367. eCollection 2016..*

2.6 Léčba STEMI v Evropě a projekt Stent for Life

Evropská iniciativa „Stent for Life“ („Stent pro život“) zaměřená na zlepšení léčby pacientů s infarktem myokardu v Evropě ukázala obrovské rozdíly v organizaci a kvalitě léčby v našem regionu. Widimským et al. (41) bylo zjištěno, že nejlépe jsou léčeni nemocní v zemích s fungujícím programem primární PCI a naopak v průměru nejhůře jsou na tom nemocní v zemích, kde primární PCI je prováděna minimálně. Tím byla relativně zpochybněna i role trombolytické léčby, jejíž podání je zdánlivě jednodušší, ale je spojeno s mnoha kontraindikacemi. Pravděpodobně ale ještě důležitějším faktorem pro neposkytnutí reperfůzní léčby bude nedostatečná nebo chybějící organizace péče o nemocné s infarktem myokardu v jednotlivých zemích. Česká republika je v tomto kontextu jednou z nejlépe zorganizovaných zemí na světě a primární PCI se využívá prakticky u všech nemocných. V práci Kristensena a kol. (viz níže) jsou výsledky léčby STEMI z původní práce Widimského a kol. porovnány s časovým odstupem 3 – 4 let a rozšířeny o dalších 7 zemí. Dalšímu směřování Stent for Life a také možnostem zapojení intervenčních kardiologů nejen do péče o pacienty se STEMI, ale i ischemickými ikty jsou věnovány úvodníky uvedené níže.

Celé texty níže uvedených publikací, na kterých jsem se podílel jako předseda Stent for Life Initiative, jsou uvedeny v přílohách 3.7., 3.8. a 3.9.

*Kristensen SD, Laut KG, Fajadet J, Kaifoszova Z, **Kala P**, Di Mario C, Wijns W, Clemmensen P, Agladze V, Antoniades L, Alhabib KF, De Boer MJ, Claeys MJ, Deleanu D, Dudek D, Erglis A, Gilard M, Goktekin O, Guagliumi G, Gudnason T, Hansen KW, Huber K, James S,Janota T, Jennings S, Kajander O, Kanakakis J, Karamfiloff KK, Kedev S, Kornowski R, Ludman PF, Merkely B, Milicic D, Najafov R,Nicolini FA, Noč M, Ostojic M, Pereira H, Radovanovic D, Sabaté M, Sobhy M, Sokolov M, Studencan M, Terzic I, Wahler S, Widimsky P; on behalf of the European Association for Percutaneous Cardiovascular Interventions; on behalf of the European Association for Percutaneous Cardiovascular*

Interventions. Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries. Eur Heart J. 2014 Aug 1;35(29):1957-1970. Epub 2014 Jan 12.

***Kala P**. Heart & brain: STEMI-like network for ischaemic stroke? EuroIntervention. 2014 Nov;10(7):778-80. doi: 10.4244/EIJV10I7A135.*

*Kaifoszova Z, **Kala P**, Wijns W. The Stent for Life Initiative: quo vadis? EuroIntervention. 2016 May 17;12(1):14-7. doi: 10.4244/EIJV12I1A3.*

2.7 Blokáda pravého raménka Tawarova (RBBB)

Vedle známých indikací reperfuzní léčby se jako vysoce riziková jeví i přítomnost nově vzniklé kompletní blokády pravého raménka Tawarova. Tato EKG patologie se v naší práci na souboru 6742 konsekutivních pacientů vyskytla v 6.3% případů, a to buď samostatně (2,8%) nebo v kombinaci s postižením levého raménka Tawarova. V obou případech kompletní blokády se jednalo o pacienty zatížené nejvyšší hospitalizační mortalitou a rizikem vzniku kardiogenního šoku. Nejen na základě této práce, by pacientům s RBBB měla být poskytnuta maximální možná léčba včetně emergentní revaskularizace.

Celý text níže uvedené publikace je uveden v příloze 3.10.

*Widimsky, P (Widimsky, Petr); Rohac, F (Rohac, Filip); Stasek, J (Stasek, Josef); **Kala, P (Kala, Petr)**; Rokyta, R (Rokyta, Richard); Kuzmanov, B (Kuzmanov, Boyko); Jakl, M (Jakl, Martin); Poloczek, M (Poloczek, Martin); Kanovsky, J (Kanovsky, Jan); Bernat, I (Bernat, Ivo); Hlinomaz, O (Hlinomaz, Ota); Belohlavek, J (Belohlavek, Jan); Kral, A (Kral, Ales); Mrazek, V (Mrazek, Vratislav); Grigorov, V (Grigorov, Vladimir); Djambazov, S (Djambazov, Slaveyko); Petr, R (Petr, Robert); Knot, J (Knot, Jiri); Bilkova, D (Bilkova, Dana); Fischerova, M (Fischerova, Michaela); Vondrak, K (Vondrak, Karel); Maly, M (Maly, Marek); Lorencova, A (Lorencova, Alena). Title: Primary angioplasty in acute myocardial infarction with right bundle branch block: should new onset right bundle branch block be added to future guidelines as an indication for reperfusion therapy? Source: EUROPEAN HEART JOURNAL Volume: 33 Issue: 1 Pages: 86-95 DOI: 10.1093/eurheartj/ehr291.*

2.8 Porovnání výsledků léčby STEMI a NSTEMI

Na rozdíl od pacientů se STEMI, je skupina s NSTEMI výrazně starší s četnějšími komorbiditami a take rozsáhlejším koronárním postižením. Na souboru 6602 konsekutivních pacientů jsme ve skupině NSTEMI prokázali častější postižení kmene levé koronární tepny (6,0% vs 1,1%; p<0,001), onemocnění všech tří koronárních tepen (53,1% vs 30%; p<0,001) a nevýznamně odlišnou nemocniční úmrtnost. Naše výsledky dále podporují volbu agresivní invazivní strategie nejen u pacientů se STEMI, ale i NSTEMI.

Celý text níže uvedené publikace je uveden v příloze 3.11.

*Knot, J (Knot, Jiri); **Kala, P (Kala, Petr)**; Rokyta, R (Rokyta, Richard); Stasek, J (Stasek, Josef); Kuzmanov, B (Kuzmanov, Boyko); Hlinomaz, O (Hlinomaz, Ota); Belohlavek, J (Belohlavek, Jan); Rohac, F (Rohac, Filip); Petr, R (Petr, Robert); Bilkova, D (Bilkova, Dana); Djambazov, S (Djambazov, Slavejko); Grigorov, M (Grigorov, Mladen); Widimsky, P (Widimsky, Petr) Title: Comparison of outcomes in ST-segment depression and ST-segment elevation myocardial infarction patients treated with emergency PCI: data from a multicentre registry. Source: CARDIOVASCULAR JOURNAL OF AFRICA Volume: 23, Issue: 9, Pages: 495-500.*

2.9 Pacienti po srdeční zástavě jako nejrizikovější skupina nemocných

Srdeční zástava představuje akutní ohrožení pacienta na životě a vzhledem ke zlepšujícímu se systému resuscitační péče se jedná o postupně narůstající skupinu pacientů. V nedávné době bylo do praxe zavedeno několik systémů pro automatickou srdeční masáž, které mohou umožnit i provedení primární PCI v jejím průběhu. Jedno z prvních využití sytému Lucas (Jolife A.B., Švédsko) v České republice bylo popsáno na našem pracovišti.

Celá komplexní problematika péče o pacienty po mimonemocniční srdeční zástavě byla námi popsána jako konsensus expertů Evropské asociace PCI. Pacienti se STEMI by měli být přímo transportováni na katetrizační sál s non-stop provozem, diagnostická koronarografie by však měla být součástí diagnosticko-léčebného algoritmu u všech pacientů po vyloučení nekardiální etiologie. Intervenční kardiologové by nyní měli být připraveni i na tyto pacienty, u kterých je akutní rozhodovací proces často mnohem komplikovanější.

Celý text níže uvedené publikace je uveden v příloze 3.12.

Kala, P., *Karlík, R., Boček, O., Neugebauer, P., Poloczek, M., Pařenica, J., Vytiska, M., Kolářová, I., Hladilová, K., Dostálová, L., Jeřábek, P. The use of automated external cardiac massage during primary PCI [Využití automatické zevní srdeční masáže při primární PCI] (2010) Intervencni a Akutni Kardiologie, 9 (4), pp. 204-207.*

Celý text níže uvedené publikace, na které jsem se podílel jako předseda Stent for Life Initiative, je uveden v příloze 3.13.

*Noc M[1], Fajadet J, Lassen JF, **Kala P**, MacCarthy P, Olivecrona GK, Windecker S, Spaulding C. Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI)/Stent for Life (SFL) groups. EuroIntervention. 2014 May 20;10(1):31-7. doi: 10.4244/EIJV10I1A7.*

2.10 Optická koherentní tomografie a STEMI

Cílem práce bylo posouzení možností využití optické koherentní tomografie (OCT) (42,43) jako v současnosti nejpřesnější invazivní zobrazovací metody s rozlišením 10 – 15 um pro vedení techniky primární PCI. Na souboru 100 pacientů bylo prokázáno, že u 20% pacientů nebylo nutné implantovat koronární stent a proceduru bylo možné ukončit po provedení manuální tromboaspirace s angiograficky optimálním výsledkem. Tato práce jako první demonstrovala příznivé klinické výsledky po využití této techniky v léčbě STEMI v průběhu 12-ti měsíčního sledování.

Celý text níže uvedené publikace je uveden v příloze 3.14.

*Cervinka, P (Cervinka, Pavel); Spacek, R (Spacek, Radim); Bystron, M (Bystron, Marian); Kvasnak, M (Kvasnak, Martin); Kupec, A (Kupec, Andrej); Cervinkova, M (Cervinkova, Michaela); **Kala, P (Kala, Petr)**. Title: Optical Coherence Tomography-Guided Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction Patients: A Pilot Study. Source: CANADIAN JOURNAL OF CARDIOLOGY Volume: 30, Issue: 4, Pages: 420-427.*

Cílem další, již randomizované multicentrické práce, bylo posouzení rozdílů při angiograficky vs OCT vedené primární PCI u 201 pacientů se STEMI do 12 hod od vzniku příznaků. Ve skupině s OCT bylo u 29% pacientů nutné pokračování v intervenci k dosažení optimálního výsledku. S odstupem 9 měsíců byla při kontrolním OCT zjištěna významně nižší „in-segment“ plocha stenózy ((6% [-11, 19] versus 18% [3, 33]; p=0.0002) ve prospěch pacientů ve skupině s OCT.

Celý text níže uvedené publikace zaslané do časopisu International Journal of Cardiology je uveden v příloze 3.15.

***Kala Petr**, Cervinka Pavel, Jakl Martin, Kanovsky Jan, Kupec Andrej, Spacek Radim, Kvasnak Martin, Poloczek Martin, Cervinkova Michaela, Bezerra Hiram, Valenta Zdenek, Attizzani Guilherme F, Schnell Audrey, Lu Hong, Costa Marco. OCT Guidance During Stent Implantation in Primary PCI: A Randomized Multicenter Study With Nine Months of Optical Coherence Tomography Follow-up. Submitted to International Journal of Cardiology 2016.*

Přesným posouzením změn radiální tepny po první transradiální PCI pomocí OCT po výkonu a s odstupem 9 měsíců u 100 pacientů jsme zjistili statisticky významný nárůst objemu intimy 33.9mm^3 (19.0; 69.4) versus 39.0mm^3 (21.7; 72.6) (p<0.001); a zmenšení objemu radiálního lumen 356.3mm^3 (227.8; 645.3) versus 304.7mm^3 (186.1; 582.7) (p<0.001).

Celý text níže uvedené publikace zaslané do časopisu Eurointervention je uveden v příloze 3.16.

***Petr Kala**, Jan Kanovsky, Tereza Novakova, Roman Miklik, Otakar Bocek, Martin Poloczek, Petr Jerabek, Lenka Privarova, Tomas Ondrus, Jiri Jarkovsky, Milan Blaha, Gary Mintz. Radial artery changes after transradial PCI – A serial optical coherence tomography volumetric study. Submitted to Eurointervention Journal 2016.*

2.11 Koncept funkční revaskularizace neinfarktových tepen

U skupiny pacientů se STEMI a onemocněním vice koronárních tepen je s výjimkou pacientů v kardiogenním šoku a trvající nestabilitou, v současnosti doporučena pouze primární PCI infarktové tepny. Při znalosti relativně časté přítomnosti dalších nestabilních koronárních lézí na neinfarktových tepnách, ale i velmi účinné sekundárně-preventivní farmakoterapie, je otázka optimální diagnosticko-léčebné strategie neinfarktových tepen jednou z velice důležitých a aktuálních otázek. Jednou z možností, vycházející z níže uvedených studií, je využití konceptu tzv. funkční revaskularizace (44), který může pacienty stratifikovat do dvou skupin. První skupinu tvoří pacienti, u kterých by měla být v případě technické a jiné schůdnosti indikována revaskularizace, druhou skupinu s funkčně nevýznamným koronárním postižením je možné bezpečně léčit konzervativně pomocí individualizované a optimálně nastavené farmakoterapie. Vedle neinvazivních testů se za zlatý standard nyní považuje invazivní posouzení funkční významnosti koronárních stenóz pomocí měření frakční průtokové rezervy myokardu (FFR) založené na poměru středních tlaků před a za stenózou v průběhu maximální, farmakologicky navozené hyperémie. Za normálních okolností je hodnota tohoto poměru v epikardiálním koronárním řečišti 1,0, hodnota ≤0,80 značí funkčně významné koronární postižení s negativním prognostickým dopadem (45–47).

U stabilních nebo stabilizovaných pacientů potvrdil De Bruyne a kol. studie FAME 2 (viz níže) předpoklad lepších klinických výsledků u pacientů s funkčně vedenou revaskularizací pomocí PCI s implantací lékových stentů 2. generace oproti pacientům léčeným konzervativně. Výsledky od 1220 pacientů, z nichž 888 bylo randomizováno a 332 bylo zařazeno do paralelně probíhajícího registru, ukázaly významně nižší riziko výskytu hlavních kardiovaskulárních komplikací ve skupině PCI (4,4% vs 12,7%; p<0,001), které bylo způsobeno vyšší nutností urgentní revaskularizace v konzervativní větvi (11,1% vs 1,6%; p<0,001). Pozitivní přínos tzv. FFR-vedené PCI byly následně potvrzeny i v průběhu 2-letého sledování.

Vedle hyperemického indexu FFR, který byl klinicky validován, se v nedávné době začal používat i další index iFR (Instantaneous wave-Free Ratio) (48), který je indexem klidovým. Práce Berryho a kol. (viz níže) pak byla první, která na souboru 206 konsekutivních pacientů prokázala nedostatečnou korelaci iFR s FFR a tento index by měl být zatím využíván pouze pro výzkumné účely, ale nikoli pro klinické rozhodování. Ve srovnání s cut-off hodnotou FFR

≤0,80 byla diagnostická přesnost 60% v případě posouzení všech tepen a pouze 51% v případě hodnot FFR mezi 0,60 – 0,90.

Celé texty níže uvedených publikací jsou uvedeny v přílohách 3.17 a 3.18.

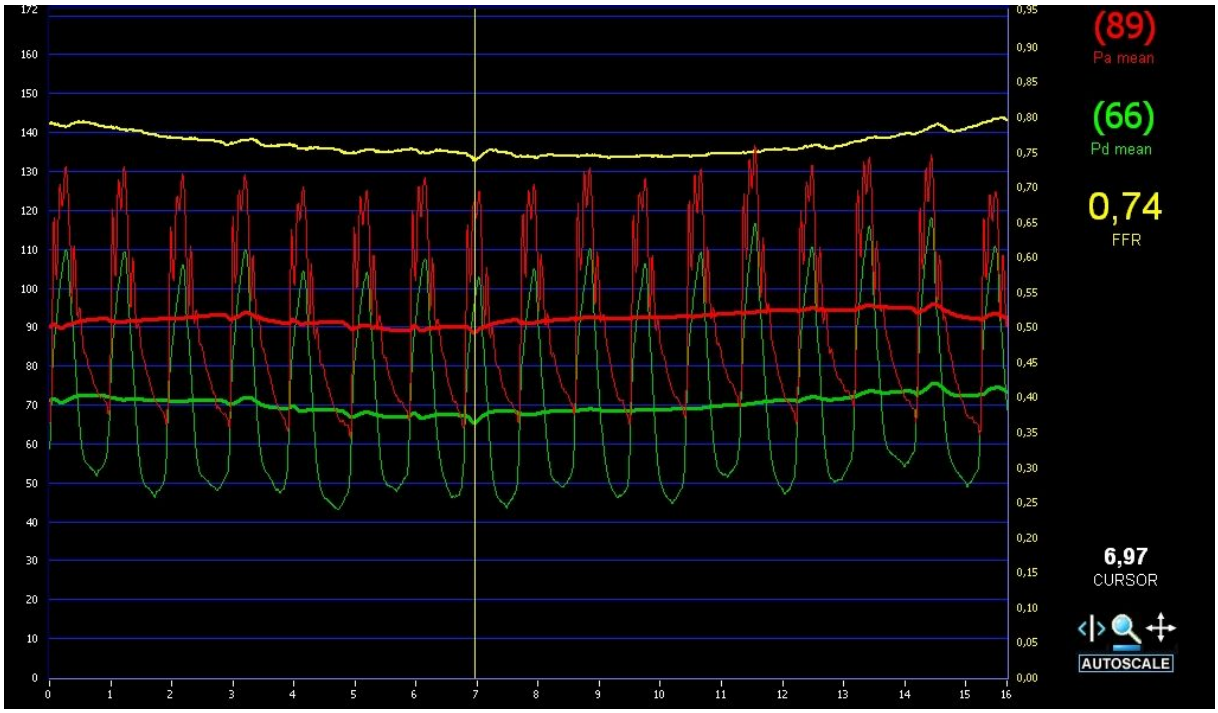
De Bruyne, B (De Bruyne, Bernard); Pijls, NHJ (Pijls, Nico H. J.); Kalesan, B (Kalesan, Bindu); Barbato, E (Barbato, Emanuele); Tonino, PAL (Tonino, Pim A. L.); Piroth, Z (Piroth, Zsolt); Jagic, N (Jagic, Nikola); Mobius-Winckler, S (Mobius-Winckler, Sven); Rioufol, G (Rioufol, Gilles); Witt, N (Witt, Nils); ***Kala, P (Kala, Petr)****; MacCarthy, P (MacCarthy, Philip); Engstrom, T (Engstrom, Thomas); Oldroyd, KG (Oldroyd, Keith G.); Mavromatis, K (Mavromatis, Kreton); Manoharan, G (Manoharan, Ganesh); Verlee, P (Verlee, Peter); Frobert, O (Frobert, Ole); Curzen, N (Curzen, Nick); Johnson, JB (Johnson, Jane B.); Juni, P (Jueni, Peter); Fearon, WF (Fearon, William F.) Group Author(s): FAME 2 Trial Investigators. Title: Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease Source: NEW ENGLAND JOURNAL OF MEDICINE Volume: 367 Issue: 11 Pages: 991-1001.*

De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, ***Kala P****, MacCarthy P, Engström T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014 Sep 25;371(13):1208-17. doi: 10.1056/NEJMoa1408758. Epub 2014 Sep 1. Erratum in: N Engl J Med. 2014 Oct 9;371(15):1465.*

Celý text níže uvedené publikace je uveden v příloze 3.19.

Berry, C (Berry, Colin); van 't Veer, M (van 't Veer, Marcel); Witt, N (Witt, Nils); ***Kala, P (Kala, Petr)****; Bocek, O (Bocek, Otakar); Pyxaras, SA (Pyxaras, Stylianos A.); McClure, JD (McClure, John D.); Fearon, WF (Fearon, William F.); Barbato, E (Barbato, Emanuele); Tonino, PAL (Tonino, Pim A. L.); De Bruyne, B (De Bruyne, Bernard); Pijls, NHJ (Pijls, Nico H. J.); Oldroyd, KG (Oldroyd, Keith G.). Title: VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice). Source: JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY Volume: 61 Issue: 13 Pages: 1421-1427.*

Obr. 12: Demonstrační obrázek invazivního posouzení funkční významnosti koronární stenózy měřením frakční průtokové rezervy myokardu (FFR). Hodnota 0,74 značí funkčně významnou stenózu vyžadující revaskularizaci (žlutá křivka - FFR jako poměr středních tlaků v průběhu maximální, farmakologicky navozené hyperémie, červená křivka – krevní tlak v aortě, zelená křivka – krevní tlak v koronární tepně distálně za stenózou)



Pa mean – střední tlak v aortě, Pd mean – střední tlak distálně od stenózy, FFR – frakční průtoková rezerva myokardu

2.12 Návrh nové klasifikace akutního koronárního syndromu

Česká kardiologická společnost, která ve svých doporučených postupech jako první v Evropě uvedla primární PCI jako metodu volby u pacientů se STEMI, se zabývá konceptem tzv. pokračující (ongoing) ischemie. Ten by měl zjednodušit praktické rozhodování o směrování pacienta do katetrizačního centra nebo spádové nemocnice. Tento koncept je v současnosti klinicky testován a v budoucnu by mohl nahradit dosavadní rozdělení pacientů na pacienty se STEMI a ostatní s probíhající koronární nestabilitou, ale s nižším rizikem.

Celý text níže uvedené publikace je uveden v příloze 3.20.

Widimský, P., Rokyta, R., Št'ásek, J., Bělohlávek, J., Červinka, P., ***Kala, P.*** Akutní koronární syndromy s pokračující ischemií myokardu versus akutní koronarní syndromy bez pokračující ischemie.Nová klasifikace akutních koronarních syndromů by měla nahradit starou klasifikaci založenou na přítomnosti nebo nepřítomnosti elevace úseku ST. Odborné stanovisko Česke kardiologické společnosti. *(2013) Cor et Vasa, 55 (3), pp. E225-E227.*

2.13 Hypotenze u pacientů po primární PCI

Výskyt hypotenze s jejím eventuálním prognostickým dopadem byl pečlivě studován před érou primární PCI. V naší prospektivní práci na 293 konsekutivních pacientech se STEMI léčenými primární PCI jsme zjistili, že významné ataky hypotenze se systolickým tlakem pod 90 mm Hg trvající 30 min a více byly pozorovány celkem u téměř 1/3 pacientů. Ženské pohlaví bylo zjištěno jako nejvýznamnější nezávislý prediktor hypotenze ($p<0,0001$). Ačkoliv se klinický osud skupin s/bez hypotenze v průběhu 20-ti měsíčního sledování celkově nelišil, významně horší celková úmrtnost byla zjištěna u pacientů netolerujících blokátory angiotensin-konvertujícího enzymu či aldosteronových receptorů.

Celý text níže uvedené publikace odeslané do časopisu American Heart Journal je uveden v příloze 3.21.

Petr Kala*, Tomas Novotny, Irena Andrsova, Klara Benesova, Maria Holicka, Jiri Jarkovsky, Katerina Hnatkova, Jan Kanovsky, Lumir Koc, Monika Mikolaskova, Tereza Novakova, Tomas Ondrus, Lenka Privarova, Marek Malik. Hypotension episodes during the sub-acute phase of ST elevation myocardial infarction: sex differences and covariates. Submitted to American Heart Journal 2016.*

3. Přílohy

3.1

Kala, P. *European society of cardiology st-segment elevation myocardial infarction guidelines in perspective - focused on primary percutaneous coronary intervention (2014) Interventional Cardiology Review, 9(1): 7-10.*

(přehledová práce – kvantitativní podíl uchazeče 100 %)

Práce byla publikována v mezinárodním recenzovaném časopise.

European Society of Cardiology ST-segment Elevation Myocardial Infarction Guidelines in Perspective – Focused on Primary Percutaneous Coronary Intervention

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Abstract

Patients suffering acute myocardial infarction with ST-segment elevation myocardial infarction (STEMI) require full attention of the whole STEMI network to save their lives and to improve the quality of life after a heart attack. Implementation of the most recent European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) STEMI Guidelines into the practice is the holy grail of the healthcare systems and all stakeholders. In relation to this, the Stent for Life Initiative can serve as one of very successful and effective models in Europe and beyond. Although the evidence-based approach may be applied to majority of patients, the tailored and updated therapy needs to be modified in concordance with the patients' risk profile, experience and availability of medical resources. Some 'hot topics', issues, differences between the ESC and ACC/AHA Guidelines, latest information and perspectives are discussed in this short review; focused on primary percutaneous coronary intervention (PCI) as the most effective reperfusion therapy.

Keywords

Acute myocardial infarction, ST-segment elevation myocardial infarction, primary percutaneous coronary intervention, clinical guidelines, thromboaspiration, radial access, ongoing ischaemia

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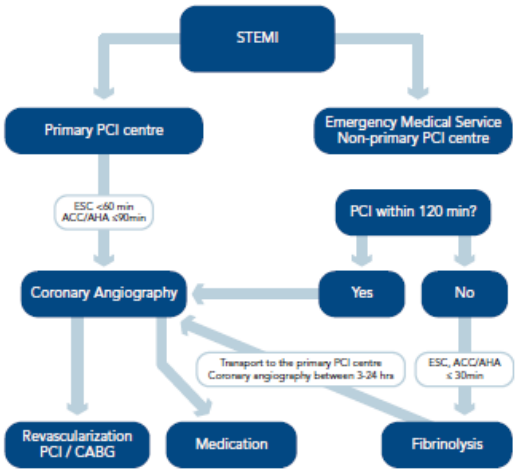
Patients suffering acute myocardial infarction with ST-segment elevation (STEMI) require full attention of the whole STEMI network to save their lives and to improve the quality of life after a heart attack. Close cooperation among all stakeholders on a national and regional level has to be established. The emergency medical service (EMS) and direct transportation to the 24 hours a day, seven days a week (24/7) catheterisation laboratory play a crucial role together with the patient-oriented public education campaigns. The most recent Clinical Practice Guidelines of the European Society of Cardiology on patients with acute myocardial infarction with ST-segment elevation (ESC STEMI Guidelines) were published in 2012 and covered the complexity of organisational and medical aspects from the emergent diagnosis and treatment until outpatient care.[1] The reason for establishing the Stent for Life Initiative and its ACT NOW. SAVE A LIFE public campaign as a joint initiative of the European Association of percutaneous coronary intervention (EAPCI) and European Percutaneous Cardiovascular Revascularization Course (EuroPCR) was the lack of implementation of the Guidelines into the practice across Europe. The incredible achievements in 16 participating countries and organisations can be followed online at www.stentforlife.com and are well documented in the recent publication of Kristensen et al.[2]

Atypical electrocardiogram (ECG) presentations that deserve prompt management in patients with signs and symptoms of ongoing myocardial ischaemia include:

- left bundle branch block (LBBB);
- ventricular paced rhythm;
- patients without diagnostic ST-segment elevation but with persistent ischaemic symptoms;
- isolated posterior myocardial infarction; and
- ST-segment elevation in augmented vector right lead (aVR).[1]

The patients with ongoing ischaemic symptoms, even in the absence of ST-segment elevations, should be managed in the same way as the STEMI patients. This recommendation, based more on experience than evidence, may shorten the delay to diagnosis and optimal treatment, and at the same time may decrease the risk of bleeding after the potent antithrombotic medication. A bit provocative is the suggestion of new and simplified classification of acute coronary syndrome with/without ongoing myocardial ischaemia (ACS w/wo OMI) instead of the currently used STEMI and non-STEMI. Such an approach may better reflect current treatment practice in some catheterisation laboratories (cath labs) and regions with the aim of facilitating the decisions made at the time of the first medical contact (FMC). The target of such simplification is the earliest selection of patients at high clinical risk that should be transported directly to the cath lab or 24/7 primary percutaneous coronary intervention (PCI) centre bypassing any other facility. Widimsky et al.[3] defined the ACS w OMI as ongoing (or recurrent) clinical signs of acute myocardial ischaemia (i.e. persistent chest pain and/or dyspnoea at rest) plus at least one of the following:

Figure 1: Timelines in the European Society of Cardiology and American College of Cardiology/American Heart Association ST-segment Elevation Myocardial Infarction Guidelines



ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass grafting; ESC = European Society of Cardiology; PCI = percutaneous coronary intervention; STEMI = ST-segment myocardial infarction.

1. ST-segment elevations in ≥2 consecutive ECG leads (≥2 mm for leads V2–V3, ≥0.5 mm for leads V7–V9 and ≥1 mm for other leads);
2. new onset bundle branch block (right or left);
3. persistent ST-segment depressions in ≥2 consecutive ECG leads (≥2 mm for chest leads and ≥1 mm for extremity leads);
4. cardiogenic shock or 'pre-shock' type of haemodynamic instability (low-to-normal blood pressure as well as tachycardia and cool extremities) due to suspected ischaemia;
5. malignant arrhythmias including resuscitated cardiac arrest with return of spontaneous circulation;
6. clinical signs of acute heart failure (Killip II–IV); and
7. new onset of a wall motion abnormality on cardiac imaging.

It is important to keep in mind that isolated findings as listed above (e.g. malignant arrhythmias without any clinical or ECG sign of acute ischaemia) do not fulfil this definition. The high clinical suspicion for acute myocardial infarction is important. Direct transport to the cath lab (bypassing any other location, e.g. intensive care unit or emergency room) is always required in groups 1–4. Patients from groups 5–7 should also be transported to a non-stop (24/7) primary PCI facility (either directly to the cath lab or they may be primarily admitted to the intensive cardiac care unit with the cath lab immediately available). Healthcare systems with multiple organisational issues may especially benefit from such practical recommendations.

Time Intervals From Onset of Symptom Until Effective Treatment

The principle aim of the medical systems in patients with STEMI is to prevent their death and to improve the quality of life after a heart attack. Besides the effective treatment of ventricular tachycardia and fibrillation in the pre-hospital phase, shortening of the total ischaemic time as much as possible is crucial. 'Patient delay' and 'system delay', where the patient delay means the delay between symptom onset and FMC followed by the system delay until reperfusion therapy.

There is one important question with potential clinical consequences: who represents the FMC? Based on the ESC Guidelines, FMC is defined as the point at which the patient is either initially assessed by a paramedic or physician or other medical personnel in the pre-hospital setting, or the patient arrives at the hospital emergency department and therefore often in the outpatient setting.[1] According to the time intervals mentioned in the ESC Guidelines, the preferred/accepted system delay from FMC to the most effective reperfusion strategy (primary PCI, i.e. wire passage) should not exceed 90/120 minutes (min) in most patients and ≤60/90 min in high-risk patients with large anterior STEMI and early presenters within two hours. In case of fibrinolysis, the recommended system delay (FMC to needle) is ≤30 min. The diagnosis of STEMI should be verified within 10 min of FMC, which in fact means that the FMC personnel has to have the 12-lead ECG available. In future, the time of the medical system activation (i.e. the time of the first phone call) should be involved in the time intervals monitoring. The definition of the FMC might be modified to the first phone or personal contact of the patient with any representative of the medical system.

Current recommendation for reperfusion and the difference between the ESC and ACC/AHA[4] STEMI Guidelines is described in *Figure 1*.

Primary Percutaneous Coronary Intervention – Procedural Aspects and Issues

Radial Over Femoral Access In Experienced Operators (Class IIa, Level of Evidence B)

The role of radial access has been investigated for 20 years[5] but in STEMI patients this topic has been especially highlighted. The Radial Versus Femoral Access for Coronary Intervention (RIVAL) STEMI subanalysis[6,7] (1,958 patients) and Radial Versus Femoral Investigation in ST Elevation Acute Coronary Syndrome (RIFLE-STEACS)[8] trial (1,001 patients) demonstrated a significant mortality benefit in a large cohort of STEMI patients treated with primary PCI via transradial approach (TRA) (44 % reduction in all-cause death in RIVAL STEMI and 60 % in cardiac death in RIFLE-STEACS). These findings were supported by two large meta-analyses published recently by De Luca et al.[9] and Karrowni et al.[10] In the contrary, no survival benefit was found in the ST Elevation Myocardial Infarction Treated by RADIAL or Femoral Approach in a Multicenter Randomized Clinical Trial (STEMI-RADIAL) in 707 patients.[11] Although the direct association between the radial access and mortality may still be doubtful, the significantly lower risk of vascular and bleeding complications should promote the TRA as the preferred access site for most operators.[12] Proper training and enough experience are necessary to achieve the optimal results that should receive the strongest level of evidence A in the upcoming guidelines.

Routine Manual Thrombus Aspiration (Class IIa, Level of Evidence B)

Recently, the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction study (TAPAS) was the only randomised trial showing the clinical benefit of routine thrombus aspiration versus conventional primary PCI. The mortality at one-year, as the secondary and not pre-specified clinical endpoint, was found less frequently in the manual thrombus aspiration group (3.6 versus 6.7 %, p=0.018).[13,14] The concerns about the single-centre experience and the technique of conventional PCI (balloon predilation

before stenting) seem to be even more relevant after the first large-scale international multicentre randomised Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial published by Fröbert et al.[15] This trial reflects the real-world practice using a unique enrolment of patients from the national comprehensive Swedish Coronary Angiography and Angioplasty Registry (SCAAR registry) and endpoints evaluation through national registries without losing a single patient to follow-up. The clot aspiration in comparison with the balloon treatment in 7,244 STEMI patients did not show any statistical difference in mortality as the primary endpoint at 30 days (3.0 versus 2.8 %; p=0.63). This finding was consistent across all pre-specified subgroups and no difference was observed in the rate of secondary endpoints obtained from the Swedish Websystem for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry and the national discharge registry (30-day rates of hospitalisation for recurrent myocardial infarction, stent thrombosis, target vessel revascularisation, target lesion revascularisation, and the composite of all-cause mortality or recurrent myocardial infarction). Currently, the routine manual thrombus aspiration seems to be not supported by the evidence and should be used only selectively. The data from the ongoing Trial of Routine Aspiration Thrombectomy With Percutaneous Coronary Intervention (PCI) Versus PCI Alone in Patients With ST-Segment Elevation Myocardial Infarction (STEMI) Undergoing Primary PCI (TOTAL) with more than 10,000 patients (ClinicalTrials.gov: NCT01149044) will probably have a definite impact on the indication of routine thrombus aspiration during STEMI.[16]

Periprocedural Pharmacotherapy

Based on the STEMI Guidelines, the dual antiplatelet therapy (Aspirin and an adenosine diphosphate [ADP] receptor blocker) is recommended together with parenteral anticoagulant as early as possible before angiography[1] (i.e. immediately after the diagnosis of STEMI is confirmed). The novel agents, prasugrel or ticagrelor, should be preferred over clopidogrel[17,18,19] in combination with bivalirudin,[20] enoxaparin[21] or unfractionated heparin.[22] The use of glycoprotein IIb/IIIa inhibitors is indicated only as bailout in high-risk clinical situations, like the presence of large thrombus burden and no-flow phenomenon after PCI. The potential advantage of intracoronary administration of abciximab has been studied but the results have to be confirmed.[23] Combination of the administration of potent drugs requires an individualised approach with respect to a patient's risk profile (prothrombotic versus bleeding), complexity of coronary pathology, selected interventional strategy and a good clinical judgement.[24] Recommendation of the ESC and ACC/AHA are shown in *Tables 1* and *2*.

Revascularisation Strategy for ST-segment Elevation Myocardial Infarction with Multivessel Disease

Culprit-only PCI has been recommended in STEMI patients except for patients in cardiogenic shock and continuous ischaemia despite successful infarct-related artery treatment.[1] Recently, Wald et al. enrolled 465 patients with STEMI, multivessel disease and primary PCI of the infarct-related artery in the Randomized Trial of Preventive Angioplasty in Myocardial Infarction (PRAMI).[25] The patients were randomly assigned to either preventive or no preventive PCI of the non-culprit vessels with at least 50 % stenoses. The study was stopped preliminary because of a highly significant decrease of the composite of death from cardiac causes, non-fatal myocardial infarction, or refractory angina in the preventive PCI group of patients (hazard ratio [HR] 0.35; p<0.001). Hazard ratios for the three components of the primary outcome were 0.34; 0.32 and 0.35, respectively. We are dealing with an exciting finding that needs further investigation. One of the unanswered questions in STEMI patients is the additional value of the functional revascularisation concept based on the fractional flow reserve measurement (ongoing Comparison Between Fractional Flow Reserve Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With multivessel disease [COMPARE-ACUTE] trial, ClinicalTrials.gov: NCT01399736).

Table 1: European Society of Cardiology Guidelines on Oral P2Y12 Antiplatelet Therapy in ST-segment Elevation Myocardial Infarction

Clopidogrel	IC*
Clopidogrel, 300 mg loading	NA
Clopidogrel, 600 mg loading	IC/B
Prasugrel	IB
Ticagrelor	IB

**When prasugrel or ticagrelor are either not available or contraindicated. NA = not available.*

Table 2: American College of Cardiology/American Heart Association Guidelines on Oral P2Y12 Antiplatelet Therapy in ST-segment Elevation Myocardial Infarction/Percutaneous Coronary Intervention

Clopidogrel (600 mg loading)	IC for primary PCI
Prasugrel (60 mg loading)	IB for primary PCI
Ticagrelor (180 mg loading)	IB for primary PCI
Clopidogrel (with thrombolytics)	IC for non-primary PCI
Clopidogrel (without thrombolytics)	IB for non-primary PCI
Prasugrel (without thrombolytics)	IB for non-primary PCI

PCI = percutaneous coronary intervention.

Conclusion

Although the evidence-based approach described in the Guidelines may be applied to the majority of STEMI patients, the tailored and updated therapy needs to be modified in concordance with the patients' risk profile, our experience and availability of medical resources. The establishment of the STEMI network and cooperation among all stakeholders can serve as the background for further improvements and new trials focused on clinical outcomes. ■

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3.2

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Pharmaco-mechanic Antithrombotic Strategies to Reperfusion of the Infarct-Related Artery in Patients with ST-Elevation Acute Myocardial Infarctions

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Abstract Primary percutaneous coronary intervention is the best treatment of patients with ST elevation myocardial infarction (STEMI). When managing a STEMI patient, our approach must be rapid and aggresive in order to interrupt the pathological process of thrombus formation and stabilization. The therapy must be initiated prior to angiography (pretreatment), continued during the procedure (periprocedural), recovery phase (in-hospital), and follow-up. The treatment strategies resulting in thrombus dissolution/extraction have focused on optimization of both pharmacological and interventional therapies. At present, there is no optimal evidence-based approach to all patients with STEMI, and the treatment of these patients needs to be modified with respect to the risk profile, availability of medical resources, and our experience. In this review, we summarize current pharmacological and interventional strategies used in the setting of STEMI and discuss potential benefits of novel dosing regimens and combinations of drugs and techniques.

Keywords Acute myocardial infarction · Thrombectomy · Antiplatelet therapy · STEMI · Thrombus management

Introduction

During the course of acute myocardial infarction with ST elevations (STEMI), where symptoms prevail and/or the time delay from the onset of chest pain to the first medical contact is <12 h, the opening of culprit coronary artery must be our major concern. One can achieve this by performing primary percutaneous coronary intervention (PCI) as early as possible or by applying fibrinolytic therapy where PCI is not available and/or the expected time delay to PCI is longer than 120 min (our goal is to achieve the time-to-treatment delay from first medical contact (FMC) to wire passage ≤90 min and in high-risk patients with large anterior infarcts and early presenters within 2 h≤60 min). If reperfusion therapy is fibrinolysis, the goal is to reduce this delay (FMC to needle) to ≤30 min [1]. Both strategies involve the use of an anticoagulant (heparin [2] or preferably enoxaparine [3, 4]) and aspirin. The outcome of patients may be improved both with the use of adjunctive antithrombotic medication—glycoprotein (GP) IIb/IIIa inhibitors, adenosine diphosphate (ADP) receptor blockers, direct thrombin inhibitors—or mechanical removal of occluding thrombotic mass. To optimize the therapy of STEMI patients, with the support of clinical trials results and our best clinical judgement and experience, we can successfully reduce both bleeding and thrombotic adverse events and improve immediate outcome (thrombolysis in myocardial infarction (TIMI) arterial flow, myocardial blush grade (MBG), ST segment resolution (STR)), short-, and long-term survival when combining pharmacological and mechanical approaches. In this review, we will summarize indications of antithombotic drugs and their potential benefit when combined with mechanical reperfusion.

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Pharmacotherapy

ADP Receptor Blockers

Ticlopidine was the first $P2Y_{12}$ ADP- receptor blocker used in combination with aspirin to reduce thrombotic events compared with warfarin after stent implantation [5]. It had never been tested in the setting of STEMI. Due to its side-effects (neutropenia, rash, gastrointestinal intolerance), ticlopidine

was gradually replaced by the ten times more potent and safer antiplatelet agent clopidogrel.

In the era of fibrinolytic therapy of STEMI, clopidogrel when added to aspirin reduced the combined cardiovascular endpoint by 9 % and death by 7 % in the COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) trial [6]. When a loading dose of 300 mg and subsequent maintenance dose of 75 mg daily were administered prior to fibrinolysis, the 20 % relative risk reduction was observed within a 30-day follow-up in STEMI patients in the CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) trial [7]. In concordance with other clopidogrel trials, dual antiplatelet therapy is indicated in STEMI patients for 12 months. An observational study of 255 consecutive STEMI patients showed a significantly lower incidence of post-PCI myocardial blush grade 0 or 1 (odds ratio, 0.64; 95 % confidence interval 0.43 to 0.96, $p=0.03$) and significantly less common no-reflow phenomenon (odds ratio, 0.38; 95 % confidence interval 0.15 to 0.98, $p=0.04$) when a 600-mg loading dose had been applied compared with a 300-mg loading dose group. Also, higher 1-year survival free of major adverse cardiac events was observed in the 600-mg group (hazard ratio, 0.57; 95 % confidence interval 0.33 to 0.98, $p=0.04$) [8]. A relatively small but randomized study in 201 STEMI patients found results supporting the use of the 600-mg loading dose in the setting of STEMI (lower median creatine kinase-myocardial band, troponin I, less TIMI flow<3 after PCI, better left ventricular ejection fraction, and fewer 30-day major adverse cardiovascular events) [9]. The 600-mg loading dose has been adopted worldwide. Moreover, the 600-mg loading dose followed by a 150-mg maintenance dose for 7 days further improves short-term outcome in STEMI patients treated with primary PCI [10]. These clinical findings might be associated with more pronounced decrease of residual platelet activity achieved with more aggressive loading dose that helps overcome clopidogrel resistance [11]. According to the results of several genetic substudies, there are two major determinants of clopidogrel resistance—polymorphism of P-glycoprotein (ACBC1, absorption) and cytochrome P450 isoenzyme CYP2C19 (two-step metabolic activation). Up to 20–40 % of patients are either non-responders or poor responders to clopidogrel therapy [12], resulting in potential negative clinical consequencies.

Prasugrel was the first out of two novel potent antiplatelet drugs to appear on the market. It also blocks thrombocytes irreversibly but requires just a single-step metabolic oxydation that is CYP2C19-independent, and as such, the activation of the prodrug is more rapid, efficient, and genetically much less determined when compared with clopidogrel [13]. In clopidogrel-naive STEMI patients in the TRITON (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel) TIMI 38 trial, prasugrel given prior to primary PCI significantly reduced the composite cardiovascular endpoint both at 30 days (hazard ratio (HR)= 0.68) and 15 months (HR=0.79) when compared with clopidogrel. The incidence of myocardial infarction and particularly stent thrombosis at 15 months was also lower with prasugrel (HR=0.75 and HR=0.58, respectively). Unlike other subgroups, the STEMI patients profited from prasugrel therapy with no increase of major and life-threatening bleeding. The concomitant use of GP IIb/IIIa inhibitors further improved patients' outcome. In patients without prior stroke, aspirin+ fractionated/unfractionated heparin+prasugrel with/without GP IIb/IIIa blocker is an evidence-based approach in the setting of STEMI [14].

Ticagrelor is a reversible ADP receptor blocker with no metabolic activation required. It is even more efficient in reducing residual platelet activity in acute coronary syndrom (ACS) patients than prasugrel [15]. When administered on top of clopidogrel or to clopidogrel-naive patients in the setting of STEMI, ticagrelor significantly reduced the incidence of myocardial infarction (HR=0.80), stent thrombosis (HR=0.66), and all-cause mortality (HR=0.87) at 12 months when compared with clopidogrel in the PLATO (PLATelet inhibition and patient Outcomes) trial [16]. There was no substantial increase of major and life-threatening bleeding but notably higher incidence of stroke (HR=1.63). Reduction of the primary composite efficacy endpoint was not observed. The concomitant use of GP IIb/IIIa inhibitors did not further improve patients' outcome.

To sum up, both prasugrel and ticagrelor are as safe as clopidogrel but more efficient in the setting of STEMI. The indirect comparison available prefers prasugrel over ticagrelor in patients presenting with STEMI.

Prasugrel or ticagrelor or clopidogrel should be administered as soon as the diagnosis has been made in most of STEMI patients prior to angiography. Respecting the fact that prasugrel pretreatment is associated with a markedly increased risk of coronary artery bypass graft-related major bleeding, both in overall ACS population and STEMI subgroup (HR=8.19), in patients where the diagnosis is doubtful (Fig. 7 on the right) or their risk profile predisposes to bleeding complications, we suggest preloading with clopidogrel or ticagrelor. In centers preferring prasugrel application, this should be held until angiografic findings have confirmed an acute thrombotic occlusion.

Glycoprotein IIb/IIIa Inhibitors (GPI)

Platelet GP IIb/IIIa receptor blockers (abciximab, tirofiban, eptifibatide) inhibit final common pathway of aggregation process by preventing fibrinogen from binding to activated thrombocytes and forming white thrombus. Depending on an agent used, the platelet inhibition achieved is selective, competitive, and short-lasting (up to 4 h) for small molecules (tirofiban, eptifibatide) and non-competitive, long-lasting (up

to 72 h), and with affinity to several other receptors of which the inhibition might be also beneficial (abciximab) [17]. Moreover, all these agents have been found to improve microcirculatory function, reduce platelet-released vasoactive molecules, and improve short- and long-term outcomes, particularly in early comers (<4 h) and diabetic patients.

Several randomized trials evaluated GPIs in the setting of STEMI. The most profound evidence has been found for abciximab in combination with heparin [18, 19]. A 30 % odd reduction in the composite ischemic endpoint was demontrated with the adjunctive use of abciximab [18]. Recently, eptifibatide was compared with abciximab in the primary PCI setting, and non-inferiority was found [20]. Tirofiban was shown to improve the composite ischemic endpoint versus placebo but seemed to perform worse than abciximab. As a consequence, abciximab remains the drug of choice [21]. Due to the increased risk of bleeding when recommended dosing of GPIs is co-administered, the combination therapy is indicated in high-risk clinical situations as bailout therapy (large thrombus, no-flow phenomenon after PCI).

In clinical trials, abciximab is usually administered as an intravenous bolus +12-h continuous infusion on top of heparin/bivalirudin. The dosing of the other drugs—eptifibatide and tirofiban—consists of one and two, respectively, weight-balanced boluses and an 18-h maintenance infusion. Recently, there have been published studies testing a potential benefit of intracoronary bolus of GPIIb/IIIa inhibitors in order to increase intracoronary concentration of the drug, resulting in more pronounced local effect on thrombus dissolution. Meta-analysis by Friedland et al. [22] demonstrated favorable effect of intracoronary bolus on TIMI flow, target vessel revascularization, and short-term mortality after PCI with no increase of bleeding complications. With a rationale that more potent ADP receptor blockers, bivalirudin, thrombus aspiration, and primary stenting are available for most of the STEMI patients and that the continuous intravenous infusion might not be benefitial to further improve outcome but increase the risk of bleeding, Gu et al. [23] applied intracoronary bolus of abciximab only with no maintenance infusion and found better blush grade and reduced infact size in those with intracoronary application of abciximab. The intracoronary application of abciximab results in lower platelet reactivity in coronary sinus blood samples when compared with intravenous dosing [24]. A randomized trial comparing these regimens with/without maintenance infusion in combination with modern mechanical reperfusion devices needs to be performed. Until then, the use of intracoronary bolus with/without subsequent infusion is questionable but supported by several studies and also by our clinical experience.

Bivalirudin

The direct thrombin inhibitor bivalirudin has been studied in various clinical settings. Many studies and meta-analyses demonstrated similar efficacy in reduction of ischemic events but much lower risk of major bleeding (45 % reduction) when compared with heparin with/without adjunctive GPI [25]. The reduction of bleeding events, no association with thrombocytopenia, no need for any co-factor for activity, and no potential to activate platelets (when compared with heparin+abciximab) might have been responsible for an overall mortality benefit in several trials. All these studies used transfemoral access site where bleeding complications are more frequent than when performing via radial artery. Secondly, comparisons of heparin+GPI versus bivalirudin and pure unfractionated heparin versus bivalirudin provide conflicting results. It seems that bivalirudin is as safe as heparin concerning major bleeding events with a trend to more frequent stent thrombosis and cardiovascular ischemic events. On the other hand, when abciximab is administered on top of heparin, this combination causes more major bleeding that drives the net clinical benefit toward bivalirudin [17]. This serves as a rationale for a bail-out therapy with GPIs in high-risk patients. Where the risk of bleeding is an issue, intracoronary bolus of GPI and no infusion strategy may be useful.

A recent study by Stone et al. demontrated a reduction of infarct size after intracoronary bolus of abciximab on top of bivalirudin anticoagulation in patients with anterior STEMI treated with drug-eluting stent implantation with/without prior thrombus aspiration [26].

Both in the TRITON and the PLATO trial, combinations of the investigational product with bivalirudin were used in just a few cases, and no subanalyses have been published describing potential benefits of prasugrel or ticagrelor on top of bivalirudin therapy. Despite this fact, with respect to clinical relevance of bivalirudin as an anticoagulant in the setting of STEMI, there is no logical reason not to apply prasugrel or ticagrelor to our patients who have had/are intended to have anticoagulation therapy with bivalirudin.

We believe that the choice of an appropriate combination of drugs needs to be individualized with respect to patient's risk profile (bleeding versus prothrombotic), coronary pathology (prognostic significance, complex leasion), selected interventional strategy (thrombus aspiration), and our good clinical judgement.

Mechanical Reperfusion for STEMI

As mentioned previously, the primary PCI is the preferred reperfusion strategy in all patients with STEMI, if the time-to-treatment delay is less than 90–120 min (Figs. 1 and 2).

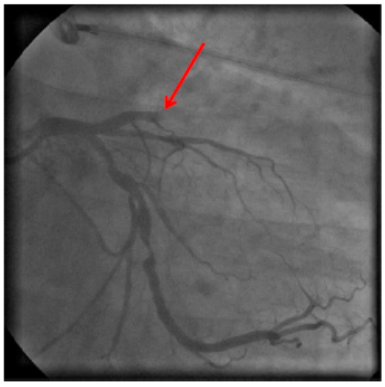

Fig. 1 Anterior STEMI with acute thrombotic occlusion of the left anterior descending artery (LAD), prior intervention

Currently, there is a large variation of reperfusion techniques available, from more historical and simple ballooning to rather complex reperfusion strategies.

Coronary Stents

Bare-Metal Stents (BMS)

Routine bare-metal stent implantation was associated with higher benefit compared with simple balloon dilation in several trials [27, 28]. Since then, based on higher effectiveness and decrease of the peri- and postprocedural risk after stenting, this strategy has been applied in majority of the STEMI patients. If feasible, the direct stenting without predilation should be preferred [29].

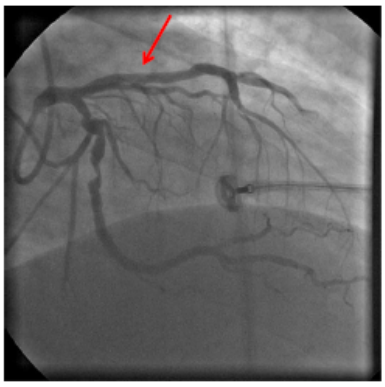

Fig. 2 Anterior STEMI with acute thrombotic occlusion of the left anterior descending artery (LAD, as on Fig. 1), treated by thromboaspiration and DES implantation, final result

Drug-Eluting Stents (DES)

The drug-eluting stent (DES) era started in 2002 in elective procedures with very promising results. The first-generation DES implantation in STEMI was safe and reduced the risk of repeat target vessel revascularization [30]. The potential higher risk of late and very late stent thrombosis raised at the ESC congress in 2006 was not clinically proved [30]. The second-generation DES was shown to be even safer than modern BMS in consecutive STEMI patients without losing the benefits [31]. Patients' compliance with the need of longer dual antiplatelet therapy has become less important with the latest types of DES. This may be the strongest argument for the DES to "win the BMS versus DES battle"—at least, until the time when fully resorbable DES for STEMI would be present.

Dedicated Stents

Managing acute clinical situations and unstable thrombotic leasions (Fig. 3) raise the need for specially designed or dedicated stents. Achievement of a really optimal result after the stent implantation on the epicardial (Fig. 4) as well as on the myocardial level is crucial for the short- and long-term patients' outcome.

Often seen spastic reaction of the infarct-related artery (IRA) and the presence of thrombus may be the reason for implanting the stents with progessive self-apposing after its implantation. The interim analysis of 600 patients in the APPOSITION III trial using the self-expanding BMS showed promising secondary endpoint results with 3.5 % rate of major cardiovascular advers events (MACE) including death, repeat target-vessel myocardial infarction, emergent bypass surgery, or clinically driven target vessel revascularisation at 30 days.

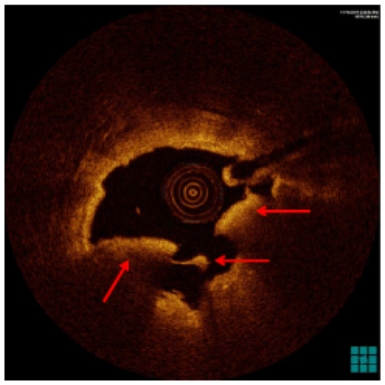

Fig. 3 Optical coherent tomography (OCT) image of acute thrombotic occlusion of LAD, showing large thrombotic mass

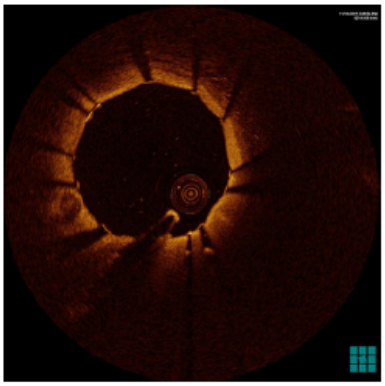

Fig. 4 OCT image of LAD (as on Fig. 3) after thromboaspiration and subsequent DES implantation with optimal stent apposition

The MACE at 12 months as the primary endpoint of the study should be available in 2013.

Managing thrombi and preventing distal embolizations is another target in STEMI where a special mesh-covered stent type can be helpful. This concept showed promising surrogate data in the multicenter single-arm MAGICAL trial (MGuard in Acute MI TriaL) in 60 patients [32], further confirmed in the randomized MASTER trial (MGuard for Acute ST Elevation Reperfusion) using the novel type of stent in 432 patients [33]. Complete ST segment resolution (STR>70 %) at 60 and 90 min together with restoring normal blood flow (TIMI-3 flow) was significantly better than after implantation of standard types of stents (57.8 % versus 44.7 %, $P=0.008$ and 91.7 % versus 82.9 %, $P=0.006$). On the contrary, no difference in the myocardial blush grade was present (MBG 2/3 83.9 % versus 84.7 %, $P=0.81$).

Thrombectomy

One of the challenging situations in interventional cardiology is the thrombus management, especially in the presence of large thrombus burden. Such situation is associated with an increased risk of distal embolization, no-reflow phenomenon, and worse clinical outcome including late mortality [34]. The role of thrombectomy during primary PCI has been tested for many years, and recently, its role has been established based on the data from randomized trials and meta-analyses. On the other hand, and especially in the era of new pharmacological regimens, it is important to know whether to use the thrombectomy in all patients or selectively and whether this adjunctive technique would have a clear impact on mortality reduction.

Manual Thrombectomy

The current Class IIa indication for manual aspiration thrombectomy during primary PCI in ESC [1] and ACC/AHA [35] Guidelines is based on two major randomized trials and several meta-analyses.

The TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study) was the first one showing the clinical benefit of manual thrombectomy using the Export catheter (Medtronic Inc., Minneapolis, MN) versus primary PCI alone in 1,071 patients, though as the secondary and not pre-specified endpoint (mortality at 1 year 3.6 % versus 6.7 %, $p=0.018$) [36, 37]. In 72 % of patients, some visible material was retracted from the IRA, and the aspiration was possible in 90 % of cases. Primary surrogate endpoint comprised the achievement of optimal reperfusion on myocardial level (MBG-3 in 46 % versus 32 %, $p<0.001$). Thromboaspiration was associated also with higher complete STR rate (57 % versus 44 %, $p<0.001$). There are two concerns about the study: single-center experience and "classical" routine balloon predilation before stenting.

Further on, using a similar design and type of aspiration catheter, the EXPIRA (thrombectomy with EXPort catheter in Infarct Related Artery during primary percutaneous coronary intervention) trial showed a significant improvement in the primary endpoints of MBG≥2 and complete STR in 175 patients (88 % versus 60 %, $p=0.001$; and 64 % versus 39 %, $p=0.001$) [38]. In a 75-patient substudy with contrast-enhanced magnetic resonance imaging, the use of aspiration was found to be effective in decreasing the infarct size both in the acute phase and at 3 months (1.7 g versus 3.7 g, $p=0.0003$ and 17 % versus 11 %, $p=0.004$). Cardiac death was less frequent in the thromboaspiration arm at 9 months (0 % versus 4.6 %, $p=0.02$).

The real clinical potential of manual aspiration technique is expected to come from the large TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) trial with more than 5,000 patients and the TOTAL (Randomized Trial of Routine Aspiration ThrOmbecTomy with Percutaneous Coronary Intervention (PCI) versus PCI ALone in Patients with STEMI Undergoing Primary PCI) trial enrolling 4,000 patients.

Mechanical Thrombectomy

Currently, there are several devices available for mechanical thrombectomy during primary PCI (e.g., AngioJet, X-Sizer, and Rescue), but mostly conflicting results of the trials do not support its routine use during primary PCI [1].

The use of AngioJet Rheolytic Thrombectomy (Medrad Interventional/Possis, Minneapolis, MN) was studied in two relatively large randomized trials. In both the AIMI (AngioJet

Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction) [39] and JETSTENT (AngioJet Rheolytic Thrombectomy Before Direct Infarct Artery Stenting in Patients Undergoing Primary PCI for Acute Myocardial Infarction) [40] trials, the primary endpoints were not met. In 480 patients in the AIMI trial, the use of rheolytic thrombectomy (RT) was associated with the increase of infarct size (p=0.03), reduction in TIMI-3 flow (p<0.05), and higher MACE rate at 30 days (p=0.01). In the JESTENT trial, the use of RT was compared with direct stenting group. Although 501 patients were selected based on the angiographic evidence of larger thrombus grades 3 to 5, co-primary endpoints (STR and infarct size) showed no difference between the two treatment strategies. It is difficult to understand the lower rate of MACE in the RT group at 6 and 12 months because of the similar infarct size (11.8 % versus 12.75 %, p=0.40) and only higher STR rate (85.8 % versus 78.8 %, p=0.043).

The X-Sizer device (eV3, White Bear Lake, MN, USA) was used in the X AMINE ST (X-Sizer for Thrombectomy in Acute Myocardial Infarction Improves ST-Segment Resolution: Results of the X-Sizer in AMI for Negligible Embolization and Optimal ST Resolution) Trial in 201 patients with occluded IRA [41]. Primary end point (partial STR>50 %) was found to be more frequent in the mechanical device group (p=0.037), but, together with lower distal embolization rate, these surrogate benefits did not result in any clinical improvement.

Manual Versus Mechanical Thrombectomy

Presently, such comparison is clinically much more relevant but with very limited data. In the TREAT-MI (A Randomized comparison of manual versus mechanical thrombus removal in primary percutaneous coronary intervention in the treatment of ST-segment elevation myocardial infarction) Trial, the X-Sizer was compared with the Export aspiration catheter [42]. Procedural parameters as well as the occurrence of primary clinical endpoint in 201 patients at 3 years were similar except for the more often successfully deployed Export catheter with a trend toward better ST-segment resolution (56.6 % versus 44 %; p=0.06) as compared with the X-sizer system. Burzotta et al. performed a meta-analysis of 2,686 patients in 11 randomized trials (from the total of 17 eligible) with manual (1,815 patients with the use of Diver CE, Pronto and Export catheters) and mechanical thrombectomy (871 patients with the use of X-Sizer, Angiojet, Rescue and TVAC devices) on an individual basis [43]. At 1 year, the clinical benefit of thrombectomy was clearly defined (p=0.049 for all-cause mortality; p=0.011 for MACE). Subgroups analysis showed better survival rate after thrombectomy also in patients treated with glycoprotein IIb/IIIa inhibitors (p=0.045), and this benefit was confined to the manual aspiration. Selection of the trials was dependent on the authors' agreement with providing the data.

On the contrary, the Bayesian meta-analysis of 21 randomized trials with manual (16 trials) and mechanical thrombectomy (4,299 patients) performed by Mongeon et al. did not show any clinical impact of thrombectomy, but there was a consistent improvement in surrogate endpoints (complete STR, final TIMI3 flow, and less no-reflow) [44].

Manual aspiration thrombectomy is currently the preferred method of thrombus extraction that is fast, broadly applicable, relatively effective, and user-friendly. The more complex mechanical extraction techniques might be useful or even required to completely manage the large thrombus burden. Nevertheless, the role of thrombectomy is less established in scenarios where the IRA is patent with initial or post-wiring TIMI 2–3 flow without angiographic evidence of larger thrombus. Direct stenting seems to be the best approach to such patients (Fig. 5).

Pharmacologic Reperfusion for STEMI=Fibrinolysis

In patients not able to be treated with primary PCI within the recommended time-interval, there is an important role of

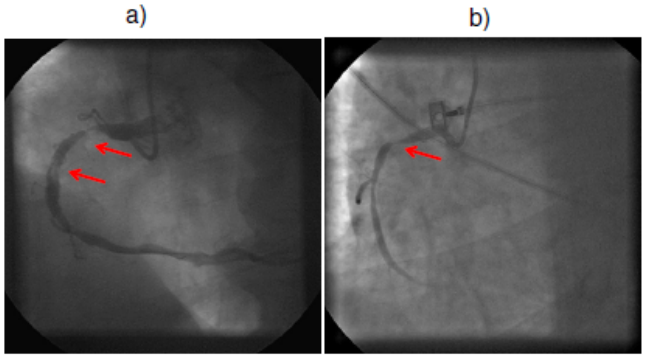

Fig. 5 Inferior STEMI with thrombotic leasions in proximal right coronary artery (RCA), initial TIMI II flow: **a** large thrombotic mass managed by thromboaspiration afterward; **b** little thrombotic mass managed by direct stenting afterward

Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction) [39] and JETSTENT (AngioJet Rheolytic Thrombectomy Before Direct Infarct Artery Stenting in Patients Undergoing Primary PCI for Acute Myocardial Infarction) [40] trials, the primary endpoints were not met. In 480 patients in the AIMI trial, the use of rheolytic thrombectomy (RT) was associated with the increase of infarct size (p=0.03), reduction in TIMI-3 flow (p<0.05), and higher MACE rate at 30 days (p=0.01). In the JESTENT trial, the use of RT was compared with direct stenting group. Although 501 patients were selected based on the angiographic evidence of larger thrombus grades 3 to 5, co-primary endpoints (STR and infarct size) showed no difference between the two treatment strategies. It is difficult to understand the lower rate of MACE in the RT group at 6 and 12 months because of the similar infarct size (11.8 % versus 12.75 %, p=0.40) and only higher STR rate (85.8 % versus 78.8 %, p=0.043).

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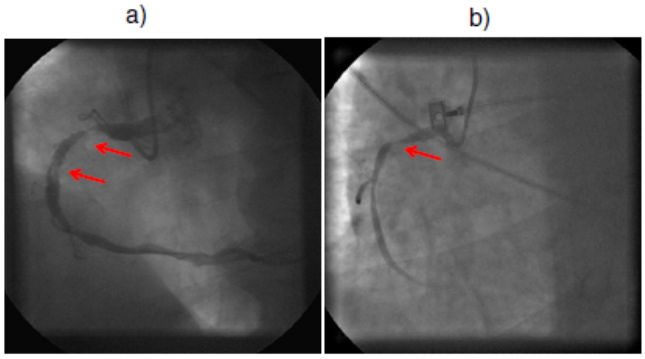

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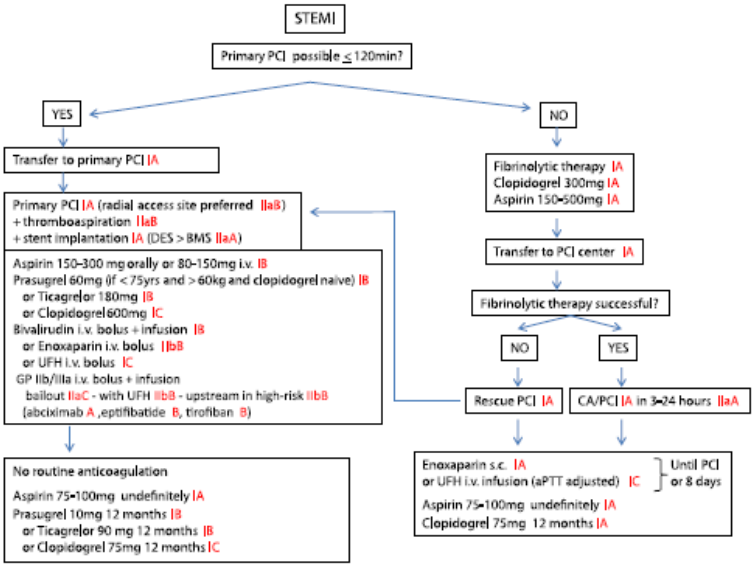

Fig. 6 Simplified algorithm of STEMI treatment based on the current European practice guidelines [1]. *STEMI* acute myocardial infarction with ST-elevation; *PCI* percutaneous coronary intervention; *i.v.* intravenous; *DES* drug-eluting stent; *BMS* bare-metal stent; *UFH* unfractionated heparin; *GP IIb/IIIa* glycoprotein receptor IIb/IIIa; *CA* coronary angiography; *s.c.* subcutaneous. Classes of recommendations: *I* = is recommended/is indicated, *IIa* = should be considered, *IIb* = may be considered; Level of evidence: *A* = data derived from multiple randomized clinical trials or meta-analyses, *B* = data derived from a single randomized clinical trial or large non-randomized studies, *C* = consensus of opinion of the experts and/or small studies, retrospective studies, registries

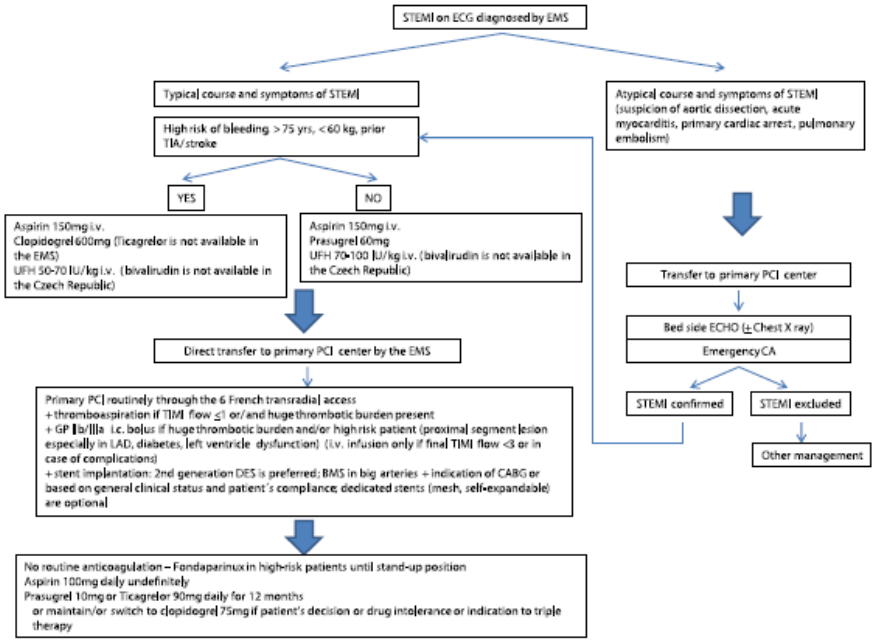

Fig. 7 Current local algorithm of the STEMI treatment in high-volume primary PCI center. *STEMI* acute myocardial infarction with ST-elevation; *ECG* electrocardiogram; *EMS* emergency medical service; *TIA* transient ischemic attack; *UFH* unfractionated heparin; *PCI* percutaneous coronary intervention; *TIMI* thrombolysis in myocardial infarction; *GP IIb/IIIa* glycoprotein receptor IIb/IIIa; *LAD* left anterior descending coronary artery; *DES* drug-eluting stent; *BMS* bare-metal stent; *CABG* coronary artery bypass graft; *ECHO* echocardiography; *CA* coronary angiography

fibrinolysis. The general limitations of fibrinolysis were well described at the beginning of the European Stent for Life Initiative in 2010 [45]. In 30 European countries, the "reperfusion paradox" was well demonstrated. In contrast to the "primary PCI countries,",a high rate of non-reperfused STEMI patients was observed in countries with the "simple and deliverable" fibrinolysis as the preferred reperfusion treatment strategy.

There are several different fibrinolytic drugs available—from the fibrin-non-specific, least effective, but broadly available streptokinase for intravenous (i.v.) infusion to the more potent and fibrin-specific tissue plasminogen activator (tPA; alteplase–i.v. bolus+infusion), reteplase (rPA–double i.v. bolus), or tenecteplase (TNK-tPA–single i.v. bolus). The major hazard of fibrinolysis is the excess risk of bleeding including the cerebral hemorhage. Moreover, with increasing time-delay, particularly after 6 h, the overall efficacy of thrombolysis decreases. Albeit the fibrinolytic facilitation of primary PCI is not indicated, the routine transportation to coronary angiography or PCI after its administration (respecting several contraindications) is routinely recommended.

It is important to realize that, because of several factors, in real life, there may be differences between the step-by-step algorithm recommended by current highly sophisticated guidelines (Fig. 6) and adjusted algorithms followed in the daily practice. We provide an example of the STEMI algorithm being used in our high-volume primary PCI center situated in one of the European "best STEMI practice countries" (Fig. 7).

Unanswered Questions

Despite the precise current data, some questions still remain unanswered: (1) the timing and method of the potent antiplatelet therapy application (pre- and in-hospital), (2) the type and method of anticoagulation agent application (LMWH, UFH, bivalirudin), (3) the optimal primary PCI technique including the thrombus-removing devices, and (4) the role of imaging.

Respecting the recommended practice guidelines, there is a continuous need for individual approach especially to high-risk patients with both tendency to bleeding, thrombotic, and ischemic events.

Conclusion

The pharmaco-mechanic approach to patients presenting with STEMI is very complex including novel potent antiplatelet drugs, new regimens of therapy, and new promising interventional techniques. There is a lot of data regarding pharmacologic and interventional treatments, but there is a lack of data showing their potential when used in mutual combination. The evidence-based approach needs to be modified to each clinical situation based on the best clinical judgment.

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RESEARCH ARTICLE Open Access

Age – related treatment strategy and long-term outcome in acute myocardial infarction patients in the PCI era

Petr Kala[1], Jan Kanovsky[1*], Richard Rokyta[2], Michal Smid[2], Jan Pospisil[2], Jiri Knot[3], Filip Rohac[3], Martin Poloczek[1], Tomas Ondrus[1], Maria Holicka[1], Jindrich Spinar[1], Jiri Jarkovsky[4] and Ladislav Dusek[4]

Abstract

Background: Older age, as a factor we cannot affect, is consistently one of the main negative prognostic values in patients with acute myocardial infarction. One of the most powerful factors that improves outcomes in patients with acute coronary syndromes is the revascularization preferably performed by percutaneous coronary intervention. No data is currently available for the role of age in large groups of consecutive patients with PCI as the nearly sole method of revascularization in AMI patients. The aim of this study was to analyze age-related differences in treatment strategies, results of PCI procedures and both in-hospital and long-term outcomes of consecutive patients with acute myocardial infarction.

Methods: Retrospective multicenter analysis of 3814 consecutive acute myocardial infarction patients divided into two groups according to age (1800 patients ≤ 65 years and 2014 patients > 65 years). Significantly more older patients had a history of diabetes mellitus and previous myocardial infarctions.

Results: The older population had a significantly lower rate of coronary angiographies (1726; 95.9% vs. 1860; 92.4%, $p < 0.0001$), PCI (1541; 85.6% vs. 1505; 74.7%, $p < 0.001$), achievement of optimal final TIMI flow 3 (1434; 79.7% vs. 1343; 66.7%, $p < 0.001$) and higher rate of unsuccessful reperfusion with final TIMI flow 0-1 (46; 2.6% vs. 78; 3.9%, $p = 0.022$). A total of 217 patients (5.7%) died during hospitalization, significantly more often in the older population (46; 2.6% vs. 171; 8.5%, $p < 0.001$). The long-term mortality (data for 2847 patients from 2 centers) was higher in the older population as well (5 years survival: 86.1% vs. 59.8%). Though not significantly different and in contrast with PCI, the presence of diabetes mellitus, previous MI, final TIMI flow and LAD, as the infarct-related artery, had relatively lower impact on the older patients. Severe heart failure on admission (Killip III-IV) was associated with the worst prognosis in the whole group of patients, though its significance was higher in the youngers (HR 6.04 vs. 3.14, $p = 0.051$ for Killip III and 12.24 vs. 5.65, $p = 0.030$ for Killip IV). We clearly demonstrated age as a strong discriminator for the whole population of AMI patients.

Conclusions: In a consecutive AMI population, the older group (>65 years) was associated with a less pronounced impact of risk factors on long-term outcome. To ascertain the coronary anatomy by coronary angiography and proceed to PCI if suitable regardless of age is crucial in all patients, though the primary success rate of PCI in the older age is lower. Age, when viewed as a risk factor, was a dominant discriminating factor in all patients.

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Background

Over the past decades the incidence of acute myocardial infarction (AMI) together with mortality have decreased dramatically in developed countries [1,2]. These favorable trends reflect an improvement in many factors that influence outcomes in patients with acute coronary syndromes (ACS) [3]. Older age, as a factor we cannot affect, is consistently one of the main negative prognostic values in most trials [4,5]. One of the most powerful factors that improves outcomes in patients with ACS is the revascularization preferably performed by percutaneous coronary intervention (PCI) [6,7]. No data is currently available for the role of age in large groups of consecutive patients with PCI as the nearly sole method of revascularization in AMI patients. The aim of this study was to assess age related differences in treatment strategies (conservative or invasive), results of PCI procedures and both in-hospital and long-term outcomes in AMI patients.

Methods

Patients' group and data collection

This multicenter, retrospective project included 3814 consecutive "all-comer" patients with a diagnosis of AMI. Age under 18 was the only exclusion criterion. Patients were enrolled in 3 tertiary complex cardiovascular university centers providing the 24/7 catheterization service (3 year period, 2005 to 2007 in two centers, and a two year period 2007 to 2008 in one center). All patients with a final diagnosis of acute myocardial infarction with/without ST elevations (STEMI / NonSTEMI) were included in the registry. The diagnosis of AMI was based on the ESC/ACC/AHA definition [8] and had to be confirmed at the time of discharge from the hospital, or post-mortem, if a patient died during hospitalization.

Admission and discharge reports of all patients were analyzed and transferred to a registry created for the project. Following parameters were collected: 1) History of diabetes and previous MI; 2) Clinical data, particularly Killip class on admission; 3) 12-lead ECG regarding the presence of ST segment changes and bundle branch blockades at the time of admission (Table 1); 4) Coronary angiography including the number of diseased vessels, initial and final Thrombolysis In Myocardial Infarction (TIMI) flow and determination of the infarct-related artery (IRA) (left anterior descending artery = LAD, left circumflex artery = LCX and right coronary artery = RCA or the disease of the left main coronary artery (LMCA) described separately) (Table 1); 5) Left ventricular ejection fraction (LVEF), assessed through echocardiography before hospital discharge or alternatively through LV angiography during catheterization. No thrombolytic therapy was used during the assessed period of time. The success of PCI was defined as a complete reperfusion of IRA represented by a final TIMI score of 3.

The World Heart Organization (WHO) definition for age reflecting also the most common retirement age in Europe was used for creating two groups of patients. The first group (younger population) included subjects ≤ 65 years of age, the second group (older population) included subjects > 65 years of age. Endpoints for this analysis were as follows: coronary angiography and PCI performed during index hospitalization, final TIMI flow after PCI, a change in TIMI flow during the PCI procedure and in-hospital mortality. Long-term mortality data independently followed by the Czech Ministry of Health were available from 2 centers. All data in the registry were anonymised and the study was provided in compliance with the Helsinki Declaration. According to the national law no ethics committee approval or signed patient informed consent were needed.

Statistical analysis

Categorical parameters were described by absolute and relative frequency of categories. Continuous parameters were described using the median and the 5^{th} – 95^{th} percentile range. Statistical significance of differences between groups of patients was analyzed using the Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical variables. Risk factors associated with long-term survival were evaluated using the Cox proportional hazard model and described using hazard ratios and their 95% confidence interval. Survival data were visualized using the Kaplan-Meier methodology. Influence of patient age on HR values within the age categories was analyzed using the interaction term in the Cox proportional hazard model. P values < 0.05 were considered statistically significant.

Results

The first group (1800 patients) included subjects ≤ 65 years of age, the second group (2014 patients) included subjects > 65 years of age. In the younger group there was a higher distribution of men, and a lower rate of diabetes mellitus and previous myocardial infarctions. Less younger patients presented with acute heart failure on admission to hospital. Consequently, Killip class II and III were more common in the older patients as well as cardiogenic shock, described as Killip class IV. STEMI was diagnosed more often in the younger group (Table 2).

More invasive therapeutic approach was observed in the younger patients in term of higher number of coronary angiographies (CAG) and PCI. In the older population there was a higher rate of unsuccessful reperfusions represented by a final TIMI score 0-1. A total of 217 patients (5.7%) died during hospitalization, significantly more in the older group

Table 1 Age-related baseline differences

Age Number of patients	≤65 years 1800	>65 years 2014	p NA
Patients' characteristics			
Males	1454 (80.8%)	1132 (56.2%)	<0.001
History of DM	389 (21.6%)	763 (37.9%)	<0.001
History of previous MI	268 (14.9%)	505 (25.1%)	<0.001
Killip class on admission			
I	1501 (83.4%)	1361 (67.6%)	<0.001
II	179 (9.9%)	410 (20.4%)	<0.001
III	54 (3.0%)	131 (6.5%)	<0.001
IV	66 (3.7%)	112 (5.6%)	0.006
Admission ECG			
STEMI + new LBBB	1060 (58.9%)	956 (47.5%)	<0.001
NonSTEMI	740 (41.1%)	1058 (52.5%)	<0.001
CAG			
CAG	1726 (95.9%)	1860 (92.4%)	<0.001
No indication for CAG	74 (4.1%)	154 (7.6%)	<0.001
Number of diseased vessels			
Single vessel disease	717 (39.8%)	463 (23.0%)	<0.001
Two vessel disease	506 (28.1%)	546 (27.1%)	0.491
Three vessel disease	478 (26.6%)	807 (40.1%)	<0.001
Left main artery disease	25 (1.4%)	44 (2.2%)	0.069
IRA (by CAG or autopsy)			
Left main	26 (1.4%)	42 (2.1%)	0.143
LAD	660 (36.7%)	763 (37.9%)	0.441
LCX	360 (20.0%)	293 (14.5%)	<0.001
RCA	585 (32.5%)	562 (27.9%)	0.002
ACB	14 (0.8%)	25 (1.2%)	0.197
Not known	155 (8.6%)	329 (16.3%)	<0.001
Initial TIMI flow			
TIMI 0-1	877 (48.7%)	781 (38.8%)	<0.001
TIMI 2	288 (16.0%)	315 (15.6%)	0.790
TIMI 3	480 (26.7%)	589 (29.2%)	0.077
PCI			
PCI total number	1541 (85.6%)	1505 (74.7%)	<0.001
No PCI	259 (14.4%)	509 (25.3%)	<0.001
PCI% of CAG	1541/1726 (89.3%)	1505/1860 (80.9%)	<0.001

Numbers in the second and third column represent absolute numbers of patients and percentage of the related group. Statistically significant difference is $p < 0.05$.
DM diabetes mellitus, *MI* myocardial infarction, *ECG* electrocardiogram, *STEMI* ST segment elevation myocardial infarction, *LBBB* left bundle branch block, *NonSTEMI* non-ST elevation myocardial infarction.

(46; 2.6% vs. 171; 8.5%, $p < 0.001$) (Table 2). Long-term mortality (calculated from data for 2847 patients from 2 centers) was higher in the older patients as well (3 and 5 years survival supplemented by 95% confidence interval: 89.6% (87.9%; 91.2%) vs. 70.8% (68.4%; 73.2%) and 86.1% (83.7%; 88.4%) vs. 59.8% (56.4%; 63.2%) respectively, $p < 0.001$; log rank test) (Figure 1). Similar risk factors significantly influenced long term survival in both the younger and older population with only a limited number of differences (Table 3). Emergent coronary-artery bypass surgery (CABG) during the first 24 hours after admission was performed in 3.4% in total (2.0% in STEMI and 4.4% in NSTEMI). Significantly more older patients were treated using emergent CABG (4.1% vs. 2.5%, $p = 0.019$).

Table 2 Age-related endpoints of the project

Age Number of patients	≤65 years 1800	>65 years 2014	p NA
Final TIMI flow			
TIMI 0-1	46 (2.6%)	78 (3.9%)	0.022
TIMI 2	64 (3.6%)	102 (5.1%)	0.026
TIMI 3	1434 (79.7%)	1343 (66.7%)	<0.001
Change of the initial TIMI flow 0-1 to the final TIMI flow 3			
1.3	118 (6.6%)	105 (5.2%)	0.084
0.3	655 (36.4%)	514 (25.5%)	<0.001
In-hospital mortality	**46 (2.6%)**	**171 (8.5%)**	**<0.001**

Numbers in the second and third column represent absolute numbers of patients and percentage of the related group, unless specified differently. Statistically significant difference is $p < 0.05$.
CAG Coronary Angiography, *PCI* Percutaneous Coronary Intervention, *TIMI* Thrombolysis In Myocardial Infarction.

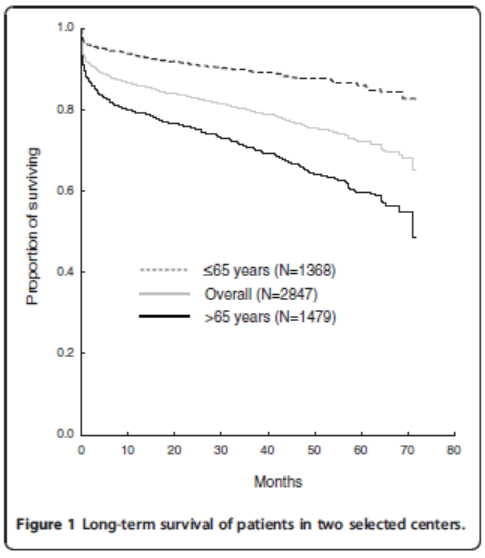

Figure 1 Long-term survival of patients in two selected centers.

Table 3 Risk factors influencing long term survival of patients in two selected centers

	≤65 years (N = 1368)			>65 years (N = 1479)			Interaction
	N	HR (95% CI)	p	N	HR (95% CI)	p	p
Age (10 years)	-	1.76 (1.35; 2.28)	<0.001	-	2.03 (1.75; 2.35)	<0.001	0.458
Men	1116	1.18 (0.78; 1.79)	0.441	856	0.90 (0.76; 1.08)	0.262	0.227
DM	303	1.91 (1.38; 2.65)	<0.001	574	1.41 (1.18; 1.68)	<0.001	0.085
Previous MI	219	2.02 (1.42; 2.87)	<0.001	385	1.46 (1.20; 1.76)	<0.001	0.189
Killip I	1114	*Basal category*		958	*Basal category*		
Killip II	155	2.52 (1.67; 3.81)	<0.001	334	1.80 (1.47; 2.22)	<0.001	0.298
Killip III	39	6.04 (3.48; 10.48)	<0.001	104	3.14 (2.36; 4.18)	<0.001	0.051
Killip IV	53	12.24 (7.94; 18.89)	<0.001	75	5.65 (4.14; 7.70)	<0.001	0.030
PCI	1169	0.60 (0.42; 0.88)	0.008	1109	0.46 (0.38; 0.55)	<0.001	0.202
No PCI	199	1.66 (1.14; 2.41)		370	2.19 (1.83; 2.63)		
STEMI + new onset of LBBB	948	1.02 (0.72; 1.43)	0.924	990	1.21 (1.00; 1.47)	0.056	0.312
NonSTEMI	420	0.98 (0.70; 1.38)		489	0.83 (0.68; 1.01)		
Final TIMI flow 2-3	1162	0.20 (0.10; 0.41)	<0.001	1096	0.32 (0.22; 0.47)	<0.001	0.151
Final TIMI flow 0-1	19	5.00 (2.43; 10.18)		46	3.13 (2.11; 4.65)		
Single vessel disease	532	*Basal category*		339	*Basal category*		
Two vessel disease	402	1.30 (0.86; 1.96)	0.223	431	1.53 (1.13; 2.06)	0.006	0.371
Three vessel disease	359	2.10 (1.43; 3.09)	<0.001	594	2.24 (1.70; 2.95)	<0.001	0.508
Left main artery disease	11	4.12 (1.28; 13.28)	0.018	8	5.85 (2.50; 13.67)	<0.001	0.564
IRA							
Left main	18	4.52 (1.77; 11.57)	0.002	28	5.26 (3.26; 8.48)	<0.001	0.995
LAD incl. its branches	490	1.77 (1.17; 2.66)	0.006	556	1.10 (0.86; 1.41)	0.431	0.093
LCX incl. its branches	269	1.36 (0.83; 2.24)	0.222	221	1.09 (0.80; 1.48)	0.608	0.546
RCA incl. its branches	444	*Basal category*		401	*Basal category*		
Bypass graft	12	0.05 (0.00; 545.31)	0.524	20	0.80 (0.30; 2.17)	0.662	-
IRA not known	135	2.69 (1.63; 4.43)	<0.001	253	2.37 (1.83; 3.05)	<0.001	0.815

N number of patients in given category.
HR hazard ratio based on Cox proportional hazards model supplemented by its statistical significance.
Influence of age category of patients on HR value within these age categories is analyzed using interaction term in Cox proportional hazards model.

Discussion

Though the age used for the definition of older or elderly patients varies among trials from 55 to 80 years [9-11] standard WHO definition of 65 years was applied for this study.

All patients were treated at academic tertiary hospitals, which provided 24/7 catheterizations. All reperfusion procedures, if indicated, were performed nearly solely by PCI; none of the patients, in either group, received thrombolysis. These conditions are unique in such a large group of consecutive, unselected patients having a diagnosis of acute myocardial infarction.

There is very limited data dealing with all types of AMI. However, in comparison with previously published data, the mortality in our cohort seems to be very low, especially in the older group. One of the reasons might be the exceptionally high catheterization (94.0%) and revascularization rate using PCI (79.9% of all study subjects). Despite the additional, known, risk factors and a worse expected prognosis in the older patients [12], the rate of diagnostic coronary angiography and PCI was found to be significantly lower in this high-risk population (92.4% vs. 95.9%, $p < 0.001$ and 74.7% vs. 85.6%, $p < 0.001$ respectively). One of the potential explanations for the lower PCI rate as well as the worse primary angiographic results in older patients might be the more complex and unfavorable anatomy. Unique data were collected from long-term survival analysis showing similar risk factors influencing the prognosis in both groups of patients with some exceptions. We clearly demonstrated age as a strong discriminating factor across the entire population of AMI patients. Though, for the most part not statistically significant, it seems to be clear that initial signs of heart failure (Killip II-IV), presence of diabetes mellitus and previous MI, final TIMI flow and the IRA are significant negative predictors but do not play as important a role in the older group as they do in younger

patients. On the contrary, PCI in the older patients seems to be even more important than in younger patients (Table 3).

A comparison with any previously published data is rather difficult because of significantly lower catheterization and revascularization rate in previously published consecutive patient groups and a lack of analyzed cohorts of unselected consecutive patients with AMI. Mehta et al. [13] evaluated in-hospital mortality in STEMI patients (age ≥ 70 y) treated with thrombolysis and described higher mortality rates compared to our findings (14.4% in PCI-treated patients vs. 17.6% in patients treated with thrombolysis). Ishihara et al. [14] recently described the outcome of a large cohort of patients with AMI divided according to the age (< 70 years or ≥ 70 years). Despite the use of a favorable methodology, i.e. involving only patients undergoing catheterization within 24 hours from admission, the in-hospital mortality rate was substantially higher in both age groups comparing to our cohort (11.7% in the patients ≥ 70 years and 5.0% in patients < 70 years). Since age is a factor that cannot be changed, we have to focus on improvement of other modalities that can be influenced, such as shortening of the times between symptom onset and primary PCI [15]. Our findings strongly support the use of PCI in all patients (HR 0.60, p = 0.008 in younger patients and HR 0.46; p < 0.001 in older patients), which was also demonstrated by Nicolau et al. [16] in the ≥ 70 years population in adjusted models (HR 0.64, p = 0.001 older patients vs. HR 0.74, p = 0.073 younger patients).

Study limitations

The study authors recognize the following limitations of the project. The registry is retrospective; however the cohort included unselected, consecutive patients with a diagnosis of AMI from multiple centers. The angiographic data were not assessed by an independent lab or in a blinded manner, although, angiographic findings were attained by experienced operators licensed in interventional cardiology. Only a limited number of coronary artery disease risk factors were followed and because of the comparison of two cohorts only univariate analysis was used to assess predictors of long-term survival.

Conclusion

In a consecutive AMI population, the older group (> 65 years) was associated with a less pronounced impact of risk factors on long-term outcome. To ascertain the coronary anatomy by coronary angiography and proceed to PCI if suitable regardless of age is crucial in all patients, though the primary success rate of PCI in the older age is lower. Age, when viewed as a risk factor, was a dominant discriminating factor in all patients.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
All authors participated in data collection and processing, all authors read and approved the final manuscript.

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3.4

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Right ventricular myocardial infarction: From pathophysiology to prognosis

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T Ondrus, J Kanovsky, T Novotny, I Andrsova, J Spinar, P Kala. Right ventricular myocardial infarction: From pathophysiology to prognosis. Exp Clin Cardiol 2013;18(1):27-30.

Right ventricle myocardial infarctions (RVMIs) accompany inferior wall ischemia in up to one-half of cases. The clinical sequelae of RVMIs vary from no hemodynamic compromise to severe hypotension and cardiogenic shock. Diagnosis is based on physical examination, electrocardiography, echocardiography and coronary angiography. Because the standard 12-lead electrocardiogram is insufficient for the assessment of RV involvement, right-sided precordial leads should always be included. Adequate fluid administration in combination with positive inotropic agents and early coronary reperfusion are crucial components of treatment, while diuretics and nitrates should be avoided. Intra-aortic balloon counterpulsation and right ventricle assist devices may be used with success in RVMIs associated with medically refractory heart failure. Right ventricular involvement appears to be an independent prognostic factor that dramatically increases in-hospital mortality, due, in part, to a significantly higher risk of hemodynamically compromising arrhythmias. Thus, using right-sided precordial leads and early RVMI identification to trigger an appropriately aggressive treatment protocol may improve patients' prognosis.

Key Words: *Arrhythmias; Revascularization; Right ventricular myocardial infarction; Treatment*

Cardiovascular disease (CVD) continues to be the main cause of mortality and morbidity in developed countries. Annually, more than one-half of the deaths in the Czech Republic are due to CVD (1), and approximately 2200 Americans die of CVD each day. CVD claims more lives each year than cancer, chronic lower respiratory disease and accidents combined (2). Coronary artery disease accounts for approximately one-half of CVD deaths.

Patients with acute coronary syndrome may present with either acute myocardial infarction (MI) with or without ST segment elevation, or unstable angina. These conditions share common pathophysiological mechanisms related to coronary plaque instability (erosion or rupture), thrombosis and vasospasm, resulting in either subendocardial or transmural ischemia.

In contrast to the lengthy historical interest in acute MIs of the left ventricle (LVMIs), the clinical consequences of right ventricular (RV) involvement were first described only in 1974 (3). Specific RV perfusion from both the right and left coronary arteries results in relatively small RVMIs, with the majority of the myocardium remaining viable even in the absence of reperfusion. Recovery from RV myocardial impairment (mainly linked to stunning or hibernation) may be rather slow and is associated with a high rate of in-hospital mortality (4).

INCIDENCE

RVMI is usually associated with LVMI and, in practice, does not exist in isolation (5). The occurrence of RV impairment depends primarily on the location of the MI, which ranges from rare cases in the anterior heart wall (6) to more common locations (depending on the type of diagnostic method used) such as in the inferior wall in 24% to 50% of cases (5-7). The relatively small percentage of RVMIs may be explained by several factors: lower oxygen requirements of the RV due to its smaller muscle mass and workload; increased blood flow during diastole and systole; more extensive collateralization of the RV, primarily from the left coronary system; and diffusion of oxygen from intrachamber blood through the thin wall of the RV and into the Thebesian veins (7-9).

The clinical sequelae of RVMI vary widely, and range from no hemodynamic compromise to severe hypotension and cardiogenic shock depending on the extent of RV ischemia (6). According to the literature, approximately 25% to 50% of RV infarctions are hemodynamically significant (7,10).

DIAGNOSTICS

Physical examination

It is important to consider a diagnosis of RVMI, particularly in the presence of an inferior wall MI. The typical triad observed on physical examination is hypotension occurring with jugular vein distention and clear lungs. Preserved left ventricular (LV) function confirms the diagnosis (3). A tricuspid regurgitation murmur, Kussmaul's sign (an increase in inspiratory central venous pressure, visible as jugular vein distention) and pulsus paradoxus are signs of significant hemodynamic effects due to RV ischemia (11). In some cases, these symptoms are not present at admission and do not occur until diuretics or nitrates are administered.

Two-dimensional echocardiography

This technique can show RV dilation with depressed systolic function (Figure 1) and RV free wall dyskinesia with paradoxical septal motion (12-16). A Doppler examination of specific pulmonary regurgitation patterns can add hemodynamic insight and confirm the diagnosis of RV involvement, especially in cases of technically inadequate two-dimensional images (17).

Radionuclide ventriculography and ^{99m}Tc pyrophosphate myocardial scintigraphy

These noninvasive techniques may be used to detect RV dysfunction. A dilated right ventricle with hypokinesia, akinesia or dyskinesia of its free wall associated with a depressed RV ejection fraction (EF) and a normal or only mildly depressed LV EF are indicative of an RVMI (7). A ^{99m}Tc pyrophosphate myocardial scintigraphy examination requires proper timing, and the scans are usually not diagnostic until 72 h after the onset of symptoms. Excessive uptake of the radionuclide in noncardiac structures (chest wall, bone, cartilage) can lead to issues regarding the interpretation of the acquired images (18).

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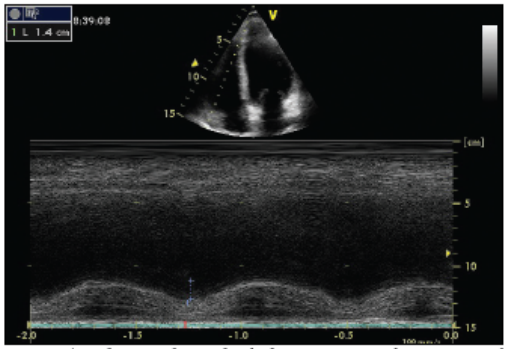

Figure 1) *Right ventricle systolic dysfunction, estimated using tricuspid annular systolic plane excursion-method echocardiography*

Hemodynamic examination

Hemodynamic examination using right-sided cardiac catheterization may reveal a disproportionate elevation of right-sided filling pressures compared with left-sided filling pressures. The generally accepted criteria for hemodynamically-significant RVMIs originate from an autopsy/hemodynamic study by Lopez-Sendon et al (19) and include right atrial pressure (RAP) >10 mmHg, a RAP to pulmonary capillary wedge pressure (PCWP) ratio >0.8, or RAP within 5 mmHg of the PCWP. However, with concomitant and significant LV dysfunction, the close relationship between the RAP and the PCWP is not preserved, although the RAP will continue to be elevated (18,19).

Coronary angiography

Angiography often reveals occlusion of the right coronary artery (RCA) proximal to the acute marginal branch (Figure 2), while more proximal occlusions usually suggest more extensive necrosis of the posterior and, potentially, the anterior RV myocardial wall (5,6). In patients with left coronary artery dominance, a left circumflex coronary artery (LCX) occlusion may also be found. Although uncommon, RV involvement may be present in patients with an occlusion in the left anterior descending artery (5). Cabin et al (20) studied 97 hearts with anterior MIs and found that 13% were RVMIs.

Electrocardiography

Because RVMIs are usually associated with an inferior wall MI, evaluation using standard 12-lead electrocardiography (ECG) often reveals corresponding ST segment elevations in leads II, III and aVF. Disproportionate ST segment elevation with greater ST elevation in lead III than in lead II is pathognomonic for an RVMI, and RV involvement should be fully and carefully considered (21). Because standard 12-lead ECG images mainly assess the LV, right-sided precordial leads should always be used. These can show ST segment elevation across the entire right precordium from V1R through V6R; a sole ST segment elevation in lead V4R >1.0 mm (Figure 3) is a reliable marker of an RV infarction, with 100% sensitivity, 87% specificity and 92% predictive accuracy (22,23). Furthermore, higher ST segment elevations in V4R have been found to be independent predictive factors for more significant RV dysfunction and higher mortality rates (24,25).

ARRHYTHMIAS

RVMIs are more often complicated by all types of arrhythmias compared with 'simple' inferior or anterior wall LVMIs (24,26-28). Barrillon et al (29) were the first to recognize the significantly higher risk of severe conduction disorders in patients with RV involvement. Complete atrioventricular (AV) or sinoatrial blocks occurred in one-half of cases in which ST segment elevation or a QS pattern in V3R and/or V4R were present. On the other hand, these complications

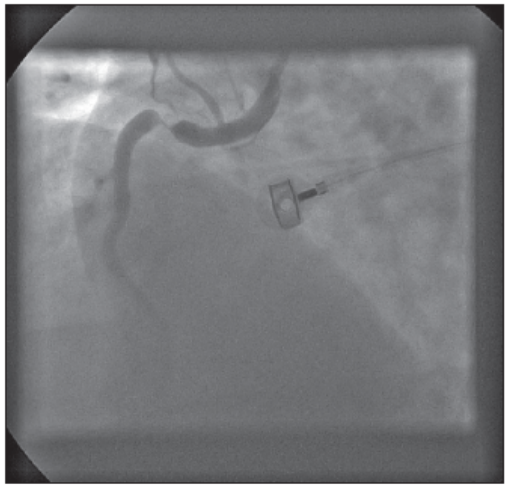

Figure 2) *Angiogram showing critical stenosis of the proximal right coronary artery*

were found in only 14% of cases in which these signs were absent. In a prospective study of 200 consecutive patients with acute inferior wall LVMI, Zehender et al (24) demonstrated a higher incidence of sustained ventricular tachycardia (16% versus 8%; P=0.08) and ventricular fibrillation (21% versus 9%; P=0.05) in patients with ECG signs of RV involvement. Significantly higher incidences of complete AV block (17% versus 4%; P=0.06) and severe bradycardias (9% versus 3%; P=0.09) with pacing requirements (18% versus 3%; P=0.01) have been reported in cases of RVMI (24). Mehta et al (26) studied complications and prognoses in a large number of patients hospitalized for anterior (n=971) and inferior LVMI with (n=491) or without (n=638) RV involvement. Anterior wall LVMI was associated with the highest overall and in-hospital mortality rates, while the number of arrhythmias (ventricular fibrillation, sustained ventricular tachycardia and high-degree AV blockade) was the highest in patients with inferior LVMI with RV involvement.

THERAPY

RV ischemia may lead to systolic and diastolic dysfunction, resulting in a serious deficit in LV preload with a subsequent drop in cardiac output and consequent systemic hypotension. Adequate filling (preload) of the impaired RV is thus crucial to maintain sufficient RV output volume and LV function (30). Initial therapy, therefore, requires the administration of sufficient volume to increase RV filling; at the same time, it is critically important to avoid drugs that cause venodilation and a decrease in RV filling (eg, nitrates, diuretics). Treatment is generally recommended to begin with a volume challenge of 300 mL to 600 mL normal saline over 10 min to 15 min through a central line or through a large-bore peripheral intravenous site (31). However, some studies have indicated that volume loading may not increase cardiac output (7,32,33). This may be due to variable initial volume status among patients. Some patients may be relatively volume-depleted and could benefit from a volume infusion, while others who present with a normal intravascular volume show no changes in cardiac index or blood pressure following a fluid load because the RV preload is already at a maximum for maintaining RV stroke output (18). Invasive hemodynamic monitoring is, therefore, recommended, because further infusion may be harmful if additional increases in RV volume prevent sufficient LV filling via interventricular interactions and intrapericardial pressure equalization. Based on hemodynamic monitoring studies, exceeding a RAP or PCWP of 20 mmHg is generally not recommended (32).

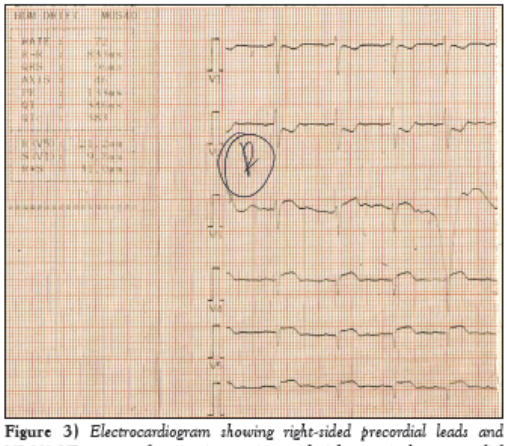

Figure 3) *Electrocardiogram showing right-sided precordial leads and V3-V6 ST segment elevation in a patient with right ventricular myocardial infarction.*

If initial volume loading fails to improve arterial pressure and cardiac output despite significant increases in RAP and PCWP, then positive inotropic agent therapy can be effective in stabilizing patients. Dell'Italia et al (32) studied the effect of dobutamine in patients with RVMI after volume loading and concluded that dobutamine produced a statistically significant increase in cardiac index, stroke volume index and RVEF.

Restoration of sufficient coronary blood flow represents the only treatment that addresses the underlying problem, and early reperfusion (Figure 4) improves RV performance as well as the clinical course and survival (4). Bowers et al (16) studied clinical outcomes and RV function using two-dimensional echocardiography in 53 patients with acute RVMI before and after reperfusion therapy. The authors reported dramatic recovery of RV performance and excellent clinical outcomes after early and complete reperfusion of the RCA using primary percutaneous coronary intervention. In contrast, unsuccessful reperfusion was associated with impaired recovery of RV function, persistent hemodynamic compromise and high mortality rates. Early reperfusion was also crucial in preventing ventricular arrhythmias, which were observed much more frequently in patients with unsuccessful coronary reperfusion (16).

In patients with refractory hypotension and low cardiac output, intra-aortic balloon counterpulsation (IABC) may be beneficial. Although IABC does not directly influence RV performance, it can increase coronary perfusion pressure and thereby improve RV function, particularly if the RCA has been recanalized. Furthermore, the performance of a dysfunctional RV is largely dependent on LV septal contraction, which can be improved using IABC (4).

The limitations of medical management of RV failure mentioned above have led to the development of a number of RV assist devices designed to bypass the impaired RV and/or pulmonary circulation to allow the right ventricle to recover. The TandemHeart Percutaneous Ventricular Assist Device (CardiacAssist Inc, USA) is an extracorporeal centrifugal pump that generates continuous flow with a minimal low amplitude pulsatile componentF. It can provide flow up to 5.0 L/min and pumps the blood from the right atrium to the main pulmonary artery, bypassing a poorly functioning RV. Kapur et al (34) studied nine patients with medically refractory RV failure and found that, although four patients died early, the Percutaneous Ventricular Assist Device was associated with significantly improved hemodynamics. Venoarterial extracorporeal membrane oxygenation systems can provide both cardiac and respiratory support. These can be fully established through the cannulation of a femoral vein and artery using the Seldinger technique; therefore, surgery is not required. In contrast to RV assist devices, this technique allows total bypassing of the pulmonary bed and, therefore, does not cause further elevation of the pulmonary pressures and relieves the RV overload. Particularly in patients presenting with an obstructive hemodynamic pattern (pulmonary artery hypertension, pulmonary embolism), extracorporeal membrane oxygenation method may be considered to be the only reasonable approach (35,36).

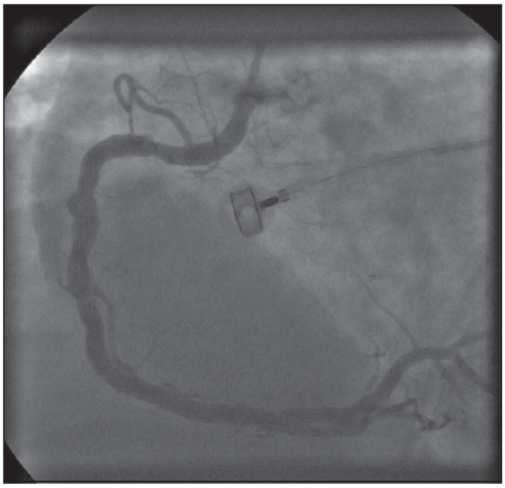

Figure 4) *Angiogram showing the right coronary artery post-revascularization*

PROGNOSIS

RV involvement significantly increased mortality in patients with inferior wall LVMIs, although it does not achieve the same rates observed in anterior wall LVMIs (26). Zehender et al (24) studied 200 consecutive patients admitted with acute inferior wall LVMI. RV involvement presenting with an ST elevation in lead V4R was found to be a highly negative predictive factor of both in-hospital mortality (31% versus 6%) and all major in-hospital complications (64% versus 28%). These included sustained ventricular tachycardia, ventricular fibrillation, myocardial rupture, second- and third-degree AV block requiring cardiac pacing, reinfarction and cardiogenic shock. Jacobs et al (37) evaluated 933 patients with acute MI presenting with cardiogenic shock due to either predominant RV (n=49) or LV failure (n=884). Despite the younger age, shorter time to shock diagnosis, higher prevalence of single-vessel coronary disease, lower prevalence of previous MI and similar revascularization outcomes in patients with RV failure, there was no significant difference in mortality between the groups (53.1% versus 60.8%; P=0.296), representing an unexpectedly high mortality rate among the RV shock patients.

On the other hand, recently published research by Foussas et al (38) found no significant difference in long-term mortality between patients with and without a RVMI. Therefore, the poor in-hospital prognosis for patients with RVMIs appears to be mainly due to the increased risk of life-threatening arrhythmias (26). Proper monitoring and appropriate antiarrhythmic treatment until hospital discharge plays a key role in the overall prognosis and survival of patients.

CONCLUSION

RVMI often accompanies an inferior wall LVMI presenting with typical clinical, ECG and echocardiographic findings. In the presence of hypotension or cardiogenic shock without signs of LV failure and 1 mm ST segment elevation in the V4R lead, a diagnosis of RVMI is highly probable. Specific treatment includes fluid loading and vasopressors, which should be administered immediately. In addition, patients with RV involvement require continuous careful monitoring because they are at

a significantly higher risk for ventricular fibrillation, sustained ventricular tachycardia and high-degree AV blockade, any of which would worsen the overall prognosis.

Thus, right-sided precordial leads should be used in all patients presenting with an acute inferior LVMI. This simple approach may facilitate early identification and risk stratification of patients with an accompanying RVMI and trigger a protocol of appropriately aggressive treatments required to manage the increased risk of life-threatening arrhythmic complications.

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Association of the right ventricle impairment with electrocardiographic localization and related artery in patients with ST-elevation myocardial infarction☆

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Abstract

Introduction: The right ventricular myocardial infarction (RVMI) has traditionally been mainly related to inferior wall ST elevation myocardial infarction (STEMI). This study assessed the RVMI electrocardiographic (ECG-RVMI) signs in relationship to ECG-based STEMI localization and to the infarct related artery in patients treated with primary percutaneous coronary intervention (pPCI).
Methods: Three hundred consecutive adult patients (107 females) were referred to catheterization laboratory with the acute STEMI diagnosis. In all patients, both the standard 12-lead ECGs and the right-sided precordial leads (V1R–V6R) were recorded. ECG-RVMI was diagnosed by ST segment elevation above 100 μV in V4R.
Results: ECG signs of RVMI were found in 35 and 31 (23.8% for both) patients with inferior and anterior wall STEMI, respectively. In 32 ECG-RVMI patients, the right coronary artery (RCA) was occluded while in 34 patients, the occlusions were in the left anterior descending (LAD) or the left circumflex artery. No statistically significant differences were found in ECG-RVMI patients when comparing clinical variables between those with anterior and inferior wall STEMI.
Conclusions: ECG signs of RVMI during acute STEMI are not uncommon. RCA was the infarction-related artery in only one half of these patients. Anterior wall STEMI and the LAD were associated with a significant proportion of ECG-RVMI cases.

Keywords: Infarction related artery; Primary percutaneous coronary intervention; Right ventricle infarction; ST elevation myocardial infarction

Introduction

In the era of treating myocardial infarction (MI) patients with thrombolysis, right ventricle (RV) involvement (RVMI) during ST elevation MI (STEMI) was associated with worsened clinical outcome [1]. In patients treated with the primary percutaneous coronary intervention (pPCI), which is currently the best available treatment option, limited outcome impact of RVMI has been reported [2]. The RV impairment has been traditionally most often related to inferior wall MI. The aim of this study was to assess the occurrence of electrocardiographic (ECG) signs of RVMI in relationship to ECG localization of STEMI and to the MI-related artery in a cohort of consecutive STEMI patients treated with pPCI.

Methods

Investigated population

A project of continuous 12-lead ECG monitoring during sub-acute MI phase enrolled consecutive STEMI patients ≥18 years old. All patients were referred to the coronary catheterization laboratory with the diagnosis of acute STEMI fulfilling the criteria for pPCI, i.e., chest pain for less than 12 h of duration and persistent ST segment elevation ≥2 consecutive leads or new left bundle branch block [3,4]. The

☆ Conflicts of interest: None.

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Table 1
Clinical characteristics of the investigated group (N = 299).

Characteristics		N (%) or median (5th–95th percentile)
Sex	Men	192 (64.2%)
	Women	107 (35.8%)
Age		62.4 (43.9; 83.8)
BMI		28.1 (22.3; 36.3)
Previous MI		28 (9.4%)
Previous PCI/CABG		28 (9.4%)
Hypertension		178 (59.5%)
Dyslipidemia		167 (55.9%)
Diabetes		66 (22.1%)
AMI localization	Anterior	130 (43.5%)
	Inferior	147 (49.2%)
	Other	22 (7.4%)
ECG signs of right ventricular impairment		66 (22.1%)
Lesion localization	RCA	114 (38.1%)
	LAD	133 (44.5%)
	LCX	52 (17.4%)
Number of diseased vessels	1 VD	152 (50.8%)
	2 VD	87 (29.1%)
	3 VD	60 (20.1%)
Time to reperfusion (hours)		3.4 (1.6; 12.8)

AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; LAD, left anterior descending artery; LCX, left circumflex artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; VD, vessel disease.

time to reperfusion therapy was defined as the interval between symptom onset and the wire passage in the culprit artery. Patients unable (in cardiogenic shock and/or unconscious on hospital admission) and those unwilling to sign an informed consent were excluded. The project was approved by the local ethics committee and all investigated patients gave a signed informed consent.

Coronary angiography

Coronary angiography was performed using Artis Zee Angiography System (Siemens Healthcare, Germany). The culprit lesion was determined as a complete vessel closure or the most significant artery stenosis. The number of diseased vessels was assessed as a count of main coronary vessels (left anterior descending artery [LAD], left circumflex artery [LCX], right coronary artery [RCA]) or its branches showing ≥50% diameter narrowing on angiography.

ECG assessment

At the admission to the catheterization laboratory, all patients had a 12-lead ECG recorded from both left (V1–6) and right (V1R–V6R) precordial leads using Artis Zee Angiography System (Siemens Healthcare, Germany). Localization of left ventricular MI was categorized as anterior (ST segment elevation in leads V_1–V_4), inferior (leads II, III, aVF), lateral (leads I, aVL and/or V_5–V_6), and septal (leads V_1–V_2). ST segment elevation above 100 μV in lead V4R was used for the diagnosis of ECG-RVMI [5,6].

Statistics

Absolute and relative frequencies are reported for categorical variables; mean ± standard deviation, and median with minimum to maximum range are used to characterize continuous variables. Differences between patients with and without ECG-RVMI were tested using Fisher's exact test for categorical variables and non-parametric Mann–Whitney U test for continuous variables. Bonferroni correction was added to multiple comparisons. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0.0.1. *P*-value below 0.05 was considered statistically significant.

Results

The study enrolled 300 consecutive patients of whom 107 were females. One male patient refused to continue in the study shortly after enrollment, thus 299 patients were studied further. Clinical characteristics of the investigated population are summarized in Table 1. ECG signs of RVMI were present in 66 patients (22.1%).

ECG signs of RVMI were found in 35 (23.8%) patients with inferior wall STEMI. In these patients, RCA and LCX were the culprit artery in 32 and 3 cases, respectively. ECG signs of RVMI were found also in 31 (23.8%) patients with anterior wall STEMI, in whom LAD was the culprit artery in all cases. ECG signs of RVMI were not found in patients with other ECG localizations of STEMI (lateral or infero-lateral). Occlusions of LCX artery were significantly less common in patients with ECG signs of RVMI. There were also no differences in number of diseased vessels (Fig. 1). The time to reperfusion therapy was not statistically different between patients with ECG-RVMI (3.3 h; 5th to 95th percentile of 1.6 to 18.7 h) and patients without ECG-RVMI (3.5; 1.6 to 12.0 h).

Further, no statistically significant differences were found in the ECG-RVMI sub-group when comparing clinical variables between patients with anterior and inferior wall STEMI (Table 2).

Discussion

In the investigated population, a noticeable ST segment elevation in lead V4R was found in 23.8% of inferior wall STEMI patients but interestingly also in 23.8% of anterior wall STEMI cases. The same results were found in assessment according to the culprit artery.

The RV impairment has been traditionally mostly related to inferior wall STEMI. Only rare cases were previously reported with other STEMI localizations [7–9]. Merely one recent report found elevations in right precordial leads V3R and V4R in 72 (65%) out of 111 STEMI patients [10].

The RV impairment can easily be explained in cases of inferior STEMI that are mostly caused by occlusion of RCA the branches of which supply the RV myocardium. The same is true for LCX occlusions in patients with left coronary artery dominance. Several pre-pPCI autopsy studies found some amount of RV necrosis in up to 94% of anterior wall STEMI despite the fact that extensive RVMI is not expected in anterior infarction because only small part of the anterior RV wall is supplied by the LAD branches [7,11,12]. Thus,

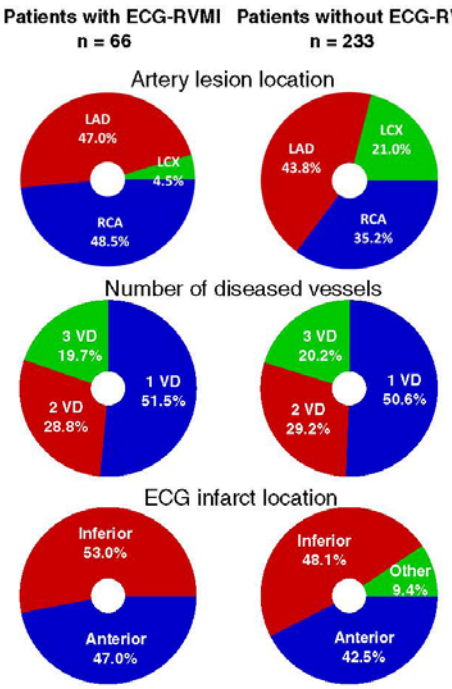

Fig. 1. Association of electrocardiographic signs of right ventricular myocardial infarction with lesion localization, number of diseased vessels and infarct location. The cases of ECG signs of right ventricular myocardial infarction (RVMI) with left circumflex artery lesion and with the "other" ECG infarct location were significantly less frequent ($p = 0.003$ and $p = 0.017$, respectively). Other parameters were not statistically significantly different. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; VD, vessel disease. (Color illustration online.)

Table 2
Comparison of clinical characteristics in patients with ECG signs of right ventricular impairment (N = 66).

Characteristics		AMI localization N (%) or median (5th–95th percentile)		P^a
		Anterior	Inferior	
Gender	Men	20 (64.5%)	21 (60.0%)	NS
	Women	11 (35.5%)	14 (40.0%)	
Age		61.6 (41.8; 86.7)	62.9 (44.9; 84.2)	NS
BMI		26.3 (21.6; 33.0)	28.0 (22.7; 38.3)	NS
Previous MI		4 (12.9%)	4 (11.4%)	NS
Previous PCI/CABG		3 (9.7%)	4 (11.4%)	NS
Hypertension		17 (54.8%)	25 (71.4%)	NS
Dyslipidemia		19 (61.3%)	19 (54.3%)	NS
Diabetes		7 (22.6%)	7 (20.0%)	NS
Lesion location	RCA	0 (0.0%)	32 (91.4%)	<0.001
	LAD	31 (100.0%)	0 (0.0%)	<0.001
	LCX	0 (0.0%)	3 (8.6%)	NS
No of diseased vessels	1 VD	17 (54.8%)	17 (48.6%)	NS
	2 VD	11 (35.5%)	8 (22.9%)	NS
	3 VD	3 (9.7%)	10 (28.6%)	NS
Time to reperfusion (hours)		3.4 (1.5; 16.8)	3.2 (1.8; 22.0)	NS

AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; LAD, left anterior descending artery; LCX, left circumflex artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; VD, vessel disease.

[a] *P*-value of Fisher's exact test or Mann–Whitney U test.

the mechanism of RV impairment in LAD occlusions is unclear. In particular (apart from lesion location) we have not only found no statistically significant differences in a number of characteristics but the numerical values shown in Table 2 were also very close between patients with anterior and inferior infarcts, suggesting that we have not missed any important difference because of small numbers of cases.

It seems reasonable to hypothesize that ECG signs of RV impairment in anterior wall STEMI are also related to the number of diseased coronary vessels. In such cases, RV can be expected to be supplied by more extensive artery collateralization, primarily from the left coronary system. Nevertheless, there were no differences in proportions of multi-vessel-disease cases in ECG-RVMI patients. There was no difference in time to reperfusion therapy. The probability of microangiopathy role is also low because of similar occurrence of diabetes in anterior and inferior STEMI groups, although other causes of microangiopathy cannot be excluded.

Several important limitations of this study need to be recognized. The number of investigated patients was relatively small. For RVMI diagnosis, ST elevations were assessed only in the V4R lead. We have no data on RV function and its correlation with the ECG findings.

In conclusion, ECG signs of RV impairment during acute phase of STEMI are not uncommon. Our findings challenge the notion that RCA is the infarct related artery in ECG-RVMI. In the investigated population, RCA was involved only in approximately a half of the ECG-RVMI patients. Anterior wall STEMI and the LAD coronary artery were associated with a significant proportion of ECG signs of RVMI. Detailed mechanism of RV involvement in these cases remains unclear.

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RESEARCH ARTICLE

Depression and Anxiety after Acute Myocardial Infarction Treated by Primary PCI

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Abstract

Aims

The main objective of the study was to find out prevalence of depression and anxiety symptoms in the population of patients with AMI with ST-segment elevation (STEMI), treated with primary PCI (pPCI). Secondary target indicators included the incidence of sleep disorders and loss of interest in sex.

Methods and results

The project enrolled 79 consecutive patients with the first AMI, aged <80 years (median 61 years, 21.5% of women) with a follow-up period of 12 months. Symptoms of depression or anxiety were measured using the Beck Depression Inventory II tests (BDI-II, cut-off value $\geq$14) and Self-Rating Anxiety Scale (SAS, cut-off $\geq$ 45) within 24 hours of pPCI, before the discharge, and in 3, 6 and 12 months). Results with the value $p<0.05$ were considered as statistically significant. The BDI-II positivity was highest within 24 hours after pPCI (21.5%) with a significant decline prior to the discharge (9.2%), but with a gradual increase in 3, 6 and 12 months (10.4%; 15.4%; 13.8% respectively). The incidence of anxiety showed a relatively similar trend: 8.9% after pPCI, and 4.5%, 10.8% and 6.2% in further follow-up.

Conclusions

Patients with STEMI treated by primary PCI have relatively low overall prevalence of symptoms of depression and anxiety. A significant decrease in mental stress was observed before discharge from the hospital, but in a period of one year after pPCI, prevalence of both symptoms was gradually increasing, which should be given medical attention.

Introduction

Depression or anxiety and ischemic heart disease (IHD) significantly more often occur together.[1–4] In the meta-analytical study of Thombs et al.[1], a structured interview

identified depressive disorder on average in 20% of patients after acute myocardial infarction (AMI); depression symptoms identified by the BDI questionnaire (Beck Depression Inventory) (score $\geq$ 10) were present in approximately 31% of patients. In the general population, depressive disorder (according to the DSM-III-R criteria) is found in 4.5%–9.3% of women and 2.3%–3.2% of men[5], and depression symptoms, but also depressive disorder are considered normal conditions after myocardial infarction (MI)[5]. In the first week after percutaneous coronary intervention (PCI), the prevalence of anxiety ranges around 25–37% [6], but up to 67% of patients after PCI may be depressed[7]. A significant portion of the data in the studies, however, is based on the evaluation of self-report questionnaires, and is often influenced by topical non-specific feelings ("unease").

The first symptoms of depression appear between 48 and 72 hours after MI and in most patients disappear within 5 or 6 days[4]. Damen et al.[8], describing intra-individual changes in depression and anxiety during the one-year follow up of patients after PCI, found that both variables are stable over time. 81% of patients after 12 months still had symptoms of depression, and 76% of patients still had symptoms of anxiety. The higher the measured score of both variables at the beginning, the more likely this score remained increased even after 12 months.

The study of the incidence of depression and anxiety symptoms is important because of the potential impact of these variables on subsequent morbidity and mortality of patients. In 1993, Frasure-Smith et al.[9] as the first ones identified depression after MI as an important predictor of 3-4-fold increase in mortality from cardiac causes, regardless of previous MI's and/or left ventricular dysfunction. Opinions concerning the influence of depression on higher mortality at the time of recovery after AMI vary; some of them confirm this relationship[10–12], others do not[13,14]. A recent study confirmed that depression 1.6-times increased the likelihood of death in the long term horizon of 7 years after PCI[15]. However, it is not certain what causal relationship this is, as treatment with antidepressants (sertralin) or with cognitive behavioural therapy (CBT) has never been associated with a favourable effect[16,17]. Possible explanations of more frequent co-occurrence of depression and IHD are being sought in more frequent occurrence of unhealthy lifestyles in depressive people[18], non-adherence to treatment[19], later seeking medical care[20], increased activation of the hypothalamic-pituitary-adrenal (HPA) axis[21], increased activation of platelets[22], abnormal endothelial function[23], etc.

The main objective of this study was to determine the prevalence of depression and anxiety symptoms in the population of patients with AMI with ST-segment elevation (STEMI) treated by currently the most effective method, which is a mechanical reperfusion using primary PCI (pPCI). This study is unique by the number of measurements throughout the year, which allows us to track trends over time. Secondary objectives were to determine co-morbidity of depression and anxiety and the difference between men and women in the level of anxiety and depression experienced during the recovery.

Materials and Methods

The study protocol was approved by the Ethical Committee of the University Hospital Brno and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Prospectively, 79 consecutive patients were enrolled in the study over 16 months, with STEMI treated by pPCI within 12 hours of the onset of problems and after signing informed consent. Exclusion criteria included AMI in the medical history, the inability to complete the questionnaire, the impossibility of finishing the 12-months follow-up, a severe chronic disease with poor prognosis (e.g. malignancy, more severe cerebral stroke, organ complications of diabetes, etc.), and the age over 80 years. These patients were followed up in the period of 1 year

after AMI in five different time intervals (within 24 hours from pPCI, before discharge from the hospital, in 3, 6, and 12 months). The project was approved by the local Ethics committee.

The symptoms of depression were measured by means of BDI-II inventory. The Czech BDI-II version was validated by Preiss and Vacíř[24]. This self-rating scale with 21 items, which does not take much time to complete (5–10 minutes), is focused on depression symptoms: affective, motivational, cognitive, and physiological. For each of 21 items, the respondent ticks the statement that best describes how he/she felt during the last 14 days. Except for two items (16 and 18), the items are on a four-point scale. Items 16 and 18 have a seven-point scale. The minimum score is 0, and the maximum 63. From 14 to 19 points (14 and 19 including), the score is interpreted as slightly depressive, 20 to 28 points as moderately depressive, and 29 to 63 as severely depressive symptoms[24].

Symptoms of anxiety were measured using the inventory of SAS (Zung's Self-Rating Anxiety Scale) [25]. It is again a method that does not take much time; it contains 20 items, identifying affective and physiological symptoms of anxiety. The final score describes, similar to BDI-II, the condition in the last two weeks, not anxiousness or a depressive state of mind as a personality trait. The respondent uses a four-point scale to assess all statements (from never / rarely, to very often / all the time). The score can be from 20 to 80 points. As a cut-off score, it is recommended to use the level of 45 points [25].

We subjected two areas, which are assessed by the self-rating scales, to a special analysis, namely sleep disturbances and loss of interest in sex.

The data was analyzed in the Statistika Cz program, version 12, and in MS Office—Excel 2007. Results with the value $p<0.05$ were considered as statistically significant. Mann-Whitney U tests were used to compare those who withdrew from the study during its course and those who continued. When analyzing BDI-II and SAS as continuous variables, the Spearman correlation coefficient was calculated to determine the relationship between the initial and subsequent rate of depression and anxiety. The same method was used to compare co-morbidity or depression and anxiety symptoms. To determine the difference between the values of both tests for men and for women, the Mann-Whitney U test was used. Kruskal Wallis ANOVA was used to determine the relationship between age groups and values of BDI-II and SAS.

Results

The research involved 79 patients (78.5% of men; median age 61 (5^{th} percentile 43.6, 95^{th} percentile 77.0, range [32–79] years).

Occurrence of depression symptoms

Within 24 hours after pPCI, depression symptoms (BDI-II $\geq$ 14) were identified in 17 patients (21.5%). In the time before the discharge (in 3–5 day after pPCI), questionnaires were handed in by 76 patients (96.2%), 7 patients (9.2%) were with depression symptoms. After 3 months, 67 patients (84.8%) responded. Of the remaining patients, 7 patients (10.4%) were with depression symptoms. After 6 months, 65 patients (82.3%) responded, 10 of this patients (15.4%) were with depression symptoms. And during the last measurement after 12 months, 9 patients of 65 (13.8%) with depression symptoms were found. (Table 1, Graph 1) There were no

Table 1. Occurrence of positivity of questionnaire BDI-II.

	Within 24h after IM	*Discharge*	*3M*	*6M*	*12M*
BDI-II score ≥14 (no. of patients)	21.5% (17/79)	9.2% (7/76)	10.4% (7/67)	15.4% (10/65)	13.8% (9/65)
Score median (5^{th}; 95^{th} percentile)	8 (1.9; 21.0)	6 (0.0; 17.0)	5 (0.0; 15.0)	6 (0.0; 21.0)	5 (0.0; 26.4)

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Table 2. Occurrence of positivity of questionnaire SAS.

	Within 24h after IM	*Discharge*	*3M*	*6M*	*12M*
SAS score ≥ 45	8.9% (7/79)	0% (0/76)	4.5% (3/67)	10.8% (7/65)	6.2% (4/65)
Score median (5^{th}; 95^{th} percentile)	34 (25.0; 48.1)	34 (22.8; 42.0)	34 (21.3; 43.7)	33 (20.0; 50.4)	33 (20.2; 45.6)

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differences between patients who did or did not follow up, at any time point, ($p = 0.51$ at discharge, $p = 0.27$ at 3 months, $p = 0.54$ at 6 months), comparing to the previous questionnaire scoring.

Occurrence of anxiety symptoms

Within 24 hours after pPCI, anxiety symptoms (SAS ≥ 45) were felt by 7 patients (8.9%). At the time of the next measurement before the discharge from the hospital, no patient was presenting anxiety symptoms. After 3 months, 3 patients (4.5%) with anxiety symptoms were found in the group. After 6 months, 7 patients (10.8%) were with anxiety symptoms. And during the last measurement after 12 months, there were 4 patients with anxiety symptoms (6.2%). (Table 2, Graph 1). There were no differences between patients who did or did not follow up, at any time point, ($p = 0.28$ at discharge, $p = 0.86$ at 3 months, $p = 0.58$ at 6 months), comparing to the previous questionnaire scoring.

Simultaneous occurrence of depression and anxiety symptoms

Both variables statistically significantly correlated in all measurements ($r = 0.61$ within 24 hours; $r = 0.44$ before discharge; $r = 0.60$ in 3 months; $r = 0.80$ in 6 months; and $r = 0.79$ in 12 months). (Fig 1)

Difference between men and women

In determining the differences between men and women it has been found that the groups statistically significantly differed from each other at the time of hospitalization. Women experienced more depression and anxiety then men in the first 24 hours after PCI ($p<0.01$; $p = 0.01$), and also more depression before hospital discharge ($p<0.01$).

Difference between age groups

In determining a depressive and anxious state of mind, the values of depression symptoms in different age groups statistically significantly ($p = 0.02$) differed in the first 24 hours after PCI in different age groups. Patients in the oldest age group between 70 and 79 years had the highest score of BDI-II in the first 24 hours after PCI (average = 12.3, SD = 5.0).

Sleep disturbances and loss of interest in sex

From the BDI questionnaire, we were further interested specifically in two aspects, which we also assessed in terms of their occurrence in patients over 12 months: changes in sleep and loss of interest in sex. On the first day of hospitalization, the values were most extreme. Changes within the 'minus' meaning, i.e. "I sleep a little less", "I sleep less", or "I wake up one to two hours earlier and cannot fall asleep again" on the first day of hospitalization were stated by 46% of respondents. Before leaving the hospital, a sharp decline in these changes was apparent—to 26% of the respondents. The third, fourth and fifth measurement stabilized at around 30%.

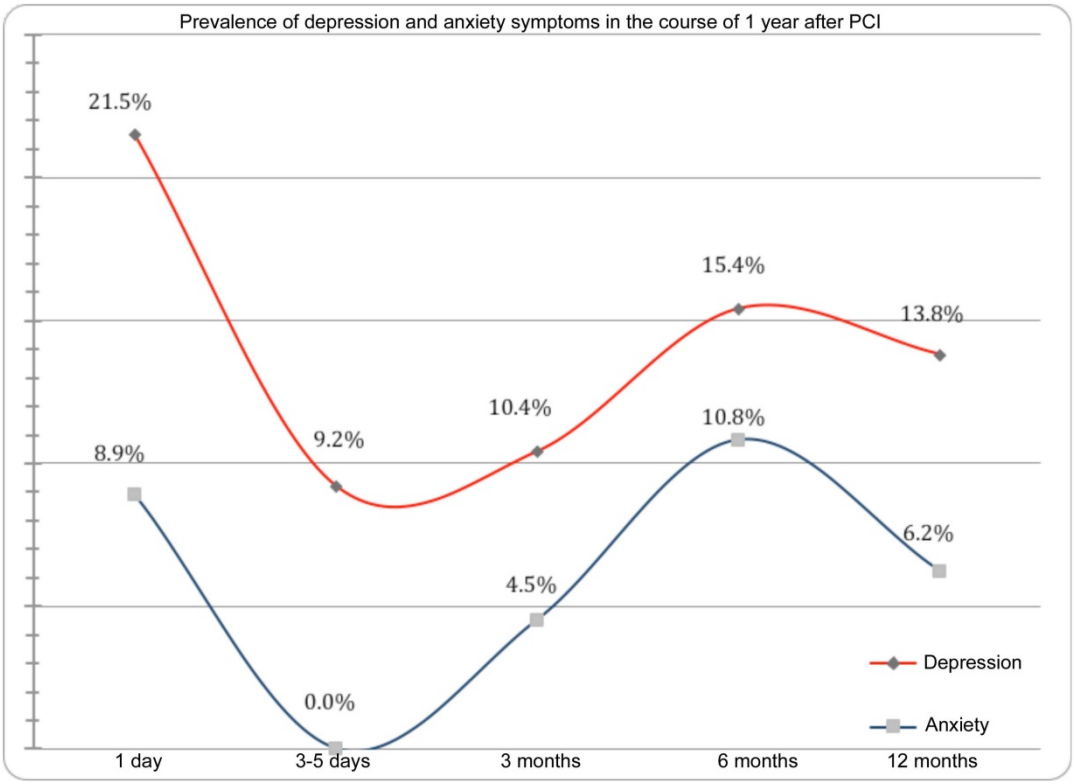

Fig 1. Prevalence of depression and anxiety symptoms in the course of 1 year after PCI.

doi:10.1371/journal.pone.0152367.g001

If we compare these sleep disorders with the incidence of depression in our sample, we can see the prevalence of sleep disorders. Changes in the sleep in the sense of "I sleep a little more than usual", and "I sleep much more than usual" occurred among the respondents during hospitalization in 22%, and before discharge in 17%. Then the values stabilized again around 30%. (Fig 2)

Partial loss of interest in sex was reported on the first day by 46%; after the 15% decline, it returned again after 12 months to 40%, with increasing tendency from month 3 to month 12. Complete loss of interest in sex was reported by 11% respondents on the first day, again with increasing tendency. Between month 6 and month 12, the incidence of complete loss of interest in sex stabilized at 20%. (Fig 3)

Discussion

Unlike previous studies, the prevalence of depression symptoms is lower. In the first 24 hours after PCI, 21.5% of patients with a depressive state of mind were recorded, while after 3–5 days after PCI before discharge from the hospital, the relative number of patients with a depressive

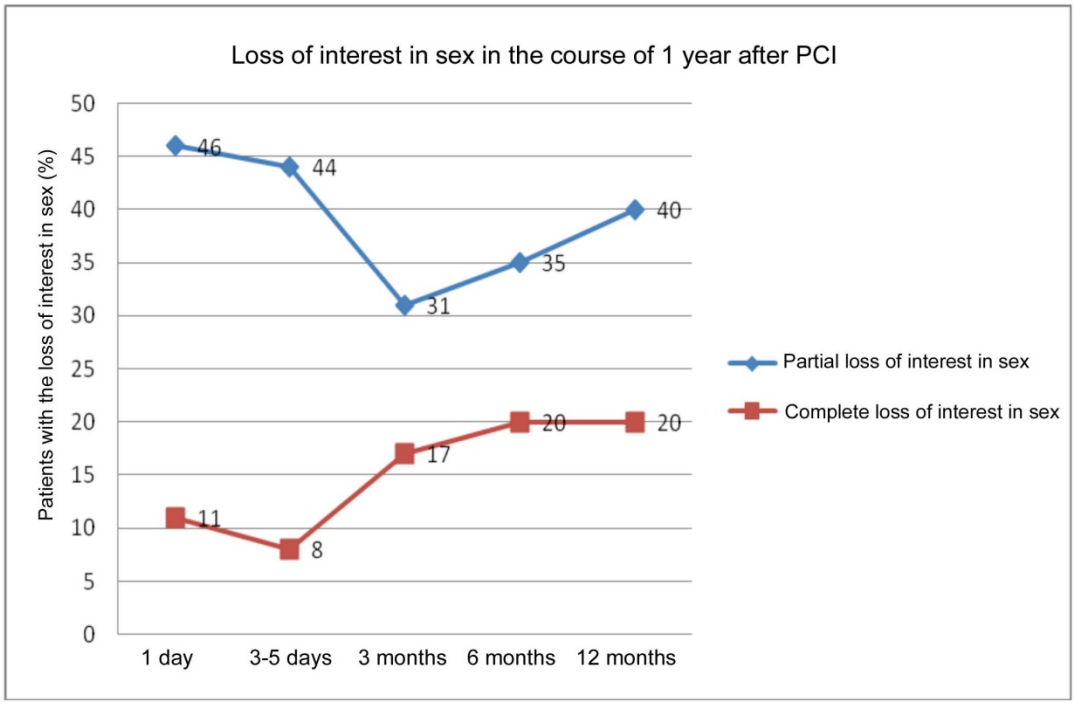

Fig 2. Changes of sleep in the course of 1 year after PCI.

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state of mind was lower than half (9.2%). This sudden drop in the incidence of depression symptoms in a short time could be explained by mental and/or physical relief after the PCI and disappearance of distressing symptoms of the ischemic heart disease, which could precede AMI. Certain limitation is the unavailability of data prior to the occurrence of MI. Partial information may be provided by first self-rating questionnaires completed within 24 hours after admission, but non-specific distress during acute cardiovascular disease surely burdens it with a certain error. Subsequently, during home treatment, there is an increase in a relative number of patients with depression symptoms—to the values 10.4%, 15.4%, and 13.8% (3, 6, and 12 months after PCI respectively). A similar curve was observed in a separate evaluation of sleep disorders and interest in sex. It can be assumed that it takes some time for the patients to fully realize consequences of severe cardiovascular disease, impaired functional capacity, and in some cases even disability caused by the new disease. This can explain to some extent a gradual increase of the symptoms in home care. In the meta-analytical study[1], 6 similar studies were assessed, ascertaining the prevalence of depression using the BDI (BDI $\geq$ 10) questionnaire. Averaged relative frequency of the incidence of depression symptoms was 31.1% (CI 29.2%–33.0%; N = 2 273). Our results are significantly lower, after one year one half. This could be partly influenced by using a different (older) version of the BDI questionnaire in these 6 studies.

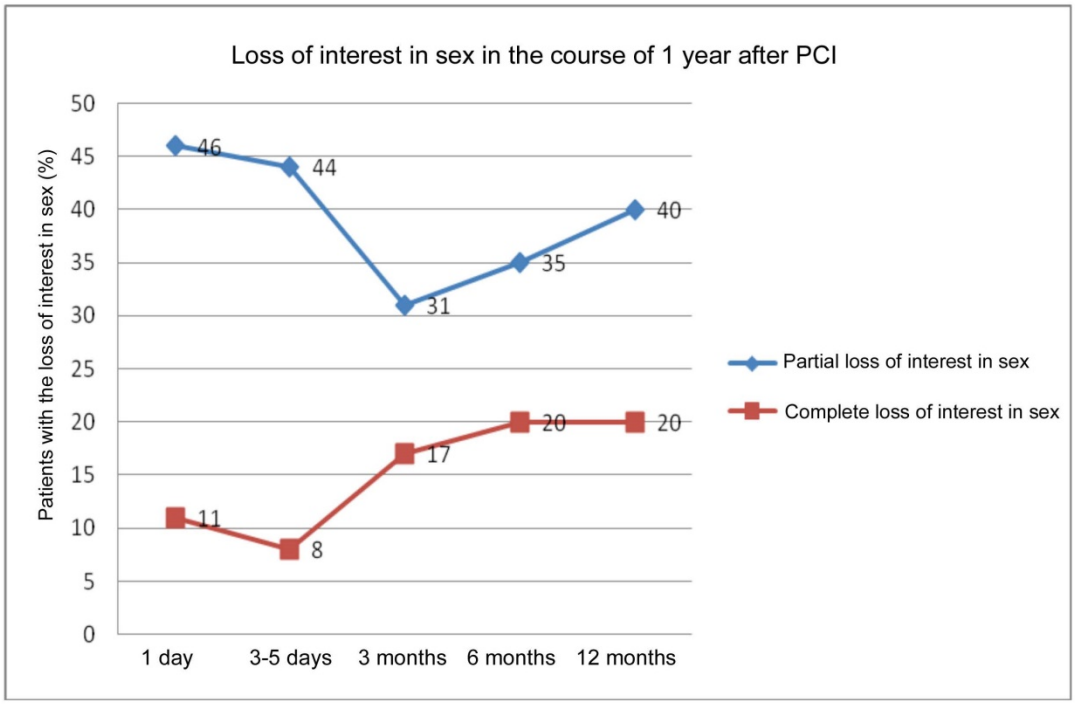

Fig 3. Loss of interest in sex in the course of 1 year after PCI.

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Prevalence of anxiety is often determined along with depression using the HADS questionnaire (the Hospital Anxiety and Depression Scale), which is divided into two subscales. For example, Furuya et al.[7] found the prevalence of anxiety in 66.7% of men and 56.3% of women, with atypical predominance of the incidence of anxiety in men. Our research group was doing better again in terms of the incidence of anxiety, when we did not use any other method of measurement. Anxiety ranged from 0% to 10.8%. Zero incidence was recorded in the period before leaving the hospital.

Patients reported depression and anxiety symptoms already on the first day after AMI, although the instructions of both self-rating scales required assessment of the condition in the last two weeks. At the same time, a rapid decline was reported immediately after 2–4 days of the completion of the first set of questionnaires. These facts suggest that both BDI-II and SAS evaluated the current condition of depression and anxiety symptoms rather than their average in the last 2 weeks.

Damen et al.[8] mentioned stability of both investigated symptoms at the time after PCI. In this study, the authors focused primarily on the research of changes of depression and anxiety symptoms over time in individual patients separately. They found relative stability of both variables. We came to similar conclusions using Spearman correlation of individual variables at all times. The results at all times were statistically significantly associated with one another.

When evaluating the relationship between depression and anxiety symptoms we came to the conclusion that the values BDI-II and SAS measured at the same time are statistically significantly related. Lane et al.[2] reached the same conclusions. The authors offer two possible explanations of this co-morbidity. These two values are either increased together in response to stress (AMI, hospitalization, PCI, etc.) without relation to any psychopathology, or they represent wrong measurement instruments, which reflect another different psychopathology[2].

By comparing men and women, predominance of depression and anxiety symptoms was explained both in the first 24 hours, and for depression, before the discharge from the hospital. Furuya et al.[7] came to opposite results with their research group. We could explain this disparity in experiencing depression and anxiety symptoms by greater reactivity of women to stressful stimuli.

Conclusion

Overall, we found a relatively low prevalence of symptoms of depression and anxiety in patients with STEMI treated with primary PCI. A favourable decline in mental stress was observed before the discharge from the hospital, but in a period of one year after PCI, the prevalence of both symptoms gradually increased. This development should be closely monitored in all patients with cardiovascular disease using simple screening methods, such as BDI-II and SAS, which in the clinical practice will allow for rapid evaluation of the risk to the patient and the use of other methods enhancing medical care.

Author Contributions

Conceived and designed the experiments: PK JK TK JP MS. Performed the experiments: JK JP LU MS. Analyzed the data: NH MJ MH. Wrote the paper: PK JK NH.

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Interventional cardiology

Reperfusion therapy for ST elevation acute myocardial infarction 2010/2011: current status in 37 ESC countries

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Aims Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion therapy in ST-elevation myocardial infarction (STEMI). We conducted this study to evaluate the contemporary status on the use and type of reperfusion therapy in patients admitted with STEMI in the European Society of Cardiology (ESC) member countries.

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Methods and results A cross-sectional descriptive study based on aggregated country-level data on the use of reperfusion therapy in patients admitted with STEMI during 2010 or 2011. Thirty-seven ESC countries were able to provide data from existing national or regional registries. In countries where no such registries exist, data were based on best expert estimates. Data were collected on the use of STEMI reperfusion treatment and mortality, the numbers of cardiologists, and the availability of PPCI facilities in each country. Our survey provides a brief data summary of the degree of variation in reperfusion therapy across Europe. The number of PPCI procedures varied between countries, ranging from 23 to 884 per million inhabitants. Primary percutaneous coronary intervention and thrombolysis were the dominant reperfusion strategy in 33 and 4 countries, respectively. The mean population served by a single PPCI centre with a 24-h service 7 days a week ranged from 31 300 inhabitants per centre to 6 533 000 inhabitants per centre. Twenty-seven of the total 37 countries participated in a former survey from 2007, and major increases in PPCI utilization were observed in 13 of these countries.

Conclusion Large variations in reperfusion treatment are still present across Europe. Countries in Eastern and Southern Europe reported that a substantial number of STEMI patients are not receiving any reperfusion therapy. Implementation of the best reperfusion therapy as recommended in the guidelines should be encouraged.

Keywords Primary percutaneous coronary intervention • STEMI • Treatment variation • Europe

Introduction

Guidelines from the European Society of Cardiology (ESC) call for timely coronary artery reperfusion in patients with ST-elevation myocardial infarction (STEMI) and stress that, if available, primary percutaneous coronary intervention (PPCI) is the preferred strategy.[1] Despite its advantages, PPCI is not universally implemented and thrombolysis is still used in many patients. Furthermore, a large group of patients presenting with STEMI are not receiving any reperfusion therapy.[2–4] The reasons for these differences in the use of reperfusion therapy in the ESC countries are poorly understood. However, prior studies suggest that clinical factors, financial concerns as well as obstacles, and organizational difficulties are key factors.[5,6] To overcome these types of barriers, systems of care have been developed such as establishment of regional STEMI networks with very encouraging results.[7,8]

This descriptive study reports the current use of reperfusion treatment in 37 ESC countries. The study is a follow-up of the survey conducted in 2007 including more countries. A total of 27 countries participated in both surveys. The present survey includes the same study variables collected in the former survey, whereas the data sources vary.[4]

Methods

This was a cross-sectional descriptive study based on aggregated survey data from 36 ESC member countries and 1 affiliated ESC country in 2010/2011. The 55 National Societies within the ESC were kindly asked to provide country-level data. Positive replies were received from 37 ESC countries, including one affiliated ESC country. The collection of data was a substantial task, and consequently, one representative/contact person from each country is listed as a co-author of this report. The study consisted of self-administered questionnaires completed by the national contact persons providing information on the following items: the number of STEMI patients per 1 000 000 inhabitants treated with (i) PPCI, (ii) thrombolysis, and (iii) patients receiving no reperfusion therapy. We also collected data on mortality assessed as overall in-hospital mortality according to the type of reperfusion therapy. Furthermore, we gained data on information on existing national STEMI or PCI registries and on the organization of treatment management (number of PPCI centres per 1 000 000 inhabitants and number of cardiologists per 1 000 000 inhabitants). Twenty-seven of the 37 countries were also participating in the survey conducted in 2007/2008, and data on the utilization of PPCI were available for comparison. Numbers of patients treated with thrombolysis and the numbers of patients not receiving reperfusion therapy were in 2007/2008 given as percentage and can therefore not be compared.

Since most of the countries in Europe at present do not have national or regional registries on PPCI or STEMI, we allowed the national contact persons to report their best estimates. The following country data were based solemnly on contact person's estimates: Azerbaijan, Bosnia and Herzegovina, Georgia, and the Netherlands. Only nine countries (Austria, Belgium, Denmark, Germany, Iceland, Italy, Poland, Sweden, and UK) have national registries covering the entire STEMI population with mandatory registration and continued data validation (*Table 1*). After conduction of the survey in 2007/2008, a substantial number of countries have taken the initiative to establish more permanent data registries with national coverage. Examples are Romania and Bulgaria with fairly new established registries covering 70% of the STEMI population. The completeness of STEMI capturing during the time period in the various registries ranged from 14.5% coverage in Greece to 100% coverage in some countries, i.e. Denmark, Sweden, and the UK. In some countries, e.g. France, Egypt, Greece, Ireland, and Slovakia, data were based on surveys and snapshots. A full description of the data sources are given in *Table 1*. Since mortality data are highly dependent on sound registration, we choose to include only mortality data from countries where a national STEMI registry and a national PCI registry exist (*Table 3*).

Data analysis

We provided descriptive analysis of the type of reperfusion utilization in 2010/2011 for each country. For the 27 countries participating in both surveys, we moreover included comparative numbers on the utilization of PPCI. The use of reperfusion therapy is presented as numbers per 1 000 000 inhabitants. Numbers of available cardiologists are presented per 1 000 000 inhabitants and numbers of available PPCI hospitals per mean population. Correlation between the number of cardiologists per 1 000 000 inhabitants and the number of performed PPCI per million inhabitants was done using Spearmans' rank correlation test. Mortality data are presented as percentages.

Table 1 Description of country data sources

Country	Data from the year	Existing national PCI registry	Existing regional PCI registry	Existing national STEMI registry	Existing regional STEMI registry	Expert estimates only	Completeness of STEMI capturing per period/ percentage of STEMI population covered by the registry	Comments to data content
Austria[a]	2011	Austrian PCI registry	PCI registry Wilhelminen Hospital Vienna	No	Vienna, STEMI registry		90% (estimate)	
Azerbaijan	2011					x		
Belgium[a]	2011	Belgian PCI registry	No	Belgian STEMI registry	No		STEMI database 50% PCI database 100%	
Bosnia and Herzegovina	2011					x		
Bulgaria	2011	Started November 2011	No	Started November 2012	No		70%	Data from various sources: The National Health Insurance Fund, National Social Security Institute, National Center of Public Health and Analyses as well as from the National PCI centres
Croatia[a]	2011	No	Yes	Yes	Yes		>90%	Croatian Institute for Public Health and regional and in-hospital ACS/STEMI/PPCI registries
Cyprus	2009	No	No	No	No		NA	Data for STEMI were based on CYPACS Study/ Registry in 2009. Data for PPCI were based on unpublished data for the year 2011, presented at the Cyprus Society of Cardiology National Congress, year 2012
Czech Republic	2011	Yes	Yes	No	Yes		92%	Register + approximation based on current and older data
Denmark	2010	The Danish Heart Registry	The Western Denmark Heart Registry, PATS (The Eastern Denmark Heart Registry	The Danish National Patient Registry	The Danish National Patient Registry		100%	
Egypt	2011	Yes	Yes				36%, 31 million people	Based on the 1st Phase of Egyptian Stent For Life registry (9 months). Four areas only: Cairo, Alexandria, Delta, and Canal. Fourteen cath labs
Finland	2011	No	Yes	No	Yes—some		Near 100%	PCI data based on registry data, STEMI data based on expert estimates

Continued

Table 1 *Continued*

Country	Data from the year	Existing national PCI registry	Existing regional PCI registry	Existing national STEMI registry	Existing regional STEMI registry	Expert estimates only	Completeness of STEMI capturing per period/ percentage of STEMI population covered by the registry	Comments to data content
France[a]	2011	ONACI	RICO, Cardio ARIF, ORBI, Center registry, PACCA registry, Alpine registry	No	RICO, Cardio ARIF, ORBI, Center Registry, PACCA registry, Alpine registry		35%	Based on the FAST-MI survey data
Georgia	2011	No	No	No	No	x		Numbers are based on data from only five PCI centres. (insured patients only)
Germany	2011	No	Yes Berlin, Essen, Hildesheim/ Association of Clinical Cardiology Directors (ALKK) Ludwigshafen/ALKK	No	Yes			Activity numbers are based on BQS: AQUA-Institut, data collection is mandatory. Staff numbers are based on Bruckenberger, the German Heart Statistics 2011
Greece	2011	No	Yes	No	No		14.5 %	Data based on Stent for Life Registry, Hellenic PCI Registry
Hungary	2011	Yes	Yes	Partially	Yes		50% Snapshot survey (2011) 92%	
Iceland	2011	Yes	Yes	Yes	Yes		PCI 100% STEMI 95%	SWEDEHEART. Data on the use of thrombolysis are based on expert estimates
Ireland	2011	No	No	No	No		NA	(1) Heartbeat voluntary STEMI database of 20 participating hospitals (July 2011 to June 2012) covering 58% of the population (in conjunction with CHAIR regional registry and HIPE national hospital administrative system) (2) Medical Council (registering body) for the number of cardiologists
Israel	2010	Yes	Record PCI	1—ACSIS ACS	1 Recode PCI		Data are extrapolated (i.e. six times) from a 2-month national ACS surveillance	ISRAEL ACSIS 2010 National ACS Registry
Italy	2010	Yes	Yes	Yes	Yes		BLITZ 1 (2 weeks snapshot in >90% Italian CCUs; BLITZ-4 a weeks snapshot representative of approximately one-fifth of total CCUs)	Data are based on GISE database[a], data on thrombolysis, and no reperfusion are based on BLIZ-4

Latvia[a]	2011	No	Yes	Yes	No	90%	
Marcedonia[a]	2011	Yes	Yes	Yes	Yes	85%	Based on national registry
Netherlands	2011	Yes	Yes	No	No	Yes	Based on expert estimate and extrapolation of data from 18 interventional centres
Portugal	2011	2 different	No	2 different	No	NA	
Poland[a]	2011	Yes	Yes	Yes	Yes		PL-ACS registry, national PCI database, thrombolysis, and number of patients not receiving any reperfusion are based on expert opinion
Romania[a]	2011	Yes	No	Yes	No	70%	Based on RO-STEMI
San Marino	2011	No	No	Yes	No	100%	
Saudi Arabia	2011	Yes	No	Yes	Yes	Representative snapshot, particularly of the governmental tertiary care hospitals	(1) National PCI Registry (CARES) (2) National ACS Registry (SPACE) (3) Regional ACS Registries (Gulf RACE-1 and Gulf RACE-2) (4) National experts estimates
Serbia[a]	2011	No	Yes	Yes	No	National registry for ACS covers all hospitalized ACS patients in Serbia	Clinical Centre of Serbia PPCI registry, National registry for ACS, Annual cath-lab reports of all PCI centres
Slovakia	2011	No	No	Yes	Yes	80–90%	Based on a 2-month snapshot covering 90% of hospitals. The results are multiplied by six to get 1-year data.
Slovenia	2011	No	In each CL	No	In each CL	100%	
Spain	2010	Yes	Yes	Yes	Yes	28.73% based on Regional STEMI Networks Registry	Spanish Society of Cardiology, PCI Registry. Prevalence of STEMI vs. non-STEMI based on MASCARA registry. Thrombolysis was based on the Spanish Society of Cardiology, PCI Registry (6% ACS non-classifiable)
Sweden[a]	2011	Yes	No	Yes	No	100%	Swedeheart, HIA
Switzerland[a]	2011	No, a nationwide annual survey of PCI	No	AMIS plus		AMIS plus ca. 30%	Information based on voluntarily hospitals participation in AMIS Plus Registry
Turkey	2011	No	No	No	No		Data sent from 25 pilot cities of SFL initiative
UK[a]	2010 and 2011	Yes MINAP BCIS	Yes	Yes	Yes	100%	BCIS PPCI data for all UK 2011. MINAP data for 2010 England and Wales—thrombolysis
Ukraine	2011	Yes (covering just 75%)	No	No	No	NA	Information based on data from 'Ukrainian Register of Percutaneous Coronary Interventions', reporting the Ministry of Health. Personal communication with PCI centres

CCU, Critical Care Unit; CL, County Level; HIA, Healt Impact Assesment.
[a]Based on the same data sources as the survey published in 2010[4].

Table 2 Number of available cardiologists, hospitals capable of performing acute and non-acute percutaneous coronary intervention, and population per centre

Country	Country population 1 January 2011	Mean number of board-certified cardiologists per million population	Numbers of PCI hospitals	Numbers of PCI hospitals with 24/7 PPCI service	Mean population per PPCI centre (24/7 service)
Austria	8 404 252	35.7	36	14[a]	600 300
Azerbaijan	9 111 078	0.22	7	4	2 280 000
Belgium	10 951 665	73.0	36	36	304 000
Bosnia and Herzegovina	3 843 183	21.1	5	2	1 922 000
Bulgaria	7 504 868	86.6	33	33	227 500
Croatia	4 412 137	NA	12	9	490 300
Cyprus	804 435	165	4	0	NA
Czech Republic	10 513 209	71.3	22	22	478 000
Denmark	5 560 628	58.4	7	5	1,112,000
Egypt[a]	82 079 632	25.8	93	31	2,654,800[a]
Finland	5 375 276	24.7	23	3	1 792 000
France[b]	65 821 885	9.1	210	210[b]	313 000[a]
Georgia[b]	4 469 250	33.6	9	4	1 117 300[a]
Germany	81 780 000	36.0	521	NA	NA
Greece[b]	10 787 690	243.8	49	15	754 000
Hungary[b]	9 985 722	40.0	17	17	587 400
Iceland	318 452	78.5	1	1	318 500
Ireland	4 480 858	22.1	16	4	1 120 200
Italy[b]	60 626 442	NA	255	211	287 300
Israel	7 873 052	72.2	24	22	311 400
Latvia	2 229 641	65.0	4	2	1 114 800
Macedonia	2 077 328	17.8	4	4	519 300
The Netherlands	16 696 000	55.7	31	22	759 000
Portugal	10 636 979	54.5	29	21	506 500
Poland	38 200 037	50.2	137	114	335 100
Romania	19 042 936	57.7	22	12	1 586 911
San Marino	31 269	191.9	1	1	31 300
Saudi Arabia	26 316 704	11.5	30	4	6 533 000
Serbia	7 276 195	NA	11	5	1 455 200
Slovakia	5 404 322	78.6	6	4	1 351 000
Slovenia	2 050 189	11.2	5	2	1 025 094
Spain	46 152 '926	46.9	126	78	591 700
Sweden	9 415 570	78.	29	12	784 600
Switzerland	7 870 134	12.6	32	26	302 700
Turkey[b]	14 283 013	13.0	27	15	952 200
UK	63 141 700	NA	117	57	1 107 749
Ukraine	45 134 707	55.5	37	11	4 103 200

[a]In Austria, further 14 centres perform PPCI in STEMI patients for 1 up to 3 days 24 h within networks that offer a rotational system of open catheter networks (e.g. STEMI networks in Vienna, LINZ, Lower Austria South).
[b]Based on survey data in selected parts of the countries—see also *Table 1*.

Results

Utilization of primary percutaneous coronary intervention in 2007 and 2010/2011

Figures 1 and 4 show the use of PPCI in the participating 37 countries. Primary percutaneous coronary intervention utilization varied considerable between countries with a range from 23 to 884 PPCI procedures per 1 000 000 inhabitants (*Figure 1*). Countries with the highest utilization of PPCI per 1 000 000 were Austria, Bulgaria, Germany, the Netherlands, and Poland. Azerbaijan, Cyprus, Egypt, Georgia, Saudi Arabia, and Ukraine had the lowest utilization (*Figure 1*). Most countries had PPCI rates around 400–600 procedures per 1 000 000 inhabitants (*Figures 1* and *4*). Twenty-seven of the total 37 countries participated in the former survey. Major

Table 3 Crude in-hospital mortality (%) of ST-elevation myocardial infarction (STEMI)

Country	STEMI	STEMI treated with PPCI	STEMI treated with thrombolysis	STEMI receiving no reperfusion
Bulgaria	12	6.1	11	19
Denmark	6	3.1	NA	11
Hungary	10	6	13.5	15.5
Iceland	5.5	NA	NA	NA
Italy	4	2.5	2.5	6.2
Macedonia	4.3	2.2	6.5	8.7
Portugal	6.7	3.3	NA	8.5
Poland	3.0	4.4	25	11.5
Romania	9.9	4.4	8.3	17.1
Spain	6.3	5	NA	13.4
Sweden	7.1	4.8	5.9	26
UK	NA	4.4	NA	NA

Based on data from countries with access to a national PCI and STEMI registry.

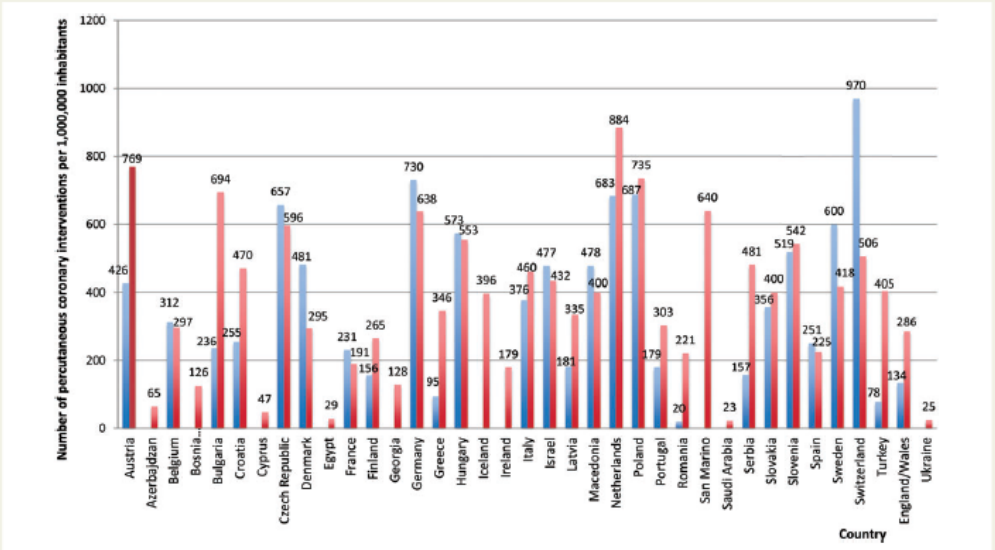

Figure 1 Primary percutaneous coronary interventions per 1 000 000 inhabitants in 37 ESC countries. Blue bars are data from 2007 and red bars are data from 2010/2011.

increases in PPCI utilization were observed in 13 countries: Austria, Bulgaria, Croatia, Greece, Italy, Latvia, the Netherlands, Portugal, Romania, Serbia, Turkey, and England/Wales (*Figure 1*). Countries like Denmark, France, and Sweden on the other hand experienced a decline in PPCI procedures.

Utilization of thrombolysis

The use of thrombolysis was highest in Bosnia and Herzegovina, Cyprus, Greece, and Serbia (*Figure 2*). The use was below 100 per 1 000 000 inhabitants in the majority of the countries.

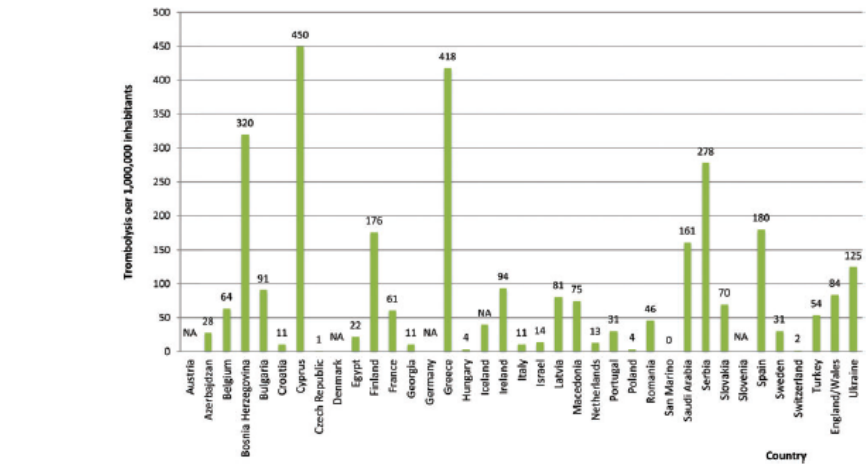

Figure 2 Thrombolysis per 1 000 000 inhabitants in 37 ESC countries 2010/2011.

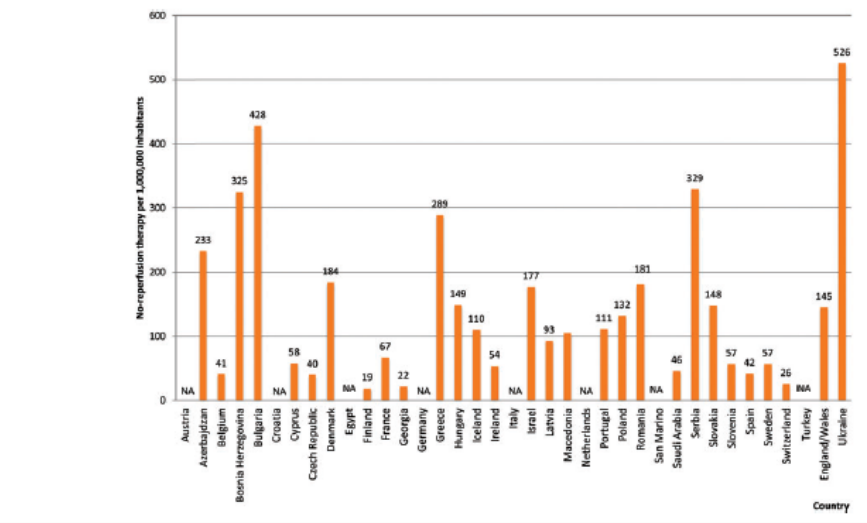

Figure 3 No reperfusion therapy per 1 000 000 inhabitants in 37 ESC Countries 2010/2011.

Number of non-reperfused patients

The number of non-reperfused patients ranged from 19 to 526 per 1 000 000 inhabitants (*Figure 3*). A large number of countries were unable to provide data on non-reperfusion.

Numbers of primary percutaneous coronary intervention centres and cardiologists

Table 2 summarizes the population of the countries, the number of board-certified cardiologists, the number of PPCI performing

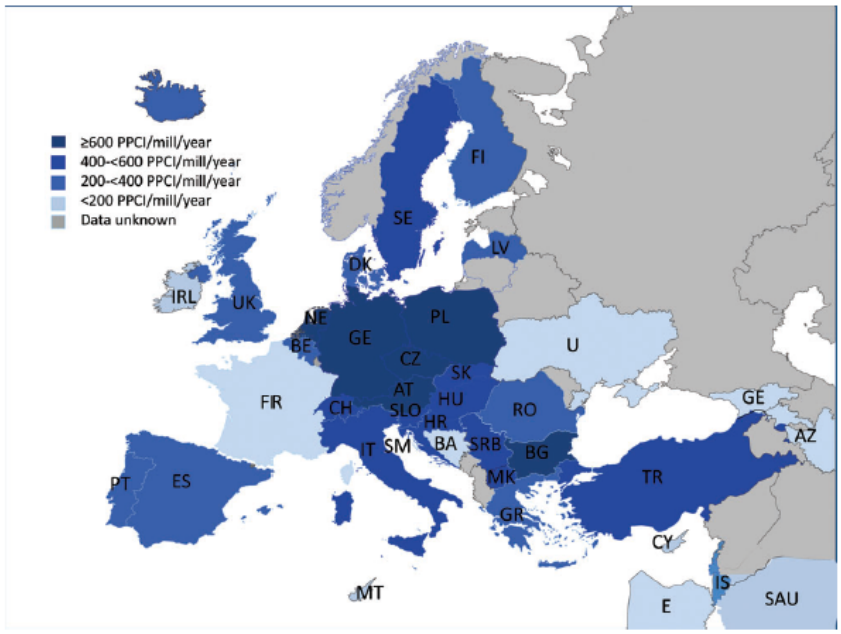

Figure 4 Numbers of Primary Percutaneous Coronary Interventions per 1 000 000 inhabitants 2010/2011 in 37 ESC member countries, grouped.

hospitals, the number of PPCI centres with a 24-h service 7 days a week (24/7), and the mean number of the population served by a 24/7 service PPCI centre for each country in the year 2011.

The mean number of board-certified cardiologists ranged from 0.2 in Azerbaijan to 243.8 board-certified cardiologists per 1 000 000 inhabitants in Greece (*Table 2*). There was no significant correlation between the number of cardiologists per 1 000 000 inhabitants and the number of PPCI procedures ($R = -0.0013$, $P = 0.99$).

The mean population served by a single PPCI centre with 24/7 services (*Table 2*) ranged from 31 300 inhabitants per centre (San Marino) to 6 533 000 inhabitants per centre (Saudi Arabia) (*Table 2*). The number of PPCI capable centres with 24/7 services was highest in Italy with 211 centres. In Cyprus, no PPCI centres existed at the time of data collection.

Mortality

Table 3 displays the in-hospital mortality for STEMI patients overall and the in-hospital mortality for STEMI patients treated with PPCI, thrombolysis, and patients receiving no reperfusion therapy. Overall in-hospital mortality in STEMI varied between 3% (Poland) and 10.0% (Hungary), whereas mortality for patients treated with PPCI was lower (range 2.2–6.1%). In countries with specific patient identifiers that allow robust-confirmation of patient-specific mortality, the reported mortality in STEMI patients treated with PPCI was 3.1% (Denmark) and 4.8% (Sweden) (*Table 3*).

Discussion

The main finding in our descriptive study of reperfusion therapy in 37 ESC countries is that large national variation in treatment strategies for patients admitted with STEMI still exists. Despite the fact that international guidelines have been recommending PPCI as the first-choice treatment for the last 10 years, this therapy is still not implemented throughout ESC countries. Moreover, a substantial number of patients are still not offered any reperfusion therapy. However, due to the variety of data collection methods and registry practices (*Table 1*), a direct comparison between countries should be performed with caution.

Utilization of primary percutaneous coronary intervention

Primary percutaneous coronary intervention as the first-choice treatment strategy is well implemented in most Northern, Western, and Central Europe countries, whereas the numbers of patients receiving this therapy still are low in some of the Southern and Eastern countries. These findings relate closely to those in the first survey based on data from 2007 published by Widimsky *et al.*[4] Twenty-seven of the 37 countries participated in this former survey. We found a major increase in the overall numbers of performed PPCIs in 13 of the countries compared with the data obtained in 2007. Especially in the majority of the countries that are participating in the Stent

for Life Initiative (Bulgaria, Greece, Italy, Portugal, Romania, Serbia, Spain, and Turkey), an important increase was evident.[3,9,10] Moreover, England/Wales reports a remarkable increase in the number of patients treated with PPCI moving from <40% of the STEMI population treated with PPCI in 2006 to >90% in 2011.[11] Countries like Denmark, Sweden, and Switzerland experienced a significant decline in PPCI utilization. On an explanation for this, evident in Denmark, would be the fact that the data from the survey in 2007/2008 were based primarily on an expert estimate, whereas that for the present survey was based exclusively on national registry data. Another plausible explanation is the decline in the incidence of STEMI over the past years in some western countries, most likely due to secondary better preventive treatments.[12–14] Explaining variation in treatment utility and comparing levels across countries remain a difficult task since it is highly influenced by multiple factors.

A gross estimate of 600 PPCI procedures per 1 million inhabitants has served as the recommended treatment goal in the development of a STEMI treatment strategy.[15] The major barrier to this type of goal setting is the lack of good nationwide registries that allow inter- and cross-country comparisons at the patient level. The underlying population demand is often unknown and such information will be a prerequisite to address the full diversity of access to treatment and to set specific treatment goals for individual countries. The importance of considering differences in the need for PPCI is apparent across Europe, where demographics vary highly and where death rates from ischaemic heart disease (both sexes, all ages) are twice as high in the UK as in Portugal.[16,17] For example, in Ireland, the ratio of elderly persons given as the number of >65 year old divided by the number of persons <65 is 17.2%, whereas in Italy this ratio is 30.9% (2011, Eurostat, Population statistics).[6,12,16] This stresses the need for good quality data at the patient level with continuous monitoring of incidence and treatment outcomes.[6,12] Future studies could benefit from reporting age standardized rates in order to make data more comparable. Also, the underlying illness burden of the population expressed as the level of co-morbidity (e.g. existing diabetes and hypertension) may vary, and influence the demand for PPCI. For example, in Saudi Arabia the percentage of people with acute coronary syndrome (ACS) suffering from diabetes is as high as 58% (2011),[18] whereas the Danish Health and Medicines Authority reports a prevalence among patients with ACS in Denmark around 30%. However, most literature finds that supply factors are the major drivers of implementation also for PPCI.[19–22] Newer studies have found that the number of physicians is associated with the level of PPCI utilization.[21,22] In our study, we found no correlation between the number of cardiologist and the number of PPCI utilization.

However, previous studies have not only shown that regions that spend more on health care on average have sicker patients, but also that higher levels of illness explain only a fraction of the overall difference in regional variations.[23–27] Another explanation for the observed variations could be the countries reimbursement schemes. Some studies have acknowledged the important influence of payment methods on technology utilization.[28,29] The reimbursement schemes for both physicians and hospitals can be strong incentives for treatment utilization and may explain some of the observed variation in PPCI utilization. Moreover, the STEMI incidence will be affected by the capability of early and correct diagnosis of STEMI. Countries with newly established registries and STEMI management strategies will most likely experience a rise in STEMI prevalence and incidence for some years due to more patients being diagnosed and registration improved. Clearly, there is a need for a re-evaluation of the recommended level of PPCI usage adjusted to the context of the country.

One other important factor that may, in part, account for the observed differences in PPCI utilization is the definition of PPCI. Some countries included procedures performed >12 h after symptom onset,[21] and also some patients with non-STEMI or cardiac arrest undergoing acute PCI. Furthermore, the data collection methods varied substantially. Some countries did provide samples or extrapolations of their STEMI total population, and thus, the actual level of PPCI in the countries must be interpreted carefully. For example, utilization rates for PPCI and thrombolysis (*Figure 1* and *2*) were considerable higher in Bulgaria than in Slovakia, despite a similar level of acute myocardial infarction discharge rates per 100 000 population (178.2 vs. 177.0, 2010, Eurostat, Health statistics).[16] Moreover, in some countries, patients treated in private hospitals may not have been included. Differences in registration practice may therefore to some extent explain the reported differences (*Table 1*). However, we do not believe that differences in data definition and data collection methods fully explain our findings of a persisting large variation in reperfusion therapy.

Thrombolysis

Thrombolysis is still widely used in some Southern and Eastern countries, whereas countries like Denmark, Czech Republic, the Netherlands, and Sweden almost have stopped using thrombolysis in STEMI patients. One plausible explanation for the existing widespread use of thrombolysis is that several countries do not have the required infrastructure and timely access to catheterization laboratories with specialized personnel.[9,30] In areas remote from PCI facilities where PPCI cannot be delivered within the recommended time limit the benefit of thrombolysis is well established and remains an important reperfusion strategy.[1,31]

Thrombolysis should preferably be administered in the pre-hospital setting and should be followed by transfer to a PCI centre as soon as possible for urgent (rescue) or subacute coronary angiography.[1,32] The optimal timing of routine angiography following successful thrombolysis is not settled, but recent trials suggest a time window of 2–12 h.[1] A well-organized system of care with clear treatment protocols and coordinated transfer systems is necessary for identifying treatment-eligible patients for on-site thrombolysis or transfer for PPCI, as treatment is highly dependent on time. Studies have shown that system delay (time from first medical contact to initiation of reperfusion) is strongly associated with mortality, and the risk of readmission to hospital with congestive heart failure.[33–36] As stated in the newly published STEMI guidelines from ESC, the time from first medical contact to reperfusion with PPCI should not exceed 120 min, and indeed, we should attempt to obtain even shorter time delays.[1]

No reperfusion

STEMI patients who do not receive reperfusion therapy have a poor outcome.[37] Our survey demonstrates that a substantial proportion of STEMI patients still are not receiving any reperfusion therapy

(*Figure 3*), which highly stresses the need for actions to improve these figures. Under-utilization of eligible STEMI patients is evident and have been reported to compress 23–30%.[38,39] The reported numbers of non-reperfused patients in our study is hampered by the fact that have very few registries on STEMI incidence exist making it difficult to make valid estimates. Delays in admission to the hospital, certain high-risk clinical features and substantial co-morbidity have all been shown to be associated with lower utilization rates of reperfusion therapy.[38,39] Moreover, the definition of non-reperfused patients may differ. For example, in Israel, the ACSIS survey showed that 33% of the examined patients had spontaneous reperfusion before reaching the catheterization laboratory and, therefore, was registered as a non-reperfused patient. In other studies, non-reperfused patients are the patients who are diagnosed after >12 h of symptom onset. It has been suggested that achieving late coronary patency in situations where patients present late might still have beneficial outcomes with PPCI. However, this is still debated.[1,32] Getting patients to call for medical help as soon as possible after symptom onset is a challenge in many countries.[9] Therefore, efforts are highly needed to increase public knowledge on the symptoms of myocardial infarction and of the awareness for immediate contact to the emergency medical system in order to shorten patient delay.

Organization of reperfusion therapy

The number of PPCI capable centres with 24/7 service and the number of cardiologists per 1 million inhabitants also varied considerable between countries. Earlier studies, like the GRACE registry, reported that the numbers of teaching hospitals and hospitals with catheterization laboratories were indicators of a higher PPCI utilization.[40] A high use of PPCI most likely depends on the presence of the necessary skills needed to perform the procedure and the availability of appropriate facilities and equipment.[41,42] Furthermore, it is possible that hospitals using PPCI have better resource allocation and an organization that allow for better overall management of all aspects of acute STEMI treatment, which most likely will lead to better outcomes and reduced health-care system delay. The formation of STEMI networks involving emergency medical services, non-PCI hospitals, and PPCI centres could be necessary to implement PPCI services effectively.[1,32,43] Besides single tertiary centres serving a specific area for 24 h, some countries and regions have developed rotational systems of STEMI care, in which three and up to five interventional cardiology centres share the PPCI function during night time. These systems have shown to be cost-effective with comparable low mortality rates as single tertiary centres offering 24/7 services, and at the same time guarantees that only experienced interventionalists are on duty.[44] Most importantly, these STEMI networks have been shown to reduce the number of non-reperfused patients. The population served by a centre must be sufficient to maintain the competency of the centre. However, setting meaningful thresholds for minimum numbers of PPCI per year to maintain the competency of both the hospital and the operator is difficult and still remains a question for future research and discussion.[45,46]

Mortality

In-hospital mortality for STEMI patients treated with PPCI varied between 3.1 and 6.1%. The reported in-hospital mortalities are consistent with evidence from other observational studies.[2,3,47,48] However, comparison of in-hospital mortality across populations is fraught with problems. Mortality data are highly dependent on the population studied and the methodologies for data collection and coding. For example, the overall mortality in patients with cardiogenic shock (usually 8–10% of patients in STEMI networks) is 40–50%, and the number of these patients will influence the mortality rate positively or negatively depending on their inclusion or absence in the registries. In well-organized networks, the in-hospital and 30-day mortality ranges from 3 to 5%.[43] The newly published FAST-MI trial from France reported a decrease in 30-day mortality from 13.7 to 4.4% in the period 1995 to 2010.[3] Moreover, they noted that overall mortality decreased irrespective of use and the type of reperfusion therapy, including the patients who did not receive any reperfusion therapy,[3] indicating that other factors such as better preventive drug therapy and changes in lifestyle are important.

Why is primary percutaneous coronary intervention not implemented?

The variation in uptake of PPCI appears to be present worldwide, and is not explained solely by economic incentives, illness severity, or patient preferences. The scant evidence within the field indicates that the barriers for PPCI implementation are a complex mix of medical, organizational, patient-related, regulatory, and economic factors.[6,21] Many factors still need to be addressed in order to understand and explain the remaining large variation in treatment utilization across Europe. The Stent for Life Initiative is, in our opinion, a good example of a joint multi-level effort identifying barriers at a national and regional level in order to change practice, and would be an example for other countries to follow.

Strength and limitations

The major strength of the study is that we were able to include a large number of countries that provided up-to-date information on the use of reperfusion therapy. STEMI is a common and well-defined clinical condition worldwide, allowing international comparison. Moreover, we provide updated information on the number of hospitals with PPCI facilities and the number of cardiologists for each country.

The major limitation of our study is the quality of the data, and several points should be highlighted. First, discrepancies in the way the data were collected; the coding of STEMI and in the definition of PPCI in the 37 countries are clearly hampering our study and may lead to both under- and overestimation of the actual reperfusion utilization and thus make cross-country comparisons difficult. Secondly, only a minority of the countries have mandatory registries, and outcomes are not based on an exhaustive collection of the STEMI population in the whole country. Moreover, the majority of countries participation in the survey changed or expanded their registration since the previous survey conducted in 2007/2008, which even makes within country comparisons difficult. Incomplete or non-compulsory reporting from hospitals may bias the factual size of the reported inequality, but the size and direction of the bias is unknown. Furthermore, data in four countries were based on best expert estimates and extrapolations, which most likely will lead to an overestimation of the actual use. Countries not participating in the survey may

be countries with less-developed STEMI programmes. This would underestimate the actual level of variation across Europe. The survey makes it possible for countries to highlight their problems regarding PPCI implementation. Mortality data are highly affected by the underlying population, e.g. the percentage of patients with out-of-hospital cardiac arrest and shock. Unfortunately, our study was based on aggregated country-level data with no access to detailed patient-level data. Thus, comparison of mortality data across countries should be done with caution.

Since STEMI incidence in most countries is unknown, we choose to present reperfusion therapies as the numbers of patients treated with the different modalities per million inhabitants instead of percentage. It can be argued that this is a crude instrument especially when populations are diverse. However, we feel that this is the most valid estimation we could obtain.

While these findings must be interpreted with caution given the limitations of the study, and the difficulties with cross-country comparisons, this mapping of the current status of reperfusion therapy across a large number of European countries is nevertheless instructive in presenting a picture of a striking international variation in the treatment strategies in patients admitted with STEMI.

Conclusions and future perspectives

In conclusion, our study demonstrates striking differences in the management of patients admitted with STEMI in 37 ESC countries. It seems that a significant deviation from the guideline recommendations is still prevailing, and an understanding of the reasons behind under-utilization of reperfusion therapy is a prerequisite for reducing or eliminating such gaps in healthcare.

In an attempt to reduce differences in a number of European countries, the Stent for Life Initiative, supporting the implementation of timely PPCI was established in 2008.[15,49] The participating countries already report striking rises in PPCI utilization, reduction in mortality, and an overall more effective management/organization of the STEMI treatment system, which strongly calls for a continuation of a strategy of implementation and supports of countries with low activities.[9,49]

A major challenge for improvement of the care and outcome of STEMI patients in Europe is the lack of accurate and comprehensive data. The availability of complete reperfusion data and patient outcome is a prerequisite to address the full diversity of access to treatment in order to improve treatment availability and outcomes for STEMI patients in the future. Systematic use of large data-based registries on STEMI treatment is highly needed. Also, the establishment of key indicators underpinned by key items of data with data definitions and clear analytical steps as used in other organizations might be helpful.

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CARDIOVASCULAR FLASHLIGHT

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Papillary fibroelastoma of the mitral valve as an unusual cause of myocardial infarction in a 20-year-old patient

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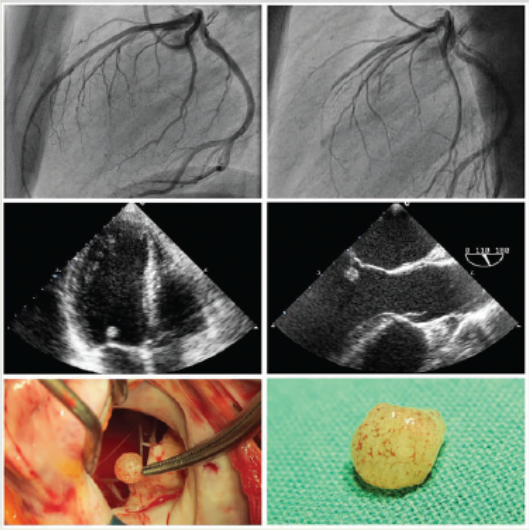
The incidence of primary cardiac tumours is <0.1% and papillary fibroelastomas are relatively rare when compared with myxomas and lipomas. Papillary fibroelastoma is generally small and single, occurs most often on valvular surfaces, and may be mobile. Despite the embolic potential of primary cardiac tumours, they are extremely uncommon cause of ischaemic vascular accidents. Patients with smaller tumours, situated on the aortic valve and in the left atrium, with minimal symptomatology and no evidence of mitral regurgitation have a higher risk of embolism. Several causes of myocardial infarction in young patients, mostly non-atheromatous origin, have been described. These are congenital coronary artery anomalies, aneurysms, spontaneous dissection, myocardial bridging, septic coronary emboli or bacteraemia, and paradoxical embolization through a patent foramen ovale. Only a few cases of acute coronary syndrome caused by papillary fibroelastoma were reported.



A 20-year-old male patient with no cardiovascular risk factors, with a history of recurrent pre-syncope was admitted to the hospital with ST-segment elevation myocardial infarction. An amputation of the left descending coronary artery was revealed and a thrombus-like mass was removed.

A following transthoracic echocardiogram showed abnormal contraction of the apex and interventricular septum and a round, hyperechoic, well-demarcated, homogenous, non-mobile tumour of 5 mm in diameter attached to the atrial side of mitral annulus, with no influence on valvular function. Transoesophageal echocardiography revealed no other masses in the heart chambers or great arteries and no patent foramen ovale. Surgical excision of the tumour was successfully performed 4 weeks after myocardial infarction and postoperative course was uncomplicated. The histological examination revealed papillary fibroelastoma.

We believe that in young patient with acute coronary syndrome echocardiography should be performed prior to initiating reperfusion therapy.

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Kala P. *Heart & brain: STEMI-like network for ischaemic stroke? EuroIntervention. 2014 Nov;10(7):778-80. doi: 10.4244/EIJV10I7A135.*

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Heart & brain: STEMI-like network for ischaemic stroke?

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When thinking about heart and brain reperfusion, several factors have to be taken into account: 1) the experience of the team, 2) the safety, effectiveness and availability of the selected therapy, 3) the appropriate therapeutic time window, and 4) the current evidence and clinical recommendations.

The heart

The joint EAPCI/EuroPCR Stent for Life Initiative began in 2008 and represents a highly successful model of care for patients with ST-elevation acute myocardial infarction (STEMI)[1,2]. Within a period of three to four years, it has been possible to develop a national STEMI network and to offer timely mechanical reperfusion (primary PCI within 12 hrs of symptom onset with maximum benefit in <3-6 hrs) to the majority of the population. Though this approach represents a seemingly simple implementation of the strongest recommendation (class I, level of evidence A) from the European Society of Cardiology clinical practice guidelines[3], *per se* it depends on the involvement of all stakeholders, widespread enthusiasm and multidisciplinary collaboration. In simple terms, to save more lives and to improve the quality of life after an acute heart attack we have to boost the whole acute healthcare system. The optimal and fastest pathway corresponding to a relatively simple pathophysiology (plaque erosion/rupture and thrombosis in >90% of cases) consists of an early diagnosis of STEMI by the emergency medical service (EMS) and direct transportation to the nearest 24/7 cathlab. Reperfusion of the infarct-related artery within 20 to 25 minutes after arrival at the cathlab is the extraordinary beauty of primary PCI. At present, the optimal primary PCI technique comprises the transradial approach, the tailored use of manual thrombectomy, drug-eluting stent implantation and a combination of potent antithrombotic medication. The role of intracoronary imaging as well as the optimal management of patients with multivessel disease have been studied intensively[4].

The brain

Unfortunately, the pathophysiology of stroke is different and more complex. Besides cerebral haemorrhage (15% of strokes) and lacunar cerebral infarctions, both intracranial and extracranial arteries may be affected (internal carotid, middle cerebral and posterior circulation arteries). In contrast to STEMI, the time window for administration of intravenous (i.v.) thrombolysis and ischaemic stroke reperfusion is only <4.5 hrs from symptom onset[5]. The pathway to reperfusion is also more complex and requires a precise multidisciplinary collaboration throughout the whole diagnostic and therapeutic process. Also, the main difference between the treatment of stroke and the STEMI fast track to cathlab is the need for neurologic and computed tomography/magnetic resonance (CT/MR) evaluation **(Figure 1)**. Another obstacle is the current lack of evidence from randomised trials supporting catheter-based thrombectomy alone. The use of the Merci®

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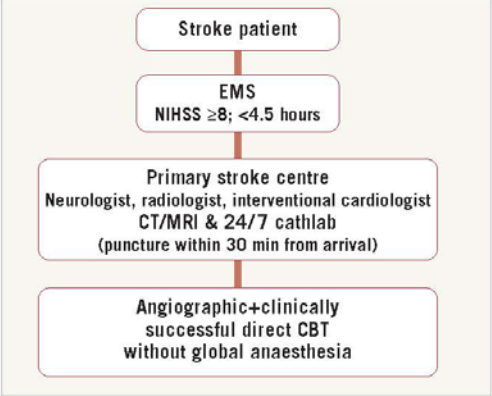

Figure 1. *STEMI-like stroke pathway perspective. CT: computed tomography; EMS: emergency medical service; MR: magnetic resonance; NIHSS: National Institutes of Health Stroke Scale*

Balloon Guide Catheter (Stryker® Neurovascular, Kalamazoo, MI, USA), the Penumbra System® (Penumbra Inc., Alameda, CA, USA), the Solitaire™ FR Revascularization Device (Covidien/ev3 Endovascular Inc., Plymouth, MN, USA), and the Trevo® Pro Retriever System (Stryker® Neurovascular) has recently been recognised as class IIa, level of evidence B in the guidelines for early management of patients with acute ischaemic stroke[5]. As with STEMI, neither intra-arterial thrombolysis nor the facilitated intervention (thrombolysis+mechanical reperfusion) provides better clinical outcome in comparison to simple i.v. thrombolysis[5-7].

Interventional cardiology as part of the stroke programme

In this issue of EuroIntervention, two original papers describe the results of catheter-based thrombectomy (CBT) in ischaemic stroke patients. These publications comprise single-centre data from relatively small cohorts of patients from the Czech Republic and Turkey. The most exciting fact is that the first authors are neither neurologists nor neuroradiologists or invasive radiologists, but interventional cardiologists. Widimsky et al in their pilot experience from the prospective PRAGUE-16 study present the results of 23 patients with moderate to severe acute ischaemic

Article, see page 869

stroke[8]. Patients were planned to be treated with direct CBT only with no previous thrombolysis within <6 hrs from the onset of typical symptoms. Nevertheless, five patients (21.7%) received thrombolysis prior to CBT. Mechanical recanalisation with three stent retriever systems (Trevo, Solitaire and Penumbra) was successful in 83% of patients after a mean of three thrombus retrieval attempts. A favourable functional clinical outcome was achieved in 48% of patients. The precise logistics of the joint programme provided by the local stroke team (interventional cardiologist, neurologist and radiologist) are very well described. Goktekin et al conducted a retrospective analysis of 38 patients treated with the Solitaire AB Neurovascular Remodeling Device (Covidien/ev3 Endovascular Inc.) by a local stroke team composed of an interventional cardiologist, neurologist, radiologist and anaesthesiologist[9]. Successful recanalisation was achieved in 89% of patients, and in 57.9% a good clinical outcome was observed at 90 days.

Article, see page 876

CBT was indicated within 4.5 hrs in patients with contraindication for i.v. thrombolysis, and within 4.5 to 6 hrs in patients with presence of penumbra confirmed by CTA/MRA. Though the results of CBT are promising, the common negative point of the presented local stroke programmes is the low number of treated patients. Twenty-three patients were enrolled in Prague within 16 months and 38 patients were treated in Istanbul within 24 months, making the mechanical stroke programme very challenging, requiring further analysis and improvements. Randomised trials comparing i.v. thrombolysis versus direct CBT are greatly needed.

Heart & brain, brain & heart questions

Q1: What can we - interventional cardiologists - offer to stroke patients?

1. A STEMI network with 24/7 cathlabs.
2. Highly experienced interventional teams.
3. Fully equipped cathlabs offering life-saving procedures and resuscitation.
4. High-quality X-ray equipment.
5. Excellent collaboration with EMS and routine use of telemedicine.

Q2: What do we - interventional cardiologists - have to learn to take an effective part in the stroke team?

1. Flow grading systems: Thrombolysis in Cerebral Infarction (TICI)[10] and Mori[11] classification.
2. Stroke severity: National Institutes of Health Stroke Scale (NIHSS) score 0-42.
3. Cerebral anatomy/function by CT/MR.
4. Dedicated diagnostic and therapeutic invasive techniques and tools.
5. Modified Rankin scale (mRS) score 0-6 [12].

Conclusion

Cardiovascular mortality, acute heart attack (especially STEMI) and ischaemic stroke represent the leading causes of death worldwide. Ischaemic stroke in particular is the most common cause of acquired disability and the third most frequent cause of death[13]. The establishment of a STEMI network, which has been supported in many countries by the Stent for Life (SFL) Initiative, may be followed by a STEMI-like network for stroke patients. The joint stroke programme, introduced by Widimsky and Goktekin[8,9], fully accomplishes the SFL motto "Working together. Saving lives".

Conflict of interest statement

P. Kala receives consultancy fees from Boston Scientific.

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The Stent for Life Initiative: quo vadis?

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Stent for Life Initiative and 2016 Stent for Life Forum

The Stent for Life Initiative (SFL), an EAPCI and EuroPCR alliance, was established in 2008 as an international network of national cardiac societies and partner organisations to address inequalities in patient access to primary PCI, a lifesaving revascularisation treatment for ST-segment elevation acute myocardial infarction (STEMI)[1-3]. SFL supports the implementation of the ESC Clinical Practice Guidelines (Guidelines) at national and regional levels through the formulation of strategies, the creation and implementation of educational programmes, and through advocacy activities and awareness campaigns[4]. Currently, 21 national cardiac societies and partner organisations from Europe, Africa, Asia and South America are part of SFL. When the SFL Forum 2016 gathered in Prague on 26 and 27 February 2016 for the 5th SFL annual conference, SFL Russia (represented by B.G. Alekyan and V. Ganyukov) and SFL South Africa (represented by R. Delport and A. Snyders) signed the SFL Declaration and joined the Initiative.

Barriers to overcome when developing an SFL regional STEMI network

Situational analyses from SFL participating countries have shown that the adherence to guidelines is influenced by many factors and varies from country to country, and from region to region[5]. An in-depth understanding of healthcare system-level barriers and unique challenges in the regional context facilitates the development of more effective strategies for improving the quality of the STEMI system of care in a given country **(Table 1)**.

Table 1. Common barriers to building a successful STEMI network of care.

Insufficient number or geographical spread of 24/7 catheterisation laboratories (cathlabs), most typically concentration in big cities, shortage in less populated large areas.
Suboptimal cathlab staffing (possibly due to insufficient funding or training).
Inadequate reimbursement for the procedures performed.
Dissimilarities in STEMI management in different regions/cathlabs.
Delayed emergency service response, or inappropriate response, for example taking STEMI patients to the nearest Emergency Room even though it does not have a cathlab (lack of straightforward transport protocol).
Inadequately equipped emergency services, for example the ambulance does not have ECG equipment as standard, or personnel are inadequately trained.
Commercial bias in areas with excessive density of 24/7 cathlabs.
Lack of effective quality control (emergency medical services and PCI centres).
Low awareness of STEMI symptoms by patients and/or family, leading to delayed contact with emergency services.
Lack of a national registry demonstrating the current situation on a nationwide and local level pointing out the areas for improvement, measuring the impact of primary PCI and showing the progress made over a certain period of time.
Ineffective communication and collaboration among key parties, e.g., healthcare professionals, government representatives and/or patients.

Importance of the role of government - experience from SFL Bulgaria, SFL Spain, SFL Turkey and SFL Egypt

Government support and involvement is crucial for the success of SFL in each country. This is why continuous efforts are needed to convince the government representatives to integrate SFL into a supported national programme. The most frequent problems are associated with difficult access to the Minister of Health, so good relationships with decision makers in the government can promote collaboration. In countries with marked decentralisation of the authorities it takes even more effort to address and iron out differences between and within regions, such as in Spain or Italy. Frequent changes in government, especially in the Ministry of Health, such as those faced in Egypt or in Saudi Arabia, can hamper ongoing political support. However, once achieved, governmental support greatly assists the accomplishment of the objectives and the action plan. In due course, SFL leaders have become

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members of national government bodies as advisors or directors, e.g., in Romania, Turkey, Spain and Saudi Arabia.

SFL results at three years and the implementation of SFL principles under complex political situations

SFL country representatives from Bosnia-Herzegovina and Ukraine, who joined SFL in 2012, reported at the SFL Forum 2016 that geographic mapping, situational analysis, proper planning and execution are critical success factors for building SFL regional STEMI networks, even under complex political conditions.

One hundred and fifty-three primary PCI/1 million inhabitants were performed in 2012 in Bosnia-Herzegovina, and 338 primary PCI/1 million were performed in 2015, representing an increase in the percentage of primary PCIs performed from 19% to 41% of all STEMI patients hospitalised, while the number of facilities providing primary PCI care increased from five to six.

Results from SFL Ukraine are encouraging as well. There were only three STEMI networks providing primary PCI in 2012 in the Ukraine, covering 13% of the country's territory. In three years, that number has increased to 14 STEMI networks involved in SFL covering 60% of the territory. The number of primary PCIs performed has increased from 75 primary PCI/1 million inhabitants to 146 primary PCI/1 million, in 2012 and 2015, respectively.

Results from SFL Bosnia-Herzegovina and SFL Ukraine, together with SFL countries who joined the programme in 2009, e.g., Bulgaria, France, Greece, Romania, Serbia and Turkey, and who presented their three-year results at the SFL Forum 2012, demonstrate that building SFL regional STEMI networks is effective and can be accomplished in relatively short periods of time. Partnerships and cooperation between STEMI referral hospitals, primary PCI hospitals and EMS teams are a prerequisite. Transportation and clinical pathway protocols and an acute coronary syndrome (ACS) registry should be developed and endorsed by regional and/or national government officials.

Delegates concluded that stakeholders in the implementation of SFL originate from different areas. They have various backgrounds (medical, industry, political, etc.), but they have a common target – to reduce mortality and morbidity in ACS patients by improving access to primary PCI. By combining their efforts towards that common target, stakeholders can boost the effect on reduced costs. It is the strength of the SFL Initiative that it is able to unite partners from different areas, with various skills, sharing common goals.

Building SFL regional STEMI networks and emergency services infrastructures in emerging countries

SFL Argentina, SFL Mexico and SFL Tunisia presented the one-year progress of SFL implementation in their respective territories. SFL leadership in Argentina focused its efforts on aligning all three cardiac societies on programme objectives and on integrating SFL into a national cardiology programme. Country situational mapping was initiated: 228 primary PCI centres and 64 non-PCI centres participated in the SFL country mapping phase. Preliminary results indicate that 39,810 PCIs and 8,470 primary PCIs were performed in 2014, and the primary PCI utilisation is 202/1 million inhabitants in Argentina. Next, 12 pilot centres were selected to initiate development of an SFL regional STEMI network. Three-year objectives will be agreed upon after barrier identification in each SFL pilot region in Argentina.

The SFL Forum expert group agreed that primary PCI should be the preferred treatment not only in developed countries, but in emerging countries as well. If a STEMI patient is located close to a primary PCI centre with a presumed short transportation time to hospital, primary PCI is the preferred treatment. For patients in rural areas, with suspected long transportation time to PCI-capable hospitals, the pharmacoinvasive strategy with thrombolytic therapy followed by catheterisation and PCI if indicated within three to 24 hours of thrombolysis would be utilised. Results from SFL emerging countries presented at the SFL Forum 2016 conference, e.g., India, Argentina, Mexico, and South Africa, revealed that building and integrating a regional emergency medical services infrastructure is a key prerequisite to support STEMI patients' access to a pharmacoinvasive strategy in those areas where primary PCI is not accessible in a given timeframe, and a mechanism for inter-hospital transfer of patients is required. The STEMI India "Hub and Spoke" model, as well as the STEMI Sri Lanka "Wagon Wheel" model were discussed and it was confirmed that priority should be given to building regional STEMI networks around existing primary PCI centres.

Results from the SFL economic model

The SFL economic model was developed to demonstrate the financial, economic, and clinical benefit of timely STEMI admissions and primary PCI treatment. The SFL economic model uses country- or region-specific data to evaluate the impact of the Stent for Life Initiative based on increased treatment with primary PCI versus the alternative approaches of thrombolytics or no reperfusion. Outcomes from an increased primary PCI mix were measured against a scenario assuming that the SFL Initiative never occurred and rates remain unchanged.

For Portugal, the SFL economic model was measuring data from 2010 to 2013. STEMI PCI was 264 per million in 2010 when the SFL Initiative began and increased to 341 per million by 2013. On-time STEMI admissions also increased over this time period. The net result of these improvements was a reduction in mortality of 414 lives and nearly 46 million USD of variable cost savings. The burden of disease also decreased by almost 150 million USD.

For Russia, we focused on the Kemerovo region where most of the SFL gains have been achieved, measuring from 2011 (the start of the SFL Initiative) to 2014. PCI, as a percent of on-time STEMI admissions, increased from 12% in 2011 to 33% in 2014 (which corresponds to 272 STEMI PCI per million inhabitants). During this time period, there was approximately 1.83 million USD of

investment in cathlabs and in the interventional cardiology workforce. However, the productivity savings of 5.7 million USD due to higher rates of PCI more than offset this amount.

For Spain, SFL looked at the Basque country region, as the data were most consistent from this area. Over the course of the SFL Initiative, the initial STEMI PCI per million was estimated at 254 in 2012 and grew to 341 by 2015, while on-time admissions improved by five percentage points. Due to the relatively high gross domestic product per capita and low inflation rate, significant cost savings of approximately three million USD were achieved in an area of less than 700,000 people.

These three impressive examples of economic analysis show the transformative power of STEMI network implementation, resulting in many lives saved along with reduced spending.

STEMI patient education - improving the quality of care of patients surviving an acute heart attack

It has been observed that a level of lay public education and patient literacy influences the access of STEMI patients to a reperfusion therapy as well as their outcomes when discharged from the hospital.

The SFL Initiative is calling for collaboration with the European Association of Cardiovascular Prevention and Rehabilitation (EACPR) and the Council of Cardiovascular Nursing and Allied Professions (CCNAP) to address the early critical phase secondary prevention after STEMI, beginning immediately after the initial cardiac event during hospital stay.

Preliminary results from situation mapping in SFL pilot countries participating in the SFL survey, Portugal, Romania, Spain, Greece and the Czech Republic, reveal that a great disparity exists among countries, country regions and hospitals, and confirms a lack of implementation of structured secondary prevention intervention at discharge from a primary PCI centre. To improve patient-related adherence to prevention therapy, Contract4Life/After a Heart Attack programme will be implemented in selected SFL pilot countries. A nurse-assisted education programme will be delivered in selected primary PCI centres to evaluate its impact on the re-hospitalisation rate of STEMI patients, and STEMI patient risk profile after 12 months.

Conclusion

The SFL Forum 2016 was, once again, a great and stimulating opportunity for SFL country delegates from four continents to share their experiences. For the first time, measurable achievements after only three years of SFL implementation were reported, highlighting the important medical and economic impact of the SFL alliance. Even greater effects can be anticipated in Russia and South Africa, two large countries which have now joined the programme.

Conflict of interest statement

Z. Kaifoszova is managing Stent for Life on behalf of EAPCI and EuroPCR. The other authors have no conflicts of interest to declare.

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Primary angioplasty in acute myocardial infarction with right bundle branch block: should new onset right bundle branch block be added to future guidelines as an indication for reperfusion therapy?

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Aims The current guidelines recommend reperfusion therapy in acute myocardial infarction (AMI) with ST-segment elevation or left bundle branch block (LBBB). Surprisingly, the right bundle branch block (RBBB) is not listed as an indication for reperfusion therapy. This study analysed patients with AMI presenting with RBBB [with or without left anterior hemiblock (LAH) or left posterior hemiblock (LPH)] and compared them with those presenting with LBBB or with other electrocardiographic (ECG) patterns. The aim was to describe angiographic patterns and primary angioplasty use in AMI patients with RBBB.

Methods and results A cohort of 6742 patients with AMI admitted to eight participating hospitals was analysed. Baseline clinical characteristics, ECG patterns, coronary angiographic, and echocardiographic data were correlated with the reperfusion therapies used and with in-hospital outcomes. Right bundle branch block was present in 6.3% of AMI patients: 2.8% had RBBB alone, 3.2% had RBBB + LAH, and 0.3% had RBBB + LPH. TIMI flow 0 in the infarct-related artery was present in 51.7% of RBBB patients vs. 39.4% of LBBB patients ($P = 0.023$). Primary percutaneous coronary intervention (PCI) was performed in 80.1% of RBBB patients vs. 68.3% of LBBB patients ($P < 0.001$). In-hospital mortality of RBBB patients was similar to LBBB (14.3 vs. 13.1%, $P = 0.661$). Patients with new or presumably new blocks had the highest (LBBB 15.8% and RBBB 15.4%) incidence of cardiogenic shock from all ECG subgroups. Percutaneous coronary intervention was done more frequently (84.8%) in patients with new or presumably new RBBB when compared with other patients with blocks (old RBBB 66.0%, old LBBB 62.3%, new or presumably new LBBB 73.0%). In-hospital mortality was highest (18.8%) among patients presenting with new or presumably new RBBB, followed by new or presumably new LBBB (13.2%), old LBBB (10.1%), and old RBBB (6.4%). Among 35 patients with acute left main coronary artery occlusion, 26% presented with RBBB (mostly with LAH) on the admission ECG.

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Conclusion Acute myocardial infarction with RBBB is frequently caused by the complete occlusion of the infarct-related artery and is more frequently treated with primary PCI when compared with AMI + LBBB. In-hospital mortality of patients with AMI and RBBB is highest from all ECG presentations of AMI. Restoration of coronary flow by primary PCI may lead to resolution of the conduction delay on the discharge ECG. Right bundle branch block should strongly be considered for listing in future guidelines as a standard indication for reperfusion therapy, in the same way as LBBB.

Keywords Acute myocardial infarction • Right bundle branch block • Left bundle branch block • Primary angioplasty • Reperfusion

Introduction

Left bundle branch block (LBBB) and right bundle branch block (RBBB) in acute myocardial infarction (AMI) patients are well known to carry the high mortality risk.[1,2] Nevertheless, the guidelines of the European Society of Cardiology (ESC) list only LBBB as an indication for urgent reperfusion therapy.[3] The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines provide similar recommendations.[4] Thus, the current guideline-recommended electrocardiographic (ECG) indications for reperfusion therapy in AMI include ST-segment elevation (STE) and LBBB of new or unknown onset. It is not well known whether also new or unknown onset RBBB should be an indication for reperfusion therapy, especially in the modern era of primary percutaneous coronary intervention (PCI). The aim of this analysis was to investigate the coronary angiographic (CAG) findings, reperfusion therapies used, and in-hospital outcomes of patients with AMI presenting with RBBB when compared with those presenting with LBBB or with other ECG patterns.

Methods

Patients

A total of 6742 consecutive patients with AMI routinely admitted to eight participating tertiary hospitals during the study period of 3 years (2006–08) were retrospectively analysed. The patients were included in this retrospective registry based on (i) diagnosis of AMI and (ii) coronary angiography. Patients with AMI, who did not undergo coronary angiography ($n = 650$, i.e. 8.8% from all AMI patients), are not subject of this analysis. Baseline characteristics studied (age, sex, diabetes, previous myocardial infarction, Killip class on admission, etc.) are listed in *Table 1*.

Table 1 Patients baselines characteristics

	STEMI	STDMI	LBBB	RBBB	Other ECG	*P*-value*	*P*-value**
$n = 6742$	3447	907	291	427	1670		
Mean age (years)	64.5 (12.4)	69.5 (10.7)	72.1 (10.1)	69.8 (11.3)	65.6 (11.4)	0.005	<0.001
Females (%)	31.2	34.6	38.1	23.2	31.6	<0.001	<0.001
Diabetes (%)	24.0	36.8	45.7	36.3	31.7	0.013	<0.001
Previous MI (%)	13.8	29.2	38.1	25.8	29.7	<0.001	<0.001
Killip class (mean)	1.44 (0.85)	1.47 (0.83)	1.86 (1.06)	1.71 (1.01)	1.23 (0.62)	0.050	<0.001
Killip I (%)	72.6	70.5	51.2	57.9	84.5	0.134	<0.001
Killip II (%)	17.0	16.0	24.6	24.1	9.9		
Killip III (%)	3.7	9.1	11.1	6.9	3.3		
Killip IV (%)	6.7	4.4	13.1	11.1	2.3		
Old BBB (%)	–	–	26.7	26.5	–	0.508	–
Unknown BBB (%)	–	–	57.5	60.8	–		
New BBB (%)	–	–	15.8	12.7	–		
QRS mean (ms)	–	–	133.7 (19.6)	133.4 (18.9)	–	0.811	–
BBB disappeared (%)	–	–	14.2	18.8	–	0.193	–
Median duration of the hospital stay	5	6	5	7	4	0.001	<0.001

Continuous data are expressed as mean values (standard deviation), categorical data are expressed as relative frequencies (percentage).
STEMI, ST elevation myocardial infarction; STDMI, ST depression myocardial infarction; LBBB, left bundle branch block; RBBB, right bundle branch block; ECG, electrocardiogram; MI, myocardial infarction; BBB, bundle branch block; QRS, QRS complex on ECG.
*P-value only applies to the comparison of LBBB vs. RBBB.
**P-values for the comparison of all five groups (null hypothesis: all five groups have the same characteristics).

Electrocardiographic patterns

Electrocardiographic reading was done by the treating cardiologist. Electrocardiograms from all patients with RBBB have been reviewed once more at the time of this manuscript preparation by another independent cardiologist. The patients were divided into the following subgroups based on the first (admission) ECG:

(i) ST-segment elevation acute myocardial infarction (STEMI, $n = 3447$, i.e. 51.1%): persistent STEs in at least two contiguous leads ($\geq$2 mm in the chest leads or $\geq$1 mm in the extremity leads),
(ii) ST-segment depression acute myocardial infarction (STDMI, $n = 907$, i.e. 13.5%): horizontal or descending ST-segment depressions in at least two contiguous leads ($\geq$2 mm in the chest leads or $\geq$1 mm in the extremity leads),
(iii) acute myocardial infarction with LBBB, irrespective of any ST-segment deviations were present on ECG (LBBB-MI, $n = 291$, i.e. 4.3%): QRS $\geq$120 ms and LBBB shape,
(iv) acute myocardial infarction with RBBB, irrespective of any ST-segment deviations were present on ECG (RBBB-MI, $n = 427$, i.e. 6.3%) with subgroups of RBBB alone (2.8%), RBBB + left anterior hemiblock (LAH) (3.2%), RBBB + left posterior hemiblock (LPH) (0.3%): QRS $\geq$120 ms and RBBB shape, electrical axis extreme left ($> -45°$) for LAH, respectively, extreme right ($> +105°$) for LPH. In all RBBB patients, a special care was taken to describe the presence or absence of STEs and all ECGs were once more analysed by an independent cardiologist.
(v) acute myocardial infarction with other ECG (other ECG-MI, $n = 1670$, i.e. 24.8%): any other ECG patterns (negative T waves, small ST shifts not fulfilling the above criteria, non-specific or even negative ECG).

The information whether any bundle branch block (BBB) is old, new, or unknown origin and whether BBB persisted or disappeared during the hospital stay was collected. Analyses in this manuscript are done with all RBBB (including bifascicular blocks) as one patient group (i.e. RBBB $\pm$ LAH or LPH).

Coronary angiography, reperfusion therapy, outcomes

Coronary angiographic or autopsy data were analysed to estimate the number of diseased major coronary arteries, to identify the infarct-related artery, and to analyse TIMI flow in the infarct-related artery before and after percutaneous coronary intervention (PCI, whenever it was performed). Coronary angiography was described by the interventional cardiologist, who performed the procedure. Pre-discharge echocardiographic ejection fraction was registered. Reperfusion therapies used during the initial hospital stay and in-hospital mortality were analysed.

Statistical analysis

For continuous variables, mean values and standard deviations were calculated. After checking normality by the Shapiro–Wilk test, Student's *t*-test was used for testing of the hypotheses about the means when two groups (RBBB and LBBB) were compared. The analysis of variance was used for comparison of more than two groups. The Mann–Whitney test was used for the ordinal variables. Categorical data were tested with the Fisher's exact test and Pearson's χ^2-test and adjusted residuals were used to identify significantly different subcategories. The multiple logistic regression and Cox's proportional hazards models were used to adjust the differences among groups for confounding factors. Following factors and covariates were entered into model: age, gender, indicators of diabetes, and previous MI, Killip class. Odds ratio (OR), hazard ratio (HR), and corresponding 95% confidence intervals (95% CI) are presented as effect estimates. All tests have been performed as two-sided on the level of significance 0.05. Statistical software Stata, release 9.2 (Stata Corp LP, College Station, TX, USA) was used for the analysis.

Results

Coronary angiographic findings

TIMI flow 0 (*Figure 1*) in the infarct-related artery was present in 51.7% of RBBB patients vs. 39.4% of LBBB patients [OR = 1.64 (95% CI 1.14–2.32), $P = 0.023$; adjusted OR 1.76 (95% CI 1.31–2.53),

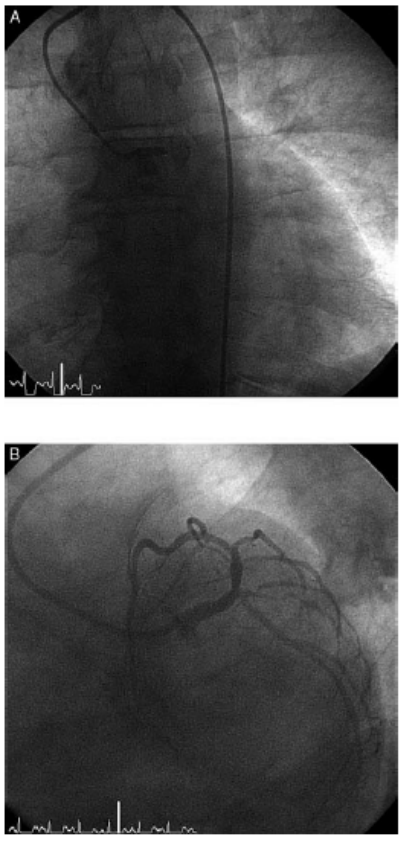

Figure 1 (*A*) Complete (100%) thrombotic occlusion of the left main coronary artery. Anterior view. (*B*) The same patient after primary percutaneous coronary intervention with stent implantation. Left inferior oblique (spider) view.

Table 2 Angiographic findings, reperfusion therapy, and outcomes

	STEMI	STDMI	LBBB	RBBB	Other ECG	P-value*	P-value**
n= 6742	3447	907	291	427	1670		
No signif. CAD (%)	0.8	0.1	2.2	2.2	2.6	0.214[a]	<0.001[a]
1-VD	37.3	17.2	21.3	27.8	29.1		
2-VD	28.2	19.9	28.3	30.1	27.5		
3-VD	30.0	53.1	41.9	35.5	35.1		
LM disease	3.7	9.7	6.3	4.4	5.7		
IRA—LMCA (% from IRAs)	1.1	6.0	5.8	3.5	2.3	0.281	<0.001
IRA-LAD	45.0	31.5	43.8	48.5	42.7		
IRA-LCX	14.0	37.5	22.1	17.2	24.0		
IRA-RCA	39.1	21.2	25.8	28.9	27.5		
IRA-bypass	0.8	3.8	2.5	1.9	3.5		
No PCI done (% of all)	10.8	38.2	31.7	19.9	32.5	<0.001	<0.001
Pre-PCI TIMI flow 0 (% from PCIs)	57.3	22.5	39.4	51.7	20.5	0.023	<0.001
TIMI-1	8.4	5.9	8.0	8.6	6.7		
TIMI-2	18.8	24.7	23.9	19.3	19.5		
TIMI-3	15.5	46.9	28.6	20.4	53.3		
Post-PCI TIMI flow 0-1 (% from PCIs)	4.4	3.8	9.6	7.0	4.2	0.409	<0.001
TIMI-2	6.4	1.7	7.5	10.0	2.4		
TIMI-3	89.2	94.5	82.9	83.0	93.4		
Reperfusion—none (%)	10.9	30.2	29.0	17.7	28.9	0.002	<0.001
TL (%)	0.4	0.0	0.3	0.5	0.0		
Primary PCI (%)	88.1	61.8	68.3	80.1	67.5		
Acute CABG (%)	0.6	8.0	2.4	1.7	3.6		
Mean EF (%)	46.3 (12.0)	50.1 (13.5)	37.5 (12.7)	42.4 (14.2)	53.4 (13.1)	<0.001	<0.001
In-hospital mortality (%)	5.4	6.3	13.1	14.3	2.9	0.661	<0.001

Continuous data are expressed as mean values (standard deviation), categorical data are expressed as relative frequencies (percentage).
STEMI, ST elevation myocardial infarction; STDMI, ST depression myocardial infarction; LBBB, left bundle branch block; RBBB, right bundle branch block; ECG, electrocardiogram; CAD, coronary artery disease; 1-VD, single vessel disease; 2-VD, two vessel disease; 3-VD, three vessel disease; LM, left main; IRA, infarct related artery; LMCA, left main coronary artery; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; TL, thrombolysis; CABG, coronary artery bypass grafting; EF, ejection fraction.
[a]None of CAD (no signif., 1,2,3-vessel) and LM disease categories differs significantly (all $P > 0.05$) in the comparison of LBBB vs. RBBB; all categories differ significantly (all $P < 0.001$) among five compared groups.
*P-value only applies to the comparison of LBBB vs. RBBB.
**P-values for the comparison of all five groups (null hypothesis: all five groups have the same characteristics).

$P = 0.005$]. Nearly 80% of RBBB patients had a complete or subtotal occlusion of the infarct-related artery (TIMI flow 0-2 was present in 79.6% of RBBB AMI patients). Furthermore, the distribution of TIMI flow grades among RBBB patients closely resembled the pattern seen among ST elevation group and this angiographic similarity between STEMI and RBBB was more distinct than between STEMI and LBBB (*Table 2*).

Left main coronary artery occlusion

Ninety-seven patients (1.4% of the entire study population) had left main, as the infarct-related, artery (*Figure 2*). In 35 of them, the left main coronary artery (LMCA) was functionally occluded (TIMI flow 0–2): most frequent ECG presentation pattern for LMCA occlusion was STE ($n = 17$), followed by RBBB [$n = 9$; with LAH in six patients (*Figures 3* and *4*) and without LAH in three patients], LBBB ($n = 6$), and ST-segment depression ($n = 3$). In other words, acute LMCA occlusion presents in 26% with RBBB, without STEs (*Figure 5*).

Reperfusion therapies

Primary PCI was performed in 80.1% of RBBB patients vs. 68.3% of LBBB patients [OR = 1.88 (95% CI 1.33–2.64), $P < 0.001$; adjusted OR = 1.71 (95% CI 1.19–2.45), $P = 0.004$]. This difference was caused by the fact that fewer LBBB patients had CAG findings suitable for primary PCI (see *Table 2* for details). In STEMI patients primary PCI was performed in 88.1%.

In-hospital outcomes

Despite the fact that RBBB patients were younger, had less frequent diabetes, less severe CAG findings, and less previous AMIs than LBBB patients, RBBB was related with a similar mortality as LBBB [14.3 vs. 13.1%, HR = 1.17 (95% CI 0.72–1.90), $P = 0.630$; adjusted HR = 1.33 (95% CI 0.80–2.21), $P = 0.268$] and was more than twice the mortality of STEMI [5.4%, HR = 2.11 (95% CI 1.45–3.07), $P < 0.001$; adjusted HR = 1.80 (95% CI 1.21–2.68), $P = 0.004$] and STDMI [6.3 %, HR = 2.49

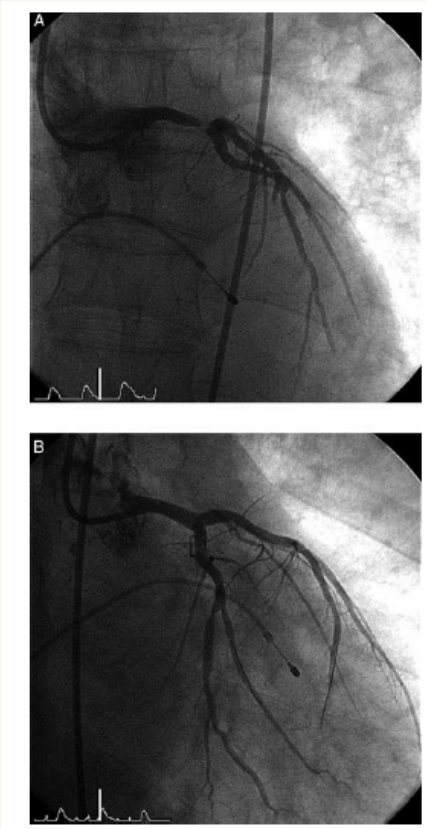

Figure 2 (*A*) Subtotal (99%) left main coronary artery occlusion. Anterior view. (*B*) The same patient after primary percutaneous coronary intervention with two stents (kissing technique) implantation. Right inferior oblique view.

(95% CI 1.70–3.64), $P < 0.001$; adjusted HR = 1.44 (95% CI 0.92–2.27), $P = 0.108$], respectively (*Table 2*).

Relation between in-hospital mortality and duration of the hospital stay

Even after taking the length of hospital stay into account, the conclusions concerning in-hospital mortality remain unchanged. We have tried the logistic regression model with length of hospital stay as a covariate and Cox's model. The overall test is significant (*P*-value for the comparison of all five groups $P < 0.001$). The comparison RBBB vs. LBBB yields $P = 0.686$, so the adjustment for length of stay brings only very small shift compared with the *P*-value presented in *Table 2*. The *P*-values for other contrasts involving RBBB group are: RBBB vs. STEMI $P < 0.001$, RBBB vs. STDMI $P = 0.014$, RBBB vs. other ECG $P < 0.001$. In fact, the median duration of hospital stay among the deceased patients was short (2 days for RBBB and 2.5 days for LBBB), confirming the clinical experience that vast majority of fatalities occurs within initial 48–72 h after hospital admission.

Bundle branch block onset time

Patients with BBBs were further divided according to the BBB onset time (*Table 3*): new or presumably new BBB (as this is the currently accepted indication for reperfusion therapy in LBBB) vs. BBB known to be old. Group of patients with new or presumably new RBBB (despite having the lowest mean age from all BBB subgroups) had high Killip class on admission (15.4% presenting with cardiogenic shock). TIMI flow 0 in the infarct-related artery was found in significantly more patients with new or presumably new RBBB (55%) than in other three subgroups (old RBBB 34.9%, old LBBB 28%, new or presumably new LBBB 41.1%). Percutaneous coronary intervention was performed in 84.8% of patients with new or presumably new RBBB, more than in other three subgroups (old RBBB 66%, old LBBB 62.3%, new or presumably new LBBB 73%). The most striking are mortality differences between these four subgroups: in-hospital mortality was highest (18.8%) among patients presenting with new or presumably new RBBB, followed by new or presumably new LBBB (13.2%), old LBBB (10.1%), and old RBBB (6.4%).

Disappearence of bundle branch block during the hospital stay

In 87 patients, the BBB (present on the admission ECG) disappeared during the hospital stay. Almost all these patients had BBB of new or unknown onset and they mostly presented to hospital with acute heart failure (mean Killip class was 1.93, cardiogenic shock was present in 19%, 86% were treated by primary PCI, which was successful in 98%). Left bundle branch block disappeared in 32 patients and their mortality was 6.2%. Right bundle branch block disappeared in 55 patients and their mortality was 12.7%.

Bifascicular blocks

Patients, in whom RBBB was combined with either LAH or LPH tended to be older, had higher incidence of diabetes, had lower ejection fraction, more frequent occurrence of three-vessel disease and LAD as an infarct-related artery, and had slightly higher mortality (*Table 4*).

Right bundle branch block and ST-segment elevations

ST-segment elevations (as defined in the methods section) were recognizable on electrocardiograms of 226 (53%) RBBB patients, while in 201 (47%) of patients presenting with AMI and RBBB no STEs could be found. TIMI flow 0-2 was found on emergent coronary angiography among 135 (67%) patients with RBBB and no STEs and 205 (91%) of those who had RBBB and STEs.

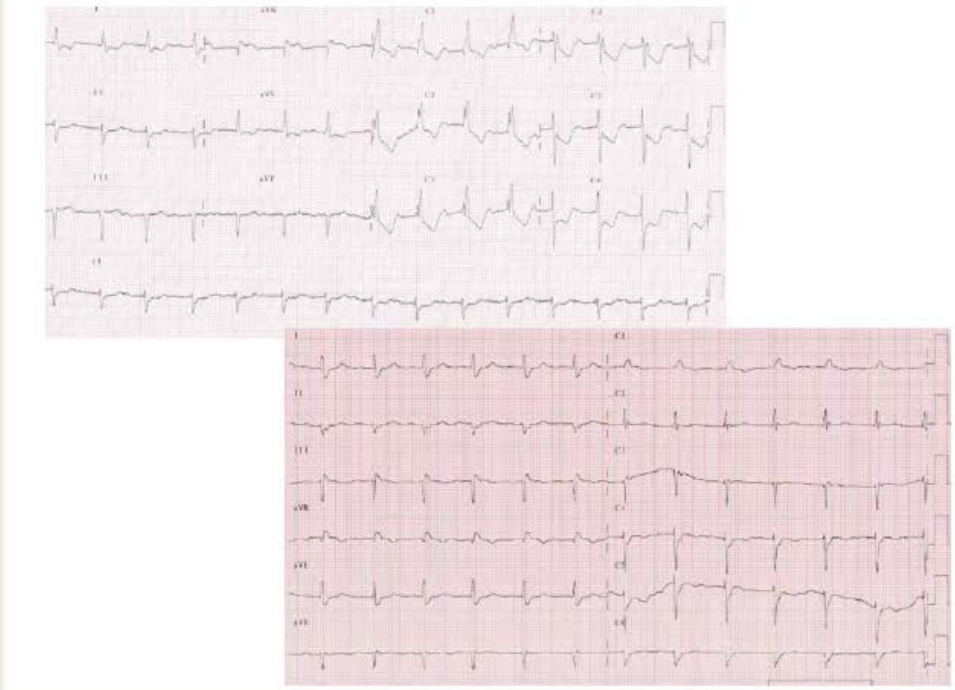

Figure 3 Electrocardiography from two patients admitted in Killip class II-III with acute 100% occlusion of the left main coronary artery (*A*) and proximal dominant right coronary artery (*B*).

Discussion

Outcomes of acute myocardial infarction patients with bundle branch block

Historically, the mortality of patients with AMI and RBBB before the thrombolytic era reached 77%.[5] A more recent study from Denmark still revealed the highest mortality of AMI among patients with BBB (left or right): 33.3% patients died in-hospital and 54.8% were dead at 1 year.[6] In the study of Dubois *et al.*,[7] patients with BBB (both left and right) had more complications and higher Killip class on admission. Both in-hospital mortality (32 vs. 10%, $P < 0.001$) and 3-year mortality (37 vs. 18%, $P < 0.001$) were higher among patients with complete BBB. In one study of 1238 consecutive patients with AMI,[8] RBBB was found in 10.9% of patients. It was newly diagnosed in 37.8%, was known to be old in 34.1%, and in 28.1% the time of RBBB origin could not be established. Right bundle branch block patients had 1-year mortality 40.7 vs. 17.6% mortality in patients without RBBB ($P < 0.001$). Mortality was significantly higher for new RBBB (43.1%, $P < 0.001$) than for old (15.5%) and indeterminate (15.3%) RBBB. For isolated RBBB vs. bifascicular block, early mortality was 14.4 vs. 40.6%, and 1-year mortality was 30.2 vs. 54.2% ($P < 0.05$ for both). Multivariate analysis showed an independent prognostic value of RBBB for early and 1-year mortality.

Bundle branch block onset time

In the usual clinical reality (at the time of decision for urgent CAG procedure), BBB frequently cannot be securely established as new or old. Thus, patients without information about previous ECG are described as 'BBB of unknown origin' and were evaluated together with patients in whom previous ECG did not show BBB.

Right bundle branch block in the guidelines

The ESC and AHA/ACC guidelines[3,4] were discussed in the introduction part. These guidelines surprisingly do not list new (or unknown) onset RBBB as an indication for reperfusion therapy. Interestingly, the guidelines of the American College of Emergency Physicians for the management of patients with suspected AMI or unstable angina[9] recommend reperfusion therapy in presence of any type of BBB. This recommendation is based on the GISSI[10] and ISIS-2 studies.[11] Also the Czech Society of Cardiology guidelines from 2009[12] recommend

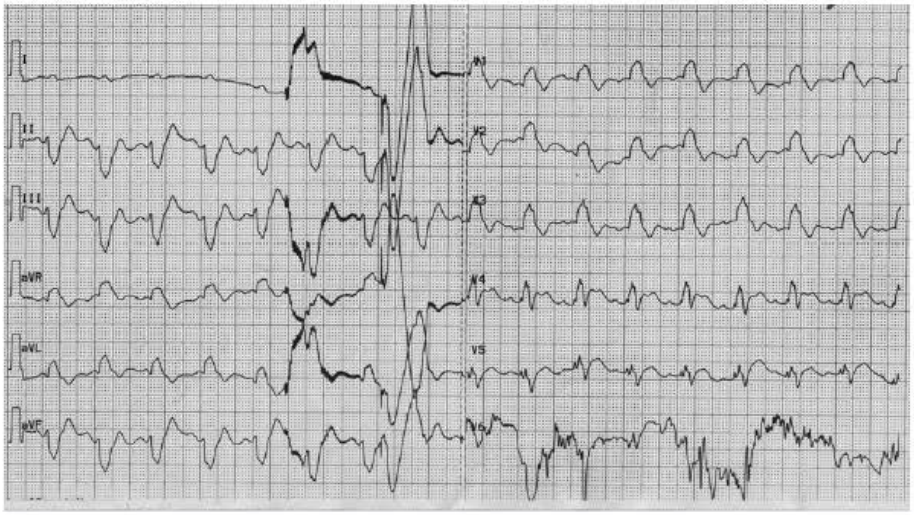

Figure 4 Electrocardiographic from a 66-year-old male acute myocardial infarction patient with cardiogenic shock, subtotal left main coronary artery occlusion, and TIMI flow 2. Again, ST-segment elevation in V4–V5 is not typical and can easily be overlooked, while the dominant feature of this Electrocardiography is wide QRS complex deformed by RBBB + LAH.

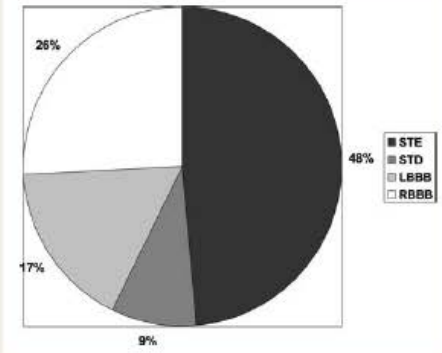

Figure 5 Electrocardiographic findings among patients with acute myocardial infarction caused by the left main coronary artery occlusion.

primary PCI strategy for all patients with new (or presumably new) BBB (left or right).

Bundle branch blocks and thrombolysis

The absolute mortality reduction from thrombolysis was greatest among patients presenting with any BBB (−4.9%), followed by anterior STE (−3.7%), ST elevation 'other' (−2.8%), ST depression (−1.4%), and ST elevation inferior (−0.9%).[13] The analysis of the GUSTO 1 and TAMI 9 cohorts[14] found that left anterior descending (LAD) artery infarcts account for 54% of all new BBBs and among anterior infarcts RBBB was more common (13%) than LBBB (7%). Thrombolytic therapy reduced mortality among patients with both BBBs (left and right).

Bundle branch blocks and primary percutaneous coronary intervention

Kurisu *et al.*[15] in patients with anterior myocardial infarction found significantly higher 30-day mortality in patients with RBBB compared with those without RBBB (14.0 vs. 1.9%, $P < 0.01$). The study of Kleeman *et al.*[16] found that patients presenting with RBBB had higher in-hospital (26 vs. 11%, $P < 0.001$) and post-discharge (19 vs. 9.2%, $P < 0.001$) mortality than patients without RBBB. After adjustment for differences in baseline characteristics, RBBB remained an independent predictor of increased mortality. Sakakura *et al.*[17] retrospectively analysed a group of 25 patients with AMI caused by the LMCA occlusion. The in-hospital mortality was 60%. Logistic regression analysis found RBBB as an independent predictor of mortality. Hirano *et al.*[18] found that 37% of patients with AMI caused by the LMCA occlusion present with RBBB, while only 3% with LBBB. We have shown that acute LMCA occlusion presents in 26% only with RBBB without STEs (*Figure 5*) being in close accordance both to previously mentioned reports and with Hirano *et al.*, who found that in 30% of LMCA occlusions no STE could be found on the admission ECG, while RBBB with left axis deviation (frequently

Table 3 Bundle branch block onset time

	LBBB old	LBBB new or unknown onset	RBBB old	RBBB new or unknown onset	*P*-value
% from all patients	1.1	3.2	1.7	4.6	
Mean age (years)	71.1 (10.0)	71.4 (10.1)	72.2 (9.9)	69.3 (11.5)	0.004
Killip class (mean)	1.68 (0.98)	1.94 (1.10)	1.45 (0.77)	1.88 (1.10)	0.001
Killip IV (%)	8.8	15.8	4.3	15.4	0.011
BBB disappeared (%)	1.6	19.4	6.8	23.2	<0.001
Pre-PCI TIMI flow 0 (% from PCIs)	28.0	41.1	34.9	55.0	<0.001
No PCI done (% of all)	37.7	27.0	34.0	15.2	<0.001
Reperfusion—none (%)	33.3	24.3	31.9	12.5	<0.001
Primary PCI (%)	62.3	73.0	66.0	84.8	
Mean EF (%)	37.3	37.8	43.4	41.5	0.003
In-hospital mortality (%)	10.1	13.2	6.4	18.8	0.015

P-value refers to the comparison of all four groups (null hypothesis: all four groups have the same characteristics). Continuous data are expressed as mean values (standard deviation), categorical data are expressed as relative frequencies (percentage).
Abbreviations same as in Tables 1 and 2.

accompanied by ST-elevation in aVR) is typical for this catastrophic type of AMI. Another study[19] found RBBB even in 52% of patients with acute occlusion of the LMCA.

In the PAMI trials,[20] patients with LBBB (1.6%) on presenting electrocardiogram were compared with patients who had RBBB (3.1%) or no BBB (95.3%). In-hospital mortality was highest with LBBB 14.6%, followed by RBBB 7.4% and no BBB 2.8% ($P < 0.0001$).

Right bundle branch block and ST-segment shifts/Q waves

Some authors[2,21] request for the diagnosis of AIM with RBBB other ECG changes (e.g. ST-segment elevations) to be present, while this is not the case for LBBB (where it is generally accepted that LBBB masks ST-segment shifts). Right bundle branch block is thought not to mask the repolarization phase changes or Q waves, therefore other ECG changes have to be present to conclude the diagnosis of AIM. However, others[22] warn before this 'clear-cut' opinion pointing out that minor ST elevations in the anterior leads (V1–V4) can be missed due to compensation by pseudo-normalization of the negative T waves. Our experience showed that even in large infarcts (caused by left main or proximal LAD coronary artery occlusion) bifascicular block (RBBB + LAH or rarely RBBB + LPH) may occur without typical STEs and thus a large life threatening AMI might be missed when ST elevations are required. Authors of this study repeatedly experienced mistakes in the clinical decision making in the real life practice, when patients with ischaemic symptoms and new or presumably new RBBB (but without STEs) were neither referred to urgent coronary angiography ± PCI nor treated by thrombolysis, sometimes with catastrophic consequences. This bad experience was the actual trigger for this study.

It has been also shown that interpretation of Q-waves can be tricky in the presence of RBBB.[23] Gussak *et al.*[24] showed that RBBB after myocardial infarction shortened Q wave duration, thus enabling false-negative diagnosis of inferior myocardial infarction. Also the term 'RBBB-dependent Q-wave' was introduced by Rosenbaum *et al.*,[25] who described appearance of new Q waves in leads V1–V2 that disappeared after restoration of normal conduction. Thus false-positive and false-negative diagnosis of myocardial infarction can be made when describing ECG with RBBB in suspicion of myocardial infarction.

Study limitations

The main study limitation is a retrospective character of analysis. However, all participating centres enrol AMI patients to their own or nationwide registries, thus minimizing the risk of losing a subject from analysis. Another limitation relates to the fact that coronary angiography analysis was not performed in a core lab and by blinded manner. However, we have analysed 'real life' data similar to other registries published and this is not a comparison of different treatment approaches.

Conclusions

Acute myocardial infarction with new or presumably new RBBB on the admission ECG is frequently related with complete occlusion of the infarct-related artery and with primary PCI treatment when compared with AMI + LBBB. In-hospital mortality of patients with AMI and new or presumably new RBBB (especially when the block is bifascicular) is highest from all ECG presentations of AMI. Restoration of coronary flow by primary PCI may lead to resolution of RBBB on the discharge ECG.

New or presumably new RBBB (± LAH or LPH) should be listed in future guidelines as a standard indication (possibly class I, level C) for reperfusion therapy, in the same way as LBBB, i.e. irrespective of the presence or absence of ST-segment denivelations.

Table 4 Right bundle branch block with/without left anterior/posterior hemiblock

	RBBB alone	RBBB + LAH	RBBB + LPH	*P*-value
% from all patients	2.8	3.2	0.3	
Mean age (years)	68.4 (11.6)	71.0 (11.2)	70.8 (9.0)	0.119
Female (%)	22.4	25.4	23.5	0.827
Diabetes (%)	30.9	36.1	29.4	0.588
Previous MI (%)	22.4	26.0	47.1	0.089
Killip class (mean)	1.69 (0.98)	1.59 (0.93)	1.41 (0.80)	0.414
Killip I (%)	57.6	36.9	70.6	0.754
Killip II (%)	26.5	21.1	23.5	
Killip III (%)	5.3	7.2	0.0	
Killip IV (%)	10.6	7.8	5.9	
No signif. CAD (%)	2.1	2.5	0.0	0.935
1-VD	28.5	27.5	17.7	
2-VD	30.5	26.2	29.4	
3-VD	34.7	39.4	52.9	
LM disease	4.2	4.4	0.0	
IRA—LMCA (% from IRAs)	3.8	5.0	0.0	0.006
IRA-LAD	39.4	51.4	38.5	
IRA-LCX	16.7	20.0	23.0	
IRA-RCA	40.1	19.3	38.5	
IRA-bypass	0.0	4.3	0.0	
Pre-PCI TIMI flow 0 (% from PCIs)	53.5	48.5	44.5	0.870
TIMI-1	8.5	9.7	0.0	
TIMI-2	17.1	21.6	22.2	
TIMI-3	20.9	20.2	33.3	
Post-PCI TIMI flow 0-1 (% from PCIs)	6.4	3.7	22.2	0.205
TIMI-2	8.8	11.1	0.0	
TIMI-3	88.8	85.2	77.8	
No PCI done (% of all)	18.7	20.1	52.9	0.008
Reperfusion—none (%)	18.0	17.7	47.1	0.014
TL (%)	0.0	0.0	0.0	
Primary PCI (%)	81.3	79.9	47.1	
Acute CABG (%)	0.7	2.4	5.8	
Mean EF (%)	44.9 (13.5)	42.1 (13.4)	41.2 (18.0)	0.189
In-hospital mortality (%)	10.5	14.8	17.7	0.438

P-value refers to the comparison of all three groups (null hypothesis: all three groups have the same characteristics).
LAH, left anterior hemiblock; LPH, left posterior hemiblock.
Abbreviations others same as in Tables 1 and 2.

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Comparison of outcomes in ST-segment depression and ST-segment elevation myocardial infarction patients treated with emergency PCI: data from a multicentre registry

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Abstract

Background: **Traditionally, acute myocardial infarction (AMI) has been described as either STEMI (ST-elevation myocardial infarction) or non-STEMI myocardial infarction. This classification is historically related to the use of thrombolytic therapy, which is effective in STEMI. The current era of widespread use of coronary angiography (CAG), usually followed by primary percutaneous coronary intervention (PCI) puts this classification system into question.**

Objectives: **To compare the outcomes of patients with STEMI and ST-depression myocardial infarction (STDMI) who were treated with emergency PCI.**

Methods: **This multicentre registry enrolled a total of 6 602 consecutive patients with AMI. Patients were divided into the following subgroups: STEMI (n = 3446), STDMI (n = 907), left bundle branch block (LBBB) AMI (n = 241), right bundle branch block (RBBB) AMI (n = 338) and other electrocardiographic (ECG) AMI (n = 1670). Baseline and angiographic characteristics were studied, and revascularisation therapies and in-hospital mortality were analysed.**

Results: **Acute heart failure was present in 29.5% of the STDMI vs 27.4% of the STEMI patients ($p < 0.001$). STDMI patients had more extensive coronary atherosclerosis than patients with STEMI (three-vessel disease: 53.1 vs 30%, $p < 0.001$). The left main coronary artery was an infract-related artery (IRA) in 6.0% of STDMI vs 1.1% of STEMI patients ($p < 0.001$). TIMI flow 0–1 was found in 35.0% of STDMI vs 66.0% of STEMI patients ($p < 0.001$). Primary PCI was performed in 88.1% of STEMI (with a success rate of 90.8%) vs 61.8% of STDMI patients (with a success rate of 94.5%) ($p = 0.012$ for PCI success rates). In-hospital mortality was not significantly different (STDMI 6.3 vs STEMI 5.4%, $p = 0.330$).**

Conclusion: **These data suggest that similar strategies (emergency CAG with PCI whenever feasible) should be applied to both these types of AMI.**

Keywords: coronary artery disease, acute myocardial infarction, primary PCI

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ST-segment elevation (STEMI) and ST-segment depression (STDMI) myocardial infarctions have a common pathogenesis – a vulnerable plaque ruptures, followed by luminal thrombus formation.[1-4] Thrombosis may lead to rapid changes in the severity of coronary artery stenosis, which may cause subtotal or total vessel occlusion. The thrombus may completely occlude the major epicardial coronary artery in cases of STEMI,[5] or cause partial or intermittent vessel occlusion in cases of non-ST-elevation myocardial infarction (NSTEMI).[6]

This traditional classification of patients with acute myocardial infarction (AMI), based on baseline electrocardiographic (ECG) recordings, has practical implications for guidelines and in clinical practice especially, as it refers to the use of reperfusion therapy. The separation of STEMI from other types of acute myocardial infarction has its historical roots in the thrombolytic era.

The current widespread use of primary percutaneous coronary intervention (pPCI) makes use of modified reperfusion treatment for myocardial infarction patients. Recently published randomised trials and meta-analyses,[7-12] as well as the guidelines of the European Society of Cardiology (ESC) for myocardial infarction in patients presenting with persistent ST-segment

elevation,[13] indicate that pPCI is the preferred reperfusion strategy in AMI patients when performed by an experienced team as soon as possible after first medical contact. The pPCI reperfusion modality remains superior to immediate thrombolysis, even if transfer to an angioplasty centre is necessary.

Similarly, an early invasive strategy with early coronary angiography and revascularisation has become the preferred approach for patients with NSTEMI.[14-17] Additionally, the ESC guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes (ACI) appropriately recognises AMI with ongoing or recurrent chest pain and ST-segment depression as the highest risk subgroup and is an indication for emergency coronary angiography, followed by revascularisation, when appropriate.[18] From the sub-analysis of two previously published trials[19,20] and a meta-analysis,[21] it has been shown that the greatest benefit of early invasive treatment was found in patients with elevated cardiac enzymes and ST-segment changes, i.e. in patients with STDMI.

The aim of this study was to analyse a large group of AMI patients presenting with different ECG records and to assess the similarities and differences between baseline and angiographic characteristics, to assess in-hospital management and mortality, and to test the hypothesis that an emergency PCI strategy should be used in both ST-segment elevation MI as well as in ST-segment depression MI.

Methods

This retrospective, multicentre, observational registry included a total of 6 602 consecutive patients admitted to five participating centres (four in the Czech Republic and one in Bulgaria; all university-type hospitals with catheterisation facilities) for an acute myocardial infarction during a three-year recruitment period (except for the centre in Bulgaria, where the recruitment period was only one year). All participating hospitals followed the guidelines of the Czech Society of Cardiology.

All patients underwent emergency coronary angiography (CAG). Patients with STEMI, new left bundle branch block (LBBB) or right bundle branch block (RBBB) and STDMI with ongoing chest pain underwent CAG immediately after hospital arrival. In all remaining cases, the procedure was performed within 24 hours of onset of AMI symptoms. Subjects had to be 18 years or older.

Based on admission ECG records, patients were divided into one of five subgroups: ST-elevation AMI (n = 3446; 52.2%), ST-depression AMI (n = 907; 13.7%), LBBB AMI (n = 241; 3.7%), RBBB AMI (n = 338; 5.1%), other baseline ECG AMI (n = 1670; 25.3%). STEMI was defined as new ST-elevation at the J-point in two contiguous leads with cut-off points of ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2–3 and/or ≥ 0.1 mV in other leads. STDMI was defined as a new horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads or transient ST-segment elevations. The other ECG group represented all remaining ECG patterns excluding STEMI, STDMI, LBBB and RBBB.

Patients entered into the registry were admitted for an acute myocardial infarction using only the ESC/ACC myocardial infarction redefinition.[22] Symptoms consistent with ischaemia, new ECG changes and a typical rise and fall of cardiac enzymes levels (troponin I and/or T and/or creatine phosphokinase-MB) were mandatory for inclusion. Moreover, the diagnosis of MI had to be confirmed at the time of discharge from hospital.

Baseline characteristics, such as age, gender, diabetes mellitus, history of previous myocardial infarction, Killip class on admission and ECG pattern (including information regarding any bundle branch blocks – old, new or of unknown origin) were analysed. Coronary angiographic (or autopsy) data were analysed to estimate the number of diseased major coronary arteries, to identify the infarct-related artery (IRA), and assess thrombolysis in myocardial infarction (TIMI) flow in the infarct-related artery before and after PCI (whenever PCI was performed).

To identify the ejection fraction, pre-discharge echo-cardiographic examinations were performed. Revascularisation strategies used during the index hospital stay were studied. Patients were followed until transfer to a referral hospital or hospital discharge/death. Death was defined as all-cause mortality during hospitalisation. The in-hospital mortality was also analysed.

Statistical analysis

Patients with STEMI and STDMI were compared based on demographics, medical history and risk factors, infarct-related artery and segment, initial and post-procedural TIMI flow, reperfusion success and in-hospital mortality. Statistical comparisons between subgroups were performed using Chi-square and Fisher's exact tests for categorical variables; data are expressed in percentages.

Continuous variables are presented as means ± standard deviations and were compared using the two-sample Student's t-test. For ordinary variables, the Mann–Whitney test was applied. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

A logistic regression model was used to adjust the differences in mortality for covariate effects. The following factors and covariates were used in the model: age, gender, previous diabetes and myocardial infarction, Killip class > I on admission, and pre-discharge ejection fraction.

Results

During the study period, a total of 6 602 patients were enrolled in the registry from five participating centres. There were 3 446 patients with STEMI and 907 with STDMI. Patients presenting with STEMI were younger than those with STDMI. The mean age in the STEMI group was 64.5 years and in the STDMI group 69.5 years ($p < 0.001$). There were more patients under 75 years in the group with STEMI than in the STDMI group (74.5 vs 63.6%, $p < 0.001$).

Compared to STEMI patients, STDMI patients were more likely to have a history of a previous MI (STDMI 29.3% vs STEMI 13.8%, $p < 0.001$) and diabetes mellitus (36.8 vs 24.1%, $p < 0.001$). The gender distribution was equal between the STEMI and STDMI groups (females 31.3 vs males 34.6%, p = 0.055). Patients in the STEMI group were more likely to be in cardiogenic shock on admission. Killip class IV on admission was present in 6.7% of STEMI patients compared to 4.4% in STDMI patients ($p < 0.001$). Acute heart failure defined as Killip class > 1 on admission (pulmonary rales or third heart sound and pulmonary oedema) was present in 29.5% of STDMI vs 27.4% of STEMI patients ($p < 0.001$) (Table 1).

TABLE 1. BASELINE CHARACTERISTICS IN STEMI AND STDMI PATIENTS

	STEMI	*STDMI*	p-*value*
Age in years ± SD	64.5 ± 12.4	69.5 ± 10.7	< 0.001
Age < 75 years (%)	74.5	63.6	< 0.001
Females (%)	31.3	34.6	0.055
Previous myocardial infarction (%)	13.8	29.3	< 0.001
Diabetes mellitus (%)	24.1	36.8	< 0.001
Killip class > I (%)	27.4	29.5	< 0.001
Killip class IV (%)	6.7	4.4	< 0.001

STEMI: ST-elevation myocardial infarction; STDMI: ST-depression myocardial infarction.

TABLE 2. ANGIOGRAPHIC CHARACTERISTICS AND PROCEDURAL OUTCOMES IN STEMI AND STDMI PATIENTS

	STEMI	*STDMI*	p-*value*
Number of involved vessels (%)			
One-vessel disease	37.3	17.2	< 0.001
Two-vessel disease	28.2	19.9	
Three-vessel disease	30.0	53.1	
Infarct-related artery (%)			
Left main	1.1	6.0	< 0.001
Left anterior descending	45.0	31.5	
Left circumflex	14.0	37.5	
Right coronary	39.1	21.2	
CABG	0.8	3.8	
Pre-PCI TIMI flow (%)			
TIMI flow 0	57.2	27.3	< 0.001
TIMI flow 1	8.8	7.7	
TIMI flow 2	18.5	24.5	
TIMI flow 3	15.5	40.6	
Post-PCI TIMI flow (%)			
TIMI flow 3	90.8	94.5	< 0.012
LVEF (%), mean ± SD	46.3 ± 12.0	50.1 ± 13.5	< 0.001

STEMI: ST-elevation myocardial infarction; STDMI: ST-depression myocardial infarction; TIMI: thrombolysis in myocardial infarction flow; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction.

STEMI patients had less-extensive coronary atherosclerosis than STDMI patients. There were more patients with three- or two-vessel disease in the STDMI group than in the STEMI group (73.0 vs 58.2%, $p < 0.001$). Severe left main stenosis was also more often present in STDMI patients compared to STEMI patients (6.0 vs 1.1%, $p < 0.001$). The left circumflex artery was more likely to be the infarct-related artery in STDMI compared to STEMI patients (37.5 vs 14%, $p < 0.001$). Moreover, nearly one-third of all STDMI patients had a TIMI 0 flow before PCI. The infarct-related artery was more often totally occluded in STEMI patients compared to STDMI patients (57.2 vs 27.3%, $p < 0.001$).

Emergency PCI was performed in 88.1% of STEMI patients versus 61.8% of STDMI patients. The success rates were higher in STDMI patients (94.5 vs 90.8%, $p < 0.012$) (Table 2). Rates of acute coronary bypass grafts were significantly higher in patients with STDMI (Fig. 1).

Despite the higher mean ejection fraction, in-hospital mortality was slightly but insignificantly higher in STDMI patients compared to STEMI patients (6.3 vs 5.4%, $p = 0.330$). There was no significant difference regarding in-hospital mortality between STEMI and STDMI patients who were treated using emergency PCI (5.3 vs 6.78%, $p = 0.274$). However, there was a large difference regarding in-hospital mortality between STDMI patients treated using PCI (6.78%) and STDMI patients without revascularisation (13.19%) ($p = 0.032$).

Using logistic regression analysis, the independent risk factor for mortality was patient age (OR 1.03, 95% CI: 1.015–1.049, $p < 0.001$); there was a 1.03-fold increased risk for every additional year of age. Killip class > I on admission was also a strong predictor of mortality (OR 2.54, 95% CI: 1.754–3.685, $p < 0.001$). A lower risk of death was associated with higher ejection fractions (OR 0.982, 95% CI: 0.967–0.997, $p < 0.024$).

Patients presenting with MI and any bundle branch block (left or right bundle branch block ± left anterior/posterior hemiblock) represented the highest risk group, with in-hospital

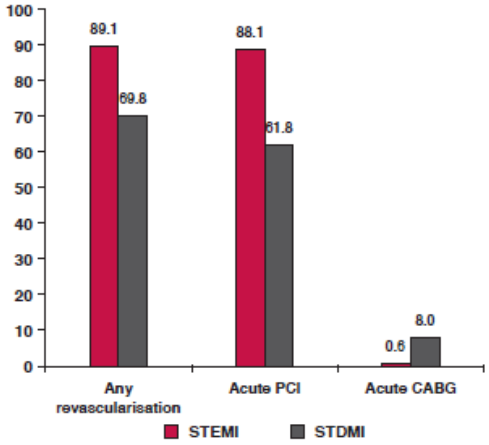

Fig. 1. Bar graphs show the type of revascularisation therapy used in ST-segment elevation (STEMI) and ST-segment depression (STDMI) myocardial infarctions. All values are percentages ($p < 0.001$). CABG: coronary artery bypass graft.

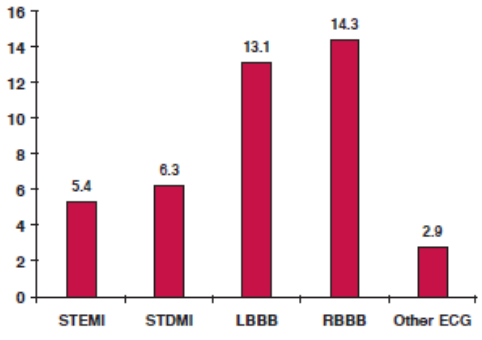

Fig. 2. Bar graph demonstrates the in-hospital mortality rates in different ECG groups of acute myocardial infarction patients. All values are percentages ($p < 0.001$). STEMI/STDMI: ST-segment elevation/depression myocardial infarction. LBBB/RBBB: left/right bundle branch block.

mortality more than double compared to patients who presented with STDMI (risk ratios 2.03, 95% CI: 1.46–2.83, $p < 0.001$) or STEMI (risk ratios 2.36, 95% CI: 1.83–3.04, $p < 0.001$). On the other hand, patients presenting with minor or no ECG abnormalities (without ST-segment shifts and without bundle branch block/s) had a significantly lower risk (acute heart failure was rare and in-hospital mortality was very low). The in-hospital mortality in this group of patients was 2.9% ($p < 0.001$).

Fig. 2 presents a comparison between patients with minor or no ECG changes and each of the other groups (STEMI, STDMI, LBBB, RBBB).

Discussion

STEMI and STDMI have a common pathogenesis: vulnerable plaque erosion or rupture followed by thrombus formation, resulting in impaired vessel patency. Impaired or no flow in a coronary artery causes ischaemic symptoms and ECG changes. The release of myocardial necrosis markers defines the diagnosis of myocardial infarction.

The current guidelines recommend different reperfusion approaches based on the admission ECG in patients with acute MI. On the other hand, ECG changes can be altered by a bundle branch block, previous MI and other conditions. Also, the infarct-related artery and infarct-related segment can influence the final ECG pattern. For example, acute occlusion of the circumflex artery may have no ST-segment elevation on a 12-lead ECG. Instead, ST-segment depressions are frequently present – this is sometimes called a hidden STEMI.

In our registry the most common IRA in STDMI patients was the circumflex branch. Moreover, nearly one-third of all STDMI patients had a TIMI grade 0 flow before PCI. Infarction in the circumflex artery bed is very often under-diagnosed and these patients undergo coronary angiography very late or not at all. Based on these facts, there is an increasing effort to find real differences or similarities between STEMI and STDMI regarding their risk factors, prognosis, mortality and appropriate revascularisation strategy.

In previously published studies, baseline characteristics of patients with STEMI compared to those without ST-segment elevation were significantly different, and the same was true in this study. Patients with STEMI were younger and had less often had a previous MI and/or diabetes mellitus. Cardiogenic shock was also found to be more common in STEMI patients.

Rosenberger *et al.*[23] investigated whether risk factors were related differently to ST-elevation and non-ST-elevation ACS. The main finding from this large survey of more than 10 000 patients was that different risk factors were related to different types of ACS. Smoking was related to STEMI patients, whereas obesity and high blood pressure were more common among MI patients without ST-elevation.

Our findings confirm the results of the Opera registry.[24] The primary objective of the nationwide Opera study was to describe the in-hospital management and cardiovascular outcomes (at one year) of MI patients. The results show that patients suffering from MI with and without ST-elevation had comparable in-hospital (4.6 vs 4.3%) and long-term prognoses (9% in STEMI vs 11.6% in NSTEMI, log-range $p = 0.09$).

Cox *et al.*[25] showed (in the Comparative early and late outcomes after primary percutaneous coronary intervention in ST-segment elevation and non-ST-segment elevation acute myocardial infarction from the CADILLAC trial) that patients with myocardial infarction without ST-elevation tended to have lower mortality rates than those with STEMI (0.4 vs 2.2%, $p = 0.06$). Similarly, the mortality rates at one year were comparable in STEMI and NSTEMI patients (3.4 vs 4.4%, respectively, $p = 0.43$). In a study by Savonitto *et al.*,[26] the 30-day mortality rate between STEMI and STDMI was not statistically different (5.1 vs 5.1%, respectively).

Granger *et al.*[27] attempted to develop a single model to assess the risk for in-hospital mortality of ACS patients. Killip class was the most powerful predictor with a two-fold increased risk of death with each worsening class. Age was associated with nearly the same prognostic significance, with a 1.7-fold increased risk for every 10 years' increase in age.

The next most important variables were systolic blood pressure, resuscitated cardiac arrest and initial serum creatinine levels. The strongest predictors of one-year mortality in the Opera study were heart failure and age. Moreover, similar predictors were found in STEMI and NSTEMI patients.[24] The same was true in our registry, with age and heart failure being strong independent in-hospital mortality risk factors.

There is no doubt that timely reperfusion of STEMI patients is critical. The current guidelines of the European Society of Cardiology appropriately recognise acute myocardial infarction with ongoing or recurrent chest pain and ST-segment depressions as the highest-risk subgroup and an indication for emergency coronary angiography, followed by revascularisation when appropriate.

Chan *et al.*[28] investigated mortality differences and timing of revascularisation of patients undergoing cardiac catheterisation for STEMI and NSTEMI. During the six-year accrual period, a total of 1 974 patients were classified as having STEMI, and 2 413 patients as having NSTEMI. NSTEMI was associated with a higher risk of long-term mortality (unadjusted mortality at one year for STEMI was 9.5 vs 14.3% for NSTEMI). Compared with no or late revascularisation, early revascularisation was associated with a similar reduction in long-term outcomes for both STEMI and NSTEMI (lower adjusted risk of mortality for STEMI and NSTEMI, $p = 0.22$).

The Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC-2) invasive trial showed for the first time a significant event rate (MI, death or both) reduction, favouring the invasive over the non-invasive strategy at six months in the NSTE-ACS population. The greatest benefit of invasive treatment, when evaluated using electrocardiography, was seen in the subset of patients with ST-segment depression MI.[19] The Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI) trial revealed that the greatest benefits of invasive treatment were achieved in patients presenting with cardiac enzyme elevation and ST-segment changes,[20] i.e. in STDMI patients. Also, a meta-analysis of seven randomised trials that included a total of 9 212 patients showed that invasive management should be considered for all patients with NSTEMI, and in particular those with ST-segment depression.[21]

In our study, there was no difference related to in-hospital mortality between STEMI and STDMI patients treated by emergency PCI (5.3 vs 6.78%, respectively, $p = 0.274$). There was a significant in-hospital mortality reduction in STDMI patients

who were treated using emergency PCI compared to STDMI patients who went without revascularisation. Moreover, the PCI success rate was significantly higher in STDMI compared to STEMI patients ($p = 0.012$). All these factors indicate that emergency CAG and PCI, when appropriate, should be used in all STDMI patients.

Early versus delayed invasive intervention in patients with ACS without ST-segment elevation was studied in the TIMACS trial.[29] Early intervention did not differ greatly from delayed intervention in preventing the primary outcome, but it did reduce the rate of the composite secondary outcome of death, MI or refractory ischaemia, and was superior to delayed intervention in high-risk patients.

Our study demonstrates the apparent positive development in invasive reperfusion treatment for acute myocardial infarction. Some form of reperfusion therapy was used in 89.1% of STEMI and 69.8% of NSTEMI patients. Of those, emergency PCI was used in 88.1% of STEMI and in 61.8% of NSTEMI patients.

By comparison, in the GRACE study (1999–2000),[30] the use of pPCI was a relatively rare reperfusion modality in STEMI. Lytic therapy was used in more than 75% of patients who received reperfusion therapy; only 62% of STEMI patients received any form of reperfusion. The in-hospital fatality rates were 7% in STEMI and 6% in NSTEMI patients ($p = 0.0459$). This positive and increasing trend of invasive treatment in AMI patients should be minimally maintained in STEMI cases, and there should be an effort made to increase the number in STDMI patients.

The presence of bundle brunch block(s) (BBBs) is associated with poor outcomes in patients suffering from an AMI. In our MI population, these patients represented the highest risk group, with in-hospital mortality more than double that of STDMI or STEMI patients. Patients with BBBs were older and more frequently had a history of diabetes mellitus. The mean left ventricular ejection fraction was lower compared with AMI patients without BBBs ($p < 0.001$). These findings support the results of Guerrero *et al*.[31] who sought to evaluate the outcome of patients with AMI and BBBs, who were treated using emergency PCI. The in-hospital mortality was significantly different (LBBB 14.6% vs RBBB 7.4% vs no BBB 2.8%).

Patients presenting with minor or no ECG abnormalities (without ST-segment shifts and without a bundle branch block) had the lowest mortality compared with all other groups (2.9%, $p < 0.001$). Additionally, heart failure was rare (Killip class I on admission was seen in 84.5% of all patients in this group).

Limitations

This study was based on the data from a registry that was retrospectively analysed. The very short follow-up period was a limitation. Our results did not evaluate long-term outcomes. No data were collected regarding previous or in-hospital drug treatment. Post-discharge treatment (secondary prevention) was also not studied.

Conclusions

The results of our study demonstrate that ST-depression AMI may represent an emergency similar to ST-elevation AMI. Therefore it would be accompanied by the same need for emergency coronary angiography and PCI when appropriate. STDMI patients in our study had comparable in-hospital mortality and were much closer, relative to treatment strategies and outcomes, to STEMI patients than to AMI patients without ST-segment shifts. Therefore, in the 'post-thrombolytic' era, emergency CAG and PCI, when appropriate, should be considered for high-risk patients with STDMI.

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Kala, P., *Karlík, R., Boček, O., Neugebauer, P., Poloczek, M., Pařenica, J., Vytiska, M., Kolářová, I., Hladilová, K., Dostálová, L., Jeřábek, P. The use of automated external cardiac massage during primary PCI [Využití automatické zevní srdeční masáže při primární PCI] (2010) Intervencni a Akutni Kardiologie, 9 (4), pp. 204-207.*

(přehledová práce s popisem případu – kvantitativní podíl uchazeče 30 % - koncept, popis případu, text publikace)

Práce s popisem případu byla publikována v r. 2010 v českém recenzovaném časopise.

Využití automatické zevní srdeční masáže při primární PCI

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Interní kardiologická klinika LF MU a FN Brno

Kardiopulmonální resuscitace je běžnou součástí práce na katetrizačním sále, a to především u pacientů s akutním infarktem myokardu. Velice problematickou je však péče o pacienty vyžadující srdeční masáž v průběhu zákroku, donedávna nutící k přerušení výkonu a manuální zevní srdeční masáži. V kazuistice uvádíme využití relativně nové techniky, automatické zevní srdeční masáže LUCAS (Lund University Cardiac Arrest System) s vysokým hemodynamickým efektem. V průběhu této masáže je, i přes určité technické limitace, možné pokračovat v provedení katetrizačního zákroku.

Klíčová slova: PCI, koronární intervence, automatická srdeční masáž, oběhová zástava.

The use of automated external cardiac massage during primary PCI

Cardiopulmonary resuscitation especially in patients with acute myocardial infarction is a common part of the cathlab work. Really problematic can be the need for cardiac massage during the procedure requiring interruption of the cathetrisation and beginning of the external cardiac massage manually. In this case we report the use of relatively new and highly effective technique – automated external cardiac massage LUCAS (Lund University Cardiac Arrest System). Despite some technical limitations it is possible to continue with the procedure during the massage.

Key words: PCI, coronary intervention, automatic cardiac massage, cardiac arrest.

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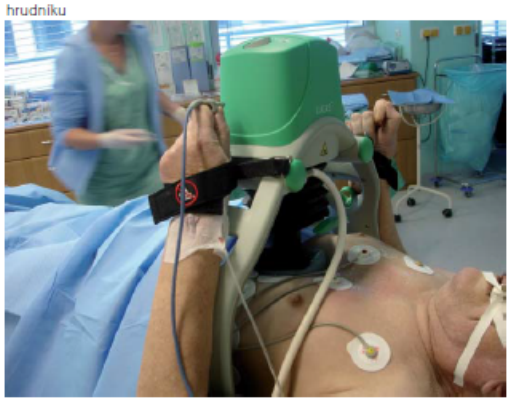
Popis případu

Šestašedesátiletému muži bez anamnézy ischemické choroby srdeční byl začátkem srpna při prvním kontaktu s týmem Zdravotnické záchranné služby (ZZS) diagnostikován akutní infarkt myokardu s ST-elevacemi v oblasti dolní stěny. Po transtelefonním přenosu EKG křivky na koronární jednotku Interní kardiologické kliniky FN Brno byl pacient letecky transportován a vezen přímo na katetrizační sál. Po převzetí pacienta do kardiologické péče ještě na heliportu došlo k náhlému vzniku atrio-ventrikulární blokády III. stupně provázené ztrátou vědomí a dechovou zástavou nutící k intubaci a umělé ventilaci pacienta. Na katetrizační sál přijíždí pacient 135 minut od vzniku obtíží, po aplikaci atropinu se sinusovou tachykardií 117/min a s hemodynamickým obrazem kardiogenního šoku s prakticky

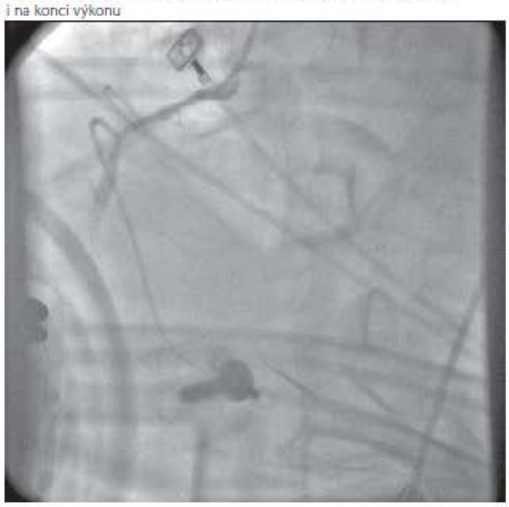
Obrázek 1. Pneumatický systém Lucas ve chvíli maximální komprese hrudníku



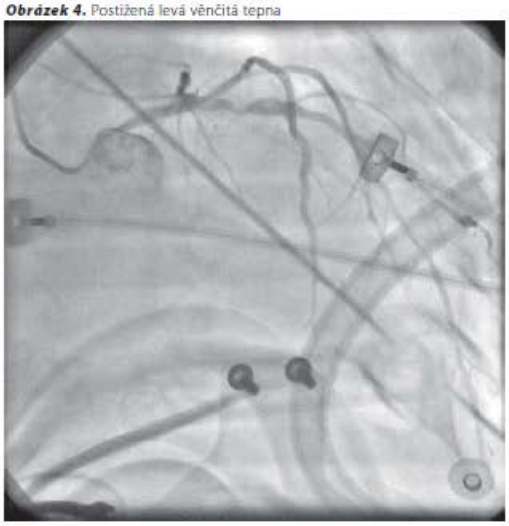
neměřitelným krevním tlakem nereagujícím na aplikaci masivních dávek katecholaminů a volumoexpanzi. Dodatečně byla doplněna anamnéza, zahrnující hospitalizaci pro schizoafektivní poruchu, diabetes mellitus II. typu na dietě, hypofunkci štítnice na substituční léčbě, prodělanou plicní embolizaci pooperačně v r. 1984 a chybění dalších rizikových faktorů ischemické choroby srdeční či jejích příznaků.

Po naslepo provedené punkci femorální tepny byl invazivně měřený systolický krevní tlak 40–45 mm Hg a pacientovi byl nasazen pneumatický systém automatické zevní srdeční masáže LUCAS (Lund University Cardiac Arrest System) (obrázek 1). Ihned po nasazení systému bylo dosaženo systolického tlaku 100–110 mm Hg při standardní frekvenci kompresí 100/minutu a jejich hloubce 5 cm. Systém zajišťuje automaticky i optimální poměr aktivní komprese a dekomprese hrudníku 1:1. Akutně byl proveden pouze nástřik pravé věnčité tepny s nálezem jejího trombotického uzávěru ve střední části nad pravou ventrikulární větví (obrázek 2). Echokardiograficky byla vyloučena srdeční tamponáda s ozřejmením dilatace a těžké systolické dysfunkce obou srdečních komor. Ani přes opakovanou manuální katétrovou tromboaspiraci se záchytem trombotického materiálu a balonkovou dilataci se nepodařilo infarktovou tepnu zprůchodnit (obrázek 3). Následně byla doplněna angiografie levé koronární tepny s nálezem již významného postižení kmene levé věnčité tepny a proximální části ramus interventricularis anterior (obrázek 4). Toto hodnocení však může být výrazně ovlivněno spastickou reakcí a tedy zatíženo velkou chybou. Kontrolní echokardiografie při dočasném zastavení zevní masáže pak doplnila původní informaci o kritickém stavu obou srdečních komor nálezem pravděpodobné ruptury závěsného aparátu mitrální chlopně a významné mitrální regurgitace (obrázek 5). Tento stav byl včetně opakované nutnosti defibrilačních výbojů se životem již neslučitelný a katetrizační výkon byl, podobně jako zevní srdeční masáž,

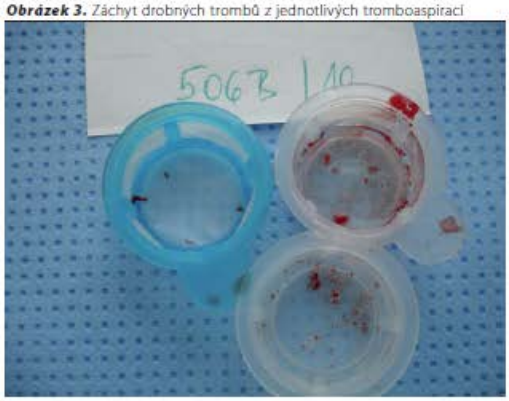
Obrázek 2. Akutně uzavřená pravá věnčitá tepna (ACD) na začátku i na konci výkonu



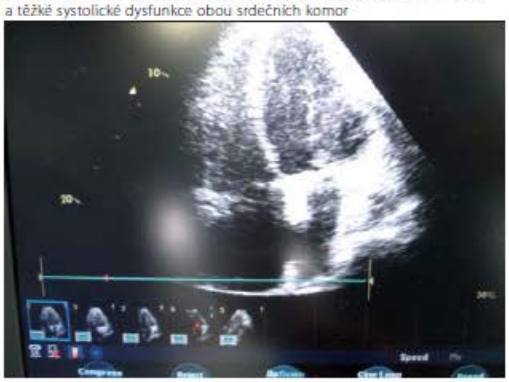
Obrázek 4. Postižená levá věnčitá tepna



Obrázek 3. Záchyt drobných trombů z jednotlivých tromboaspirací



Obrázek 5. Echokardiografie s nálezem susp. ruptury papilárního svalu a těžké systolické dysfunkce obou srdečních komor



ukončeny. Autoptický nález v celém rozsahu potvrdil naše klinická pozorování, tzn. rozsáhlý akutní srdeční infarkt stěny levé i pravé srdeční komory a rupturu závěsného aparátu mitrální chlopně u premorbidně silně poškozeného a dilatovaného srdečního svalu.

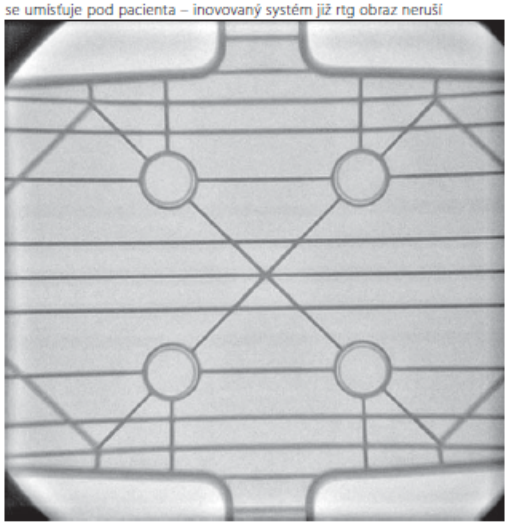
I přesto, a nebo právě proto, je však nutno zdůraznit, že ***pacient v kritickém stavu přežil celých 120 minut na kontinuální zevní srdeční masáži***, která umožnila provedení všech výše uvedených zákroků a vyšetření. Vlastní nasazení a spuštění popsaného systému je velmi jednoduché a u trénovaného týmu trvá méně než 30 sekund, během kterých je z větší části prováděna masáž manuálně. V průběhu vlastní srdeční masáže je nutné počítat i s některými „limitacemi", kterými jsou výrazně omezená možnost pohybu rtg lampy, silné exkurze hrudníku a doprovodný zvukový efekt. Dalším problémem, kterým je kontrastní struktura podkladové části rušící angiografický obraz koronárních tepen (obrázek 6), byl již technologicky vyřešen změnou materiálu.

V případě, že by nález na srdci skýtal určitou šanci na přežití, přicházelo by v úvahu napojení pacienta na některý z pokročilejších systémů mechanické podpory oběhu a následné definitivní kardiochirurgické řešení. Velmi dobré zkušenosti z katetrizačních laboratoří jsou popsány s perkutánním zavedením axiální pumpy Impella (Abiomed, Inc., USA) do levé komory, která je v ideálních podmínkách schopna přečerpat až 2,5 či 4,5 l krve za minutu v závislosti na zvoleném typu katétru/pumpy. Tento systém využívá několik let i pracoviště autorů. Další potenciální možností, kterou však autoři nedisponují, je napojení pacienta na veno-arteriální systém ECMO (extracorporeal membrane oxygenation) dočasně zajišťujícím až 75 % srdečního oběhu.

Diskuze

Oběhový kolaps je stav vyžadující okamžitý léčebný zásah, kam vedle defibrilace, umělé plicní ventilace a farmakoterapie nepochybně patří i optimálně vedená a nepřerušovaná srdeční masáž (1). I pro dobře trénovaný tým je velmi obtížné dosáhnout doporučené frekvence a hloubky komprese, a to nejen při déletrvající resuscitaci, ale i při té krátkodobé, v trvání méně než 10 minut. Snaha o vytvoření systému pro bezpečnou a efektivní automatickou zevní srdeční masáž se datuje hluboko do 20. století (2), z praktického hlediska využitelné výsledky s popsaným systémem ale byly publikovány až po roce 2002, kdy byl systém poprvé předsta-

Obrázek 6. Rtg obraz standardně dodávané části systému Lucas, který se umísťuje pod pacienta – inovovaný systém již rtg obraz neruší



ven (2). V České republice se tento systém začal využívat teprve v nedávné době zkušenosti ze zahraničí však vyzývají k jeho nasazení především při prvním kontaktu s nemocným v oběhové zástavě, tzn. ve vozech ZZS (3, 4). V rámci nemocniční péče by jako optimální modelový příklad mohla posloužit naše nemocnice, kde stejným systémem automatické zevní srdeční masáže LUCAS disponují týmy urgentního příjmu, koronární jednotky i katetrizačního centra. Naše vlastní, více než roční zkušenosti, pak mohou jen potvrdit literární údaje o chybění závažných komplikací, které se poměrně běžně vyskytují u masáže manuální.

Z pohledu intervenční kardiologie je velice cennou inovací změna materiálu podkladové části systému, která na rozdíl od standardně dodávané neruší rtg obraz. Vedle popsaného pneumatického systému označovaného jako typ 1 LUCAS™ 1, je nově dostupný i typ 2, tzn. systém elektrický poháněný na baterie.

Závěr

V kazuistice je popsáno bezpečné a dlouhodobě efektivní použití pneumatického automatizovaného systému pro zevní srdeční masáž u pacienta v kardiogenním šoku z důvodu komplikovaného akutního infarktu s ST-elevacemi. I přes určité technické limitace, bylo v průběhu srdeční masáže možné provést primární koronární intervenci a další vyšetření.

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Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI)/Stent for Life (SFL) groups

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The references can be found in the online version of this paper at the following website: http://www.pcronline.com/eurointervention/72nd_issue/7

KEYWORDS

- cardiac arrest
- coronary angiography
- PCI

Abstract

Due to significant improvement in the pre-hospital treatment of patients with out-of-hospital cardiac arrest (OHCA), an increasing number of initially resuscitated patients are being admitted to hospitals. Because of the limited data available and lack of clear guideline recommendations, experts from the EAPCI and "Stent for Life" (SFL) groups reviewed existing literature and provided practical guidelines on selection of patients for immediate coronary angiography (CAG), PCI strategy, concomitant antiplatelet/anticoagulation treatment, haemodynamic support and use of therapeutic hypothermia. Conscious survivors of OHCA with suspected acute coronary syndrome (ACS) should be treated according to recommendations for ST-segment elevation myocardial infarction (STEMI) and high-risk non-ST-segment elevation -ACS (NSTE-ACS) without OHCA and should undergo immediate (if STEMI) or rapid (less than two hours if NSTE-ACS) coronary invasive strategy. Comatose survivors of OHCA with ECG criteria for STEMI on the post-resuscitation ECG should be admitted directly to the catheterisation laboratory. For patients without STEMI ECG criteria, a short "emergency department or intensive care unit stop" is advised to exclude non-coronary causes. In the absence of an obvious non-coronary cause, CAG should be performed as soon as possible (less than two hours), in particular in haemodynamically unstable patients. Immediate PCI should be mainly directed towards the culprit lesion if identified. Interventional cardiologists should become an essential part of the "survival chain" for patients with OHCA. There is a need to centralise the care of patients with OHCA to experienced centres.

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Introduction

Sudden out-of-hospital cardiac arrest (OHCA) remains the leading cause of death in developed countries with an annual incidence of between 36 and 81 events per 100,000 inhabitants[1]. Pre-hospital treatment is initiated with a sequence of critical events known as the "chain of survival" which includes the early recognition of symptoms, bystander cardiopulmonary resuscitation, early defibrillation and advanced cardiac life support. Re-establishment of spontaneous circulation (ROSC) before hospital arrival is currently achieved in 40-60% of patients in whom advanced cardiac life support is attempted. Due to significant improvement in the pre-hospital "chain of survival" in Europe, an increasing number of initially resuscitated patients are being admitted to hospitals.

According to autopsy and immediate coronary angiography (CAG) data, significant coronary artery disease may be documented in more than 70% of patients with resuscitated OHCA[2,3]. These data are well known by the physicians caring for these patients. Furthermore, the 2012 European Society of Cardiology (ESC) guidelines on ST-segment elevation myocardial infarction (STEMI) included recommendations on the management of survivors of OHCA[4]: "In patients with resuscitated cardiac arrest, whose electrocardiogram (ECG) shows STEMI, immediate CAG with a view to primary percutaneous coronary intervention (PCI) is the strategy of choice, provided that the guidelines mandated times can be met (class I, level B). Given the high prevalence of coronary occlusions and potential difficulties in interpreting the ECG in patients after cardiac arrest, immediate CAG should be considered in survivors of cardiac arrest having a high index of suspicion of ongoing infarction (class IIa, level B)". Interventional cardiologists in "24-7" STEMI centres are therefore being increasingly alerted for immediate CAG and PCI. Because of the limited data available, the 2012 ESC STEMI guidelines could not address several important practical issues while treating patients with resuscitated OHCA:

1) Should a coronary angiogram be performed immediately at admission in all survivors of an OHCA with STEMI or should a selection be performed on the basis of neurological status on admission, prognostic criteria such as the duration of no-flow, initial rhythm, age and pre-arrest comorbidities?
2) Should patients without STEMI be admitted directly to the catheterisation laboratory or should a rapid assessment be performed before to exclude a non-cardiac cause of arrest?
3) Which anticoagulation and antiplatelet treatment should be administered before, during and after PCI?
4) Should PCI be performed only on the culprit artery or on all lesions during the initial procedure or subsequently, and what stents should be used?
5) What are the current indications for cardiac assist devices in OHCA?
6) What are the indications for a coronary artery spasm provocation test in survivors of OHCA?

The aim of this statement paper on CAG and PCI after resuscitated OHCA, designated as invasive coronary strategy, is to provide practical guidelines on the management for interventional cardiologists based on the limited current data and an expert consensus. This paper should therefore be regarded as complementary to the existing ESC guidelines for STEMI and NSTE-ACS.

Literature review on invasive coronary strategy in resuscitated OHCA

It is now well known that, in the presence of STEMI, defined as an ST elevation of >1 mm in two contiguous standard leads or >2 mm in precordial leads on the early post-resuscitation ECG, acute thrombotic lesions, such as those usually apparent in acute coronary syndromes (ACS) without preceding cardiac arrest, may be found in up to 90% of cases[5-9]. However, the absence of STEMI on the ECG performed in the pre-hospital setting or on admission does not exclude obstructive or even thrombotic "ACS" coronary stenosis, which may be present in 25% to 58% of cases[3,7,9,10]. These ECG patterns include ischaemic ST-T changes, bundle branch block, non-specific intraventricular delay and non-specific ST-T changes[9,10].

There are no randomised trials investigating the possible benefits of an immediate invasive coronary strategy in patients with resuscitated OHCA. In fact, patients with preceding sudden cardiac arrest have been systematically excluded from major randomised trials which unequivocally demonstrated the benefits of primary PCI in STEMI[11] and early PCI in non-ST-elevation acute coronary syndrome (NSTE-ACS)[12]. We therefore performed a "PubMed" search using the key words "cardiac arrest" and "coronary angiography". Each paper was reviewed and possible additional references within the text identified. If patients undergoing urgent coronary angiography and PCI were identified, they were included in the pooled analysis **(Table 1)**. Forty-two studies with 3,665 patients confirmed the high prevalence of >1 obstructive coronary lesion and the feasibility and safety of an immediate invasive coronary strategy[3,5-10,13-46]. The fact that seven of these studies with a total of 1,110 patients have been published since 2012 points to the growing utilisation of an invasive coronary strategy in patients with OHCA[40-46].

Recently, Larsen and Ravkilde[47] performed a meta-analysis of 10 observational studies comparing the survival of patients with resuscitated OHCA in relation to an immediate invasive coronary strategy. In 3,103 patients, an immediate invasive strategy was associated with improved survival (pooled unadjusted OR 2.78; 95% CI: 1.89-4.10; p<0.001). Because of the heterogeneity of studies and lack of data for adjusted analysis, this finding should be interpreted with caution.

More recently, investigators from the United States analysed 3,981 patients with OHCA admitted after ROSC of whom 19% and 17% underwent coronary angiography and PCI within 24 hours, respectively[48]. There was very wide variability among the 151 admitting hospitals in the frequency of these procedures. However, survival and favourable neurological outcome were independently associated with early coronary angiography (adjusted OR 1.87; 95% CI: 1.15-3.04) and reperfusion (adjusted OR 2.14; 95% CI: 1.46-3.14).

Table1. Published cohort studies on immediate invasive coronary strategy in patients with resuscitated cardiac arrest.

Author	Year	N	Comatose (%)	STEMI (%)	PCI (%)	PCI success (%)	MIH	Survival (%)	CPC 1 or 2 (%)
Kahn[13]	1995	11	7 (64)	11/11 (100)	11 (100)	7/11 (64)	N	6/11 (55)	6/11 (55)
Spaulding[3]	1997	84	NA	34/84 (40)	37 (44)	28/37 (76)	N	32/84 (38)	30/84 (36)
Lin[14]	1998	10	NA	10/10 (100)	10 (100)	10/10 (100)	N	9/10 (90)	NA
Bulut[15]	2000	10	NA	10/10 (100)	10 (100)	8/10(80)	N	4/10 (40)	NA
McCollough[16]	2002	22	NA	22/22 (100)	22 (100)	22/22 (100)	N	9/22 (41)	NA
Keelan[17]	2003	15	13 (87)	15/15 (100)	15 (100)	14/15 (93)	N	11/15 (73)	9/15 (60)
Bendz[5]	2004	40	36 (90)	40/40 (100)	40 (100)	38/40 (95)	N	29/40 (73)	NA
Quintero-Moran[18]	2006	27	NA	27/27 (100)	27 (100)	23/27 (85)	NA	18/27 (67)	NA
Sunde[19]	2007	47	NA	NA	30 (64)	NA	Y	NA	NA
Gorjup[6]	2007	135	86 (64)	135 (100)	109 (81)	102/109 (94)	Y	90/135 (67)	74/135 (55)
Garot[20]	2007	186	NA	186 (100)	186 (100)	161/186 (87)	Y	103/186 (70)	89/186(48)
Richling[21]	2007	46	NA	46 (100)	46 (100)	NA	NA	24/46 (52)	22/46 (48)
Markusohn[22]	2007	25	18 (72)	25 (100)	25 (100)	22/25 (88)	Y	19/25 (76)	17/25 (68)
Werling[23]	2007	24	NA	NA	13 (54)	NA	NA	16/24 (67)	NA
Hovdenes[24]	2007	49	49 (100)	NA	36 (73)	NA	Y	41/49 (84)	34/49 (69)
Valente[25]	2008	31	31 (100)	31 (100)	31 (100)	NA	NA	23/31 (74)	NA
Mager[26]	2008	21	NA	21 (100)	21 (100)	NA	NA	18/21 (86)	NA
Wolfrum[27]	2008	16	16 (100)	16 (100)	16 (100)	16/16 (100)	Y	12/16 (75)	NA
Pleskot[28]	2008	20	NA	NA	19 (95)	17/19 (89)	NA	NA	NA
Peels[29]	2008	44	NA	44 (100)	44 (100)	38/44 (86)	NA	22/44 (50)	NA
Merchant[30]	2008	30	NA	13 (43)	30 (20)	17/19 (89)	NA	22/30 (80)	NA
Hosmane[8]	2009	98	73 (74)	98 (100)	64 (65)	62/64 (97)	Y	63/98 (64)	57/98 (58)
Anyfantakis[10]	2009	72	NA	23 (32)	27 (38)	24/27 (89)	NA	35/72 (49)	33/72 (46)
Reynolds[31]	2009	96	NA	42 (44)	NA	NA	Y	52/96 (54)	NA
Lettieri[32]	2009	99	NA	99 (100)	99 (100)	79/99 (80)	NA	77/99 (78)	72/99 (73)
Pan[33]	2010	49	NA	49 (100)	49 (100)	42/49 (86)	NA	31/49 (63)	NA
Batista[34]	2010	20	NA	10 (50)	20 (100)	NA	Y	8/20 (40)	6/20 (30)
Dumas[7]	2010	435	NA	134 (31)	202 (46)	177/202 (88)	Y	171/435 (39)	160/435 (37)
Stub[35]	2011	62	62 (100)	27 (44)	31 (50)	29/31 (94)	Y	NA	NA
Tomte[36]	2011	252	NA	NA	NA	NA	NA	140/252 (56)	NA
Radsel[9]	2011	212	171 (81)	158 (75)	165 (78)	150/165 (91)	Y	154/212 (73)	108/212 (51)
Mooney[37]	2011	101	NA	68 (67)	56 (55)	NA	NA	NA	NA
Cronier[38]	2011	91	NA	50 (55)	46 (51)	43/46 (93)	Y	60/91 (66)	NA
Moellmann[39]	2011	65	NA	36 (55)	65 (100)	64/65 (98)	NA	46/65 (71)	NA
Nanjayya[40]	2012	35	35 (100)	31 (89)	21 (60)	NA	Y	20/35 (57)	14/35 (40)
Bro-Jeppesen[41]	2012	360	360 (100)	116 (32)	198 (55)	101/122 (83)	Y	219/360 (61)	207/360 (58)
Zanuttini[42]	2012	93	93 (100)	32 (34)	NA	NA	Y	50/93 (54)	36/93 (39)
Liu[43]	2012	81	24 (30)	81 (100)	49 (60)	42/49 (86)	N	36/81 (44)	NA
Zimmermann[44]	2013	48	48 (100)	48 (100)	44 (92)	37/44 (84)	Y	32/48 (67)	16/48 (33)
Hollenbeck[45]	2013	269	269 (100)	0 (0)	122 (45)	NA	Y	151/269 (56)	NA
Velders[46]	2013	224	108 (48)	224 (100)	217 (97)	NA	Y	183/218 (84)	168/218 (77)
Total		3,655	1,499/1,804 (83%)	2,012/3,263 (62%)	2,253/3,179 (71%)	1,373/1,553 (88%)		2,036/3,384 (60%)	1,158/2,241 (52%)

CPC 1 or 2: cerebral performance category 1 or 2 indicating survival with good neurological outcome; MIH: mild induced hypothermia for post-resuscitation coma; N: number of patients in the study; PCI: percutaneous coronary intervention

Selection of patients for immediate coronary invasive strategy

Because of the lack of appropriate trials and unequivocal guideline recommendations, there is considerable variability in the selection of patients for immediate invasive coronary strategy among different hospitals and countries. In this context, it is also important to notice that there are two very different populations of resuscitated patients at hospital admission. Because of typical delays in the pre-hospital "chain of survival", up to 80% of resuscitated patients present in coma despite ROSC, which indicates post-resuscitation

brain injury, the severity of which may vary from no or mild disability to permanent vegetative state or brain death. Importantly, this cannot be predicted on hospital admission. Only a minority of fortunate patients regain consciousness immediately after ROSC if chest compression and defibrillation have been initiated immediately, which is usually the case if the emergency medical team is already present at the scene or if the patient has received well performed cardiopulmonary resuscitation immediately before the arrival of the medical team. Conscious survivors of OHCA, in contrast to comatose survivors of cardiac arrest, have little or no post-resuscitation brain injury and represent a less complex subpopulation in terms of post-resuscitation treatment. Pooling published studies on conscious survivors of OHCA triggered by ACS who underwent immediate invasive coronary strategy, 117 out of 119 (98%) patients survived to hospital discharge with good neurological outcome[6,8,9,13].

Based on the described observational studies and by extrapolation from "ACS-no cardiac arrest" interventional trials, we suggest recommendations for interventional cardiologists for decision making regarding selection of patients for immediate coronary invasive strategy in a hospital with an immediately available catheterisation laboratory and an intensive care unit **(Figure 1)**. There is little doubt that conscious survivors of OHCA with suspected ACS should be treated according to recommendations for STEMI and high-risk NSTE-ACS which also includes life-threatening ventricular arrhythmias[4,12]. Accordingly, patients with ST-segment elevation on the post-resuscitation ECG should undergo immediate CAG and patients without STEMI rapid CAG in less than two hours. Comatose survivors of OHCA with ECG criteria for STEMI on the post-resuscitation ECG should follow the "STEMI fast track" and go directly to the catheterisation laboratory[4]. For patients without STEMI ECG criteria, whilst coronary disease is likely, there are many other possible causes of cardiac arrest. We advise a short "emergency department or intensive care unit stop" to exclude non-coronary causes, such as respiratory failure, shock of non-cardiogenic aetiologies, cerebrovascular event, pulmonary embolism and intoxication, by performing the appropriate diagnostic procedures. These include more detailed information from bystanders regarding possible symptoms before cardiac arrest and review of previous medical history if available. Echocardiography is very useful to document cardiac tamponade, acute "cor pulmonale" due to massive pulmonary embolism and aortic dissection which can be subsequently confirmed by contrast CT scan of the thorax. Head CT should not be routinely performed but, if a cerebrovascular event is suspected as a cause of cardiac arrest, this should be the first diagnostic procedure. Although attractive, we believe that selective diagnostic tests rather than a routine total body CT scan are currently more validated and are a cheaper way to approach the cause of cardiac arrest. In the absence of an obvious non-coronary cause, CAG should be performed as soon as possible, within two hours according to the guidelines for high-risk NSTE-ACS[12]. This is particularly important in haemodynamically unstable patients and in patients with recurrent malignant ventricular arrhythmias[12]. Coma on admission should not automatically represent a contraindication for immediate coronary angiography. However, unfavourable pre-hospital settings related to cardiac arrest and initial resuscitation indicating a remote likelihood for neurological recovery should be strongly considered and argue against an invasive coronary strategy regardless of post-resuscitation ECG. These include unwitnessed cardiac arrest, late arrival of a pre-hospital team without lay basic life support (>10 minutes), presence of an initial non-shockable rhythm, and more than 20 minutes of advanced life support without ROSC[49]. As we already mentioned, there is currently no parameter which can adequately predict neurological outcome at hospital admission when the decision for immediate invasive coronary strategy is taken. Also, severe pre-arrest comorbidities and limited life expectancy should be taken into account. All these factors should be analysed on a per patient basis and the decision-making process individualised.

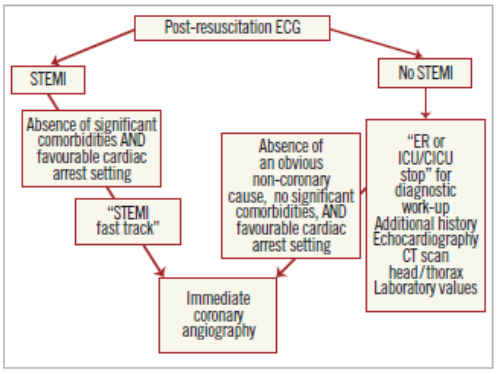

Figure 1. *Selection of patients for immediate coronary invasive strategy. CICU: specialised cardiac intensive care unit; CT scan: computed tomography scanner; ECG: electrocardiogram; ER: emergency room; ICU: intensive care unit; STEMI: ST-segment elevation myocardial infarction. See text for the definition of favourable cardiac arrest setting.*

Pre-hospital triage and regional networks among hospitals for the management of OHCA should be encouraged. Referral centres for OHCA with at least an intensive care unit and a "24-7" interventional cardiology department should be identified. Direct admission of survivors of OHCA to these centres is recommended. If a survivor of OHCA is admitted to a hospital without an interventional cardiology department, and the expected "time to reperfusion by PCI" is less than two hours[4], transfer decisions to a catheterisation laboratory should be taken immediately with the referral centres, based on the same criteria as described previously. If the patient is more than two hours from a referral centre, transfer decisions are taken on a per patient basis. Thrombolytic therapy should only be considered if the patient cannot be transported within the appropriate delays for PCI, presents with clinical evidence suggestive of STEMI within 12 hours of symptom onset, and if there are no contraindications

to thrombolytic therapy, such as prolonged and traumatic CPR[21]. However, one should keep in mind that assessment of contraindications to such therapy is often difficult after an OHCA. If thrombolysis is administered, the patient should then be transported to a centre with PCI capability and a CAG performed three to 24 hours after the administration of thrombolysis[4].

Cardiac arrest PCI (CA-PCI)

CAG after resuscitated OHCA may reveal very heterogeneous findings particularly in patients without ST-elevation. These include angiographically normal coronary arteries, non-obstructive disease (<50% diameter stenosis), intermediate disease (50-70%), obstructive disease with angiographically stable appearance, and presence of typical culprit "ACS" lesion (TIMI 0 or 1 flow with an abrupt closure, or TIMI 2 or 3 flow with angiographic images suggesting thrombus or ulcerated plaques). The aim of CA-PCI is to reduce the incidence of recurrent cardiac arrest, to reduce infarct size in case of an acute occlusion and thereby to improve the haemodynamic status. In comatose survivors, who represent a major subgroup of resuscitated OHCA patients, stabilised haemodynamic status may allow enough time for possible neurological recovery during the following days.

There is a lack of studies addressing different revascularisation strategies in relation to angiographic characteristics, completeness of revascularisation and outcome. Again, we are left mainly with extrapolation of interventional "ACS" studies to this much higher-risk population of patients with resuscitated OHCA. We suggest an algorithm which integrates the angiographic characteristics of a lesion, its cause-effect relationship to the cardiac arrest, the haemodynamic status of a patient and the presence of post-resuscitation brain injury to obtain the maximal benefit and avoid futility at the time of the index intervention **(Figure 2)**.

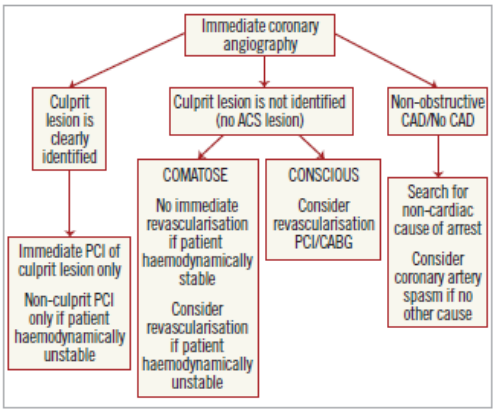

Figure 2. *Revascularisation strategies in survivors of out-of-hospital cardiac arrest. ACS: acute coronary syndrome; CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; PCI: percutaneous coronary intervention*

Clear "ACS" lesions obviously represent the cause of cardiac arrest, and successful CA-PCI is likely to decrease the incidence of recurrent cardiac arrest, reduce infarct size and improve haemodynamic stability. Immediate CA-PCI should therefore be performed in clear "ACS" lesions and, in the absence of data, non-culprit PCI should probably be postponed despite very recent evidence indicating possible benefit in STEMI without OHCA[50]. Index CA-PCI of additional non-culprit but obviously obstructive lesions with stable angiographic appearance may be beneficial if the patient is haemodynamically unstable[51]. Immediate coronary artery bypass grafting (CABG) is a realistic option only in conscious survivors of OHCA on hospital admission with severe multivessel disease and not in comatose patients in whom the ultimate neurological outcome is difficult to predict.

Significant obstructive disease with angiographically stable appearance may also be the cause of cardiac arrest even though the cause-effect relationship is much less certain. Possible mechanisms include transient ischaemia caused by plaque thrombosis - spontaneous reperfusion, coronary spasm or decrease in perfusion pressure across the lesion or collaterals in case of sudden drop in arterial pressure. On the other hand, obstructive lesions may also be "innocent bystanders" without direct cause-effect relationship to the cardiac arrest. While in "conscious survivors" of cardiac arrest revascularisation by either PCI or CABG should be considered, decision making becomes more complex in comatose patients with uncertain neurological prognosis. We suggest that immediate CA-PCI of obviously obstructive "stable" lesion(s) be performed only in haemodynamically unstable patients[51]. If, on the other hand, a comatose survivor is haemodynamically stable, the decision for revascularisation, either by PCI or CABG, should be postponed and planned if the patient survives with no or minimal neurological sequelae.

Angiographic absence or presence of non-obstructive disease (<70%) is also important because a negative result should immediately trigger a search for alternative causes of OHCA. For example, if an acute cerebrovascular event or a massive pulmonary embolism is suspected, CT of the head and thorax should be performed on the way from the catheterisation laboratory to the intensive care unit. If an alternative cause of OHCA is not identified, coronary artery spasm should be considered, since several studies have shown that spasm may trigger lethal arrhythmias and lead to sudden death[52-54]. Accordingly, if the index procedure reveals normal coronary arteries, if the patient survives with no or minimal neurological sequelae, and if there is no other obvious cause of arrest, a coronary artery spasm provocation test may be performed during a second coronary angiogram by an experienced operator using either intracoronary acetylcholine or ergonovine[54,55].

There are no published data regarding stent selection in the setting of CA-PCI. We believe contemporary drug-eluting stents should be preferred to bare metal stents in patients with a high likelihood of good neurological recovery. This includes conscious and selected comatose survivors of OHCA with favourable predictive factors for survival with no or minimal neurological sequelae

(presence of initially shockable rhythm and short delays to advanced cardiac life support and ROSC).

There are no randomised data comparing the radial and femoral approaches for coronary procedures in survivors of OHCA. Radial access reduced mortality in the subgroup of patients with STEMI without OHCA[56]. We suggest using the radial approach as the default strategy in survivors of OHCA if the operator is experienced and if the radial pulse is present. However, femoral access may have an advantage in haemodynamically compromised patients who may require insertion of a percutaneous assist device. The introducer can be left at the end of the procedure to monitor blood pressure in the intensive care unit. There are no data on the use of femoral arterial closure devices in the setting of CAG or CA-PCI in survivors of OHCA.

Periprocedural anticoagulation and antiplatelet therapy

PCI with stenting is obviously associated with the need for anticoagulation and antiplatelet therapy to prevent stent thrombosis. In conscious survivors of OHCA, this treatment should be used according to the current guidelines[4,12]. No randomised studies are available for comatose survivors of cardiac arrest. Furthermore, these patients are often at high risk for bleeding complications due to chest compression and intubation before admission and often develop renal failure. Based on expert consensus, the following strategy is suggested for comatose patients:-

1) Intravenous administration of acetylsalicylic acid and anticoagulant therapy, for which we recommend unfractionated heparin (UFH), are generally advised after the assessment of coronary anatomy. However, in patients with clear STEMI on the post-resuscitation ECG who have a high likelihood of thrombotic occlusion and subsequent CA-PCI, this can be done prior to the CAG. UFH should be closely monitored during and after the procedure.
2) While acetylsalicylic acid, UFH and GP IIb/IIIa inhibitors may be administered by an intravenous route, P2Y12 inhibitors are available only in tablets. Since comatose survivors are intubated and mechanically ventilated during and after PCI when hypothermia is also initiated, administration of crushed tablets via a nasogastric tube remains the only option[57]. Early post-resuscitation state and ongoing hypothermia may significantly affect P2Y12 absorption and metabolism leading to delayed onset of action not only after clopidogrel loading[58,59] but also in case of newer agents such as prasugrel and ticagrelor[60] which result in no or suboptimal platelet inhibition. In cases with a high thrombotic burden, complex stenting, or "bail-out" situations, GP IIb/IIIa inhibitors may therefore be considered. There is very recent evidence that administration of eptifibatide in these settings results in profound platelet inhibition measured by both the VerifyNow IIb/IIIa and the Multiplate TRAP tests for at least 22 hours[59]. Even a bolus of GP IIb/IIIa without additional infusion might be sufficient to bridge the delayed effect of P2Y12 inhibitors, as demonstrated in patients with STEMI without cardiac arrest[61,62].

Cangrelor may represent an attractive pharmacological solution to inhibit platelet reactivity temporarily in these patients but further studies are needed[63]. However, profound inhibition in platelet reactivity should always be weighed against the increased risk of bleeding due to possible traumatic injury related to chest compression and endotracheal intubation.

There are few and conflicting data regarding the rate of stent thrombosis after PCI in survivors of OHCA. A recent observational study suggests no increase compared to STEMI patients[57], while other investigators found a 10.9% incidence of acute and subacute stent thrombosis in comatose survivors of OHCA, which was five times more than in a comparable group of patients with ACS but without cardiac arrest[64].

Invasive haemodynamic support in survivors of OHCA and haemodynamic compromise

Post-resuscitation shock appears in 30 to 40% of survivors of OHCA, most often four to six hours after the arrest. The mechanisms are multifactorial and include vasoplegia and myocardial stunning. Immediate PCI seems to reduce the rate and intensity of post-resuscitation shock[65]. The role of haemodynamic support in patients with resuscitated OHCA and haemodynamic compromise has not been specifically studied. Feasibility and safety of the intra-aortic balloon pump (IABP) have been demonstrated in comatose survivors of OHCA with cardiogenic shock[24]. Such support was beneficial only in small and uncontrolled studies, while the SHOCK IABP trial, which included around 40% of patients with resuscitated cardiac arrest and cardiogenic shock[66], and the CRISP AMI trial[67] did not demonstrate any benefit of IABP. In the absence of proven benefit, routine periprocedural implantation of IABP cannot therefore be recommended in this setting and should be decided on an individual basis. This is true also for haemodynamically more effective devices including Impella™ (Abiomed, Inc., Danvers, MA, USA), TandemHeart™ (CardiacAssist, Inc., Pittsburgh, PA, USA) and venous-arterial extracorporeal membrane oxygenation (VA ECMO) which may be considered in this setting in conscious patients on admission and in comatose patients with a high likelihood for survival with no or minimal neurological sequelae and absence of severe pre-arrest comorbidities.

Refractory cardiac arrest

The number of patients admitted to hospital with refractory OHCA and no ROSC despite prolonged and ongoing advanced cardiac life support by manual or automated chest compression is increasing. Since there are only case reports or small case series of successful PCI performed during ongoing chest compression (which are clearly biased by mainly reporting survivors[68]), this strategy cannot be recommended as a universal clinical routine. However, it may be used in selected patients by experienced interventional cardiologists with a skilled resuscitation team taking care of the ongoing resuscitation. VA ECMO[69,70] or Impella™[71] have been successfully implemented in refractory cardiac arrest to restore perfusion promptly, to allow for subsequent CAG and PCI and to bridge until

recovery of cardiac function. The potential benefits of such an aggressive strategy are currently being addressed by the controlled Prague OHCA randomised trial[72]. Another option is the pre-hospital implantation of VA ECMO[73]. However, due to the lack of data, these strategies should be either assessed in trials or applied to selected cases in experienced centres.

Induced hypothermia

The benefit of mild induced hypothermia between 32 and 34°C in comatose survivors of OHCA was demonstrated with the publication in 2002 of two randomised trials showing a marked increase in survival[74,75]. A recent randomised trial, however, demonstrated that maintaining a target core temperature at 36°C may be sufficient to facilitate neurological recovery[76]. While the debate regarding the optimal temperature is still ongoing, we suggest measuring the body temperature of survivors of OHCA when they are admitted to the catheterisation laboratory. In most cases the temperature will be less than 36°C either spontaneously or if cooling has been initiated before the arrival to the hospital or during the "emergency department or intensive care unit stop". Interventional cardiologists may facilitate induction and maintenance of hypothermia by infusion of cold saline or the use of ice packs. The use of endovascular cooling catheters through the femoral vein into the inferior vena cava with the tip at the entrance of the right atrium has been suggested[77]. It is important to emphasise that angiographic success of CA-PCI seems not to be compromised by ongoing hypothermia[27,57,78].

Call for interventional cardiologists to become members of the "post-resuscitation team"

Interventional cardiologists should become an essential part of the "survival chain" for patients with OHCA which includes bystander cardiopulmonary resuscitation, pre-hospital emergency medical units, emergency departments, acute cardiac care units and electrophysiology departments. Because immediate CAG and PCI are best achieved within existing STEMI networks, this system can also be used to become a "fast track" for patients with OHCA. The history and evolution of primary PCI for STEMI shows that there is a need to centralise the care of patients with OHCA to centres of excellence with a high-volume "24-7" interventional cardiology service, an intensive care unit, on-site cardiac and vascular surgery with a cardiac assist programme, and an integrated electrophysiology department. Indeed, there is evidence that patients with resuscitated OHCA admitted to such specialised cardiac arrest centres have better outcomes[79,80].

Organisation of hospital "post-resuscitation team"

Because of the involvement of different specialists, it is very important to decide who will direct the treatment and take responsibility after hospital admission. Because of different hospital size, organisation and resource availability, this varies significantly among hospitals and countries. Our general recommendation is that an intensive care (ICU)/cardiac intensive care (CICU) physician or anaesthesiologist who ultimately admits the patient should take the lead. Since monitoring and treatment of the patient during the CAG and PCI procedure are crucial, ICU/CICU or anaesthesiology teams experienced in managing such patients should manage the patient in the catheterisation laboratory. This team should take care of therapeutic measures including mechanical ventilation, vasopressor/inotropic drug administration, cardiac rhythm management and induction of hypothermia if indicated. Uncontrolled movements of arms and legs (which may occur in some patients) can be managed by increasing sedation. This allows the interventional cardiologist to be focused on decision making based on angiographic findings and patient condition and to perform CA-PCI in optimal conditions. The interventional cardiologist together with ICU/CICU physicians/anaesthesiologists should also decide on the use of an invasive haemodynamic support. After the procedure, the patient should be admitted by the ICU/CICU physician/anaesthesiologist who is already familiar with the patient situation and who will take responsibility for further diagnostic procedures and treatment. After ICU/CICU discharge, the patient can be transferred to a cardiology unit. A "Heart Team" approach is necessary to discuss further revascularisation (PCI or CABG), spasm provocation studies, and diagnostic procedures such as MRI. The electrophysiology specialist is an essential part of the team to discuss electrophysiology testing, arrhythmia ablation or the implantation of an internal cardiac defibrillator.

Further research

Closer involvement of the interventional community is essential to stimulate appropriate randomised studies which will provide definitive answers about optimal patient selection for immediate CAG and guidance for optimal revascularisation strategy. While randomisation of patients with clear STEMI in post-resuscitation ECG does not seem to be ethical, there is undoubtedly a great need for a trial in patients presenting with no-STEMI post-resuscitation ECG patterns. CA-PCI strategy should be explored and the possible benefits of non-culprit PCI during the index procedure versus staged procedure should be addressed. Periprocedural pharmacology including antiplatelet effects of newer P2Y12 inhibitors and cangrelor in these settings is largely unknown. More reliable information is needed regarding stent thrombosis in this setting.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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The references can be found in the online version of the paper.

Online data supplement

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Clinical Research

Optical Coherence Tomography-Guided Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction Patients: A Pilot Study

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ABSTRACT

Background: The objective of our study was to assess whether optical coherence tomography (OCT) guidance could guide intervention to avoid balloon angioplasty and stenting during primary percutaneous coronary intervention.

Methods: One hundred patients with ST-segment elevation myocardial infarction and thrombus-containing lesion were enrolled in this study. Thrombus aspiration was performed in all cases followed by an OCT study. After thrombectomy, no stent was implanted in residual significant stenosis (> 50%) if examination using OCT suggested that the occlusion was mostly thrombotic, provided that the patient was symptom-free and the Thrombolysis In Myocardial Infarction (TIMI) flow was ≥ 2. All patients managed only using thrombectomy underwent 1-week and 9-month angiography and OCT. Patients with significant lesion or those in whom thrombectomy failed to re-establish flow underwent standard treatment.

Results: Based on the OCT information, 20 patients (20%) were treated only with aspiration even in the presence of angiographically

RÉSUMÉ

Introduction : L'objectif de notre étude était d'évaluer si la tomographie par cohérence optique (TCO) pourrait guider l'intervention afin d'éviter l'angioplastie par ballonnet et l'implantation d'endoprothèse vasculaire au cours de l'intervention coronarienne percutanée primaire.

Méthodes : Cent (100) patients ayant subi un infarctus du myocarde avec sus-décalage du segment ST et ayant une lésion thrombotique participaient à cette étude. L'aspiration du thrombus était réalisée dans tous les cas et suivie d'une étude TCO. Après la thrombectomie, aucune endoprothèse n'était implantée dans le cas de sténose résiduelle importante (> 50 %) si l'examen par TCO montrait que l'occlusion était surtout d'origine thrombotique, et ce, pourvu que le patient n'ait pas de symptômes et que le débit selon la TIMI (*Thrombolysis in Myocardial Infarction*) soit ≥ 2. Tous les patients pris en charge par la thrombectomie seule subissaient l'angiographie et la TCO après 1 semaine et après 9 mois. Les patients ayant une lésion importante ou ceux chez qui la thrombectomie n'avait pas pu rétablir le débit subissaient le traitement standard.

Primary percutaneous coronary intervention (PCI) with stent implantation is currently the most effective method of treatment for patients with ST-segment elevation myocardial infarction (STEMI).[1,2] Although drug-eluting stents (DES) represent a breakthrough technology in interventional cardiology because of their reduction of restenosis, concerns have recently been raised concerning possible higher rate of late stent thrombosis in patients with STEMI treated with DES, especially when a large burden of thrombus is present.[3,4] It has also been previously shown that stent implantation might result in slow or even no-reflow phenomenon in the infarct-related artery with an increase in short- and long-term mortality.[5,6] Acute thrombotic occlusion of a coronary artery due to plaque rupture or erosion of thin-cap fibroatheroma (TCFA; fibrous cap thickness ≤ 65 μm) are thought to be the most important mechanisms leading to STEMI.[7–9] Moreover, most clinical events do not occur in plaques that produce high-grade stenosis[10,11]; therefore, routine plain old balloon angioplasty (POBA) or stent implantation could eventually be obviated in these cases. Optical coherence tomography (OCT) is the imaging technique available for clinical use with the highest axial resolution, hence, enabling unprecedented detailed assessment of plaque and thrombus. Several studies have recently demonstrated the potential of OCT to identify TCFA.[12,13] However, data are lacking on the clinical role of OCT in patients with STEMI. The aim of this pilot study was

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detected "high-grade stenosis." Angiogram and OCT performed at 1 week and 9 months showed a "normal vessel" without significant stenosis in all 20 cases. There were no cases of major adverse cardiovascular event (including death, myocardial infarction, and target lesion revascularization) during the in-hospital period or at the 12-month follow-up.

Conclusions: The results of our pilot study suggest that ST segment elevation myocardial infarction patients with TIMI 2/3 flow in the angiogram and without significant coronary narrowing using OCT examination (even in the presence of angiographically detected "high-grade stenosis"), in whom thrombus aspiration is performed in addition to optimal medical therapy might benefit only from thrombus aspiration without plain old balloon angioplasty/stenting during primary percutaneous coronary intervention. Validation of these preliminary data in larger randomized studies is warranted.

Résultats : Selon l'information obtenue par la TCO, 20 patients (20 %) avaient été traités par l'aspiration seule même en présence d'un « degré de sténose élevé » détecté à l'angiographie. L'angiogramme et la TCO réalisés après 1 semaine et après 9 mois montraient un « vaisseau normal » sans sténose importante pour l'ensemble des 20 cas. Il n'y avait aucun cas d'événement cardiovasculaire indésirable majeur (incluant la mort, l'infarctus du myocarde et la revascularisation de la lésion cible) au cours de la période d'hospitalisation ou au suivi après 12 mois.

Conclusions : Les résultats de notre étude pilote montrent que les patients ayant subi un infarctus du myocarde avec sus-décalage du segment ST dont le débit selon la TIMI est de 2-3 à l'angiogramme et le rétrécissement coronarien n'est pas significatif selon l'examen par TCO (même en présence d'un « degré de sténose élevé » détecté par l'angiographie), et chez lesquels l'aspiration du thrombus est réalisée en plus du traitement médical, pourraient bénéficier de l'aspiration seule du thrombus sans avoir recours à l'angioplastie traditionnelle par ballonnet et à l'implantation d'endoprothèse vasculaire au cours de l'intervention coronarienne percutanée primaire. La validation de ces données préliminaires au cours de plus vastes études aléatoires est justifiée.

to assess whether OCT could guide intervention to avoid balloon angioplasty and stenting during primary PCI in STEMI patients with single vessel disease and larger burden of thrombus (at least **T**hrombolysis **i**n **M**yocardial **I**nfarction [TIMI] 3 according to definition of TIMI thrombus grade).[14]

Methods

Between January 2011 and June 2012, 536 patients were treated with primary PCI for STEMI at the Department of Cardiology, Masaryk hospital in Ústí nad Labem. Among these, 100 consecutive patients with angiographically detected 1-vessel disease and thrombus formation > TIMI 3 according to the TIMI thrombus scale were enrolled in this study. The patient flow and treatment flow is shown in Figure 1. STEMI was defined as chest pain lasting longer than 20 minutes and less than 12 hours and ST-segment elevation > 0.1 mV in ≥ 2 contiguous leads on 12-lead electrocardiogram. The inclusion criteria were as follows: (1) STEMI according to the previously mentioned definition; (2) single-vessel disease; (3) a thrombus-containing lesion (thrombus at least TIMI 3 according to the TIMI thrombus scale); (4) reference diameter 2.5-4.0 mm; and (5) the patient was able to sign the inform consent. Exclusion criteria were as follows: (1) reference diameter > 4 mm; (2) left main disease; (3) cardiogenic shock; and (4) ostial lesions. A radial approach using a 6-French sheath and guiding catheter were used in all patients. The study was approved by a local ethical committee and all patients signed the informed consent before the procedure. All patients were pretreated with aspirin 500 mg intravenously, heparin 5000 IU intravenously, and clopidogrel 600 mg orally. If the duration of the entire procedure exceeded 30 minutes, the activated clotting time was measured and additional heparin was given to keep it within 250-300 seconds. Glycoprotein IIb/IIIa receptor antagonists (double bolus of eptifibatide, followed by an infusion) were administered in all patients. Pre- and post-procedural angiography was performed at least at 2 orthogonal projections with quantitative coronary analysis using Quantcore software (Pie Medical, The Netherlands). Furthermore, the use of an aspiration catheter (Export, Medtronic) before each procedure was mandated in all patients. If the thrombectomy catheter did not cross the target lesion, predilatation was allowed with the use of a small balloon (≤ 1.5 mm) according to discretion of the physician. After the thrombus aspiration, the OCT study was performed in all patients. After thrombectomy, no stent was implanted in residual significant lesion stenosis (> 50%) if OCT suggested that the occlusion was mostly thrombotic, provided that patients were symptom-free and the TIMI flow was ≥ 2.[15] In case of a significant lesion (≥ 50%) or in patients in whom thrombectomy failed to re-establish flow, balloon angioplasty with stenting was performed. All patients were scheduled for 30-day, and 6-, 9-, and 12-month clinical follow-up with major adverse cardiovascular event (including death, myocardial infarction, and target lesion revascularization) (MACE) assessment. Death was reported as cardiac or noncardiac death. Q-wave myocardial infarction was defined as the development of new, pathologic Q waves in 2 or more electrocardiogram leads, with postprocedural creatine kinase (CK) levels of 3 times the upper limit of normal (< 2.9 μcatal/l) and CK-MB > 10% CK levels. Non-Q-wave myocardial infarction was defined as an elevation of postprocedural CK levels of 3 times the upper limit of normal, with CK-MB level above normal and no-Q-waves target lesion revascularization was defined as revascularization within 5 mm to stent edges (in-segment) on angiography. All target lesion revascularizations required a significant stenosis and objective evidence of ischemia related to the restenotic artery before treatment. Stroke was defined as clinical evidence of cerebral injury based on symptoms persisting > 24 hours or until death.

An exercise stress test was performed at the 9-month follow-up in all patients. Patients treated only with thrombus aspiration were also scheduled for 1-week and 9-month follow-up angiography and OCT imaging. Standard landmarks (bifurcation, calcification) were used for serial OCT analysis. The OCT images were obtained using a C7-XR intravascular imaging system (LightLab Imaging, St. Jude Medical Company, St.

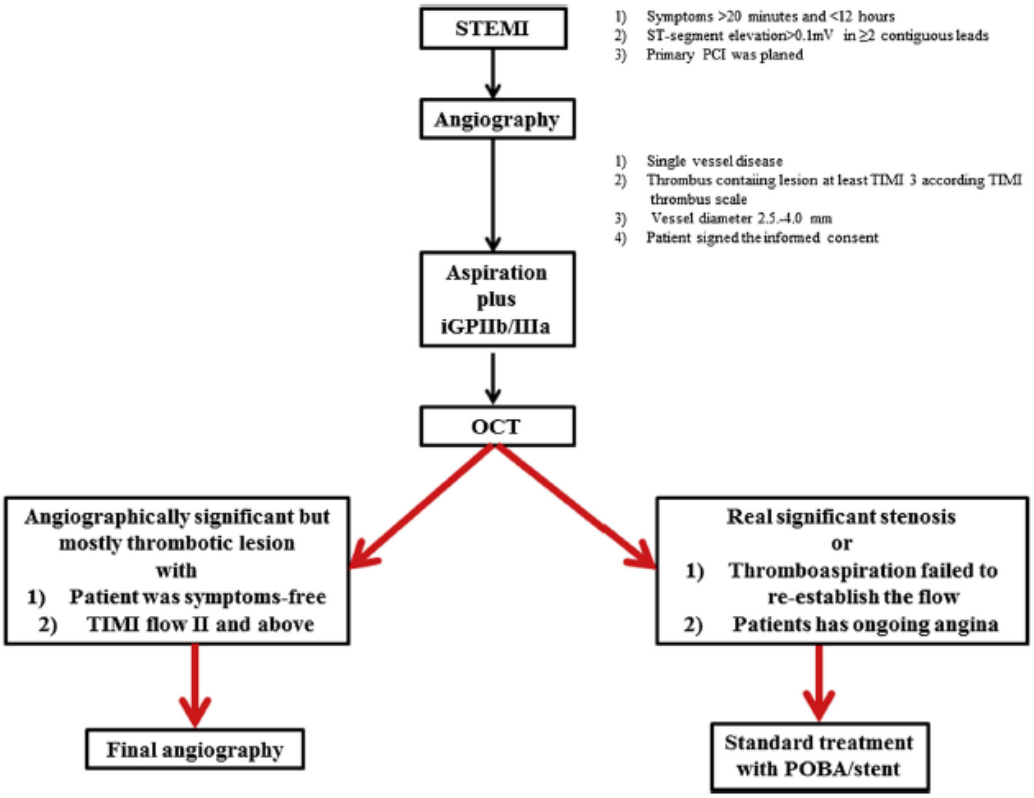

Figure 1. Patient and treatment flow. iGPIIB/IIIA, inhibitors glycoprotein IIB/IIIA; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

Paul, MN) using a C7 Dragonfly intravascular imaging catheter. Before introducing the OCT catheter, 0.1 mg of isosorbide dinitrate was given intracoronary. A nonocclusive technique was used in all patients with continuous flushing of the artery with contrast dye (total amount of 15 cc) through the guiding catheter using a injector with the speed of 4 cc/s. Motorized pullback was performed at a rate of 20 mm/s for a length of 54 mm. The images were recorded in the OCT system console and analyzed immediately by 2 observers with good interobserver reproducibility ($r = 0.84$) for characterizing TCFA from a previous study.[16] The presence of TCFA, plaque rupture, and intracoronary thrombus was noted. TCFA was defined as a lipid-rich plaque with a fibrous cap < 65 µm. The size of plaque was quantified as the number of quadrants displaying the lipid pool on the cross-sectional OCT image. When lipid was present in > 1 quadrant in any of the images within a plaque, it was considered a lipid-rich plaque. The covering fibrous cap was measured at its thinnest part 3 times and the average value represented the thickness of the fibrous cap. A plaque rupture was defined as a plaque containing a cavity that was in contact with the lumen that had any overlying residual fibrous cap fragment. Thrombus was defined as intraluminal mass > 200 µm, with no direct continuity with the surface of the vessel wall or a highly backscattered luminal protrusion in continuity with the vessel wall and resulting in signal-free shadowing.[17,18] In patients with significant stenosis, PCI was performed according to standard practice with stent implantation at low pressure (≤ 10 atm) with high-pressure (≥ 15 atm) noncompliant balloon after dilatation intrastent. Either biolimus A9-eluting (BioMatrix, Biosensors International, Biosensors Europe, Morges, Switzerland) or everolimus-eluting (Promus, Boston Scientific, Natick, MA) stents were used. Dual antiplatelet therapy (aspirin and clopidogrel) was recommended for 12 months in both groups. Low–molecular-weight heparin was given for 1 week after the index procedure (primary PCI + index OCT) to 1 week follow-up OCT study.

Statistical analysis

Statistical analysis was performed using NCSS 97 program (NCSS, Kaysville, UT). Discrete data are presented as frequencies, numbers and percentages, whereas continuous variables are presented as median values and corresponding 25th and 75th percentiles, as is standard for nonparametric data.

Continuous variables were compared using Mann-Whitney 2-sample test. Categorical variables were compared by using the χ^2 test (or the Fisher exact test, when an expected cell count was < 5). A 2-tailed value of $P < 0.05$ was considered statistically significant.

Results

No procedural-related complications were seen in this study. Baseline, angiographic, and procedural characteristics are presented in Tables 1 and 2. Based on the OCT imaging, 20 patients (20%) were treated only with thrombus aspiration. TIMI 2/3 was observed in all these patients (4 patients had TIMI 2 and 16 patients had TIMI 3 flow). Moreover, ST-segment resolution > 50% immediately after procedure was also observed in all 20 patients vs 66 patients (83%) ($P < 0.001$) in the POBA/stent group. At the end of procedure, various degrees of thrombus was apparent in all 20 patients but with a good flow, as previously mentioned. Mean ejection fraction on discharge was 48% without differences between groups. No differences in the mean peak of troponin level was found between both groups. In the infarct-related/culprit lesion, TCFA was found in 100% of cases. The mean thickness of the fibrous cap was 50 ± 9 μm. Furthermore, thrombus was also apparent in all cases. Plaque rupture was recognized in 75% (15 patients) in the aspiration thrombectomy group vs 78% (62 patients) in the POBA/stent group (P = not significant). The mean thickness of the fibrous cap of the lesions of patients treated with thrombo-aspiration was 48 ± 8 μm. One-week angiogram showed a "normal vessel" without significant stenosis in all 20 cases. Furthermore, the 1-week OCT study presented non-obstructive TCFA also in all cases. Surprisingly, no thrombus was revealed in any patient, and plaque rupture was still present in all patients. Nine-month angiography and OCT follow-up examinations showed nonsignificant (< 50%) soft plaques without thrombus or plaque rupture (Figs. 2, 3, and 4) in the thrombus-aspiration group. The thickness of the fibrous cap increased nonsignificantly to 59 ± 11 μm. No MACE occured at 30 days, or at the 9-month and 12-month follow-up in both groups (P = not significant). However, during the hospital stay, there were 2 cases of heart failure in the POBA/stent group with a prompt reaction to the pharmacological treatment. There was 1 case of paroxysm of atrial fibrillation in the aspiration group with spontaneous conversion to sinus rythm. Between the 6- and 9-month follow-up, 1 patient from the POBA/stent group was hospitalized for bronchopneumonia.

Discussion

To the best of our knowledge, this is the first prospective study using OCT as guidance for primary PCI in patients with evolving STEMI. The present study revealed that OCT during primary PCI is safe and useful. Based on the OCT study, 20% of patients were managed only with thrombus aspiration without either balloon dilatation or stent implantation even in the presence of angiographically detected "high-grade stenosis."

It is well known that angiography itself has limited capability to differentiate between real stenosis and thrombus formation. In contrast, OCT represents a tool that enables unprecedented detailed assessment of plaque and thrombus.

Table 1. Baseline characteristics

Characteristic	Aspiration	POBA/stent	P
n	20	80	
Age, years	47.5 [35-60]	49 [36-64]	0.45
Male sex	15 (75)	62 (78)	0.25
Smoking	15 (75)	66 (83)	0.42
DM	6 (28)	26 (33)	0.32
HY	15 (75)	62 (78)	0.25
Previous MI	0	0	
Localization			
AS	10 (50)	30 (38)	0.09
Lateral	5 (25)	25 (31)	1.00
Inferior	5 (25)	25 (31)	1.00
Killip class I	20 (100)	80 (100)	1.0
Treated vessels			
LAD	10 (50)	30 (38)	0.09
RCA	5 (25)	25 (31)	1.0
LCx	5 (25)	25 (31)	1.0

Data are presented as n (%) except where otherwise noted. Values in square brackets represent quartiles 1-3.

AS, anteroseptal; DM, diabetes mellitus; HY, hypertension; LAD, left anterior descending; LCx, left circumflex; MI, myocardial infarction; POBA, plain old balloon angioplasty; RCA, right coronary artery.

In the present study, all patients were event-free at the 12-month follow-up. OCT performed 1 week after primary PCI showed the vessel without signs of thrombus at the site of the previous culprit lesion. However, the plaque rupture was apparent in all patients. At the 9-month follow-up, the angiography showed nonsignificant (< 50%) stenosis in all patients. OCT showed fibrous plaque with nonsignificant stenosis (< 50%) and minimal lumen area > 5 mm^2 in all patients. All plaque ruptures were healed at this time point.

Our results are in agreement with data very recently presented by Prati et al. In their article, fully 40% of patients with STEMI were treated using aspiration thrombectomy with dual antiplatelet therapy without percutaneous revascularization. All patients were asymptomatic at a median follow-up of 753 days.[19] Furthermore, a meta-analysis of 5 nonrandomized studies and 1 randomized trial (n = 590) on deferred stenting has recently been presented,[20] showing that avoiding

Table 2. Angiographic and procedural characteristics

Characteristic	Aspiration only	POBA/stent	P
n	20 (20)	80 (80)	
TIMI flow			
0-I	0	0	1.0
II-III	20 (100)	80 (100)	1.0
MLD, mm	2.2 [1.83-2.67]	3.6 [3.15-4.1]	0.0003
GP IIb/IIIa-i	20 (100)	80 (100)	1.0
DS, %	48 [35-61]	10 [1-19]	0.0001
Aspiration	20 (100)	80 (100)	1.0
ST resolution > 50%	20 (100)	66 (83)	< 0.001
TnI maximum (ng/mL)	98.5 [14.6-178.9]	89.5 [12.3-170.5]	0.12
EF, %	42 [32-54]	44 [33-56]	0.25
TCFA (μm)	48 [39-58]	51 [40-59]	0.22
Thrombus	20 (100)	80 (100)	1.0
Plaque rupture	15 (75)	55 (69)	0.08

Data are presented as n (%) except where otherwise noted. Values in square brackets represent quartiles 1-3.

DS, diameter stenosis; EF, ejection fraction; GP, glycoprotein; MLD, minimal lumen diameter; POBA, plain old balloon angioplasty; TCFA, thin cap fibroatheroma; TIMI, Thrombolysis in Myocardial Infarction; TnI, troponin I.

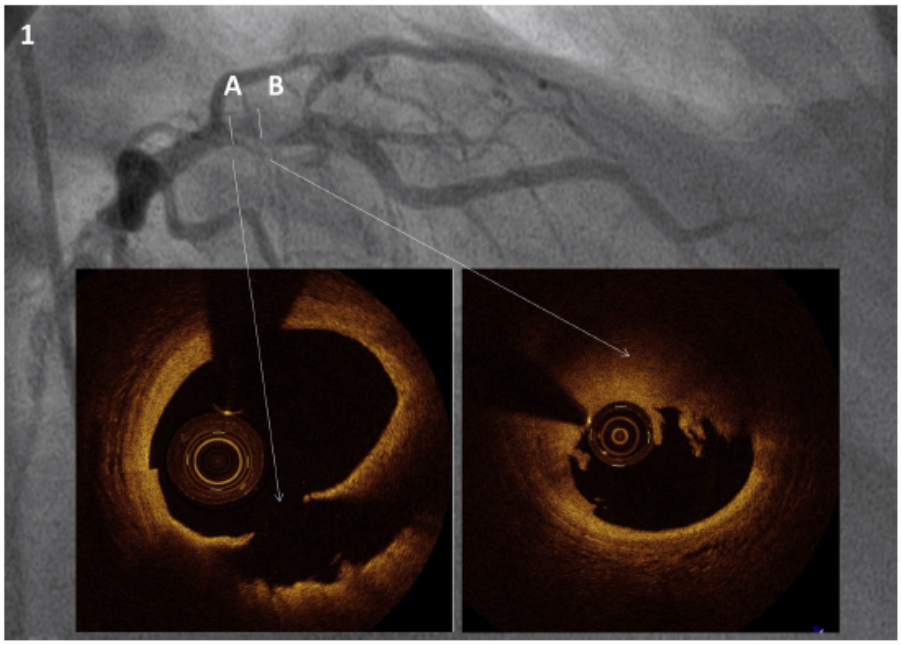

Figure 2. Left coronary angiography in a patient with anterior ST-elevation myocardial infarction showing a large burden of thrombus in the proximal part of the left anterior descending artery. **A** indicates the spot of plaque rupture with the corresponding optical coherence tomography image. **B** indicates a large thrombus (with the corresponding optical coherence tomography image) located downstream to the plaque rupture. OCT, optical coherence tomography.

immediate stenting across the whole acute coronary syndrome spectrum might lead to fewer periprocedural complications. However, the rate of MACEs in our study was substantially lower than in the previously mentioned meta-analysis in which the rate of MACEs varied widely from 5% to 43% in the delayed stenting group and 15% to 66% in the immediate stenting group. Whether the low rate of MACEs in our trial is because of selection bias or it is just play of chance because of the small population of patients enrolled is unclear. Our findings also support data very recently published by Escaned and colleagues.[21] They clarified the role of thrombectomy without additional angioplasty or stenting as an adequate treatment for STEMI in carefully selected cases. Among 1737 consecutive patients treated using primary PCI for evolving STEMI, 757 (44%) underwent thrombectomy and 28 (1.6%) had thrombectomy only. At the 40-month follow-up, 80% of the patients remained asymptomatic and free of cardiac events. It has been shown that the most important mechanism leading to STEMI is an acute thrombotic occlusion of a coronary artery either due to plaque rupture or erosion of thin cap fibroatheroma.[7-9] Davies and Thomas[10] and Fuster et al.[11] have lately shown that clinical events can occur at plaques without high-grade stenosis. In contrast, routine stenting is thought to be a "gold standard" during primary PCI[22] without consideration of lesion severity or thrombus occurrence. However, some trials have shown that stent implantation might even worsen flow of the infarct-related artery with an increase of short- and long-term mortality.[5,6] Although the introduction of DES in clinical practice represents a revolution in interventional cardiology because of their reduction in restenosis, there are some possible concerns linked to this technology, such as high rates of late stent thrombosis in patients with STEMI, especially when a large burden of thrombus is present.[3,4] Although the results of the **T**hrombus **A**spiration in **ST**-Elevation Myocardial Infarction in Scandinavia (TASTE) study published recently shed doubt on the role of routine thrombectomy during STEMI, there is a cohort of patients (with a large burden of thrombus) who could benefit from this treatment.[23]

However, until recently it was very difficult to clearly differentiate plaque and thrombus due to known limitations of angiography and other intravascular imaging tools.[24] OCT is the latest imaging technique with the highest resolution for plaque and thrombus assessment.[17,18] Recently, many studies have also shown that the OCT modality might be the best imaging technique for the identification of TCFA/plaque rupture.[12,13,25,26] In the present study, OCT allowed clear differentiation between real lesion and thrombus formation in the setting of STEMI and led to the avoidance of POBA and stenting in 20 out of 100 patients (20%). These patients were treated only with thrombus aspiration with good TIMI flow at the end of the procedure and without adverse events. One can argue that OCT does not bring any further clinical information needed for treatment and increases the cost of the procedure when compared with coronary angiography. However,

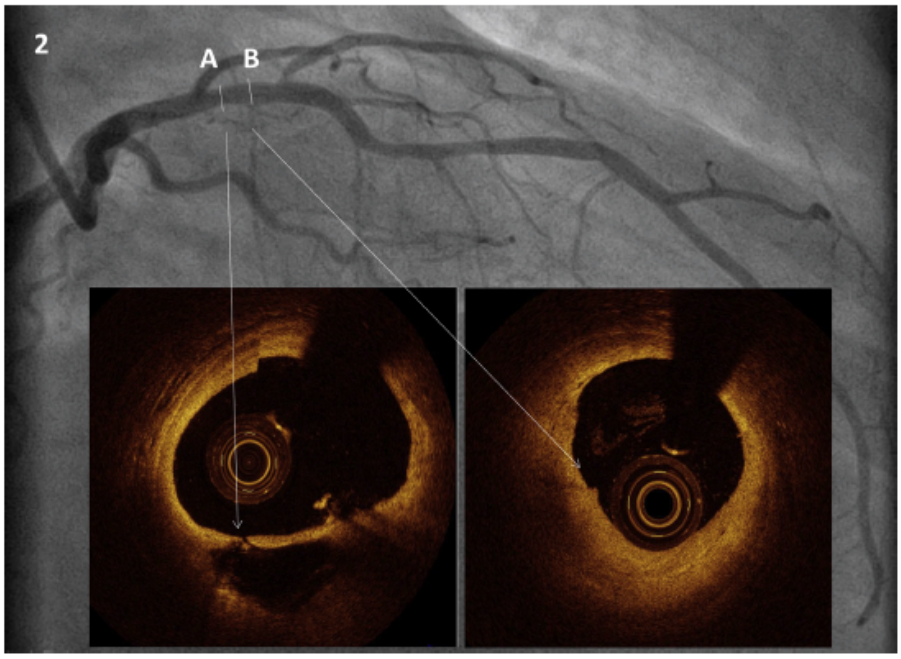

Figure 3. A 1-week follow-up angiography and OCT study. Angiography showed good lumen diameter. Plaque rupture was still present (**A** with corresponding OCT image). However, the thrombus was completely resolved (**B** with corresponding OCT image). OCT, optical coherence tomography.

we believe that at this early period, in-depth understanding of the patient cohort who might derive the greatest benefit, or the ability to identify risk markers for vessel reocclusion, requires the use of an invasive imaging modality with the highest resolution.

DeWood at al.[7] have shown that the rate of vessel occlusion decreases with the time since the event onset. In the present study, the OCT study performed at 1 week also showed no thrombus presence at the site of the culprit lesion. Whether this is a result of activity of the intrinsic thrombolytic system or potent antiplatelet/anticoagulant treatment is unclear. However, plaque ruptures were seen in all 20 patients at the 1-week OCT follow-up. The findings might validate the role of potent dual antiplatelet therapy after acute coronary syndrome to improve outcomes as shown in large clinical trials. Interestingly, 9-month OCT and angiography follow-ups showed nonsignificant lesions at the culprit spot. Moreover, the OCT study showed that all plaques became "stabilized"—ruptures were healed and the thickness of plaques increased. Moreover, 30-day, 6-month, 9-month, and 12-month follow-up were uneventful in our study and all patients were asymptomatic. The explanation is only speculative. It might also be that intensive pharmacological medication after the procedure stabilized initially unstable plaques. Our study was underpowered for individual clinical end points because of the small cohort of patients included. This remains to be assessed in prospective larger trials with a sufficient number of patients with serial OCT study and long-term follow-up.

Limitations

There are limitations of our study. First, this was a small pilot study underpowered for clinical end points. Second, balloon predilatation could modify the morphology of the culprit lesion in some patients. Third, only midterm follow-up was available for patients involved in this study. The long-term follow-up (beyond 1 year) is essential to confirm that avoidance of POBA/stenting is safe in some patients with STEMI. One should also take into account the low-risk profile of our cohort of patients because all patients were Killip class I. Fourth, it is also possible that the presence of thrombus formation itself might also affect OCT imaging of the lesions. Fifth, the play of chance in addition to case selection might have played a role in the low rate of MACEs in our study.

Conclusions

In conclusion, our pilot study documents the safety and usefulness of OCT guidance during primary PCI in patients with STEMI. Based on our data, avoiding POBA/stenting while performing manual aspiration thrombectomy is safe in some patients with STEMI despite the presence of "angiographically significant" stenosis. Because not all STEMIs are

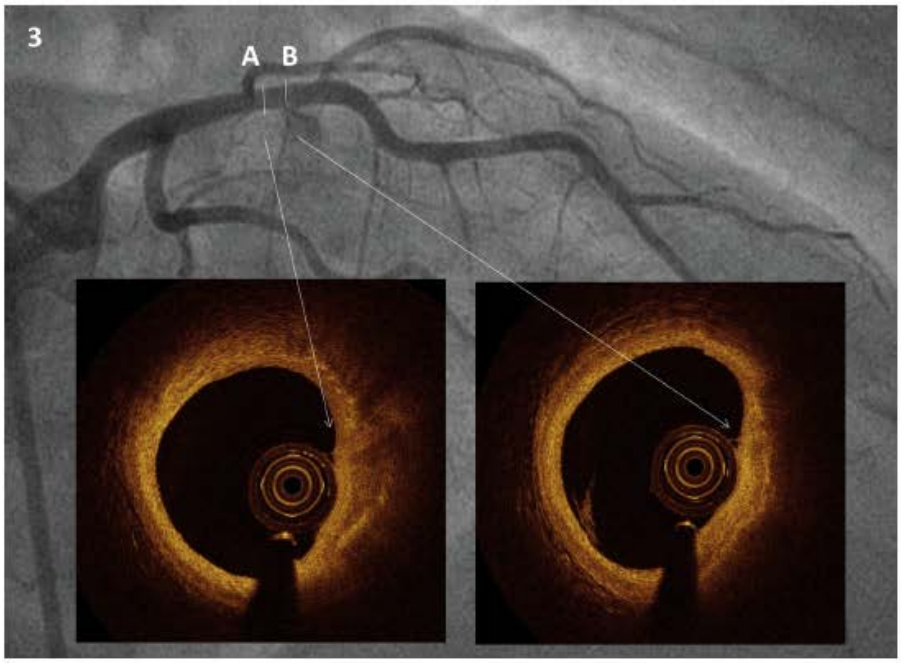

Figure 4. A 9-month follow-up angiography and optical coherence tomography study. Left coronary angiogarphy shows a normal vessel without a significant lesion. Optical coherence tomography analysis shows a healed and hemodynamically nonsignificant fibrotic plaque with good minimal lumen area (letters **A** and **B**, respectively).

alike, it is likely that a uniform therapeutic approach consisting of coronary stenting in this complex disease might not necessarily always be appropriate. Larger randomized studies with serial OCT study and long-term follow-up are needed to confirm our findings.

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Disclosures

The authors have no conflicts of interest to disclose.

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OCT Guidance During Stent Implantation in Primary PCI: A Randomized Multicenter Study With Nine Months of Optical Coherence Tomography Follow-up

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[#]this author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation; *statistical analyses; [†]patient enrollment and data acquisition; [‡]manuscript critital reading

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Abstract

Aims: To assess the possible merits of optical coherence tomography (OCT) guidance in primary percutaneous coronary intervention (pPCI).

Methods and results: 201 patients with ST-elevation myocardial infarction (STEMI) were enrolled in this study. Patients were randomized either to pPCI alone (angio-guided group, n=96) or to pPCI with OCT guidance (OCT-guided group, n=105) and also either to biolimus A9 or to everolimus-eluting stent implantation. All patients were scheduled for nine months of follow-up angiography and OCT study. OCT guidance led to post-pPCI optimization in 29% of cases (59% malapposition and 41% dissections). No complications were found related to the OCT study. OCT analysis at nine months showed significantly less in-segment area of stenosis (6% [-11, 19] versus 18% [3, 33]; p=0.0002) in favor of the OCT-guided group. The rate major adverse cardiovascular events was comparable at nine months in both groups (3% in the OCT group versus 2% in the angio-guided group; p=0.87).

Conclusions: This study demonstrates the safety of OCT guidance during pPCI. The use of OCT optimized stent deployment in 1/3 of patients in this clinical scenario and significantly reduced in-segment area of stenosis at nine months of follow-up. Whether such improvements in OCT endpoints will have a positive impact on late clinical outcomes demands both a larger and longer-term follow-up study.

Keywords: optical coherence tomography, OCT, primary PCI, ST-segment elevation myocardial infarction, drug-eluting stents, STEMI.

Introduction

Drug-eluting stents (DES) siginficantly reduce the rate of restenosis, but concerns have recently been raised regarding a possible increase in late stent thrombosis in patients with ST-segment elevation myocardial infarction (STEMI) treated with DES. (1, 2). Stent underexpansion, malapposition, incomplete lesion coverage and residual plaque burden are well-recognized as major contributors of late-stent thrombosis (3, 4, 5, 6, 7, 8). Intravascular imaging, namely intravascular ultrasound (IVUS), showed in a recently published meta-analysis that IVUS-guided DES implantation significantly reduces adverse clinical outcomes compared with angiography-guided PCI (9).

The optical coherence tomography (OCT) has the highest resolution (~10 µm, i.e., 10-fold greater than IVUS) imaging technique available for clinical use, hence, it enables an unprecedented level of detail in the assessment of plaques and thrombi (10, 11). For example, OCT allows for direct measurements of the fibrous cap covering a lipid plaque, thus enabling a precise assessment of thin-cap fibroatheroma in vivo (12, 13, 14). While some observational data support the role of OCT guidance during primary PCI (15, 16, 17), a randomized study is lacking to further expand our knowledge in this setting. The objective of this randomized study was, therefore, to assess the safety and efficacy of OCT- versus angio-guided primary PCI with second-generation DES implantation at nine months.

Methods

Study population, study design and PCI procedures. The present study was a subanalysis of the ROBUST trial (NCT 00888758), a multicenter, randomized interventional trial comparing biolimus A9-eluting and everolimus-eluting stents with OCT-guided stent implantation in STEMI with nine months of angiographic and OCT follow-up. A two-stage randomization scheme (angio-guided versus

OCT-guided pPCI and everolimus versus biolimus A9 drug eluting stent) was applied in this trial. Between February 2011 and October 2012, 201 STEMI patients treated with primary PCI were enrolled. The study design (***Figure 1)*** was approved by the appropriate national and institutional regulatory authorities and ethics committees, and all patients provided written informed consent. Patients between 18-85 years of age admitted with STEMI in a native coronary artery (diameter range 2.5-3.75 mm) with a lesion suitable for stenting were included. Exclusion criteria were as follows: 1) reference diameter >4 mm, 2) left main coronary artery disease, 3) cardiogenic shock, and 4) ostial lesions. Interventions were carried out by the radial approach using a 6-French sheath and guiding catheters. All patients were pre-treated with 500 mg aspirin intravenously, 5000 IU heparin intravenously, and 600 mg clopidogrel orally. If the duration of the entire procedure exceeded 30 min, the activated clotting time (ACT) was measured and additional heparin was given to keep it within 250-300 seconds. After diagnostic angiography, at least at two orthogonal projections with quantitative coronary analysis (QCA) employing Quantcore software (Pie Medical, The Netherlands), patients were randomly assigned (using a sealed envelope) to either angiography-guided primary PCI according to the standard practice (angio-guided group, N=96) or to primary PCI with adjunctive OCT guidance (OCT-guided group, N=105). Patient enrolment was stopped prematurely, however, the sample size was adequate for OCT and QCA analysis. The use of glycoprotein IIb/IIIa receptor antagonists and manual thrombus aspiration were strongly recommended. If the thrombectomy catheter did not cross the target lesion, pre-dilatation was allowed, employing a small balloon (≤1.5 mm) according to the physician's discretion. Either biolimus A9- (BioMatrix®, Biosensors International, Biosensors Europe, Morges, Switzerland) or everolimus-eluting (Promus, Boston Scientific, Natick, MA, USA) stents were used. Dual antiplatelet therapy (aspirin plus clopidogrel) post-procedure was recommended for 12 months in both groups. Primary PCI was performed according to standard practice with stent implantation at low pressure (≤10 atm) with high pressure (≥15 atm) non-compliant balloon post-dilatation inside the stent. After stent implantation was considered optimal, final angiography was performed, using at least two orthogonal projections.

OCT image acquisition and analysis. In the OCT-guided group, OCT (C7-XR™ intravascular imaging system, LightLab® Imaging, St. Jude Medical Company, St. Paul, Minnesota, USA with a C7 Dragonfly™ intravascular imaging catheter) was performed after stent deployment with "optimal angiographic result" after administration of 0.1 mg of intracoronary isosorbide dinitrate. A non-occlusive technique was used in all patients, with continuous flushing of the artery with contrast dye (total amount of 15 cc) through the guiding catheter using an injector with a speed of 4 cc/s. Automated pullback was performed at a rate of 20 mm/s for a length of 54 mm. The images were recorded in the OCT system console and analyzed on-line in the cathlab and off-line in CoreLab. All cross-sectional images (frames) were initially screened for quality assessment and excluded from analysis if any portion of the stent was off the screen or if the image was of poor quality due to residual blood, artifacts, or reverberation. A second and/or third image was obtained to obtain an image of good quality. Optimal OCT criteria for stent deployment were as follows: 1) minimal lumen area (MLA) >80% of the mean proximal and distal vessel lumen references; 2) in cases without proximal vessel references, MLA was >90% of the distal reference lumen area; 3) no significant malapposition; and 4) no dissection at the edges of the stented segment. Strut/stent malapposition was determined when the negative value of the strut-level intimal thickness (SIT) was greater than the strut thickness (plus the thickness of the abluminal polymer for biolimus A9 and everolimus-eluting stents), according to the stent manufacturer's specifications (127 μm for the BioMatrix® stent and 89 μm for the Promus Element™ stent) corrected for strut blooming thickness. The final cut-off value for malapposition was 144 μm for BioMatrix® and 106 μm for Promus Element™. The therapeutic decision was based on acute online OCT imaging in the cathlab and was left to the discretion of highly experienced pPCI operators. To determine the reproducibility of OCT analysis, a quantitative analysis of 100 struts were performed by these two operators. The interobserver difference for SIT was $0.01 \pm 0.03\ \mu m$ ($r = 0.0897$). After the final OCT study, final angiography was performed. All the images were digitally stored and independently analyzed by blinded analysts at the Cardiovascular Imaging Core Lab, Harrington Heart & Vascular Institute, University Hospitals, Case Medical Center, Cleveland, OH, USA.

Patient follow-up, clinical outcomes, endpoints, and definitions. All patients were scheduled for 30 days of clinical and nine months of clinical, angiographic, and OCT follow-up. Major adverse cardiovascular events (MACE; including death, myocardial infarction [MI], and target lesion revascularization) were assessed. Death was reported as cardiac or non-cardiac. Q-wave MI was defined as the development of new, pathologic Q waves in two or more ECG leads, with post-procedural creatine kinase (CK) levels three times higher than the upper limit of normal (<2.9 µkatal/l) and CK-MB >10% of CK levels. Non-Q-wave MI was defined as an elevation of post-procedural CK levels three times higher than the upper limit of normal, with CK-MB above normal, and no-Q-wave target lesion revascularization (TLR) was defined as revascularization within 5 mm to the stent edges (in-segment) on angiography. All TLR required significant stenosis and objective evidence of ischemia related to the restenotic artery before treatment. The features captured in the QCA and OCT analyses at nine months of follow-up are mentioned in ***Table 2***. The reference area was defined as the average of 5 mm (25 frames) proximal and distal to the stent edge, except for slices of bad quality, with image distorting side branches, or severe dissection. The inter-slice distance was 200 µm along the entire target segment (***Figure 1 online***). Dedicated semiautomated software developed at the Cardiovascular Imaging Core Lab, Harrington Heart &Vascular Institute, University Hospitals, Case Medical Center, Cleveland, OH, USA was used for the OCT analysis (OCTivat-Stent) ***(Figure 2 online)*** in this study to delineate the lumen contours of each cross-sectional image. For a more detailed description, we refer to the original paper (18). OCT endpoints were the percentage of uncovered stent struts, the percentage of malapposed stent struts, in-stent area of stenosis and in-stent minimal lumen diameter at nine months.

Statistical analysis. Categorical variables were described as group counts and relative frequencies (percentages), while continuous variables were described as group means, standard deviations (SDs), and totals (N). Tests of statistical hypotheses in contingency tables were performed using the Fisher Exact Test based on a hypergeometric distribution. Since most of the continuous variables subject to statistical testing showed significant departures from normality (as expressed by e.g. the Shapiro-Wilk normality test), the non-parametric Wilcoxon Rank-Sum Test was used to compare continuous

outcomes across different groups defined by either of the treatment arms (OCT- versus angio-guided pPCI, stent type Biomatrix versus Promus). McNemar's test was applied for comparisons of binary categorical variables between the individual stages of follow-up (e.g. baseline vs. 30 days of follow-up). The level of statistical significance was set to alpha=0.05 for all tests. In multiple testing scenarios (e.g. a battery of tests performed in a certain table), Bonferroni corrections of the nominal level of statistical significance were applied in individual tests in order to keep the family-wise Type I error rate alpha at 0.05. The statistical analysis was conducted using dedicated software (R version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline demographic and procedural characteristics. Baseline demographic and procedural characteristics were well-balanced in both groups ***(Table 1)***. We did not observe any complications related to the OCT studies, either during the index procedure or at follow-up. More stents and higher mean implantation pressures were used in the OCT-guided group. Interestingly, suboptimal results not fulfilling at least one of the four defined criteria were found on-line in almost one-third of the patients (29/105) randomized to the OCT-guided group. Malapposition was found in 17 (59%) and any dissection in 12 (41%) out of 29 patients. In the case of malapposition, a larger balloon and/or higher pressure had been used to optimize the result. Any dissection had been managed with the implantation of an additional stent. However, the detailed core lab analysis showed that suboptimal results was even more frequent (34%; 36/105). Physicians missed malapposition in 7 out of 11 patients, and the suboptimal area of stenosis was not corrected in 16 out of 20 patients. On the other hand, significant dissections were treated correctly in all patients (5/5 patients). Some degree of thrombus formation was found in all patients in the OCT-guided group. The fluoroscopy time was significantly shorter in the angio-guided group compared to the OCT-guided group (10 [7-14] min versus 7 [5-10] min; p=0.0001). TIMI flow post-procedure, the diameter of stenosis and the extent of STEMI were comparable in both groups ***(Table 2)***.

MACE and angiographic analysis at nine months of follow-up. MACE rates were comparable between both groups at 30 days and nine months of follow-up (2% versus 0%, p=0.499 and 3% versus 1%, p=0.623, respectively). One stent thrombosis was found in each group (both were deemed early and definite). Angiographic data were available for 90% (95/105) patients of the OCT-guided group and 95% (91/95) of the angio-guided pPCI group. Binary restenosis was very low and comparable in both groups (2% versus 3%; p=0.671). Furthermore, in-stent and in-segment angiographic late lumen loss at nine months did not differ significantly between the groups, although there was a trend towards both smaller in-stent and in-segment late lumen loss in the OCT-guided group (0.06±0.49 mm vs. 0.18±0.32 mm respectively; p=0.055) ***(Table 2, Figure 2)*.**

OCT analysis at nine months of follow-up. At nine months of follow-up, appropriate OCT data were available for 88% (92/105) of patients in the OCT-guided group and 90% (86/96) of the angio-guided pPCI group. ***(Table 2)***. A significantly smaller in-segment area of stenosis was revealed in the OCT-guided group compared with the angio-guided group (6% [-11, 19] versus 18% [3, 33]; p=0.0002). The total number of assessed struts was 71,578 in angio-guided pPCI and 84,882 struts in OCT-guided pPCI. The number of either uncovered or malapposed struts, in-segment minimal lumen diameter, in-segment minimal lumen area, and mean in-stent neointimal hyperplasia did not differ significantly between groups. No residual thrombi were found in the target segment in both groups. Interestingly, 15% (out of 84,882 struts) late-acquired malapposed strutswaer found in OCT-guided pPCI at nine months; however, the rate of malapposed struts using the index procedure decreased by 44%.

Discussion

This is the first randomized study comparing both the safety and efficacy of OCT guidance during primary PCI for STEMI with second-generation DES implantation. Furthermore, 90% of patients in both groups underwent OCT assessments at nine months of follow-up. Routine use of OCT guidance during primary PCI was associated with reduced in-segment area of stenosis at nine months of follow-up. The rate of malapposed struts was very low and did not differ between the groups. During the

acute phase of STEMI and based on the OCT imaging, the operators decided more often (in 30% of cases) to perform further procedure optimization despite the optimal angiographic result. This approach was associated with a higher number of implanted stents with no difference in the rate of MACE during follow-up. There were no complications related to OCT imaging in the present study, either during pPCI or at follow-up.

Our data are in concordance with the results of recently presented non-randomized observational studies. In pioneering work, Imola et al. first demonstrated that OCT guidance during PCI is feasible and safe, even in patients with complex lesions (19), later supported by Stefano et al. (15). Undoubtedly, the progress in OCT instrumentation and the non-occlusive technique have played major roles in reducing the OCT-related complications (19). Recently, the results of a meta-analysis (N=24,849) on IVUS-guided DES implantation have been published (9). In the pooled analysis of non-randomized trials, IVUS-guided DES implantation was associated with significantly lower rates of MACE compared with angiography guidance (OR: 0.79;95% CI:0.69 to 0.91; p=0.001), including a reduction in all-cause mortality, myocardial infarction, target vessel revascularization, and stent thrombosis. Since OCT provides even higher resolution imaging; we hypothesized that compared with angio-guided pPCI, OCT-guided pPCI would optimize the results and improve outcomes related to DES implantation during STEMI. In the present study, the use of OCT resulted in further post-OCT interventions in 28% of patients. In the majority of cases (59%), additional post-dilatation was performed for malapposed struts. Dissections were found in 41% of cases and, according to the protocol, all significant dissections were treated with the implantation of another stent. This therapeutic decision was left to the pPCI operator's discretion and led to a significantly higher number of stents bring used in the OCT-guided group (1.4 versus 1.2; p=0.03). Prati et al. reported additional post-OCT interventions in 34% of patients receiving OCT (11). Stefano et al. demonstrated stent malapposition in 39% of cases despites the routine use of high-pressure balloon inflation; additional balloon dilatation was performed in 90% of these cases (15). In this study, high-pressure post-dilatation with non-compliant balloons was mandatory as part of the protocol. Despite this, the difference between the minimal lumen diameter and the minimal stent area doubt the optimal circular

shape at the end of pPCI. Very recently, Im et al. (20) in their observational study demonstrated acute stent malapposition in 62% of lesions with a favorable clinical outcome. Acute stent malapposition with a volume >2.56 mm^3 differentiated late-persistent stent malapposition from resolved acute stent malapposition. Late-acquired stent malapposition was detected in 15% of all lesions. Whether such findings from the elective procedures would correspond with a completely different pathomorphology of STEMI remains unclear (21). . Recently, in a study by Stefano et al., among 29% of dissections, 76% were deemed benign and only 24% (4/17) were treated. There were no complications associated with untreated edge dissections. It seems that dissection with a longitudinal length <1.75 mm, with <2 concomitant flaps, flap depth <0.52 mm, flap opening <0.33 mm, and not extending deeper than the media layer have favorable outcomes and can be left untreated (22). In the present trial, all dissections evaluated by the operator as significant were treated with the implantation of an additional stent.

So far, there is no clear evidence that OCT-guided PCI improves outcomes. However, some observational studies have reported better clinical outcomes with OCT guidance compared to angiography-guided interventions (16). The mechanism of the beneficial effects of OCT guidance in the DES era might be the ability to identify factors associated with periprocedural complications and guide optimization. Low and comparable MACE rates observed in our study were supported by the low rate of “surrogate” findings in both groups such as angiographic binary restenosis (2% versus 3%; p=0.671) and late lumen loss both in-stent and in-segment with a trend to reduced late loss in the OCT-guided group (0.05±0.5 vs. 0.15±0.34, p=0.119 and 0.06±0.49 vs. 0.18±0.03, p=0.055, respectively). However, it is important to consider that our sample size was not powered to detect differences in clinical outcomes. In-stent late lumen loss reported in present study was one of the lowest reported ever (23) and means that both second-generation DES used in this trial represent further improvements in this innovative technology. There was one case of early stent thrombosis in each group. Both were deemed definite (confirmed by angiography). Careful offline analysis of the index OCT study did not reveal any procedure-related issues associated with the development of stent thrombosis in this patient.

OCT assessment and clinical implications. The endpoints of the present study were those assessed by OCT at nine months of follow-up. The only difference found in this study was a significantly smaller in-segment area of stenosis in the OCT-guided group compared with the angio-guided group (6% [-11, 19] versus 18% [3, 33]; p=0.0002). Whether these findings will be translated into better clinical outcomes has to be confirmed in future larger randomized trials with long-term follow-up. The number of either uncovered or malapposed struts, in-segment minimal lumen diameter, in-segment minimal lumen area and the value of mean in-stent neointimal hyperplasia did not differ significantly between groups (13% [5, 18] versus 17% [4, 27]; 1% [0, 1] versus 1% [0, 1]; 2.9 mm [2.6, 3.0] versus 2.8 mm [2, 3] and 6.7 mm^2 [5.0, 8.0] versus 6 mm^2 [5.0, 8.0]; 1.2 $mm^2 \pm 0.6$ versus 1.3 $mm^2 \pm 0.7$; p=0.6), respectively). While OCT may refine PCI precision by means of identifying stent underexpansion and malapposition, as well as incomplete lesion coverage otherwise not depicted by angiography, it is still unclear as to what the thresholds are (i.e., how much malapposition should be treated, how much of underexpansion should be further dilated) regarding OCT findings. Interestingly, in this study, the rate of malapposed struts at the index procedure decreased by 44% at nine months in OCT-guided pPCI at nine months this group. On the other hand, 15% of new (clinically silent) late-acquired stent malappositions were found in this group, probably as a result of positive vessel remodeling. This finding will be further analyzed in the upcoming comprehensive stent strut analysis.

Importantly, pre-procedure OCT imaging can identify thrombi, lumen contours, and nearby structures. Although we did not evaluate the role of pre-intervention OCT in our study, a customized approach, such as appropriate stent selection based on OCT findings concerning the plaque distribution and lumen dimensions, performing additional thrombus aspiration, or selective infusion of anti-platelet drugs in the case of a large thrombus burden and vasoconstriction shown by OCT could help further refine the results and eventually reduce the adverse outcomes of primary PCI (12). Recently, Wijns et al. published the results of the ILUMIEN 1 study which enrolled patients with stable angina, unstable angina, or non-ST-elevation MI (24). In this study, physician decision-making was affected by OCT imaging prior to PCI in 57% and after PCI in 27% of all cases. Further investigation is required in this setting.

Study limitations. There are limitations to our study. First, this study was underpowered for the clinical endpoints. Nonetheless, it is the first randomized study to compare angio- vs. OCT-guided primary PCI. Second, only mid-term follow-up was available for the patients involved in this study. Third, one has to take into account the low-risk profile of our cohort of patients because of the majority of patients were Killip I; patients with left main coronary artery disease and cardiogenic shock were excluded from the study. On the other hand, the design of the protocol represents real-life practice in high-volume 24/7 primary PCI cathlabs, where the site or individual issue was part of the study.

Conclusions

The present study demonstrates the safety and possible merit of OCT guidance during second-generation DES deployment in patients who present with STEMI and undergo primary PCI. OCT analysis post-primary PCI affected physician decision-making in about 30% of cases. At nine months, OCT guidance led to a significantly reduced in-segment area of stenosis. Larger randomized trials with longer-term follow-up are warranted.

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Legends

Figure 1: Patient flow and treatment flow

PCI=percutaneous coronary interventions, OCT=optical coherence tomography

Figure 2: Cumulative distribution of mean in-stent late lumen loss at nine months of follow-up

OCT=optical coherence tomography; FU= follow-up

Table 1: Baseline demographic and procedural characteristics

OCT=optical coherence tomography; pPCI=primary percutaneous coronary intervention; CAD=coronary artery disease; MI=myocardial infarction; CABG=coronary artery bypass graft; LAD=left anterior descending; RCA=right coronary artery; LCx=left circumflex; values in square brackets represent quartiles 1-3; pPCI=primary percutaneous coronary intervention; MLD=minimal lumen diameter; GPIIb/IIIa i=glycoprotein IIb/IIIa inhibitors; DS=diameter stenosis; DAPT=dual antiplatelet treatment.

Table 2: Angiographic data at nine months of follow-up

OCT=optical coherence tomography; pPCI=primary percutaneous coronary intervention; Mean, (STD), Median (Q1, Q3).

Table 1: Baseline demographic and procedural characteristics

	OCT-guided pPCI	Angio-guided pPCI	P value
N	**105**	**96**	
Age (years)	57 [46-70]	59 [47-72]	0.960
Male (%)	83	87	0.556
Smoking (%)	64	59	0.822
Diabetes mellitus (%)	17	26	0.264
Hypertension (%)	50	52	0.778
History of CAD Previous MI (%) Previous PCI (%) Previous CABG (%)	 1 4 0	6 4 0	0.910 1.000 -
Killip class I (%) II (%) III (%)	 98 2 0	98 0 2	0.916 0.156 0.158
Treated vessels LAD (%) RCA (%) LCx (%)	 39 48 16	 32 52 12	 0.491 0.623 0.402
Number of diseased vessels **1 (%)** **2** **3**	 88 11 1	 91 8 1	 P=0.563 P=0.864 P=0.962
TIMI flow (%) **0-II**	94	93	0.075
MLD (mm)	0.29	0.51	0.007
GP IIb/IIIa i (%)	34	30	0.648
DS (%)	92	87	0.012

Aspiration (%)	45	39	0.393
DAPT before (%)	100	98	0.227
Number of stents/patients	1.4	1.2	0.03
Direct stenting (%)	59	60	0.86
Max. implant pressure (atms)	18[16-20]	16[16-18]	0.020
Fluoroscopy time (minutes)	10[7-14]	7[5-10]	<0.0001
Rates and types of abnormal findings post-PCI OCT imaging	29/105 (28%)		
- Malapposition	17/29 (59%)		
- Any dissection	13/29 (41%)		

Table 2: Angiographic and OCT data at nine months of follow-up

	OCT-guided pPCI	**Angio-guided pPCI**	**P value**
ANGIOGRAPHY			
N	95	91	
Binary in-stent restenosis (%)	2 (2%)	3 (3%)	0.320
Diameter stenosis in-stent (%)	17.0 ±13.68	16.0 ±9.99	0.951
Diameter stenosis in-segment (%)	27.8 ±16.5	27.5 ±13.3	0.887
Late lumen loss in-stent (mm]	0.05 ±0.5	0.15 ±0.34	0.119
Late lumen loss in-segment (mm)	0.06±0.49	0.18±0.32	0.055
Minimal in-stent diameter (mm)	2.7±0.47	2.6±0.52	0.263
Minimal in-segment diameter (mm)	2.3±0.51	2.3±0.59	0.754

Reference stent diameter (mm)	3.2±0.55	3.1±0.52	0.453
Reference segment diameter (mm)	3.1±0.7	3.2±0.6	0.868
OCT			
N	92	86	
Mean lumen diameter (mm)	3.33 (0.46) 3.30 3.00, 3.62)	3.21 (0.56) 3.17 (2.89, 3.60)	0.14
Minimal lumen diameter (mm)	2.87 (0.50) 2.88 (2.60, 3.18)	2.75 (0.53) 2.72 (2.39, 3.13)	0.11
Mean lumen area (mm^2)	8.89 (2.43) 8.58 (7.10, 10.30)	8.40 (2.86) 7.93 (6.54, 10.20)	0.18
Minimal lumen area (mm^2)	6.67 (2.21) 6.47 (5.28, 8.00)	6.13 (2.25) 5.70 (4.51, 7.69)	0.13
Area of stenosis (%)	6.21 (23.44) 8.00 (-10.72, 19.19)	17.84 (21.08) 18.03 (2.88, 33.05)	0.0002
Number of uncovered struts (%)	12.78 (13.01) 7.57 (4.48, 18.34)	16.79 (15.80) 11.85 (3.65, 26.72)	0.19
% Malapposed struts	0.82 (2.85) 0.12 (0.00, 0.69)	0.82 (1.43) 0.14 (0.00, 1.15)	0.63

Figure 1: Patient flow and treatment flow

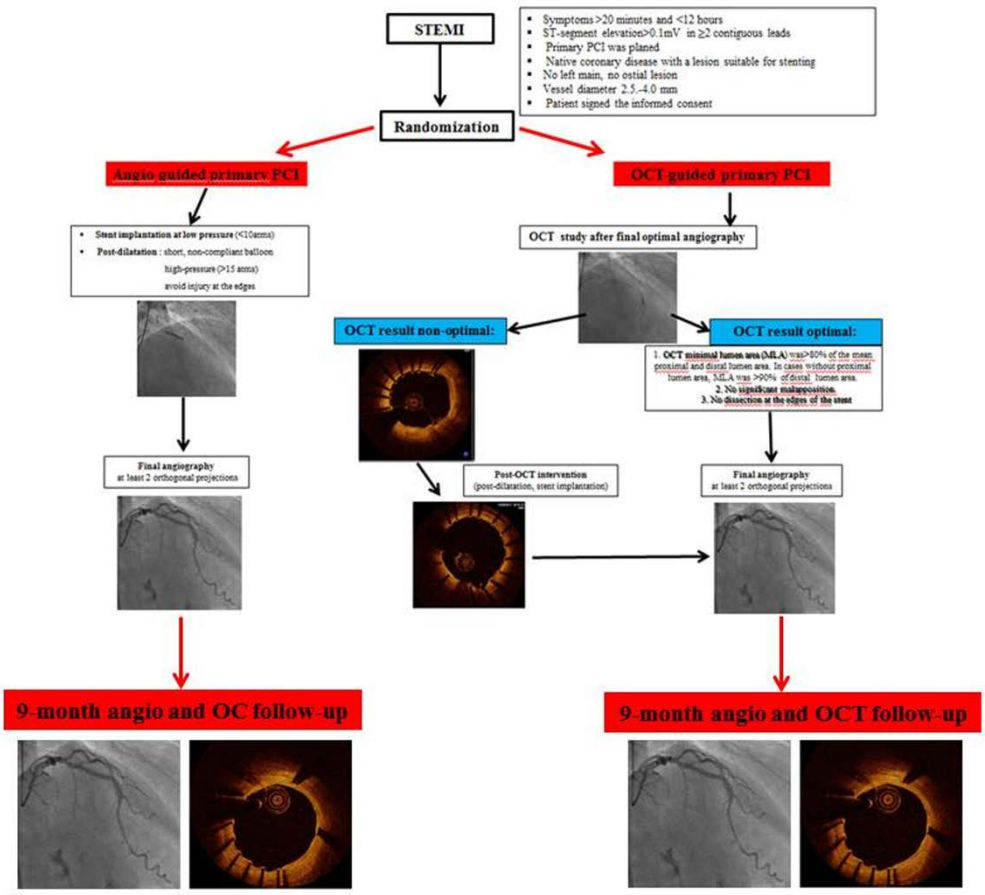
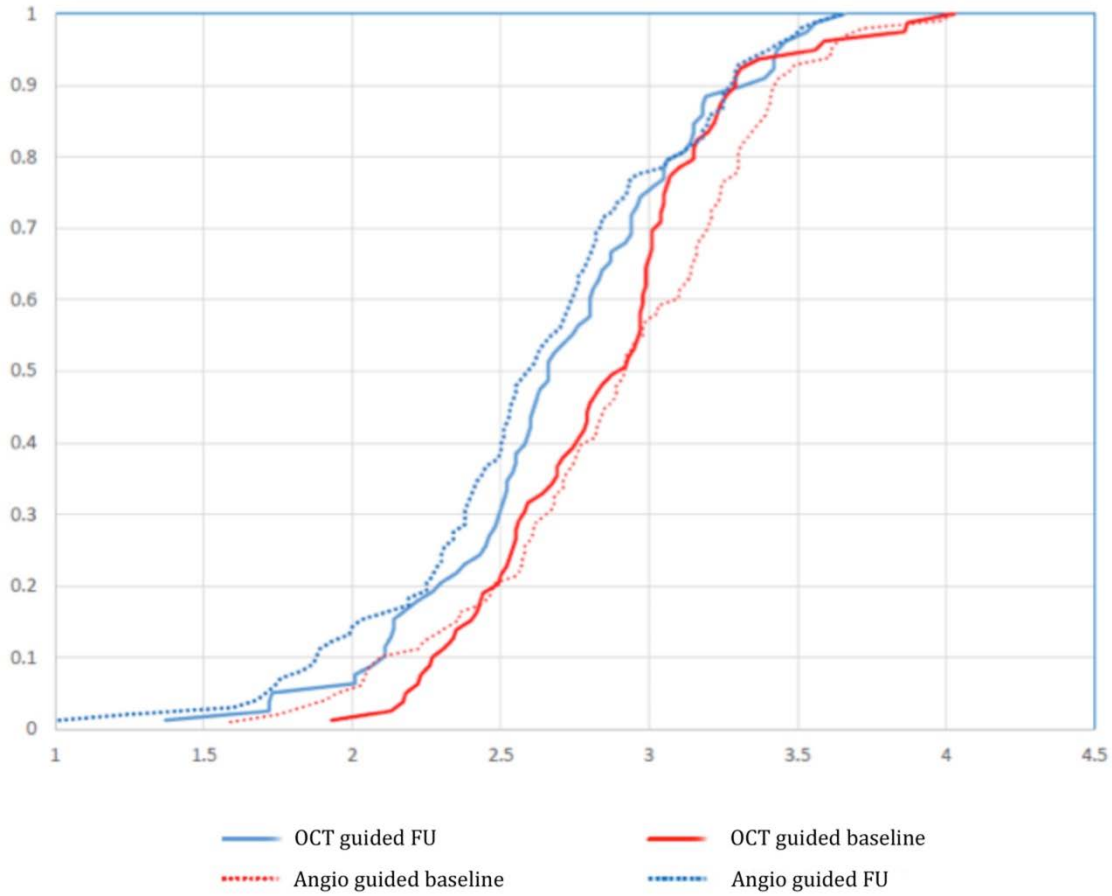


Figure 2: Cumulative distribution of mean in-stent late lumen loss at nine months of follow-up


1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
1.5
2
2.5
3
3.5
4
4.5
OCT guided FU
OCT guided baseline
Angio guided baseline
Angio guided FU

3.16

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Radial artery changes after transradial PCI – A serial optical coherence tomography volumetric study

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Abstract

Aims: Transradial catheterization (TRC) is a dominant access site for coronary catheterization and percutaneous coronary interventions (PCI) in many centers. Previous studies reported higher intimal thickness of the radial artery (RA) wall in patients with a previous history of TRC. In this investigation the aim was to assess the intimal changes of RA using the optical coherence tomography (OCT) intravascular imaging in a serial manner.

Methods and results: 100 patients with the diagnosis of non-ST-elevation myocardial infarction (nSTEMI) treated by PCI were enrolled. An 54mm long OCT run of the RA was performed immediately after the index PCI and repeated 9 months later. Volumetric analyses of the intimal layer and lumen changes were conducted. Median intimal volume at baseline versus 9 months was 33.9mm^3 (19.0; 69.4) versus 39.0mm^3 (21.7; 72.6) ($p<0.001$); and median arterial lumen volume was 356.3mm^3 (227.8; 645.3) versus 304.7mm^3 (186.1; 582.7) ($p<0.001$). There was no significant difference in the effect of any clinical factor on the RA volume changes.

Conclusions: OCT volumetric analyses at baseline and 9 months showed a significant increase in the radial artery intimal layer volume and a decrease in lumen volume after transradial PCI. No significant factors affecting this process were identified.

Keywords

Optical coherence tomography; Neointimal hyperplasia; PCI; Radial artery

Abbreviations list

FD-OCT	frequency domain optical coherence tomography
nSTEMI	non-ST segment elevation myocardial infarction
PCI	percutaneous coronary intervention
RA	radial artery
STEMI	ST segment elevation myocardial infarction

TRA transradial access

TRC transradial catheterization

Introduction

Many interventional cardiologists have adopted transradial catheterization (TRC) the last decade. The first TRC was performed by Campeau in 1989[1], and the first coronary stent was implanted via radial artery by Kiemeneij and Laarman in 1993[2]. Nowadays, the rate of transradial access (TRA) for percutaneous coronary interventions (PCI) is higher than transfemoral in many centers although the prevalence is higher in Asia and Europe than in the USA[3,4]. Compared to the femoral artery, TRA offers lower rate of complications such as bleeding[5] and even death[6]. However, the RA is smaller than the femoral artery[3], and TRA is associated with a higher prevalence of subclinical damage[7]. Previous studies investigated qualitative RA vessel wall changes after TRC. A greater thickness of the RA intimal layer was reported in patients with a history of TRC[7,8]. We performed the first prospective serial (baseline and 9-month follow-up) frequency-domain optical coherence tomography (FD-OCT) study of the RA after first-time transradial PCI in consecutive patients. FD-OCT uses near-infrared light for tissue imaging and has a spatial resolution close to 10 microns[9]. Conversely, the method is limited by the tissue penetration of near-infrared light; and during imaging the vessel has to be continuously flushed, usually with a 100% contrast, to clear the optical environment of blood cells. For RA vessel wall imaging, OCT is currently the best option to assess discreet changes of the RA wall intimal layer.

Methods

Patient group

One hundred consecutive patients were included in the project, as a part of larger group of patients (140 subjects) enrolled into a study focusing on OCT analysis of the coronary vessels in patients with the diagnosis of myocardial infarction without ST segment elevation (nSTEMI). The following inclusion criteria were applied: diagnosis of nSTEMI, first-in-life transradial coronary

catheterization, and PCI during the index procedure. Exclusion criteria included myocardial infarction with ST segment elevation (STEMI), left main coronary artery lesion, renal insufficiency with creatinine level above 150umol/l, acute heart failure, and refusal to sign the informed consent. All patients signed written informed consent. The project was approved by the local Ethics Committee.

Coronary angiography and PCI procedure

Cardiac catheterization was performed in accordance with the local medical standards in an 24/7 tertiary PCI center. The center has wide experience with transradial catheterizations and interventions with a 97% rate of transradial procedures in 2014. All the procedures were performed via 6F *Radiofocus Introducer II* kit (Terumo, Japan) with an intravascular sheath length of 7 cm. The RA was punctured with the kit according to local standards. A vasodilating drug (typically 2.5mg of verapamil) was administered in all cases. Solely 6F guide catheters were used for the coronary interventions. Unfractioned heparin with the target ACT ≥250 was used for the anticoagulation.

OCT procedure protocol

After the index coronary angiography and subsequent PCI, OCT of the RA was performed. The standard coronary wire and OCT catheter were placed in the radial artery through the 6F guiding catheter and the guiding catheter was pulled out from the radial sheath. Overall, 3cm of the sheath was withdrawn from the artery (distally), leaving 4cm inside the RA. An X-ray contrast ruler was used to identify the start of OCT imaging and pullback 8cm proximal to the actual sheath tip position. From that point, OCT pullback recording was performed using a 100% contrast fluid to flush the vessel. The standardized length of the pullback was 54mm (Figure 1). We used the *Dragonfly Duo catheter* and *Optis Ilumien OCT system* (St.Jude, Minneapolis, MN, USA) to perform the OCT procedure. The puncture site was covered with a compress band for two hours to allow hemostasis after the procedure.

The standard data acquisition speed was 18mm per second, getting high resolution data from the vessel in 3 seconds (for the 54mm pullback record length).

The procedure was repeated 9 months after the index procedure during follow-up coronary catheterization. The same OCT protocol as described above was used.

OCT analysis

OCT images of the entire 54 mm segment for each patient were analyzed offline manually by two experienced OCT analysts (Figure 2) at baseline and follow-up. The lumen border and intima-media border was segmented every 3 mm. Simpson's rule was applied to create a volumetric model of lumen and intimal layer of the radial artery. This model was used to compare the baseline and follow-up volumes of both the lumen and the intimal layer of the radial artery. If some frames were not of sufficient quality for evaluation, the analysis was normalized for the standard length of 54mm. The percentage of analysed frames was 94.7% both in baseline and follow-up pullbacks (Table 1). An analysis of factors affecting the volume changes was performed.

Statistical analysis

Standard descriptive statistical methods were applied in the analysis; absolute and relative frequencies for categorical variables and median with 5th-95th percentile range for continuous variables. Statistical significance of differences between various subgroups of patients in baseline and follow-up measurements was tested using a non-parametric Mann-Whitney U test and Kruskal-Wallis test. Intra-individual differences in arterial volumes were assessed using a Wilcoxon signed-rank test. Influence of duration of catheterization on change of volume was tested by Mann-Whitney U test. Correlation between duration of catheterization and change of volume was tested by Pearson's correlation coefficient. Statistical analyses were computed using SPSS 22.0.0.1 (IBM Corporation, 2014).

Results

Radial artery OCT was well tolerated by patients with a general mild discomfort in the forearm during the contrast flush, but no clinically significant adverse events occurred.

Overall, 96 RA data records were of sufficient quality for the analysis. The median age of the group was 66.5 years. More men (67.7%) than women were enrolled. The baseline characteristics of the patient population have been listed in Table 2.

Irrespective of the fact that 54mm of artery was imaged in each patient, distributions of intimal layer volume were relatively wide, from 20mm^3 to 80mm^3 (Figure 3). Similarly, distributions of lumen volume were also wide, from 200mm^3 to 800mm^3 (Figure 4).

Median intimal layer volume at baseline was 33.9mm^3 (19.0; 69.4) versus 39.0mm^3 (21.7; 72.6) measured 9 months later. This difference of 3.0mm^3 (-9.4; 21.3) was highly statistically significant ($p<0.001$, Table 3). The intimal volume increased in 66.7% of patients; no change or decreased volume occurred in 33.3% of patients (Table 4, Figure 5). Median lumen volume at baseline was 356.3mm^3 (227.8; 645.3) versus 304.7mm^3 (186.1; 582.7) 9 months later. The difference of -54.0mm^3 (-210.6; 87.2) was highly statistically significant ($p<0.001$, Table 3). The lumen volume decreased in 79.2% of patients; there was no change or increased volume in 20.8% of patients (Table 4, Figure 6).

Analysis of multiple factors affecting intimal and lumen volume changes was performed (gender, age, body-mass index, clinical risk factors and duration of cathetrization). No significant risk factor associated with the intimal and lumen volume changes was identified (Tables 5, 6, 8a and 8b).

Discussion

In our study, we analysed the effect of the first-in-life TRC in 100 patients, using serial OCT analysis. The results showed significant changes of the vessel in the period of 9 months after the first catheterization.

Wakeyama et al. used intravascular ultrasound (IVUS) to assess 100 radial arteries for intimal-medial changes in 2002[8]. There was intima-media thickening in repeat-TRI patients compared to the first-time TRI patients, especially in the distal radial artery. In 2008, Burris et al. used OCT for graft quality evaluation of the cadaverous radial artery after endoscopic and open harvesting[10]. The first OCT study investigating RA changes in vivo was conducted by Yonetsu et al. in 2010[7], enrolling 69 patients, dividing them into first-time and repeat-TRC groups. By measuring multiple cross-section areas of the RA, they found intimal areas to be significantly greater in the repeat-TRC RA group. Older time-domain OCT technology (TD-OCT) was used together with longer (16cm) sheath introduction.

In our study, we enrolled solely "TRC-naive" patients. Our results proved previously suggested hypothesis that even uncomplicated and relatively short TRC affects the radial artery as a complex part of the arterial vascular system. Recent publication by Nakata et al.[11] proved that 6F sheath insertion into the RA impaired vascular endothelial function the day after the procedure. The impaired changes assessed by reactive hyperemia peripheral arterial tonometry lasted for 6 months. Taken together, these results suggest that every diagnostic and therapeutic catheterization should be performed in a minimally invasive manner, preferably using smaller (possibly also shorter) sheaths and small size catheters (where possible).

Due to the fact that no other factors have proved to have a strong effect on the radial artery changes, it may be observed that the RA was affected solely by TRC. Recently, a comprehensive review on minimizing RA damage has been published[12].

Limitations

The analysis was limited to 54mm, and the OCT was performed only at baseline and 9 month follow-up; therefore, we could not assess the true time-course of post-TRC changes.

Conclusion

The volumetric model of the radial artery lumen and the arterial wall intimal layer after transradial PCI assessed by OCT at baseline and at 9-month follow-up showed a significant effect of transradial catheterization. The intimal layer volume increased significantly, while the volume of the lumen decreased. No significant clinical factors affecting this process have been found.

Impact on daily practice:

The study brings a new light into the field and describes the sub-macroscopic changes in the radial artery used for the catheterization access. The results could be interesting for a wide population of acute and interventional cardiologists as well as for the specialists working in the intensive care units and cardiovascular surgeons seeking for full arterial revascularization, especially in terms of arterial graft quality evaluation.

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Figures

1. Optical coherence tomography of RA – procedure scheme

   Legend: A-Sheath tip position during the OCT procedure, B-Original sheath tip position during the PCI, C-Start position of the OCT probe

2. Representative OCT cross-section frame of the radial artery and its analysis

   Legend: A-intimal layer, B-media, C-adventitia

3. Distributions of RA intimal layer volume in baseline and follow-up measurements

4. Distributions of RA luminal volume in baseline and follow-up measurements

5. Change in the volume of intima layer of the arterial wall in individual patients (mm^3)
6. Change in the volume of arterial lumen in individual patients (mm^3)

Table 1 Evaluability of artery volumes (N = 96)

	Mean ± SD	**Median (min-max)**
Baseline measurement		
Evaluable part of artery (%)	**90.4 ± 12.3**	**94.7 (52.6; 100.0)**
Number of invalid frames	**1.8 ± 2.3**	**1.0 (0.0; 9.0)**
Follow-up measurement		
Evaluable part of artery (%)	**89.4 ± 13.7**	**94.7 (47.4; 100.0)**
Number of invalid frames	**2.0 ± 2.6**	**1.0 (0.0; 10.0)**

Table 2: Baseline characteristics

Characteristics		**N (%) or median (5^{th}-95^{th} percentile)**
Gender	Man	65 (67.7 %)
	Woman	31 (32.3 %)
Age	(N = 96)	66.5 (45.0; 80.7)
Body-mass index	(N = 92)	28.2 (23.1; 37.1)
Hypertension		65 (67.7 %)
Dyslipidemia		31 (32.3 %)
Diabetes mellitus		33 (34.4 %)
Peripheral vasculopathy		4 (4.2 %)
Smoking	Smoker	26 (27.7 %)
	Former smoker	29 (30.9 %)

	Never smoked	39 (41.5 %)
Alcohol	≥ 1 drink / week	14 (14.9 %)
	≥ 1 drink / month	33 (35.1 %)
	< 1 drink / month	47 (50.0 %)
Creatinine (µmol/l)	(N = 82)	87.5 (52.0; 118.0)

Table 3: RA arterial wall and lumen changes

	N	Baseline[1]	Follow-up[1]	Difference[1]	p
Arterial wall volume (mm^3)	96	33.9 (19.0; 69.4)	39.0 (21.7; 72.6)	3.0 (-9.4; 21.3)	**< 0.001**
Arterial lumen volume (mm^3)	96	356.3 (227.8; 645.3)	304.7 (186.1; 582.7)	-54.0 (-210.6; 87.2)	**< 0.001**

[1] Median (5^{th}-95^{th} percentile);

Table 4: Change of volume (N = 96)

Volume change	Increase	Decrease
Intima layer	64 (66.7%)	32 (33.3%)
Arterial lumen	20 (20.8%)	76 (79.2%)

Table 5: Influence of risk factors on RA arterial wall changes

		N	Arterial wall volume		
			Baseline[1]	Follow-up[1]	Difference[1]
Gender	Man	65	36.5 (22.2; 69.7)	41.7 (25.5; 69.1)	4.3 (-9.8; 18.2)
	Woman	31	30.4 (15.9; 49.1)	34.5 (18.3; 72.6)	2.0 (-7.2; 27.2)

		p			**0.664**
Age	< 60	29	26.6 (16.5; 69.0)	28.6 (21.7; 60.0)	2.9 (-12.8; 19.2)
	60-69	38	35.6 (19.2; 58.4)	39.5 (19.9; 64.6)	1.8 (-9.8; 19.6)
	≥ 70	29	36.4 (22.0; 77.1)	44.4 (22.5; 84.0)	7.1 (-8.1; 27.2)
		p			**0.307**
Body-mass index	< 25	12	25.8 (15.9; 43.3)	33.0 (17.4; 59.9)	7.9 (-4.7; 23.6)
	25-29	48	36.4 (19.8; 69.7)	41.8 (24.1; 69.1)	3.7 (-8.1; 18.2)
	≥ 30	32	34.3 (19.1; 58.4)	35.0 (20.5; 75.0)	2.4 (-12.8; 27.2)
		p			**0.368**
Hypertension	Yes	65	34.7 (19.2; 69.7)	42.2 (22.7; 75.0)	4.3 (-8.7; 19.6)
	No	31	30.4 (16.5; 52.7)	31.7 (21.7; 60.0)	2.3 (-12.6; 21.8)
		p			**0.692**
Dyslipidemia	Yes	31	34.1 (22.1; 77.1)	38.7 (22.7; 84.0)	4.7 (-8.1; 19.2)
	No	65	33.7 (18.4; 59.4)	39.3 (21.7; 69.1)	2.7 (-9.8; 21.8)
		p			**0.848**
Diabetes mellitus	Yes	33	36.4 (19.0; 69.7)	43.3 (22.7; 75.0)	4.8 (-9.8; 27.2)
	No	63	33.3 (19.1; 69.0)	36.1 (21.7; 60.0)	2.2 (-9.3; 18.2)
		p			**0.159**
Smoking	Smoker	26	33.2 (18.4; 55.7)	38.2 (23.7; 63.4)	6.9 (-9.3; 19.2)
	Former smoker	29	37.1 (23.8; 77.1)	39.9 (26.7; 84.0)	2.9 (-9.4; 21.3)
	Never smoked	39	33.7 (19.0; 59.4)	38.7 (18.3; 69.1)	1.5 (-8.1; 23.6)
		p			**0.707**
Alcohol	≥ 1 drink / week	14	32.5 (12.8; 59.4)	40.7 (19.9; 63.4)	6.7 (-8.7; 21.8)
	≥ 1 drink / month	33	36.6 (19.1; 69.0)	44.4 (21.7; 75.0)	1.3 (-9.4; 21.3)
	< 1 drink / month	47	33.7 (19.0; 73.6)	37.7 (22.5; 72.6)	4.3 (-7.2; 19.6)

	p				**0.726**
Creatinine	< 100 µmol/l	63	33.8 (19.0; 59.4)	37.6 (20.5; 68.9)	2.7 (-8.1; 19.2)
	≥ 100 µmol/l	19	33.0 (16.5; 81.5)	39.9 (21.7; 88.9)	6.6 (-4.5; 17.3)
	p				**0.527**

[1] Median (5^{th}-95^{th} percentile);

Table 6: Influence of risk factors on RA lumen changes

		N	Arterial lumen volume		
			Baseline[1]	**Follow-up[1]**	**Difference[1]**
Gender	Man	65	404.6 (252.8; 675.9)	321.8 (194.2; 603.8)	-61.6 (-233.2; 87.2)
	Woman	31	305.0 (203.1; 503.6)	252.3 (173.7; 445.3)	-53.1 (-192.0; 87.2)
	p				**0.538**
Age	< 60	29	353.0 (173.8; 675.9)	302.4 (198.0; 530.3)	-42.2 (-153.9; 94.0)
	60-69	38	367.3 (231.0; 640.5)	310.6 (156.0; 571.6)	-53.5 (-325.3; 133.9)
	≥ 70	29	353.6 (227.8; 645.3)	271.1 (195.0; 603.8)	-62.6 (-192.0; 8.5)
	p				**0.673**
Body-mass index	< 25	12	268.3 (212.7; 566.5)	206.3 (149.1; 498.3)	-60.8 (-126.0; 33.8)
	25-29	48	369.1 (228.4; 684.2)	317.2 (194.8; 623.2)	-33.0 (-233.2; 74.9)
	≥ 30	32	404.5 (231.0; 622.8)	300.5 (201.7; 571.6)	-68.3 (-192.0; 87.2)
	p				**0.123**
Hypertension	Yes	65	368.9 (234.5; 645.3)	314.2 (194.0; 582.7)	-58.8 (-192.0; 87.2)
	No	31	343.5 (173.8; 635.3)	270.3 (175.3; 530.3)	-43.0 (-210.6; 94.0)

		p			**0.922**
Dyslipidemia	Yes	31	369.2 (228.4; 628.1)	306.9 (175.3; 603.8)	-54.2 (-192.0; 87.2)
	No	65	353.0 (227.8; 675.9)	299.5 (194.2; 571.6)	-46.0 (-210.6; 74.9)
		p			**0.947**
Diabetes mellitus	Yes	33	369.2 (203.1; 628.1)	314.2 (194.2; 571.6)	-58.4 (-157.2; 87.2)
	No	63	353.0 (231.0; 675.9)	302.4 (175.3; 582.7)	-46.0 (-233.2; 87.2)
		p			**0.826**
Smoking	Smoker	26	372.3 (173.8; 675.9)	271.4 (194.2; 521.7)	-58.1 (-198.4; 94.0)
	Former smoker	29	404.4 (237.0; 628.1)	377.1 (173.7; 603.8)	-60.8 (-210.6; 87.2)
	Never smoked	39	337.3 (212.7; 645.3)	306.9 (175.3; 582.7)	-39.1 (-173.4; 87.2)
		p			**0.604**
Alcohol	≥ 1 drink / week	14	332.2 (145.4; 790.8)	290.0 (149.1; 521.7)	-62.4 (-519.7; 162.9)
	≥ 1 drink / month	33	391.5 (212.7; 675.9)	367.1 (208.4; 645.8)	-60.8 (-183.4; 94.0)
	< 1 drink / month	47	349.5 (228.4; 599.7)	271.1 (175.3; 582.7)	-53.1 (-198.4; 87.2)
		p			**0.637**
Creatinine	< 100 µmol/l	63	368.9 (212.7; 640.5)	307.0 (186.1; 538.3)	-53.9 (-192.0; 94.0)
	≥ 100 µmol/l	19	338.2 (227.8; 645.3)	287.7 (156.0; 672.1)	-39.1 (-325.3; 87.2)
		p			**0.513**

[1] Median (5^{th}-95^{th} percentile);

Table 7a *Influence of duration of catheterization on change of volume (N = 96)*

	Volume increase	**Volume decrease**	**p**

Intima layer			
Duration of catheterization (in minutes, median (min-max))	50.5 (23.0; 163.0)	47.5 (24.0; 108.0)	0.892
Arterial lumen			
Duration of catheterization (in minutes, median (min-max))	51.0 (24.0; 163.0)	48.0 (23.0; 130.0)	0.346

Table 7b *Correlation between duration of catheterization and change of volume (N = 96)*

Volume change	**r**	**p**
Intima layer		
Duration of catheterization (in minutes)	0.080	0.436
Arterial lumen		
Duration of catheterization (in minutes)	0.043	0.680

3.17

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Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

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ABSTRACT

BACKGROUND

The preferred initial treatment for patients with stable coronary artery disease is the best available medical therapy. We hypothesized that in patients with functionally significant stenoses, as determined by measurement of fractional flow reserve (FFR), percutaneous coronary intervention (PCI) plus the best available medical therapy would be superior to the best available medical therapy alone.

METHODS

In patients with stable coronary artery disease for whom PCI was being considered, we assessed all stenoses by measuring FFR. Patients in whom at least one stenosis was functionally significant (FFR, ≤0.80) were randomly assigned to FFR-guided PCI plus the best available medical therapy (PCI group) or the best available medical therapy alone (medical-therapy group). Patients in whom all stenoses had an FFR of more than 0.80 were entered into a registry and received the best available medical therapy. The primary end point was a composite of death, myocardial infarction, or urgent revascularization.

RESULTS

Recruitment was halted prematurely after enrollment of 1220 patients (888 who underwent randomization and 332 enrolled in the registry) because of a significant between-group difference in the percentage of patients who had a primary end-point event: 4.3% in the PCI group and 12.7% in the medical-therapy group (hazard ratio with PCI, 0.32; 95% confidence interval [CI], 0.19 to 0.53; P<0.001). The difference was driven by a lower rate of urgent revascularization in the PCI group than in the medical-therapy group (1.6% vs. 11.1%; hazard ratio, 0.13; 95% CI, 0.06 to 0.30; P<0.001); in particular, in the PCI group, fewer urgent revascularizations were triggered by a myocardial infarction or evidence of ischemia on electrocardiography (hazard ratio, 0.13; 95% CI, 0.04 to 0.43; P<0.001). Among patients in the registry, 3.0% had a primary end-point event.

CONCLUSIONS

In patients with stable coronary artery disease and functionally significant stenoses, FFR-guided PCI plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the need for urgent revascularization. In patients without ischemia, the outcome appeared to be favorable with the best available medical therapy alone. (Funded by St. Jude Medical; ClinicalTrials.gov number, NCT01132495.)

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*The investigators in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial are listed in the Supplementary Appendix, available at NEJM.org.

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Percutaneous coronary intervention (PCI) improves the outcome in patients with acute coronary syndromes.[1] In contrast, for the treatment of patients with stable coronary artery disease, controversy persists regarding the extent of the benefit from PCI, as compared with the best available medical therapy, as an initial management strategy.[2-5] The potential benefit of revascularization depends on the presence and extent of myocardial ischemia.[6-8] Performing PCI on nonischemic stenoses is not beneficial[9] and is probably harmful.[10] Thus, careful selection of ischemia-inducing stenoses is essential for deriving the greatest benefit from revascularization in patients with stable coronary artery disease.

Fractional flow reserve (FFR) is a pressure-wire–based index that is used during coronary angiography to assess the potential of a coronary stenosis to induce myocardial ischemia.[11-14] The usefulness of FFR-guided PCI as compared with PCI guided by angiography alone is supported by robust clinical outcome data.[9,10,14-17]

The aim of this trial was to determine whether FFR-guided PCI with drug-eluting stents plus the best available medical therapy is superior to the best available medical therapy alone in reducing the rate of death, myocardial infarction, or unplanned hospitalization leading to urgent revascularization among patients with stable coronary artery disease.

Methods

Study Design and Oversight

The Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) study is a randomized "all comers" trial (i.e., involving the consecutive enrollment of all eligible patients with stable coronary artery disease). The trial was conducted at 28 sites in Europe and North America and was approved by the institutional review board at each participating center. The members of the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study without involvement of the sponsor, St. Jude Medical. The sponsor was involved in the collection and source verification of the data but not in the conduct of the trial or in the decision to terminate it. An independent data and safety monitoring board (see the Supplementary Appendix) oversaw the trial and met twice a year or more frequently, as necessary for the oversight of the trial. No formal stopping rules were specified. The academic members of the steering committee had full access to all the data in the study, vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol, wrote the manuscript, and had final responsibility for the decision to submit it for publication. The research protocol is available at NEJM.org.

Patients

Patients in stable condition who were appropriate candidates for PCI and who had angiographically assessed one-, two-, or three-vessel coronary artery disease suitable for PCI were included in the trial. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix. The investigator first indicated which stenoses were thought to require stenting on the basis of the clinical and angiographic data. FFR was then measured with a coronary guidewire (PressureWire Certus or PressureWire Aeris, St. Jude Medical) during adenosine-induced hyperemia to assess the hemodynamic severity of each indicated stenosis. Patients who had at least one stenosis in a major coronary artery with an FFR of 0.80 or less were randomly assigned, by means of an interactive voice-response system, to FFR-guided PCI plus the best available medical therapy (hereinafter called the PCI group) or to the best available medical therapy alone (hereinafter called the medical-therapy group). The randomization schedule was computer-generated; randomization was stratified according to site and performed in blocks, with block sizes varied randomly. Patients with an FFR of more than 0.80 in all vessels with indicated stenoses were enrolled in a registry and received the best available medical therapy. A random sample of 50% of the registry patients underwent the same follow-up as the patients in the randomized trial. The treatment assignments were known to the patients. All patients provided written informed consent.

Treatment

All patients were prescribed aspirin at a dose of 80 to 325 mg daily, metoprolol at a dose of 50 to 200 mg daily (or any other beta-1–selective blocker, alone or in combination with a calcium-channel blocker or a long-acting nitrate), lisinopril (≥5 mg daily, or another angiotensin-converting–enzyme [ACE] inhibitor or an angiotensin II–receptor

blocker if the patient had unacceptable side effects with the ACE inhibitor), and atorvastatin (20 to 80 mg daily, or another statin of similar potency alone or in combination with ezetimibe, to reduce the low-density-lipoprotein [LDL] level to less than 70 mg per deciliter [1.8 mmol per liter]).

Patients who were randomly assigned to PCI received a loading dose of clopidogrel (600 mg) and aspirin immediately before the procedure if they were not already taking these medications. All stenoses with an FFR of 0.80 or less were treated with second-generation drug-eluting stents.[18-20] After PCI, all patients received clopidogrel at a dose of 75 mg per day for at least 12 months in addition to the best available medical therapy. All patients were given a medication tracking form for recording weekly medication use and doses. Patients who smoked were counseled regarding smoking cessation. Patients with diabetes were referred to a diabetes specialist to receive the best available treatment for that disease.

FOLLOW-UP

Electrocardiography (ECG) was performed with the patient at rest, and the creatine kinase level and the MB fraction of creatine kinase were measured in all patients before angiography was performed and between 12 and 24 hours after enrollment. Follow-up visits were scheduled at 1 and 6 months and at 1, 2, 3, 4, and 5 years. At baseline and all follow-up visits, we obtained information regarding the presence or absence (and, if present, the severity) of angina, the patient's work status, and the number and doses of cardiac medications and assessed the patient's quality of life with the use of the European Quality of Life–5 Dimensions [EQ-5D] instrument.[21] In addition, we performed resting ECG, measured the levels of total cholesterol and cholesterol fractions, and assessed the patient's utilization of medical resources.

END POINTS

The prespecified primary end point was a composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization during the first 2 years. Secondary end points included individual components of the primary end point, cardiac death, nonurgent revascularization, and angina class. All outcomes were adjudicated by an independent clinical events committee (see the Supplementary Appendix) whose members were unaware of the treatment assignments. For each revascularization procedure, a detailed description was included. Revascularization was considered to be urgent when a patient was admitted to the hospital with persistent or increasing chest pain (with or without ST-segment or T-wave changes or elevated biomarker levels) and the revascularization procedure was performed during the same hospitalization.

STATISTICAL ANALYSIS

The trial was powered to determine whether PCI with the best available medical therapy was superior to the best available medical therapy alone with respect to the primary end point at 24 months. On the basis of findings from previous studies and using binomial proportions, we estimated that the cumulative incidence of the primary end point at 24 months would be 12.6% in the PCI group[18-20] and 18.0% in the medical-therapy group,[3] corresponding to a relative risk reduction with PCI of 30%, and that with 816 patients in each group, the study would have more than 84% power to detect that relative risk reduction, at a two-sided type I error rate of 0.05. Continuous variables are presented as means and standard deviations, and categorical data are presented as numbers and percentages. All patients were included in the analysis according to the groups to which they were originally assigned (intention-to-treat analysis). We used the Mantel–Cox method to calculate hazard ratios and 95% confidence intervals for the between-group comparisons of clinical outcomes and the log-rank test to calculate corresponding P values. We constructed Kaplan–Meier curves for the primary end point and its components.

In an exploratory analysis, we also calculated the hazard ratio for urgent revascularization triggered by a myocardial infarction or by unstable angina with evidence of ischemia on ECG. We used a chi-square test to assess the interaction between treatment effect and these characteristics. Landmark analyses were performed according to a landmark point at 7 days, with the hazard ratio calculated separately for events that occurred up to 7 days after randomization and events that occurred between 8 days and the end of the follow-up period. We then performed a test for the interaction between treatment and time (first 7 days vs. subsequent period). In all time-to-event analyses (i.e., overall and landmark), for each type of event, data for a patient

Table 1. Baseline Clinical, Angiographic, and Fractional Flow Reserve (FFR) Characteristics.*

Variable	Randomly Assigned Groups		Registry Cohort	P Value†
	PCI plus Medical Therapy	Medical Therapy Alone		
Patient characteristics				
Total no. of patients	447	441	166	
Age — yr	63.52±9.35	63.86±9.62	63.58±9.75	0.90
Male sex — no. (%)	356 (79.6)	338 (76.6)	113 (68.1)	0.005
Body-mass index‡	28.29±4.27	28.44±4.55	27.83±3.94	0.14
Family history of coronary artery disease — no. (%)	216 (48.3)	207 (46.9)	76 (45.8)	0.65
Current smoking — no. (%)	89 (19.9)	90 (20.4)	35 (21.1)	0.79
Hypertension — no. (%)	347 (77.6)	343 (77.8)	136 (81.9)	0.23
Hypercholesterolemia — no. (%)	330 (73.8)	348 (78.9)	118 (71.1)	0.15
Diabetes mellitus — no. (%)				
Any	123 (27.5)	117 (26.5)	42 (25.3)	0.65
Insulin-dependent	39 (8.7)	39 (8.8)	10 (6.0)	0.24
Renal insufficiency — no. (%)§	8 (1.8)	12 (2.7)	7 (4.2)	0.14
Peripheral vascular disease — no. (%)	43 (9.6)	47 (10.7)	8 (4.8)	0.03
History of stroke or transient ischemic attack — no. (%)	33 (7.4)	28 (6.3)	10 (6.0)	0.69
History of myocardial infarction — no./total no. (%)	164/442 (37.1)	165/436 (37.8)	60/164 (36.6)	0.83
History of PCI in target vessel — no. (%)	80 (17.9)	76 (17.2)	34 (20.5)	0.37
Angina — no./total no (%)¶				0.64
Asymptomatic	53/447 (11.9)	46/440 (10.5)	17/166 (10.2)	
CCS class I	82/447 (18.3)	98/440 (22.3)	42/166 (25.3)	
CCS class II	204/447 (45.6)	197/440 (44.8)	74/166 (44.6)	
CCS class III	80/447 (17.9)	65/440 (14.8)	23/166 (13.9)	
CCS class IV, stabilized	28/447 (6.3)	34/440 (7.7)	10/166 (6.0)	
Silent ischemia — no. (%)	73 (16.3)	73 (16.6)	27 (16.3)	0.96
Left ventricular ejection fraction <50% — no./total no. (%)	83/423 (19.6)	56/410 (13.7)	27/150 (18.0)	0.69
Angiographic findings				
Angiographically significant lesions — no. per patient	1.87±1.05	1.73±0.94	1.32±0.59	<0.001
Vessels with at least one significant lesion — no. of patients (%)				<0.001
1	251 (56.2)	261 (59.2)	136 (81.9)	
2	156 (34.9)	146 (33.1)	26 (15.7)	
3	40 (8.9)	34 (7.7)	4 (2.4)	
At least one significant lesion in proximal or middle left anterior descending artery — no. (%)	291 (65.1)	276 (62.6)	74 (44.6)	<0.001
FFR findings				
Functionally significant lesions — no. per patient	1.52±0.78	1.42±0.73	0.03±0.17	<0.001
Vessels with at least one significant lesion — no. of patients (%)				<0.001
1	331 (74.0)	343 (77.8)	5 (3.0)‖	
2	102 (22.8)	85 (19.3)	0	
3	14 (3.1)	13 (2.9)	0	
At least one significant lesion in proximal or middle left anterior descending artery — no. (%)	279 (62.4)	263 (59.6)	1 (0.6)	<0.001

Table 1. (Continued.)

Variable	Randomly Assigned Groups		Registry Cohort	P Value†
	PCI plus Medical Therapy	Medical Therapy Alone		
Lesion characteristics				
Total no. of lesions	890	815	241	
Angiographic findings				
Lesions with stenosis of >50% of diameter — no. (%)	837 (94.0)	764 (93.7)	219 (90.9)	0.13
Stenosis — no. (%)				<0.001
<50% of diameter	53 (6.0)	51 (6.3)	22 (9.1)	
50–69% of diameter	317 (35.6)	331 (40.6)	176 (73.0)	
70–90% of diameter	383 (43.0)	331 (40.6)	38 (15.8)	
>90% of diameter	101 (11.3)	80 (9.8)	0	
Total occlusion	36 (4.0)	22 (2.7)	5 (2.1)	
FFR findings				
Lesions with FFR ≤0.80 — no. (%)	679 (76.3)	625 (76.7)	5 (2.1)‖	<0.001
Mean FFR in lesions with FFR ≤0.80	0.68±0.10	0.68±0.15	0.50±0.00	0.01

* Plus–minus values are means ±SD. There were no significant differences between the two randomly assigned groups in any of the baseline characteristics, with the exception of left ventricular ejection fraction of less than 50% (P=0.04). PCI denotes percutaneous coronary intervention.
† The P values are for the combined groups that underwent randomization (the group assigned to PCI plus the best available medical therapy and the group assigned to the best available medical therapy alone) as compared with the group of patients who did not undergo randomization (patients in whom all stenoses had an FFR of more than 0.80) and were enrolled in a registry. In patient-level analyses, the P values were calculated with the use of a chi-square test except when cell numbers were small (<15 patients), in which case Fisher's exact test was used. In lesion-level analyses, mixed maximum-likelihood logistic-regression models were used for between-group comparisons of dichotomous variables, and mixed maximum-likelihood linear-regression models were used for comparisons of continuous variables, to account for the correlation of multiple lesions within patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Renal insufficiency was defined as a creatinine level of more than 2.0 mg per deciliter (176.8 μmol per liter).
¶ Angina was classified according to the Canadian Cardiovascular Society (CCS) functional classification, in which classes range from I to IV, with higher classes indicating greater limitations on physical activity owing to angina.
‖ Five totally occluded arteries supplied infarcted areas and were therefore not considered for revascularization by means of PCI.

were censored at the time of the first event that occurred in that patient. All analyses were performed by an independent statistician from an academic clinical trials unit (CTU Bern, University of Bern, Switzerland) with the use of Stata software, version 11.2.

RESULTS

Study Termination and Patient Follow-up

At the recommendation of the independent data and safety monitoring board, patient recruitment was stopped on January 15, 2012, owing to a highly significant difference in the incidence rates of the primary end point between the PCI and medical-therapy groups. Between May 15, 2010, and January 15, 2012, a total of 1220 patients were enrolled (Fig. S1 in the Supplementary Appendix). A total of 888 patients had at least one stenosis with an FFR of 0.80 or less in a large epicardial artery: 447 patients were randomly assigned to FFR-guided PCI plus the best available medical therapy, and 441 patients to the best available medical therapy alone. In 332 patients with angiographically significant stenoses, none of the stenoses had an FFR of 0.80 or less; these patients were enrolled in the registry and received the best available medical therapy alone. The mean (±SD) duration of follow-up was 213±128 days among patients assigned to PCI plus the best medical available therapy, 214±127 days among patients assigned to the best available medical therapy alone, and 206±119 days among patients enrolled in the registry.

Baseline Characteristics

Table 1 shows the baseline clinical, angiographic, and FFR characteristics of the patients who under-

went randomization, as compared with the patients who were enrolled in the registry. There were higher percentages of men, patients with peripheral vascular disease, and patients with multivessel disease in the groups that underwent randomization than in the registry cohort. More than 25% of the patients had diabetes, and 68% of the patients had angina of class II to IV on the Canadian Cardiovascular Society (CCS) scale (which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina). There were more lesions per patient and more lesions with stenosis of more than 70% of the diameter of the artery among patients who underwent randomization than among patients in the registry. A total of 1601 stenoses in the patients who underwent randomization were considered for PCI on the basis of angiographic findings, whereas 1304 were considered for PCI on the basis of an FFR of 0.80 or less. Among the latter, the FFR ranged from 0.19 to 0.80. Table S1 in the Supplementary Appendix shows the medications the patients were taking at baseline and during the follow-up period.

PRIMARY END POINT

By January 15, 2012, a total of 75 patients in the randomized groups had had at least one primary end-point event. The percentage of patients who had a primary end-point event was lower in the PCI group than in the medical-therapy group (4.3% vs. 12.7%; hazard ratio with PCI, 0.32; 95% confidence interval [CI], 0.19 to 0.53; P<0.001) (Fig. 1A and Table 2). In the registry cohort, 5 patients had at least one primary end-point event (3.0%). There was little difference in the incidence of a primary end-point event between patients in the PCI group and patients in the registry (hazard ratio for the PCI group, 1.29; 95% CI, 0.49 to 3.39; P=0.61), but there was a large difference between patients in the medical-therapy group and patients in the registry (hazard ratio for the medical-therapy group, 4.32; 95% CI, 1.75 to 10.66; P=0.001) (Table S2 in the Supplementary Appendix).

SECONDARY END POINTS

The Kaplan–Meier curves for the individual components of the primary end point are shown in Figures 1B, 1C, and 1D. Neither the rate of death from any cause nor the rate of myocardial infarction differed significantly between the PCI group and the medical-therapy group, but the rate of urgent revascularization did differ significantly between the groups (hazard ratio with PCI, 0.13; 95% CI, 0.06 to 0.30; P<0.001). Among the 56 patients who underwent urgent revascularization, the procedure was triggered by a myocardial infarction in 12 patients (21.4%), by unstable angina accompanied by evidence of ischemia on ECG in 15 patients (26.8%), and by unstable angina diagnosed on the basis of clinical features in 29 patients (51.8%). In an exploratory analysis, 4 patients in the PCI group (0.9%) and 23 patients in the medical-therapy group (5.2%) underwent an urgent revascularization that was triggered by a myocardial infarction or by unstable angina with evidence of ischemia on ECG (hazard ratio with PCI, 0.13; 95% CI, 0.04 to 0.43; P<0.001). As compared with patients in the medical-therapy group, patients in the PCI group were significantly less likely to undergo any revascularization (hazard ratio with PCI, 0.14; 95% CI, 0.08 to 0.26) or nonurgent revascularization (hazard ratio, 0.17; 95% CI, 0.08 to 0.39) (Table 2, and Fig. S2 in the Supplementary Appendix). Among patients in the registry, the rates of death from any cause, myocardial infarction, urgent revascularization, and nonurgent revascularization were all low (Fig. 1, and Table S2 in the Supplementary Appendix).

Figure 2 shows the results from landmark analyses of the primary end point and its components. PCI plus the best available medical therapy was shown to be consistently more beneficial after the landmark point of 7 days after randomization than before; there were significant interactions between time and treatment with respect to the primary end point, the individual components of death and myocardial infarction, and the composite of death or myocardial infarction, as well as a trend toward an interaction with respect to urgent revascularization. Corresponding Kaplan–Meier curves are presented in Figure S3 in the Supplementary Appendix. Stratified analyses according to patient characteristics are shown in Figure S4 in the Supplementary Appendix. Effects were similar across most subgroups; however, the benefit of PCI appeared to be more pronounced among patients who had lesions with an FFR of less than 0.65 than among patients who had only lesions with larger FFR values (P=0.01 for the interaction). The reduction from baseline in the percentage of patients with angina of CCS grade II to IV was greater in the PCI group than in the medical-therapy group and the registry cohort (Fig. 3).

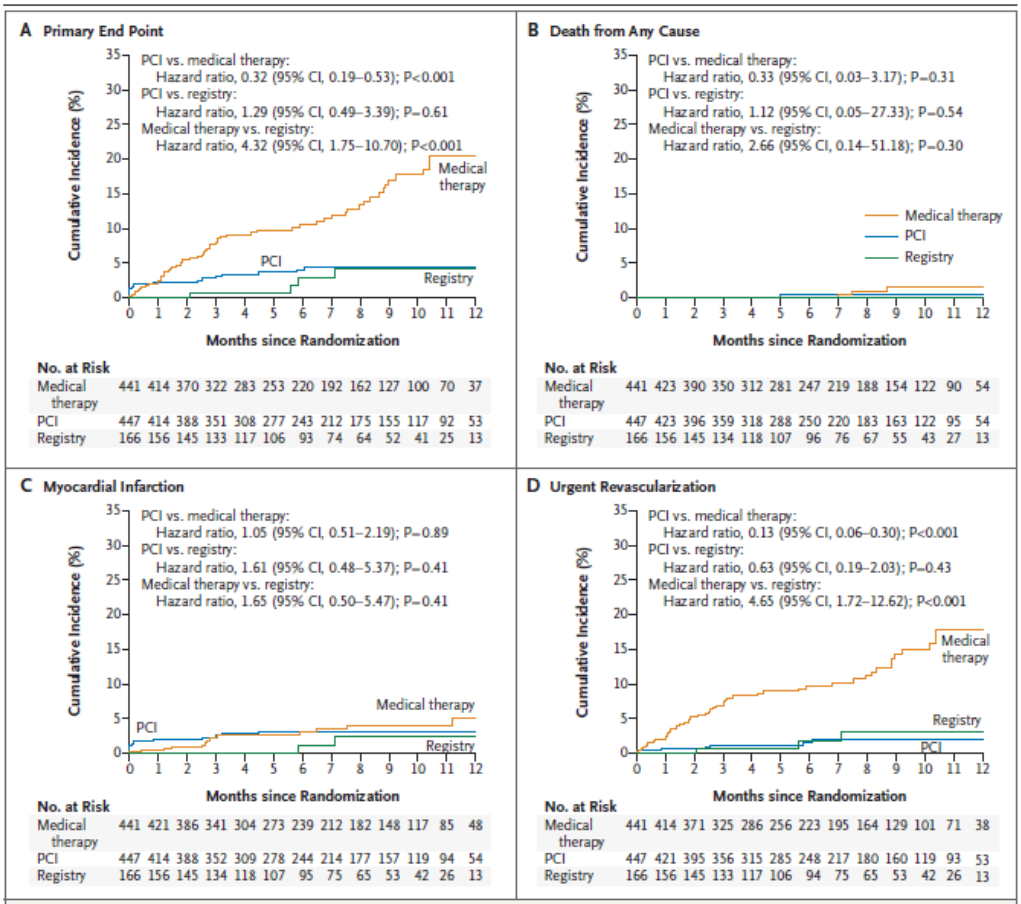


Figure 1. Cumulative Incidence of the Primary End Point and Its Components.

Kaplan–Meier curves are shown for the cumulative incidence of the primary end point of death, myocardial infarction, or urgent revascularization (Panel A) and the individual components of the primary end point (Panels B, C, and D) in the group that was randomly assigned to PCI and the best available medical therapy (PCI), the group that was randomly assigned to the best available medical therapy alone (medical therapy), and the group that did not undergo randomization and was enrolled in a registry (registry). After 12 months, a total of two primary end-point events occurred in the PCI group, none in the medical-therapy group, and one in the registry cohort. No deaths occurred after 12 months in any of the groups. Two patients in the PCI group, none in the medical-therapy group, and one in the registry cohort had a myocardial infarction after 12 months. One patient in the registry cohort, and none in the other two groups, had an urgent revascularization performed after 12 months.

DISCUSSION

In the FAME 2 trial, we compared the treatment strategy of PCI, performed according to current quality standards, plus the best available medical therapy with the best available medical therapy alone in patients with stable coronary artery disease and hemodynamically significant stenoses. FFR-guided PCI with drug-eluting stents plus the best available medical therapy, as compared with the best available medical therapy alone, resulted in significantly improved clinical outcomes. The difference between the two strategies was driven by an increase by a factor of 8 in the need for

Table 2. Clinical Events.

Event	Randomly Assigned Groups				Registry Cohort (N=166)
	PCI plus Medical Therapy (N=447)	Medical Therapy Alone (N=441)	Hazard Ratio with PCI (95% CI)	P Value	
	no. (%)				*no. (%)*
Primary end point	19 (4.3)	56 (12.7)	0.32 (0.19–0.53)	<0.001	5 (3.0)
Components of primary end point					
Death from any cause	1 (0.2)	3 (0.7)	0.33 (0.03–3.17)	0.31	0
Myocardial infarction	15 (3.4)	14 (3.2)	1.05 (0.51–2.19)	0.89	3 (1.8)
Urgent revascularization	7 (1.6)	49 (11.1)	0.13 (0.06–0.30)	<0.001	4 (2.4)
Death or myocardial infarction	15 (3.4)	17 (3.9)	0.61 (0.28–1.35)	0.22	3 (1.8)
Cardiac death	1 (0.2)	1 (0.2)	0.96 (0.06–15.17)	0.98	0
Revascularization					
Any	14 (3.1)	86 (19.5)	0.14 (0.08–0.26)	<0.001	6 (3.6)
Nonurgent revascularization	7 (1.6)	38 (8.6)	0.17 (0.08–0.39)	<0.001	2 (1.2)
Stroke	1 (0.2)	2 (0.5)	0.49 (0.04–5.50)	0.56	1 (0.6)
Definite or probable stent thrombosis	5 (1.1)	1 (0.2)	4.98 (0.59–42.25)	0.10	1 (0.6)

urgent revascularization in the medical-therapy group. In the case of half of these urgent revascularizations, the need for the procedure was triggered by an increase in biomarker levels, ischemic changes on ECG, or both. When we performed a landmark analysis, we found that the strategy of PCI plus the best available medical therapy was more beneficial 8 days or more after randomization than 7 days or less after randomization, with interactions between time and treatment with respect to the primary end point, as well as with respect to death and myocardial infarction, suggesting that the benefit of PCI plus the best available medical therapy might become more pronounced with an increasing duration of follow-up. The percentage of patients with angina of CCS class II to IV was markedly lower among patients in the PCI group than among patients in the medical-therapy group. Moreover, in 25% of the patients in whom PCI was considered, none of the stenoses that were visible on an angiogram were hemodynamically significant as assessed by means of the measurement of FFR. Among these patients, the strategy of providing the best available medical therapy alone was associated with a very low event rate.

Several factors may explain the differences between results in the present study and those in previous trials involving patients with stable coronary disease.[3,4] First, in previous trials in which various revascularization methods were compared with the best available medical therapy, patient enrollment was based primarily on angiographic findings, with or without noninvasive documentation of ischemia. It is likely that a sizable proportion of the patients had only limited ischemia. Even in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, in which noninvasive testing was performed in 85% of the patients,[3] less than one third of the patients had more than 10% ischemia on myocardial perfusion imaging.[8] In daily clinical practice, less than half of patients undergo noninvasive stress testing before elective PCI.[22] In the current trial, all the patients who underwent randomization had at least one functionally significant stenosis. Moreover, a mean FFR value of 0.68 in large epicardial arteries suggests that there were large areas of myocardium that were at risk for ischemia. The low-risk patients with nonischemic FFR values were not randomly assigned to a study group but were followed in a registry — a study design that was unlike that of previous trials.

Second, among patients in the PCI group who had several stenoses, PCI was performed only in

End Point	PCI	Medical Therapy	Relative Risk (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Primary end point					<0.001
≤7 days	9/447 (2.0)	4/441 (0.9)	2.24 (0.69–7.31)	0.17	
8 days to maximum follow-up	10/427 (2.3)	52/428 (12.1)	0.17 (0.09–0.35)	<0.001	
Death or myocardial infarction					0.003
≤7 days	8/447 (1.8)	1/441 (0.2)	7.99 (0.99–64.57)	0.04	
8 days to maximum follow-up	7/428 (1.6)	16/431 (3.7)	0.42 (0.17–1.04)	0.053	
Death					—
≤7 days	0/447	0/441			
8 days to maximum follow-up	1/436 (0.2)	3/432 (0.7)	0.33 (0.03–3.17)	0.37	
Myocardial infarction					0.007
≤7 days	8/447 (1.8)	1/441 (0.2)	7.99 (0.99–64.57)	0.04	
8 days to maximum follow-up	7/428 (1.6)	13/431 (3.0)	0.52 (0.21–1.32)	0.16	
Urgent revascularization					0.09
≤7 days	2/447 (0.4)	4/441 (0.9)	0.49 (0.09–2.70)	0.45	
8 days to maximum follow-up	5/434 (1.2)	45/428 (10.5)	0.10 (0.04–0.26)	<0.001	

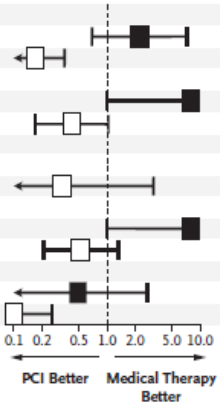


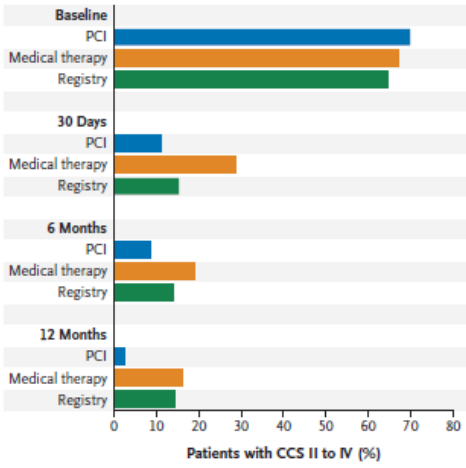
Figure 2. Landmark Analysis of the Primary End Point and Its Components.

The relative risk of the primary end point of death, myocardial infarction, or urgent revascularization and of components of the primary end point are shown, according to the time from randomization (7 days or less vs. 8 days or more). The solid boxes represent relative-risk estimates for 7 days or less after randomization, and the open boxes represent relative-risk estimates for 8 days to the maximum follow-up. Arrows indicate that the lower end of the confidence interval is less than 0.1. (The lower end of the confidence interval for urgent revascularization at 8 days to maximum follow-up, which could not be shown on the plot, was 0.04.) P values were calculated with the use of a log-rank test, except for the following, which were calculated with the use of Fisher's exact test: death or myocardial infarction at 7 days or less; death at 8 days to maximum follow-up; myocardial infarction at 7 days or less; and urgent revascularization at 7 days or less. P values for the interaction between time and treatment with respect to the end points were calculated with the use of the Mantel–Cox method. A total of 10 patients randomly assigned to PCI plus the best available medical therapy and 8 patients assigned to the best available medical therapy alone underwent randomization during the week before January 15, 2012, and their data were censored for the analysis of 8 days to maximum follow-up. In addition, 1 patient in each of those groups withdrew consent during the first week of follow-up, and their data were also censored in the analysis of the subsequent period.

lesions with an FFR of 0.80 or less. This FFR-guided approach is associated with a better clinical outcome than that with PCI performed on the basis of angiographic results alone.[10] These features probably explain the similarity of event rates between patients who were treated with PCI plus the best available medical therapy and patients with equivalent baseline characteristics but no functionally significant lesions who were enrolled in the registry and treated with the best available medical therapy alone.

Third, we used drug-eluting stents in patients who underwent PCI, a strategy that resulted in a low number of repeat revascularizations.[18-20] The use of anti-ischemic medication was similar to that reported in the COURAGE trial[23] and was most likely much higher than that in routine clinical practice.[24] Nevertheless, receipt of the best available medical therapy did not preclude a significantly higher number of unplanned hospitalizations with urgent revascularization among patients randomly assigned to the best available medical therapy alone than among those assigned to PCI plus the best available medical therapy.

Finally, the primary end point of the present study included not only death and myocardial infarction but also urgent revascularization, a component that was not included in the primary end point of previous trials. The definition of urgent revascularization was stringent in order to distinguish it from nonurgent — albeit clinically justified — revascularizations. Among patients who underwent urgent revascularization, the clinical presentation met the criteria of an acute coronary syndrome as assessed by an independent clinical events committee whose members were unaware of the treatment assignments. In half the patients who underwent an urgent revascularization, the unstable nature of the symp-



	Randomly Assigned Groups			Randomly Assigned Groups vs. Registry	
	No. of events/ total no.	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
Baseline			0.42		
PCI	312/447	1.04 (0.95–1.13)		1.08 (0.95–1.23)	0.22
Medical therapy	296/440	Reference		1.04 (0.92–1.19)	0.52
Registry	107/166	—		Reference	
			<0.001		
30 Days					
PCI	46/413	0.39 (0.28–0.53)		0.72 (0.45–1.15)	0.17
Medical therapy	119/412	Reference		1.87 (1.25–2.81)	0.002
Registry	23/149	—		Reference	
			0.002		
6 Months					
PCI	21/238	0.46 (0.28–0.74)		0.62 (0.33–1.19)	0.16
Medical therapy	46/239	Reference		1.36 (0.77–2.40)	0.29
Registry	13/92	—		Reference	
			0.07		
12 Months					
PCI	1/41	0.15 (0.02–1.19)		0.17 (0.01–2.42)	0.19
Medical therapy	6/37	Reference		1.14 (0.16–8.03)	0.90
Registry	1/7	—		Reference	

Figure 3. Patients with Angina Class II to IV and Corresponding Relative Risks.

The percentage of patients with angina of class II to IV on the Canadian Cardiovascular Society (CCS) scale (which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina) and the corresponding relative risks are shown at various time points for the group that was randomly assigned to PCI and the best available medical therapy (PCI), the group that was randomly assigned to the best available medical therapy alone (medical therapy), and the group that did not undergo randomization and was enrolled in a registry (registry). A total of 414 patients in the PCI group, 417 in the medical-therapy group, and 151 in the registry cohort were eligible for follow-up at 30 days; the corresponding numbers at 6 months were 238, 241, and 92, and the corresponding numbers at 1 year were 41, 38, and 7.

toms was evidenced by ST-segment depression, biomarker elevation, or both. The occurrence of an acute coronary syndrome necessitates hospitalization and is associated with an unfavorable prognosis, and it should therefore be considered to be a treatment failure. More important, revascularization has been shown to improve the rate of survival and decrease the risk of myocardial infarction among high-risk patients with an acute coronary syndrome.[25-27]

The trial has several limitations. First, because of the premature termination of enrollment, there was an unusually short follow-up period — too short to see restenosis emerge as a complication of PCI. Differences in the rates of death and myocardial infarction between the strategies of PCI and medical therapy alone that were seen in one recent registry study[28] could not be confirmed. However, the difference in the primary outcome between the two treatment groups was large and was steadily increasing over time; therefore, the data and safety monitoring board believed that exposing more patients with functionally significant stenoses to the risk of urgent revascularization was inappropriate. Second, although randomization was concealed,[29] it is possible that the awareness of the presence of a stenosis influenced decisions regarding revascularization. Third, even though the adherence to medications was high, the best available medical therapy did not include interventions by nurse case managers that were aimed at lifestyle changes and risk-factor reduction, interventions that were included as part of the best available medical therapy in the COURAGE trial.[23] Fourth, the strategic nature of the trial meant that we followed contemporary guidelines,[30] which require dual antiplatelet treatment only for patients who undergo stenting. It is unlikely that this difference in drug regimen between the two groups could explain the magnitude of the observed difference with respect to the primary end point.

In conclusion, among patients with stable coronary artery disease and at least one stenosis with an FFR of 0.80 or less, FFR-guided PCI with drug-eluting stents plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the rate of urgent revascularization. Among patients with stenoses that were not functionally significant, the best available medical therapy alone resulted in an excellent outcome, regardless of the angiographic appearance of the stenoses.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

Fractional Flow Reserve–Guided PCI for Stable Coronary Artery Disease

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ABSTRACT

BACKGROUND

We hypothesized that in patients with stable coronary artery disease and stenosis, percutaneous coronary intervention (PCI) performed on the basis of the fractional flow reserve (FFR) would be superior to medical therapy.

METHODS

In 1220 patients with stable coronary artery disease, we assessed the FFR in all stenoses that were visible on angiography. Patients who had at least one stenosis with an FFR of 0.80 or less were randomly assigned to undergo FFR-guided PCI plus medical therapy or to receive medical therapy alone. Patients in whom all stenoses had an FFR of more than 0.80 received medical therapy alone and were included in a registry. The primary end point was a composite of death from any cause, nonfatal myocardial infarction, or urgent revascularization within 2 years.

RESULTS

The rate of the primary end point was significantly lower in the PCI group than in the medical-therapy group (8.1% vs. 19.5%; hazard ratio, 0.39; 95% confidence interval [CI], 0.26 to 0.57; P<0.001). This reduction was driven by a lower rate of urgent revascularization in the PCI group (4.0% vs. 16.3%; hazard ratio, 0.23; 95% CI, 0.14 to 0.38; P<0.001), with no significant between-group differences in the rates of death and myocardial infarction. Urgent revascularizations that were triggered by myocardial infarction or ischemic changes on electrocardiography were less frequent in the PCI group (3.4% vs. 7.0%, P=0.01). In a landmark analysis, the rate of death or myocardial infarction from 8 days to 2 years was lower in the PCI group than in the medical-therapy group (4.6% vs. 8.0%, P=0.04). Among registry patients, the rate of the primary end point was 9.0% at 2 years.

CONCLUSIONS

In patients with stable coronary artery disease, FFR-guided PCI, as compared with medical therapy alone, improved the outcome. Patients without ischemia had a favorable outcome with medical therapy alone. (Funded by St. Jude Medical; FAME 2 ClinicalTrials.gov number, NCT01132495.)

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*A complete list of investigators and committee members in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial is provided in the Supplementary Appendix, available at NEJM.org.

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The benefit of percutaneous coronary intervention (PCI) as an initial treatment strategy in patients with stable coronary artery disease remains controversial.[1-3] The potential result from revascularization depends on the extent and the degree of myocardial ischemia.[4,5] A fractional flow reserve (FFR) value of 0.80 or less (i.e., a drop in maximal blood flow of 20% or more caused by stenosis), as measured with the use of a coronary pressure wire during catheterization, indicates the potential of a stenosis to induce myocardial ischemia.[6-8]

In such cases, robust clinical-outcome data favor FFR-guided revascularization, as compared with revascularization guided by angiography alone.[9-16] In previous trials comparing PCI with medical therapy alone in patients with stable coronary artery disease,[1,2] investigators did not use FFR guidance or contemporary drug-eluting stents.

In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial, we investigated whether contemporary PCI plus medical therapy would be superior to medical therapy alone in patients with stable coronary artery disease and functionally significant stenoses, as determined by the FFR. This report describes the prespecified 2-year results for the primary outcome.

METHODS

PATIENTS

We enrolled patients with clinically stable coronary artery disease involving up to three vessels (as determined on angiography) that was suitable for treatment with PCI. The inclusion and exclusion criteria have been described previously.[17] Using a centralized randomization method, we assigned patients who had at least one stenosis in a major coronary artery with an FFR of 0.80 or less to undergo FFR-guided PCI (with the use of the PressureWire Certus or PressureWire Aeris, St. Jude Medical) plus medical therapy (PCI group) or to receive medical therapy alone (medical-therapy group). Patients with an FFR of more than 0.80 in all stenoses received medical therapy alone and were included in a registry. All patients provided informed written consent. The study protocol is available with the full text of this article at NEJM.org.

STUDY DESIGN AND OVERSIGHT

We conducted this open-label, randomized trial at 28 sites in Europe and North America. The trial was approved by the institutional review board at each participating center. The members of the steering committee designed the study without involvement of the sponsor, St. Jude Medical. The sponsor was involved in the collection and source verification of the data but not in the conduct of the trial. An independent data and safety monitoring board oversaw the trial. The members of the steering committee had full access to all the data in the study, wrote the manuscript, and made the decision to submit it for publication.

STUDY TREATMENTS

Patients were prescribed daily aspirin, a beta-blocker (alone or in combination with a calcium-channel blocker, a long-acting nitrate, or both), an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker, and atorvastatin alone or in combination with ezetimibe to achieve a low-density lipoprotein cholesterol level of less than 70 mg per deciliter (1.8 mmol per liter). Among patients in the medical-therapy group and the registry patients, the prescription of clopidogrel was left to the discretion of the treating clinician. Among patients in the PCI group, all stenoses with an FFR of 0.80 or less were treated with second-generation drug-eluting stents. These patients received clopidogrel (at a dose of 75 mg per day) for at least 12 months in addition to standard medical therapy. Smokers were counseled regarding smoking cessation, and patients with diabetes were referred to a specialist in order to optimize their treatment.

STUDY END POINTS AND FOLLOW-UP

The primary end point was a composite of death from any cause, nonfatal myocardial infarction, or unplanned hospitalization leading to urgent revascularization within 2 years. Fifty percent of registry patients were randomly selected to be followed up in the same manner as the study patients. For each outcome event, a detailed narrative was produced. All events were adjudicated by an independent clinical-events committee whose members were unaware of the assigned treatment.

Revascularization was considered to be urgent when a patient was admitted to the hospital

with persistent or increasing symptoms (with or without changes in the ST segment or T wave or elevated biomarker levels) and the revascularization procedure was performed during the same hospitalization. All urgent revascularizations were adjudicated by two independent cardiologists, who were unaware of the assigned treatment, to determine the type of trigger (myocardial infarction, electrocardiographic evidence of ischemic changes, or clinical features only) and the severity of angina (according to the criteria of the Canadian Cardiovascular Society [CCS]) that led to the procedure.

ADVERSE EVENTS

Serious adverse events were defined as any event that resulted in death or was life-threatening, required hospitalization or prolongation of a hospital stay, or resulted in persistent or substantial disability. Also included were all protocol-specified clinical end-point events.

STATISTICAL ANALYSIS

The trial was powered to determine the superiority of FFR-guided PCI plus medical therapy over medical therapy alone with respect to the primary end point at 2 years. We estimated that the cumulative incidence of the primary end point would be 12.6% in the PCI group[18-20] and 18.0% in the medical-therapy group,[1] which would correspond to a relative risk reduction of 30% in the PCI group. We determined that the enrollment of 816 patients in each study group would provide a power of more than 84% to detect a relative risk reduction of 30% at a two-sided type I error rate of 0.05.

We used the Mantel–Cox method to calculate hazard ratios and 95% confidence intervals for between-group comparisons of clinical outcomes and the log-rank test to calculate corresponding P values. All patients were included in the intention-to-treat analysis. We constructed Kaplan–Meier curves for the primary end point and its components. In exploratory analyses, we separately plotted cumulative urgent-revascularization events triggered by myocardial infarction, unstable angina with evidence of ischemia on electrocardiography, or clinical features only, stratified according to the CCS class, and used the Mantel–Cox method to calculate hazard ratios with 95 confidence intervals and log-rank tests to calculate P values.

We performed separate analyses according to a landmark (cutoff) point of 7 days after randomization, with hazard ratios calculated separately for events that occurred within 7 days and those that occurred between 8 days and the end of follow-up at 2 years. For each type of event, data for patients were censored at the time of the first event — for example, data for a patient who had an event that contributed to the primary composite end point during the first 7 days were censored at the time of the event and excluded from the analysis of subsequent years after the landmark point. Landmark analyses were accompanied by a chi-square test for interaction between treatment effect and time (first 7 days vs. subsequent period). All analyses were performed by two independent statisticians at an academic clinical-trials unit (CTU Bern, University of Bern).

RESULTS

PATIENTS

Among 1220 patients who were enrolled between May 15, 2010, and January 15, 2012, a total of 888 had at least one stenosis with an FFR of 0.80 or less in a large epicardial artery. These patients were randomly assigned to undergo FFR-guided PCI plus medical therapy (447 patients) or to receive medical therapy alone (441 patients). In the remaining 332 registry patients, all stenoses that were visible on angiography had an FFR of more than 0.80. On the basis of the highly significant between-group difference in the primary end point, patient recruitment was halted on January 15, 2012, after the randomization of 54% of the patients in the initially planned study sample (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The characteristics of the patients at baseline, which have been described previously,[17] were well balanced between the two treatment groups (Table S1 in the Supplementary Appendix). Among the 888 patients, 1601 stenoses were eligible for PCI on the basis of angiography, whereas 1304 stenoses were eligible for PCI on the basis of an FFR of 0.80 or less, with a mean (±SD) FFR of 0.64±0.13 (range, 0.19 to 0.80).

PRIMARY END POINT

At 2 years, at least one primary outcome event had occurred in 36 patients (8.1%) in the PCI group and in 86 patients (19.5%) in the medical-therapy group (hazard ratio in the PCI group,

Table 1. Clinical Events and Triggers of Urgent Revascularization.*

Variable	PCI (N=447)	Medical Therapy (N=441)	Hazard Ratio (95% CI)†	P Value‡
	no. (%)			
Primary end point	36 (8.1)	86 (19.5)	0.39 (0.26–0.57)	<0.001
Death from any cause	6 (1.3)	8 (1.8)	0.74 (0.26–2.14)	0.58
Myocardial infarction	26 (5.8)	30 (6.8)	0.85 (0.50–1.45)	0.56
Urgent revascularization	18 (4.0)	72 (16.3)	0.23 (0.14–0.38)	<0.001
Death or myocardial infarction	29 (6.5)	36 (8.2)	0.79 (0.49–1.29)	0.35
Other end points				
Death from cardiac causes	3 (0.7)	3 (0.7)	0.99 (0.20–4.90)	0.99
Revascularization				
Any	36 (8.1)	179 (40.6)	0.16 (0.11–0.22)	<0.001
Nonurgent	18 (4.0)	117 (26.5)	0.13 (0.08–0.22)	<0.001
Stroke	7 (1.6)	4 (0.9)	1.74 (0.51–5.94)	0.37
Definite or probable stent thrombosis	7 (1.6)	2 (0.5)	3.48 (0.72–16.8)	0.10
Triggers of urgent revascularization according to Canadian Cardiovascular Society class§				
Any trigger				
All classes	18 (4.0)	72 (16.3)	0.23 (0.14–0.38)	<0.001
0, I, or II	4 (0.9)	7 (1.6)	0.56 (0.16–1.93)	0.35
III	3 (0.7)	20 (4.5)	0.14 (0.04–0.49)	<0.001
IV	11 (2.5)	47 (10.7)	0.22 (0.11–0.42)	<0.001
Myocardial infarction or changes on ECG				
All classes	15 (3.4)	31 (7.0)	0.47 (0.25–0.86)	0.01
0, I, or II	3 (0.7)	4 (0.9)	0.74 (0.17–3.31)	0.69
III	2 (0.4)	7 (1.6)	0.28 (0.06–1.35)	0.09
IV	10 (2.2)	21 (4.8)	0.46 (0.22–0.98)	0.04
Clinical features only				
All classes	3 (0.7)	43 (9.8)	0.07 (0.02–0.21)	<0.001
0, I, or II	1 (0.2)	3 (0.7)	0.33 (0.03–3.17)	0.31
III	1 (0.2)	14 (3.2)	0.07 (0.01–0.53)	0.001
IV	1 (0.2)	27 (6.1)	0.03 (0.00–0.26)	<0.001

* ECG denotes electrocardiography, and PCI percutaneous coronary intervention.
† Hazard ratios are for the PCI group as compared with the medical-therapy group.
‡ P values were calculated with the use of the log-rank test.
§ Patients could have more than one event. The Canadian Cardiovascular Society grades the severity of angina as follows: class I, angina only during strenuous or prolonged physical activity; class II, slight limitation, with angina only during vigorous physical activity; class III, symptoms with activities of everyday living (moderate limitation); and class IV, inability to perform any activity without angina or angina at rest (severe limitation).

0.39; 95% confidence interval [CI], 0.26 to 0.57; P<0.001) (Table 1, and Table S2 in the Supplementary Appendix). In the registry group, at least one event in the primary end point occurred in 15 patients (9.0%), with little difference between the PCI group and registry patients (hazard ratio, 0.90; 95% CI, 0.49 to 1.64; P=0.72) but a large difference between the medical-therapy group and registry patients (hazard ratio, 2.34; 95% CI, 1.35 to 4.05; P=0.002) (Table S2 and Fig. S2 in the Supplementary Appendix).

LANDMARK ANALYSES

Within 7 days after randomization, there were more primary end-point events in the PCI group than in the medical-therapy group (2.2% vs.

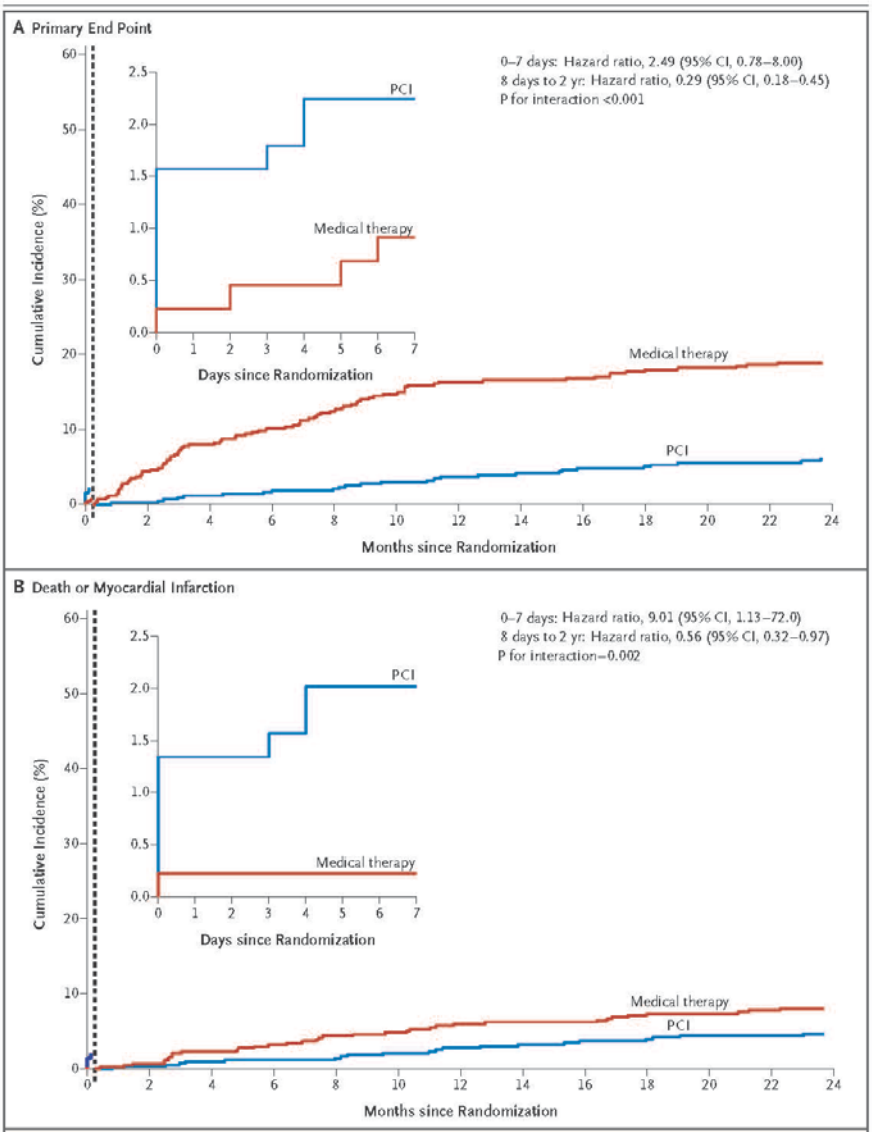

Figure 1. Kaplan–Meier Curves for the Landmark Analyses.

Shown are the cumulative incidences of the primary end point (a composite of death from any cause, nonfatal myocardial infarction, or urgent revascularization) (Panel A) and of death or myocardial infarction (Panel B) in the two study groups, stratified on the basis of a landmark point at 7 days after randomization (vertical dashed line). Hazard ratios for PCI versus medical therapy were calculated separately for events that occurred within 7 days and those that occurred between 8 days and the end of follow-up at 2 years. Data for the first 7 days are not included in the period after 7 days. The insets show the data for days 0 to 7 on an expanded y axis. P values for interaction were calculated from tests of heterogeneity between time periods. Hazard ratios below 1.00 denote a lower incidence of the primary end point in the PCI group than in the medical-therapy group.

0.9%; hazard ratio, 2.49; 95% CI, 0.78 to 8.00; P=0.11) (Fig. 1A, and Table S3 in the Supplementary Appendix). Six out of 10 primary end-point events in the PCI group were periprocedural myocardial infarctions. During the period from 8 days to 2 years after randomization, patients undergoing PCI had a 44% relative risk reduction for the composite of death or myocardial infarction (4.6% vs. 8.0%; hazard ratio, 0.56; 95% CI, 0.32 to 0.97; P=0.04) (Fig. 1B) and a 79% relative risk reduction for urgent revascularization (3.6% vs. 15.6%; hazard ratio, 0.21; 95% CI, 0.12 to 0.37; P<0.001), with a significant interaction between treatment and time for the composite of death or myocardial infarction (P=0.002 for interaction) but not for urgent revascularization (P=0.34 for interaction).

URGENT REVASCULARIZATION

The between-group difference in the primary end point was driven by a 77% reduction in the need for urgent revascularization in the PCI group, as compared with the medical-therapy group (4.0% vs. 16.3%; hazard ratio, 0.23; 95% CI, 0.14 to 0.38; P<0.001) (Table 1). Figure 2 shows the cumulative numbers of unplanned rehospitalizations with urgent revascularization according to the type of trigger and angina class over time. Eighteen urgent revascularizations were performed in 18 patients in the PCI group (2.1 events per 100 patient-years), whereas 79 revascularizations were performed in 72 patients in the medical-therapy group (10.4 events per 100 patient-years).

In these 90 patients in the two study groups, revascularizations were triggered by a myocardial infarction in 28 patients (31%), by unstable angina with ischemic changes on electrocardiography in 18 patients (20%), and by clinical features only in the remaining 44 patients (49%), with a predominance of CCS class IV angina, regardless of the trigger. There were significant differences between the PCI group and the medical-therapy group with respect to urgent revascularizations triggered by a myocardial infarction or ischemic electrocardiographic changes (3.4% vs. 7.0%; hazard ratio, 0.47; 95% CI, 0.25 to 0.86; P=0.01) and those triggered by CCS class IV angina (2.5% vs. 10.7%; hazard ratio, 0.22; 95% CI, 0.11 to 0.42; P<0.001). Figure 3 shows the cumulative incidence of revascularization for any reason.

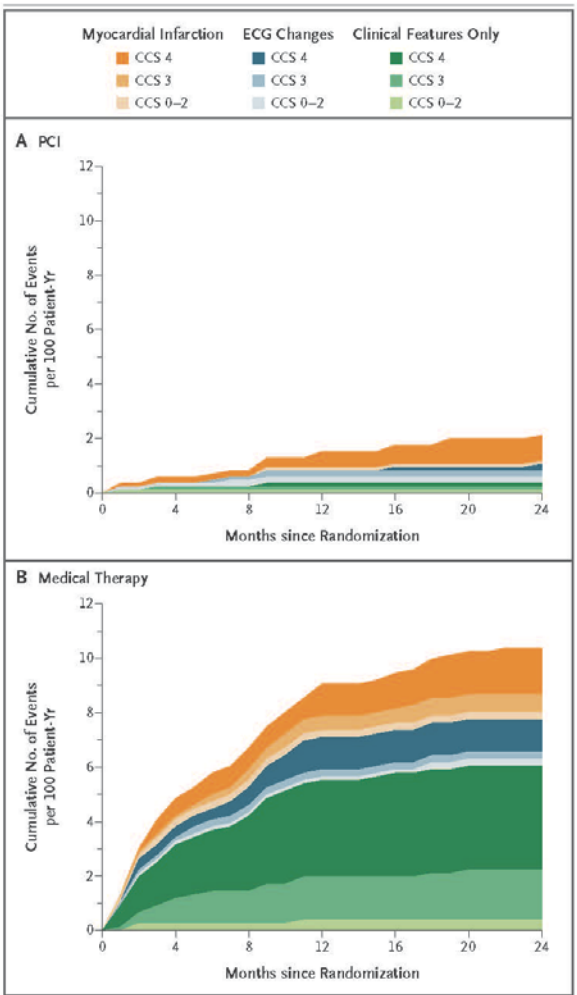

Figure 2. Urgent Revascularizations, According to Type of Trigger.
Cumulative events of urgent revascularization are shown for patients in the PCI group (Panel A) and those in the medical-therapy group (Panel B), according to whether the procedure was triggered by myocardial infarction, electrocardiographic (ECG) changes, or clinical features only and according to the severity of angina at presentation, as indicated by Canadian Cardiovascular Society (CCS) class.

OTHER END POINTS

After 2 years, 179 patients (40.6%) in the medical-therapy group had crossed over to undergo PCI, whereas 36 patients (8.1%) in the PCI group had undergone repeat revascularization (hazard

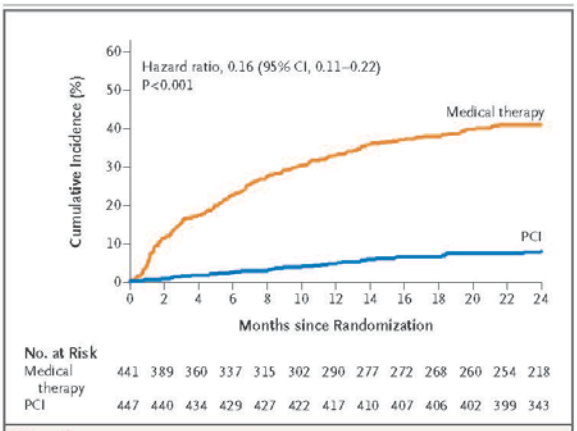

Figure 3. Kaplan–Meier Curves for Total Revascularizations.
Shown are the cumulative incidences of total revascularizations in the two study groups during the 2-year study period. Hazard ratios and the corresponding 95% confidence intervals are based on a Mantel–Cox comparison of revascularizations with PCI versus medical therapy alone, and the P values were calculated with the use of a log-rank test. Additional details are provided in Figure S5 in the Supplementary Appendix.

ratio, 0.16; 95% CI, 0.11 to 0.22; P<0.001). Table S2 in the Supplementary Appendix presents a comparison of end points for patients in the two study groups and the 166 registry patients who were followed for up to 2 years; 20 registry patients (12.0%) crossed over to undergo PCI. Figure S3 in the Supplementary Appendix presents stratified analyses of the primary end point according to the characteristics of the patients at baseline. The reduction from baseline in the percentage of patients with angina of CCS grade II, III, or IV was greater among patients in the PCI group than among those in the medical-therapy group and those in the registry group at all time points during 2 years of follow-up (Fig. S4 in the Supplementary Appendix). After 2 years, 69% of patients were still receiving a combination of aspirin, beta-blockers, and statins (Table S4 in the Supplementary Appendix).

SERIOUS ADVERSE EVENTS

At least one clinical event or other serious adverse event was reported in 151 patients (33.8%) in the PCI group and in 232 patients (52.6%) in the medical-therapy group (hazard ratio, 0.55; 95% CI, 0.44 to 0.67; P<0.001) (Table 1, and Table S5 in the Supplementary Appendix). The same percentage of patients in the two groups (17.2%) had noncardiovascular serious adverse events, including clinical events (hazard ratio, 1.00; 95% CI, 0.73 to 1.38; P=0.98), whereas serious cardiovascular adverse events (defined as death from cardiac causes, myocardial infarction, stent thrombosis, any revascularization, or any other cardiovascular serious adverse event) were reported in 110 patients in the PCI group as compared with 204 patients in the medical-therapy group (24.6% vs. 46.3%; hazard ratio, 0.45; 95% CI, 0.36 to 0.57; P<0.001).

DISCUSSION

In our study involving patients with stable coronary artery disease and stenosis, the rate of the primary end point (death, myocardial infarction, or urgent revascularization at 2 years) among those who underwent FFR-guided PCI with contemporary drug-eluting stents was less than half the rate among patients who received medical therapy alone. Urgent revascularizations triggered by a myocardial infarction or ischemic changes on electrocardiography were half as frequent in the PCI group as in the medical-therapy group. Although there was no significant between-group difference in the overall rate of death or myocardial infarction, patients who underwent PCI, as compared with those who received medical therapy alone, had a significant reduction in the rate of death or myocardial infarction after the initial 7 days following randomization.

More than 25% of patients with stable coronary artery disease who were scheduled to undergo PCI on the basis of clinical and angiographic data had no stenosis with an FFR value of 0.80 or less and were thus unlikely to have had ischemia. These patients had a favorable clinical outcome at 2 years with medical therapy alone, a finding that is similar to results in patients with at least one clinically significant stenosis who were treated with PCI plus medical therapy. The degree of angina at 2 years was significantly lower in the PCI group than in the medical-therapy group, even though almost 50% of patients who were initially assigned to the medical-therapy group had died, had had a myocardial infarction, or had undergone revascularization.

In daily clinical practice, less than half of patients undergo noninvasive stress testing be-

fore elective PCI,[21] and the decision to perform revascularization is based primarily on the angiographic appearance of a stenosis. There is a growing awareness of the poor accuracy of coronary angiography for identifying lesions responsible for myocardial ischemia and the inaccuracy of noninvasive stress testing in patients with multivessel coronary artery disease.[22,23] In our randomized trial, we enrolled only patients with an FFR of 0.80 or less in at least one large epicardial artery. In contrast to all previous trials comparing PCI with medical therapy in patients with stable coronary artery disease, this FFR-driven selection process excluded patients without clinically significant ischemia, who are known to be at lower risk than are those with ischemia. The inclusion of these low-risk patients in previous trials limited the potential for showing any benefit from PCI. In our study, the measurement of FFR in patients with multivessel coronary artery disease allowed for the determination of which lesions were hemodynamically significant. Such lesions were shown to benefit from PCI, as compared with hemodynamically nonsignificant stenoses, for which PCI is unnecessary or even harmful.[9,10] The resolution of ischemia in the patients treated with FFR-guided PCI probably explains the similar event rates among registry patients who had coronary artery disease and similar baseline characteristics but who received medical therapy alone because they had no ischemia-producing lesions.

Multiple studies have suggested that periprocedural infarctions rarely have an effect on the long-term prognosis for patients undergoing PCI,[24,25] whereas spontaneous infarctions are predictive of an increased risk of death. In our study, the rate of death or myocardial infarction was significantly higher in the medical-therapy group than in the PCI group after the initial 7 days following randomization because of a higher rate of spontaneous myocardial infarction in the medical-therapy group.

The primary end point of our study included not only death and myocardial infarction but also unplanned hospitalization for urgent revascularization. The definition of urgent revascularization was stringent in order to distinguish urgent from nonurgent procedures. Severe angina was present in more than 90% of patients who underwent urgent revascularization, and in more than 40% of these patients, there was an increase in biomarkers or dynamic changes on electrocardiography, which are criteria for performing PCI according to both American and European guidelines.[26,27] Therefore, urgent revascularization in our study should be considered a failure of the treatment to which the patient has been assigned.

In contrast to previous trials comparing PCI with medical therapy,[1,2] we used second-generation drug-eluting stents.[18-20] This factor may partially explain the improved outcome in patients with stable coronary artery disease who were treated with PCI as compared with the outcome in the medical-therapy group.[28,29]

Our trial has several limitations. First, enrollment was interrupted early after interim analyses by the data and safety monitoring board disclosed a large excess of primary end-point events in the medical-therapy group. Second, patients and treating physicians were aware of study-group assignments. It is possible that the awareness of the presence of a functionally significant stenosis influenced the decision of the physician or the patient during follow-up. Yet, the fact that the group of registry patients with angiographically significant coronary artery disease had a lower number of events than those in the medical group suggests that the awareness of having an unstented coronary blockage cannot explain the high event rates among patients in the medical-therapy group. Moreover, the significantly higher rates of death and myocardial infarction that occurred more than 7 days after randomization in the medical-therapy group than in the PCI group and the registry group cannot be explained by the lack of blinding. Third, stenoses were located in large coronary arteries and the mean FFR value was 0.64, which suggests both profound and extensive ischemia. Thus, these results should not be extended to patients with smaller vascular areas at risk.

In conclusion, among patients with stable coronary artery disease and ischemia, as shown by the presence of at least one stenosis with an FFR of 0.80 or less in a large epicardial artery, the clinical outcome at 2 years was improved by FFR-guided PCI with second-generation drug-eluting stents plus the best available medical therapy, as compared with medical therapy alone. In patients without hemodynamically significant stenosis, the best available medical therapy alone

was associated with an excellent 2-year clinical outcome, regardless of the angiographic appearance of the stenoses.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice)

A Multicenter Study in Consecutive Patients

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Objectives This study sought to compare fractional flow reserve (FFR) with the instantaneous wave-free ratio (iFR) in patients with coronary artery disease and also to determine whether the iFR is independent of hyperemia.

Background FFR is a validated index of coronary stenosis severity. FFR-guided percutaneous coronary intervention (PCI) improves clinical outcomes compared to angiographic guidance alone. iFR has been proposed as a new index of stenosis severity that can be measured without adenosine.

Methods We conducted a prospective, multicenter, international study of 206 consecutive patients referred for PCI and a retrospective analysis of 500 archived pressure recordings. Aortic and distal coronary pressures were measured in duplicate in patients under resting conditions and during intravenous adenosine infusion at 140 μg/kg/min.

Results Compared to the FFR cut-off value of ≤0.80, the diagnostic accuracy of the iFR value of ≤0.80 was 60% (95% confidence interval [CI]: 53% to 67%) for all vessels studied and 51% (95% CI: 43% to 59%) for those patients with FFR in the range of 0.60 to 0.90. iFR was significantly influenced by the induction of hyperemia: mean ± SD iFR at rest was 0.82 ± 0.16 versus 0.64 ± 0.18 with hyperemia ($p < 0.001$). Receiver operating characteristics confirmed that the diagnostic accuracy of iFR was similar to resting Pd/Pa and trans-stenotic pressure gradient and significantly inferior to hyperemic iFR. Analysis of our retrospectively acquired dataset showed similar results.

Conclusions iFR correlates weakly with FFR and is not independent of hyperemia. iFR cannot be recommended for clinical decision making in patients with coronary artery disease. (Comparison of Fractional Flow Reserve Versus Instant Wave-Free Ratio for Assessment of Coronary Artery Stenosis Severity in Routine Practice; NCT01559493) (J Am Coll Cardiol 2013;61:1421–7) © 2013 by the American College of Cardiology Foundation

Fractional flow reserve (FFR) is a pressure-derived index of coronary stenosis severity and represents the ratio of maximal blood flow in a stenotic artery to maximal flow in the same artery in the absence of any stenosis (1–4). It has been well validated (5–7), and in patients with multivessel coronary disease undergoing percutaneous intervention (PCI), FFR guidance improves health and economic outcomes

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Abbreviations and Acronyms

ACC = American College of Cardiology
ESC = European Society of Cardiology
FFR = fractional flow reserve
iFR = instantaneous wave-free ratio
Pa = aortic pressure
Pd = distal coronary pressure
PCI = percutaneous coronary intervention

compared to treatment based on angiography alone (8–10). As a result, FFR guidance during PCI has received a class 1A recommendation from the European Society of Cardiology (11) and a class IIA recommendation from the American College of Cardiology (12). FFR measurements require that myocardial resistance is minimal and constant. In clinical practice, intravenous adenosine infusion is used to establish these conditions. Although most patients experience some breathlessness and chest tightness during adenosine infusion, these symptoms are generally well tolerated (13). The instantaneous wave-free ratio (iFR) has been proposed as an index of stenosis severity that is independent of hyperemia and can be measured without the need for adenosine (14). The concept of iFR is based on the hypothesis that there is a diastolic "wave-free" period (WFP) when microvascular resistance is already constant and minimal. An iFR value of ≤0.83 has been suggested as having diagnostic accuracy comparable to the commonly used FFR cutoff of ≤0.80. We studied consecutive unselected patients referred for angiography with or without PCI to compare FFR to iFR and to determine whether iFR is independent of hyperemia.

Methods

The study protocol was approved by the institutional review board or ethics committee at each participating center, and all patients provided written informed consent. This study is registered at the National Institutes of Health Clinical Trials website (NCT01559493). All consecutive patients referred for FFR-guided angiography with or without PCI during a 5-week period from January 4 to February 10, 2012,

Table 1 Baseline Characteristics (n = 206)

Age (yrs)	65.2 ± 10.2
Male	146 (71)
Mean body mass index (kg/m^2)	27.7 ± 4.6
Risk factors	
Cigarette smoker	64 (31)
Diabetes	50 (24)
Hypercholesterolemia	127 (62)
Treated hypertension	137 (67)
Family history	71 (35)
Mean % of left ventricular ejection fraction	56 ± 11
Stable angina	140 (68)
Unstable angina	46 (22)
No. of previous MIs in the culprit artery territory	28 (14)
Index artery	
LAD	133 (64)
Cx	28 (14)
RCA	45 (22)
No significant disease	16 (8)
Single-vessel disease	85 (41)
Two-vessel disease	64 (31)
Three-vessel disease	41 (20)
Medication	
Aspirin	181 (88)
Clopidogrel or ticagrelor or prasugrel	94 (46)
ACE inhibitor or ARB	139 (68)
Beta-blocker	161 (78)
Statin	169 (82)
Calcium antagonist	49 (24)
Long-acting nitrate	45 (22)
Insulin	19 (9)
Oral antidiabetes medication	33 (16)

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; MI = myocardial infarction; RCA = right coronary artery.

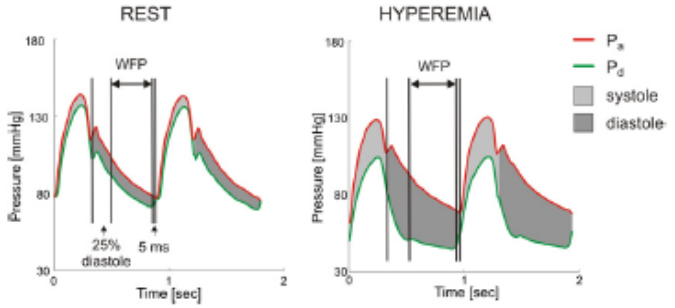

Figure 1 Pressure Tracings of 2 Sequential Heartbeats at Rest and During Hypermia Induced by Adenosine

The wave-free period (WFP) begins 25% into diastole and ends 5 ms before the end of diastole. Aortic pressure is in **red** and distal coronary artery pressure is in **green**. Both the systolic pressure gradient (**light shade**) and diastolic pressure gradient (**dark shade**) increase substantially during hyperemia.

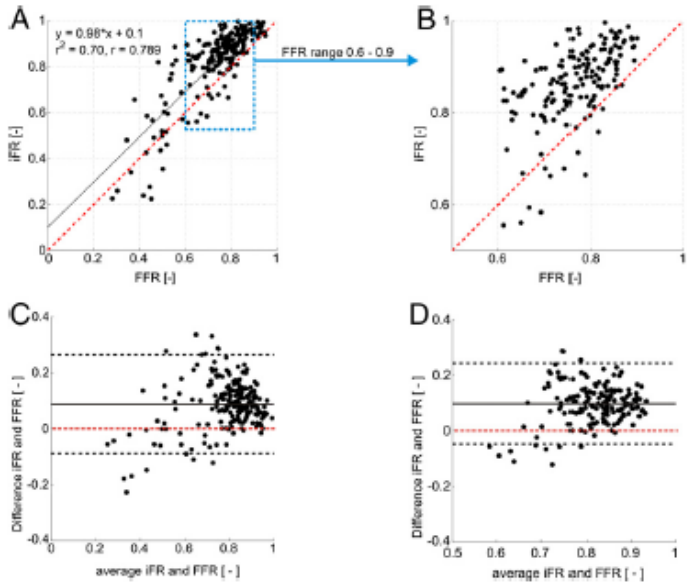

Figure 2 Scatterplots and Bland-Altman Plots of FFR Versus iFR for the Prospective Dataset (n = 206)

(A and C) All vessel; **(B and D)** vessels with FFR 0.60 to 0.90. Lines of identity are shown as **dashed red lines**. In addition to the linear regression shown **(A, solid black line)**, a hinged regression line (not shown) was fitted by least squares and gave a slope of 0.67 above the hinge point of FFR = 0.60 (x-axis) and 0.75 (**y-axis**) and a slope below it of 1.65; r is Spearman's correlation. Limits of agreement, −0.08 to 0.27 **(B)** and −0.05 to 0.24 **(D)**, are shown as **dashed lines**, and average differences are shown as **solid lines**. When FFR is low (<0.60), the 95% mean ± SD limits of agreement (±1.96) are wide (−0.36, 0.23).

were included. Exclusion criteria were a history of coronary artery bypass surgery, extremely tortuous coronary arteries, an occluded coronary artery, severely calcified lesions, or a history of acute myocardial infarction within 5 days. Retrospective analysis was conducted using archived pressure recordings from 500 unselected patients from three of the participating centers.

FFR was measured in one coronary artery in each patient after the operator had identified potential targets for PCI. The RadiAnalyzer Xpress instrument (St. Jude Medical, Uppsala, Sweden) and a coronary pressure wire (Certus, St Jude Medical, Uppsala, Sweden) were used in all cases. After the coronary angiogram was obtained, the pressure wire was zeroed, equalized, and positioned with the sensor in the distal third of the target artery. Two minutes after the last injection of contrast medium, pressure recording commenced. After approximately 10 cardiac cycles, an intravenous infusion of adenosine (140 μg/kg/min) was administered through a large antecubital or central vein. The response to adenosine was confirmed by changes in heart rate and blood pressure and development of typical symptoms. After a stable minimum value of FFR was established, the adenosine infusion and pressure recording were stopped. Following a 2-min rest period, the sequence was repeated to test reproducibility of all indices. Finally a pullback recording was performed to exclude wire drift.

iFR was measured as the ratio of mean distal coronary pressure to mean aortic pressure during the diastolic WFP

Table 2 Diagnostic Performance and Accuracy of iFR ≤0.80

Diagnosis	% of FFR ≤0.80 (n)	% of Sensitivity (95% CI)	% of Specificity (95% CI)	% of PPV (95% CI)	% of NPV (95% CI)	% of Accuracy (95% CI)
Prospective study						
All FFRs (n = 206)	65 (134)	40 (31–48)	99 (93–100)	98 (90–100)	47 (39–55)	60 (53–67)
FFRs 0.6–0.9 (n = 160)	64 (103)	25 (17–35)	98 (91–100)	96 (81–100)	42 (34–51)	51 (43–59)
Retrospective study						
All FFRs (n = 497)	68 (339)	40 (35–46)	99 (97–100)	99 (96–100)	44 (38–49)	59 (54–63)
FFRs 0.6–0.9 (n = 392)	70 (275)	28 (22–33)	99 (95–100)	99 (93–100)	37 (31–42)	49 (44–54)

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

Table 3 Diagnostic Performance and Accuracy of iFR ≤0.83

Diagnosis	% of FFR ≤0.80 (n)	% of Sensitivity (95% CI)	% of Specificity (95% CI)	% of PPV (95% CI)	% of NPV (95% CI)	% of Accuracy (95% CI)
Prospective study						
All FFRs (n = 206)	65 (134)	54 (45–62)	96 (88–99)	96 (89–99)	53 (44–62)	68 (61–75)
FFRs 0.6–0.9 (n = 160)	64 (103)	41 (31–51)	95 (85–99)	93 (82–99)	47 (38–56)	60 (52–68)
Retrospective study						
All FFRs (n = 497)	68 (339)	55 (49–60)	98 (95–99)	98 (95–100)	50 (44–56)	68 (64–72)
FFRs 0.6–0.9 (n = 392)	70 (275)	45 (39–52)	97 (93–99)	98 (93–100)	43 (37–49)	61 (56–66)

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

as described by Sen et al. (14) (Fig. 1). In order to determine whether iFR was independent of hyperemia, mean Pd/Pa during this period was also measured during adenosine infusion ("hyperemic" iFR). All analyses were performed in a fully automated manner without manual selection of data time points.

Data management and statistics. For the prospective study, a sample size of 189 subjects provided 90% power at the 5% significance level to confirm a difference of 10% in the diagnostic accuracy of iFR compared to FFR from a null hypothesis value of 80%. We planned to recruit 200 patients to account for any missing data. Clinical data without patient identifiers and coronary pressure recordings were submitted to a core laboratory (Department of Biomedical Engineering, University of Technology, Eindhoven, the Netherlands). Coronary pressure recordings were exported from RadiView software (version 2.2, St Jude Medical, Uppsala, Sweden) and analyzed using Matlab (Mathworks, Inc., Natick, Massachusetts). The relationship between FFR and iFR was quantified with a coefficient of determination (r^2). Agreement between the methods was assessed by Bland-Altman plots and 95% limits of agreement. The performance of iFR was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (the percentage of patients correctly diagnosed by iFR), together with their 95% confidence intervals (CIs). iFR was compared to hyperemic iFR and other measures by using receiver operating characteristics (ROC) area under the curve (AUC) analysis using the method described by DeLong et al. (15). Analyses were performed with the entire dataset and with the subgroup of patients with an FFR in the range 0.60 to 0.90. Statistical analysis was performed by an independent statistician (J.M.) with IBM SPSS version 19.0 (IBM Corp., Armonk, New York), Minitab version 16.0

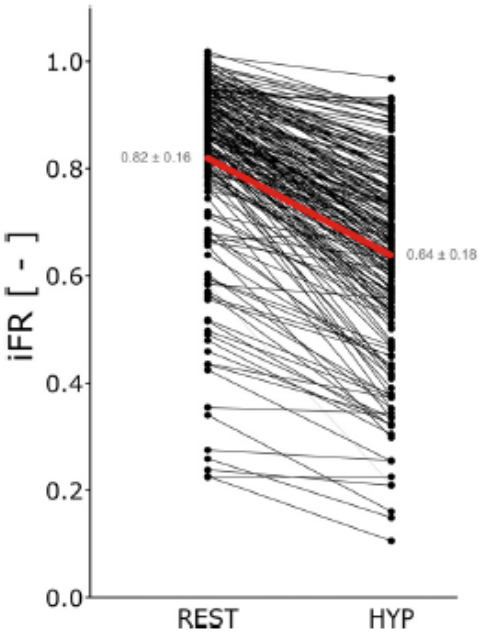

Figure 3 iFR During Rest and Hypermia With Mean ± SD for Each Group

Mean difference: 0.18 (95% CI: 0.17 to 0.20), p < 0.0001.

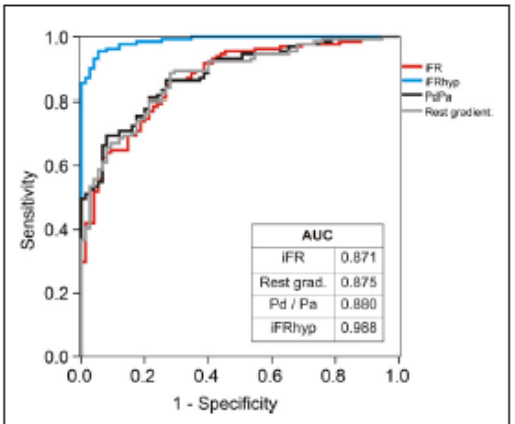

Figure 4 ROC Curves for iFR (AUC = 0.87), Hyperemic iFR (iFRhyp; AUC = 0.99, p < 0.000001), Distal Coronary/Aortic Pressure Ratio at Rest (Pd/Pa; AUC = 0.88, p = 0.52), and Resting Gradient Between Aortic and Distal Coronary Pressures (AUC = 0.87, p = 0.77)

All p values are comparisons with iFR.

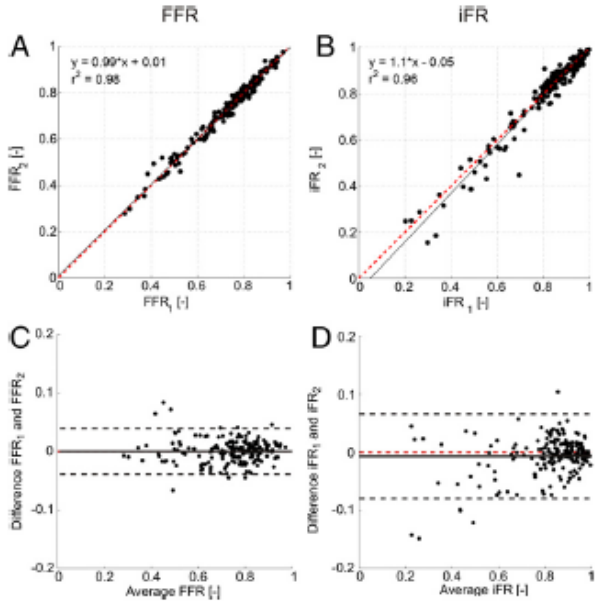

Figure 5 Scatterplots and Bland-Altman Plots Showing the Reproducibility of FFR and iFR

Line of identity is in **red (dashed)**. **(A and B)** Linear regression equation line is shown in **solid black.** **(C and D)** Mean differences **(solid black line)** and 95% limits of agreement **(dashed black lines)** are shown.

(Minitab Inc., State College, Pennsylvania), and R (R Foundation, Vienna, Austria) software.

Results

The clinical characteristics of the patients in the prospective study are shown in Table 1. The relationships between FFR and iFR are shown in Figure 2. Compared to the commonly used FFR cut-off value of ≤0.80, the diagnostic performance of iFR of ≤0.80 is shown in Table 2. Overall accuracy was 60% (95% CI: 53% to 67%) for all vessels studied and 51% (95% CI: 43% to 59%) for those with FFR in the range of 0.60 to 0.90. Sen et al. (14) proposed that iFR of ≤0.83 has diagnostic performance equivalent to an FFR of ≤0.80. The diagnostic performance of iFR at ≤0.83 in our prospectively acquired dataset is shown in Table 3. Overall accuracy was 68% (95% CI: 61% to 75%) for all vessels studied and 60% (95% CI: 52% to 68%) for those with FFR in the range of 0.60 to 0.90. iFR decreased significantly with hyperemia: mean ± SD iFR at rest 0.82 ± 0.16 versus 0.64 ± 0.18 with hyperemia (95% CI for difference 0.17 to 0.20; p<0.0001) (Fig. 3). ROC confirmed that the diagnostic performance of iFR was similar to that of resting Pd/Pa (p = 0.52) and trans-stenotic pressure gradient (p = 0.77) and inferior to that of hyperemic iFR (p < 0.0001) (Fig. 4). Both iFR and FFR showed excellent reproducibility (Fig. 5). However, FFR had significantly better reproducibility (p < 0.000) with the iFR differences having between 2.5 and 4.4 times larger variance than FFR differences (95% CI and F-test to compare two variances). The FFR 95% limits of agreement were −0.04 to 0.04; iFR 95% limits of agreement were wider (−0.07 to 0.08), particularly when iFR <0.8 (−0.08 to 0.14). The relative error (iFR − FFR/FFR) for heart rate (p = 0.032) and pressure rate product (p = 0.032) indicated that iFR was susceptible to variations in heart rate and blood pressure during resting conditions. This is illustrated by the wider spread of points in the iFR scatter plot than in the FFR scatter plot (Fig. 5). Results of the analysis of our retrospectively acquired dataset were consistent with those of the prospective study (Table 2 and 3, Fig. 6). In Figure 6A (as in Fig. 2A), in addition to the simple linear regression shown (solid black line), a hinged regression line was fitted by least squares and gave a slope of 0.62 above the hinge point of FFR = 0.63 (x-axis) and 0.78 (y-axis), and a slope below it of 1.19.

Discussion

Our results show a moderate overall correlation between FFR and iFR but only a weak correlation in the clinically important range for decision making of 0.60 to 0.90. Sen et

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Widimský, P., Rokyta, R., Št'ásek, J., Bělohlávek, J., Červinka, P., ***Kala, P.*** *Akutní koronární syndromy s pokračující ischemií myokardu versus akutní koronarní syndromy bez pokračující ischemie. Nová klasifikace akutních koronarních syndromů by měla nahradit starou klasifikaci založenou na přítomnosti nebo nepřítomnosti elevace úseku ST. Odborné stanovisko České kardiologické společnosti. (2013) Cor et Vasa, 55 (3), pp. E225-E227.*

(přehledová práce jako konsensus expertů České kardiologické společnosti – kvantitativní podíl uchazeče 20 % - koncept, text publikace)

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Odborné stanovisko ČKS | Expert consensus statement

Akutní koronární syndromy s pokračující ischemií myokardu versus akutní koronární syndromy bez pokračující ischemie. Nová klasifikace akutních koronárních syndromů by měla nahradit starou klasifikaci založenou na přítomnosti nebo nepřítomnosti elevace úseku ST.

Odborné stanovisko České kardiologické společnosti

(Acute coronary syndromes with ongoing myocardial ischemia (ACS with OMI) versus acute coronary syndromes without ongoing ischemia (ACS without OMI). The new classification of acute coronary syndromes should replace old classification based on ST segment elevation presence or absence—Expert consensus statement of the Czech Society of Cardiology)

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SOUHRN

V tomto dokumentu navrhuje Česká kardiologická společnost novou klasifikaci akutních koronárních syndromů v době prvního kontaktu s lékařem. V tomto návrhu se doporučuje zrušit termíny „infarkt myokardu s elevacemi úseku ST" a „akutní koronární syndrom bez elevací úseku ST" a nahradit je označením „akutní koronární syndrom s pokračující ischemií myokardu" a „akutní koronární syndrom bez pokračující ischemie myokardu". Nová navrhovaná klasifikace lépe odráží současné léčebné postupy a usnadní rozhodování při prvním kontaktu s lékařem.

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Úvod

Současná klasifikace akutních koronárních syndromů (AKS) ve dvou hlavních kategoriích (akutní infarkt myokardu s elevacemi úseku ST [STEMI] a akutní koronární syndromy bez elevací úseku ST [non-STE AKS]) historicky vychází z potřeby definovat pacienty indikované k trombolytické léčbě. Je prokázáno, že trombolytická léčba je sice účinná u STEMI, ne však u non-STE AKS [1,2]. V současnosti je však trombolytická léčba u STEMI ve většině evropských zemí a stále více i jinde ve světě nahrazována účinnějším léčebným postupem – primární perkutánní koronární intervencí (p-PCI) [3,4]. Na rozdíl od trombolýzy je akutní PCI užitečná u širšího spektra AKS. Dilema v první linii rozhodování tak dnes již nezní, ***„zda provést trombolýzu"*** (toto rozhodnutí se řídilo přítomností nebo nepřítomností elevací úseku ST), ale spíše ***„zda odeslat pacienta přímo na katetrizační sál"***. Při tomto rozhodování se nesmí vycházet z přítomnosti/nepřítomnosti elevací úseku ST, ale spíše ze známek probíhající ischemie nebo hemodynamické nestability bez ohledu na vstupní EKG záznam.

Podle nedávno publikovaných doporučení Evropské kardiologické společnosti [5,6] se emergentní invazivní strategie (podobná p-PCI) indikuje nejenom v případě STEMI, ale i u nejrizikovějších podskupin pacientů s non-STE AKS. Navíc se u řady pacientů s kritickým (život ohrožujícím) angiografickým nálezem často neobjevují elevace úseku ST (kritické léze kmene levé věnčité tepny, uzávěr r. circumflexus atd.), i když u těchto pacientů (stejně jako u řady dalších s probíhajícím akutním infarktem myokardu bez elevací úseku ST) by provedení emergentní koronarografie (coronary angiography – CAG) a PCI [7] bylo bezpochyby přínosné. Odkládání koronarografie kvůli nepřítomnosti elevací úseku ST v těchto kritických situacích může v běžné praxi vést ke zhoršení klinického stavu (včetně zbytečných případů úmrtí).

Česká kardiologická společnost se na základě těchto skutečností rozhodla navrhnout novou klasifikaci akutních koronárních syndromů vycházející z přítomnosti nebo nepřítomnosti probíhající ischemie v době prvního kontaktu s lékařem nebo při příjezdu na jednotku neodkladné péče. Tato klasifikace je zaměřena na první projevy (včetně nutnosti okamžitého rozhodnutí, zda pacienta (ne)převézt na katetrizační sál pro provedení p-PCI), a ne na konečnou diagnózu – a proto primárně není součástí počátečního rozhodovacího algoritmu stanovení biomarkerů. Některá česká pracoviště terciární péče již do svých léčebných protokolů tuto klasifikaci zařadila [8].

Navrhovaná nová klasifikace akutních koronárních syndromů (obr. 1)

Akutní koronární syndromy je nutno ***klasifikovat podle rozhodnutí, kam je třeba převézt pacienta již při prvním kontaktu s lékařem***: (a) bezprostředně (během < 2 hodin od prvního kontaktu s lékařem) ***na katetrizační sál nejbližší nemocnice s vybavením pro PCI***, nebo (b) ***na nejbližší koronární jednotku*** (včetně nemocnic bez vybavení pro PCI). Do kategorie (a) spadají v podstatě všichni pacienti s probíhajícími (rozvíjejícími se nebo recidivujícími) známkami akutní ischemie myokardu bez ohledu na výsledek vstupního EKG záznamu (elevace nebo deprese úseku ST, blokáda raménka Tawarova, nebo dokonce nediagnostický výsledek EKG vyšetření při vážném klinickém podezření, např. uzávěru r. circumflexus) a pacienti s jakoukoli formou akutního koronárního syndromu komplikovaného hemodynamickou nebo elektrickou nestabilitou (Killipova třída II–IV nebo maligní arytmie – samozřejmě pouze v kombinaci s klinickými symptomy možného akutního koronárního syndromu). Kategorie (b) zahrnuje všechny ostatní formy akutních koronárních syndromů, tedy situace, kdy odklad rozhodnutí o provedení CAG/PCI o 24–72 hodin nejspíše nebude pro pacienta znamenat žádné riziko.

a) ***Akutní koronární syndrom s probíhající ischemií myokardu*** je definován jako probíhající (nebo recidivující) *klinické známky akutní ischemie myokardu* (tzn. přetrvávající bolest na hrudi a/nebo dyspnoe v klidu) ***plus*** *alespoň jedna* z následujících situací:

1. elevace úseku ST ve ≥ 2 po sobě jdoucích EKG svodech (≥ 2 mm u svodů V_2–V_3, ≥ 0,5 mm u svodů V_7–V_9 a ≥ 1 mm u ostatních svodů);
2. nově vzniklá blokáda raménka Tawarova (pravého nebo levého);

A: Současná klasifikace akutních koronárních syndromů

Diagnóza při prvním kontaktu s lékařem		Konečná diagnóza (při propuštění pacienta)		
STEMI	Non-STE AKS	Q-IM	Non-Q-IM	Nestabilní angina pectoris

B: Nově navržená klasifikace akutních koronárních syndromů

Diagnóza při prvním kontaktu s lékařem		Konečná diagnóza (při propuštění pacienta)		
AKS s pokračující ischemií myokardu	AKS bez pokračující ischemie myokardu	Q-IM	Non-Q-IM	Nestabilní angina pectoris

Obr. 1 – Schéma staré (A) a navržené nové (B) klasifikace akutních koronárních syndromů. Zkratky jsou uvedeny textu.

3. přetrvávající deprese úseku ST ve ≥ 2 sousedních EKG svodech (≥ 2 mm u svodů na hrudníku a ≥ 1 mm u svodů na končetinách);
4. kardiogenní šok nebo „předšokový" typ hemodynamické nestability (nízký až normální krevní tlak + tachykardie + studené končetiny) při podezření na ischemii;
5. maligní arytmie včetně resuscitované zástavy srdce s obnovou spontánního krevního oběhu;
6. klinické známky akutního srdečního selhání (Killipova třída II–IV);
7. abnormální pohyb srdeční stěny nově zjištěný zobrazovacími metodami.

Je třeba mít na paměti, že izolované nálezy situací/stavů uvedených výše v bodech 1–7 (např. maligní arytmie bez jakýchkoli klinických nebo EKG známek akutní ischemie) uvedenou definici nesplňují. Je třeba mít vysoké klinické podezření na akutní infarkt myokardu. Pacienty ze skupin 1–4 je vždy nutno dopravit přímo na katetrizační sál (bez ztráty času kdekoli jinde v řetězci zdravotní péče, např. na jednotce intenzivní nebo neodkladné péče). Pacienty z kategorií 5–7 je rovněž nutno převézt do zařízení s vybavením pro p-PCI s nepřetržitou službou (24/7) (buď přímo na katetrizační sál, nebo nejdříve na kardiologickou jednotku s následným okamžitým převozem na katetrizační sál).

b) ***Akutní koronární syndrom bez probíhající ischemie myokardu*** zahrnuje všechny ostatní akutní koronární syndromy. Konkrétně jde o nemocné s nestabilní anginou pectoris a malým akutním infarktem myokardu (zvýšení troponinu) bez výše uvedených známek probíhající ischemie v době prvního kontaktu s lékařem.

Hlavní přednost této nově navržené klasifikace spočívá v možnosti okamžitého rozhodnutí, zda pacienta převézt přímo na katetrizační sál (nemocnice s dostupností PCI v nonstop režimu) jako neodkladný případ („strategie primární PCI"), nebo zda odložit provedení koronarografie na další (pracovní) den. Tato klasifikace bude mít praktický význam pro lékaře všech specializací, kteří přicházejí jako první do styku s pacienty s AKS. Česká kardiologická společnost představila částečně podobnou klasifikaci již ve svých doporučených postupech pro léčbu STEMI publikovaných v roce 2002 [9]. V těchto doporučených postupech z roku 2002 byl akutní infarkt myokardu s depresí úseku ST považován za urgentní stav s odpovídajícím postupem (tzn. indikací k okamžitému invazivnímu vyšetření a léčbě v zařízení s vybavením pro PCI v nonstop režimu) jako při STEMI.

Význam stanovení srdečních troponinů je pro konečné potvrzení diagnózy akutního infarktu myokardu i nadále velký. Tato klasifikace není s definicí akutního infarktu myokardu v rozporu. Smyslem této klasifikace je nabídnout jasný a jednoduchý praktický doporučený postup pro ***rozhodování při prvním kontaktu s lékařem***.

Poděkování

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Hypotension episodes during the sub-acute phase of ST elevation myocardial infarction: sex differences and covariates

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Abstract

Background: The introduction of primary percutaneous coronary intervention (PPCI) has modified the profile of ST elevation myocardial infarction (STEMI) patients. Occurrence and prognostic significance of hypotension episodes are not known in PPCI treated STEMI patients. It is also not known whether and/or how the hypotension episodes correlate with the degree of myocardial damage and whether there are any sex differences.

Methods: Data of 293 consecutive STEMI patients (189 males) treated by PPCI and without cardiogenic shock were analyzed. Blood pressure was measured noninvasively. A hypotensive episode was defined as a systolic blood pressure below 90 mmHg over a period of at least 30 minutes.

Results: A hypotensive episode was observed in 92 patients (31.4 %). Female sex was the strongest independent predictor of hypotension episodes ($p < 0.0001$), while there was no relationship to electrocardiographic STEMI localization. Hypotensive patients had significantly higher levels of troponin T and BNP; hypotensive episodes were particularly frequent in women with increased troponin T. Treatment with angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) and betablockers was less frequent in hypotensive patients. After a mean 20-month follow-up, all-cause mortality did not differ between hypotensive patients and others. However, mortality in hypotensive patients who did not tolerate ACEI/ARB therapy was significantly higher compared to other hypotensive patients ($p=0.016$).

Conclusion: Hypotension episodes are not uncommon in the sub-acute phase of contemporarily treated STEMI patients with a striking difference between sexes. Hypotensive episodes may lead to a delay in pharmacotherapy which influences prognosis.

Keywords: hypotension; sex differences, ST elevation myocardial infarction.

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INTRODUCTION

Arterial hypotension is an important complication in ST elevation myocardial infarction (STEMI).1 The majority of existing data and experience with hypotension in STEMI patients were mainly obtained prior to the introduction of primary percutaneous coronary intervention (PPCI). In particular, hypotension has long been recognized as a complication of streptokinase administration to STEMI patients.2 Compared to the thrombolytic treatment, PPCI improved the prognosis of STEMI patients substantially.3,4 Consequently, PPCI is presently the standard treatment of choice in all acute STEMI patients. This change of clinical practice has modified the sub-acute profile of STEMI patients. Among others, occurrence and prognostic significance of hypotension episodes are not known in PPCI treated STEMI patients. It is also not known whether and/or how the hypotension episodes correlate with the degree of myocardial damage and whether there are any sex differences. Having this in mind, we monitored the incidence of hypotension episodes in a consecutive population of STEMI patients hospitalized between December 2012 and April 2015.

METHODS

Patients

From total of 300 patients enrolled in the bilateral Holter-ECG project, data of 293 consecutive STEMI patients (189 males) were analyzed (7 patients were excluded from the analysis because of very short period of blood pressure monitoring). All the patients were referred to our coronary catheterization laboratory with the diagnosis of acute STEMI fulfilling the criteria for PPCI according

to guidelines.5,6 Localization of infarction was categorized as anterior (leads V_1-V_4), inferior (II,III,aVF), lateral (I,aVL and/or V_5-V_6), posterior (V_7-V_9), and septal (V_1-V_2). Patients in cardiogenic shock and/or unconscious on admission and/or unable to sign an informed consent were excluded. The time to reperfusion was defined as the interval between symptom onset and the wire passage in the culprit artery. Time of acute MI onset was defined as that of first chest pain symptoms. After the PPCI procedure, the patients were hospitalized in the coronary care unit for at least 72 hours. An attempt of an initiation of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and/or betablocker therapy was done immediately after transfer of a patient to coronary care unit (in the absence of contraindications). The project was approved by the local Ethics committee, all patients signed an informed consent.

Clinical measurements

Noninvasive blood pressure monitoring was performed automatically (Dash 4000 Patient Monitor, GE Medical Systems, Milwaukee, WI, U.S.A.) at least every 30 minutes. A hypotensive episode was defined as a systolic blood pressure below 90 mmHg over a period of at least 30 minutes when criteria for cardiogenic shock were not fulfilled.5 If a patient suffered from repeated hypotension episodes, only the timing of the first episode was considered. The decision of therapeutic intervention was based on individual opinion of a particular physician on duty.

Troponin T levels were measured 24 hours after the chest pain onset (Troponin T high sensitivity assay, Roche Diagnostics, Basel, Switzerland). Brain natriuretic peptide (BNP) levels were assessed in the morning of the second hospitalization day (Architect BNP assay, Abbott Laboratories, Chicago, IL, USA). Left ventricular ejection fraction (LVEF) was measured by echocardiography before discharge. Body mass index (BMI) was calculated as the body mass divided by the square of the body height. Data on all-cause mortality were retrieved from the Nation-wide health insurance registry.

Statistics

Absolute and relative frequencies were obtained for categorical variables; mean±standard deviation and median with minimum to maximum range were used to characterize continuous variables. Differences between patients with and without hypotension were tested using Fisher's exact test for categorical variables and non-parametric Mann-Whitney U test for continuous variables. To associate hypotension episodes with age, troponin T levels, and BNP levels, the incidence of the episodes was compared between patients above and below median of the respective variables. The tests were also repeated separately for female and male patients with median cut-offs obtained separately in females and males. Incidence of hypotension episodes and all-cause mortality were evaluated by Kaplan-Meier survival event-free curves and compared by the log-rank test. Multivariable backwards stepwise regression analysis of prediction of hypotension episodes was performed in two modes: using original values of numerical variables and dichotomizing non-binary variables at population medians. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0.0.1, and in Statistica package, Version 6.1. P level <0.05 was considered statistically significant.

RESULTS

Table 1 shows clinical characteristics of the population and the principal results. The PPCI procedure of infarction artery was successful in all investigated individuals. No patient developed cardiogenic shock during hospitalization.

During the 72 hours a hypotension episode was observed in 92 patients (31.4 %). In 17 (18.5 %) of them, hypotensive values were present immediately after the transfer from catheterization laboratory. Approximately two thirds of the episodes occurred during the first 24 hours compared to fewer than 10% during the third hospitalization day (Figure 1A).

Univariable correlates

Hypotension episodes were significantly more frequent in females (Figure 1B). Simple statistical comparison (Table 1) suggested that hypotension was also more frequent in elderly patients. However, (Figure 1C) only a non-significant trend towards more frequent episodes was observed in patients aged above and below 62.1 years (complete population median). Moreover, female patients were significantly older than males (68.0±10.4 vs. 59.9±11.8 years, $p < 0.0001$) and when distinguishing women and men above and below median age of 67.5 and 58.8 years, respectively, no trend towards more frequent hypotension episodes in older patients was visible (Figure 1D).

Occurrence of hypotension was not related to electrocardiographic STEMI localization. There was no relationship to the time to reperfusion.

Hypotensive patients had significantly higher levels of troponin T (population median of 2.39 ng/ml, Figure 2A) and BNP (population median of 284 pg/ml, Figure 2B), and lower LVEF. Women had troponin T levels similar to those in men (3.33±3.17 vs. 3.41±3.43 ng/ml, p=NS). Nevertheless, when distinguishing women and men above and below the sex-specific medians of troponin T (2.38 and 2.41 ng/ml, in women and men, respectively) the separation of the hypotension incidence became more apparent (Figure 2C). In particular, there was no difference in hypotension incidence between women with lower and men with higher troponin T levels. Such a distinction was not observed for BNP levels that were much higher in women than in men (550±392 vs. 338±405 pg/ml, $p<0.0001$). While there was a difference in the incidence of hypotension episodes in men with BNP levels above and below sex-specific BNP median of 212 pg/ml, the incidence did not differ between women with BNP levels above and below 510 pg/ml (median in women) (Figure 2D).

Hypotensive individuals had also a lower BMI. However, separating patients with lower and higher BMI did not show any significant difference in hypotension incidence (the same was true for the separate sex-groups; women and men did not differ in BMI). Of the medical history data, the only difference between patients with and without hypotension episodes was a less common dyslipidemia in hypotensive patients.

Multivariable analyses

The multivariate regression analysis considered sex, age, BMI, hypertension, troponin T, BNP, and LVEF values as predictors of hypotension episodes. Dichotomized analysis used the following population medians for age, BMI, troponin T, BNP, and LVEF: 62.1 years, 28.1 kg/m^2, 2.39 ng/ml, 283.9 pg/ml, and 55%, respectively.

With both analysis models, only sex and troponin T levels were significant predictors of hypotension ($p < 0.0001$). In both models, sex differences were stronger predictor (F statistics of 27.9 and 28.3 for continuous and dichotomized models, respectively) than the troponin T levels (F of 14.9 and 19.2, respectively).

Treatment effects

In 29 (31.5%) patients with hypotension, the event required therapy by volume expansion and/or vasoactive drugs (Table 1). Of all 92 hypotension patients, 28 (30.4%) suffered from repeated episodes.

The proportion of ACEI/ARB and betablocker therapy was lower in hypotensive individuals during hospitalization. At discharge the difference remained significant in ACEI/ARB. A trend for lower use of ACEI/ARB in women at discharge was non-significant (86.4% vs 92.1%, p=NS). However, when distinguishing hypotensive and non-hypotensive patients, the proportions of ACEI/ARB and betablocker therapy did not differ between women and men. However, prior ACEI/ARB treatment was more frequent in women compared to men (p=0.036 and p=0.048 for patients without and with hypotension, respectively). Consequently, the difference in discharge versus prior ACEI/ARB treatment in women with hypotension (30%) was much lower compared to men with hypotension (54.2%) (Figure 3).

Follow-up

After an average 20-month follow-up, the all-cause mortality was similar in patients with and without hypotension episodes (Figure 4A). Nevertheless mortality of hypotensive patients who did not tolerate ACEI/ARB was significantly higher compared to other hypotensive patients (Figure 4B).

DISCUSSION

STEMI patients with impaired hemodynamics are at increased risk of life-threatening complications and their prognosis is uncertain.5,6 Although hypotension is a well-recognized risk factor in the early stage of STEMI, its significance in the subacute phase is much less known.1

In our population of PPCI treated STEMI patients, hypotension episodes were not uncommon and occurred in approximately one third of all patients. Increased levels of troponin T and BNP suggested higher amount of damaged myocardium,7 as further supported by lower LVEF at discharge.

The female sex was found to be the strongest independent predictor of hypotension episodes. The reasons for this striking sex-related difference are not immediately obvious. It has been hypothesized that the stiffer and thicker ventricles in women tolerate less the volume shifts often occurring during early STEMI phases.8 While women were substantial older than men, age had no influence on the incidence of the episodes in sex-separated sub-groups.

Troponin levels after STEMI correlate with myocardial performance by echocardiography.9 Not surprisingly, increased troponin levels were also independently predicting hypotension episodes. In healthy population or stable coronary disease, women have generally lower troponin T levels.10,11 There are no such data in PPCI treated STEMI patients. In our study, troponin T levels were similar in both sexes suggesting similar myocardial damage. However, women with higher troponin T levels had markedly higher incidence of hypotension episodes. Levels of BNP in women were significantly higher but the incidence of hypotension was not different with values above and below median. On the contrary this difference was apparent in men. There are limited data on sex-specific BNP differences during acute coronary syndromes. In a large registry, women had higher BNP at admission due to heart failure than men, when stratified by LVEF.12 These observations suggest that women develop more pronounced heart failure (measured by BNP levels) compared to men with similar amount of myocardial damage (measured by troponin T levels) and these women are also more prone to hypotension.

Apart from the observations of greater myocardial damage, there are no clear mechanistic explanations for these findings as there was no difference in time to reperfusion and no relationship to MI localization although it would be plausible to expect higher occurrence of hypotension particularly in anterior MI, traditionally indicating increased infarction size. It could be speculated that such

paradigms are changing with PPCI therapy. Often assessed comorbidities of hypertension, diabetes, previous MI, previous PCI, and coronary artery bypass surgery, did not differ between hypotensive and normotensive patients (Table 1). The observation of less frequent dyslipidemia among hypotensive patients was likely only a collateral chance finding.

Numerous studies have demonstrated a benefit of early initiation of betablocker and ACEI/ARB therapy in STEMI patients.13,14 In our study, episodes of hypotension prevented early administration of ACEI, ARB and betablockers in a substantial sub-group of patients. With decreasing occurrence of hypotensive events during the first 72 hours after MI, the proportion of treated patients was increasing. At discharge, more than 90% of hypotensive as well as normotensive patients were treated by betablockers. However, the proportions of ACEI/ARB treated patients were different. In the hypotensive group, a proportion of ACEI/ARB treatment reached 79.1 % at discharge. Although this percentage was not particularly low, it was significantly lower compared to the normotensive group (95%). Multiple studies have shown that women with acute coronary syndrome are less likely to be treated with guideline-directed medical therapies.15, 16 In our study, a simple statistical assessment showed a similar trend for lower use of ACEI/ARB treatment in all women at discharge.

The all-cause mortality was low. After a mean 20-months follow up, it did not differ between hypotensive and normotensive patients. Nevertheless in the hypotensive patients without ACEI/ARB, the mortality was significantly increased despite relatively short follow-up. These findings emphasize the necessity for efforts to initiate ACEI/ARB therapy even in hypotensive patients.

Limitations

This is a single center experience, the number of investigated patients was relatively small preventing many sub-group analyses. Blood pressure was not measured continuously. No distinction of how deep systolic blood pressure decreased below 90mmHg was considered but none of the patients suffered from a newly developed cardiogenic shock. Durations of the hypotensive episodes were not considered. The averaged follow-up was only 20 month. The incidence of hypotension was measured from MI onset although the regular blood pressure measurement started only after hospitalization. Multivariable regression models do not consider the time between index MI and the hypotension episodes. Nevertheless, we also calculated proportional hazard Cox regression models and obtained the very same results.

Conclusion

In spite of these limitations, the study permits to conclude that hypotension episodes are not uncommon in the sub-acute phase of PPCI treated STEMI patients. Striking gender specific differences in hypotension incidence and its relationship to troponin levels were observed. Episodes of hypotension may delay the start of pharmacotherapy. Patients in whom hypotension prevented administration of ACEI/ARB had a significantly poorer prognosis.

Authorship contributions: PK – design of the project, article writing; TN – design of the project, article writing; IA – data collection and analysis, KB – statistics, graphics, MH – data collection and analysis, JJ - statistics, graphics, KH - statistics, graphics, JK – data collection, LK – data collection, MM - data collection, TN - data collection, TO - data collection, LP - data collection, MM – article writing and critical reading.

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Figure legends

Fig 1. Probability of hypotension episodes in 92 patients (Panel A). Panel B - differences between females (grey line) and males (black line). Panel C - the differences in patients above (continuous line) and below (dotted line) median age in the complete population. Panel D - the age-related analysis shown separately in females (grey lines) and males (black lines). Continuous and dashed lines show patients above and below age median, respectively. AMI – acute myocardial infarction.

Fig 2. Panel A - probability of hypotension episodes in patients above (continuous line) and below (dashed line) troponin T median of the complete population. Panel B - the differences according to BNP values above (continuous line) and below (dashed line) median of the complete population. Panel C - troponin T-related analysis shown separately in females and males. Panel D - BNP-related analysis shown separately in females and males. In panels C and D, grey and black lines show female and male

subgroups, respectively, the continuous and dashed lines show patients above and below sex-specific median values, respectively. BNP - brain natriuretic peptide, AMI – acute myocardial infarction.

Fig 3. Proportions of patients treated with ACEI/ARB and betablockers are shown before the admission due to acute STEMI (previous treatment), during first and second day of hospitalization, and at discharge separately in women (top panels) and men (bottom panels). Statistically significant differences between patients with and without hypotension are marked with asterisk. STEMI - ST elevation myocardial infarction, ACEI - angiotensin-converting enzyme inhibitor, ARB - angiotensin receptor blocker.

Fig 4. Kaplan-Meier analysis of probability of death in study patients. Panel A - comparison of patients without (grey line) and with hypotension episodes (black line). Panel B - a comparison of hypotension patients with (grey line) and without ACEI/ARB treatment (black line) at discharge. ACEI - angiotensin-converting enzyme inhibitor, ARB - angiotensin receptor blocker.

Table 1 Comparison of patients with and without hypotension

Parameter		**Total (N = 293)**	**No hypotension (N = 201)**	**Hypotension (N = 92)**	**P**
Sex	Men	189 (64.5%)	148 (73.6%)	41 (44.6%)	**< 0.001**
	Women	104 (35.5%)	53 (26.4%)	51 (55.4%)	
Age	(N = 293)	62.8 ± 12.0	61.6 ± 11.7	65.5 ± 12.1	**0.015**
		62.1 (30.7; 89.5)	61.2 (30.7; 88.4)	65.6 (35.5; 89.5)	
BMI	(N = 292)	28.6 ± 4.6	29.0 ± 4.3	27.6 ± 5.1	**0.002**
		28.1 (19.5; 51.0)	28.6 (21.1; 48.4)	27.3 (19.5; 51.0)	
Previous MI		27 (9.2 %)	17 (8.5 %)	10 (10.9 %)	0.519
Previous PCI/CABG		27 (9.2 %)	19 (9.5 %)	8 (8.7 %)	0.999
Hypertension		173 (59.0 %)	123 (61.2 %)	50 (54.3 %)	0.306
Dyslipidemia		163 (55.6 %)	123 (61.2 %)	40 (43.5 %)	**0.005**
Diabetes		64 (21.8 %)	47 (23.4 %)	17 (18.5 %)	0.366
AMI localization*	Anterior	127 (43.3%)	88 (43.8%)	39 (42.4%)	0.899
	Inferior	144 (49.1%)	95 (47.3%)	49 (53.3%)	0.379
	Lateral	48 (16.4%)	33 (16.4%)	15 (16.3%)	0.999
	Septal	6 (2.0%)	6 (3.0%)	0 (0.0%)	0.182
	Posterior	11 (3.8%)	8 (4.0%)	3 (3.3%)	0.999
Troponin T max.	(N = 290)	3.4 ± 3.3	2.9 ± 3.0	4.4 ± 3.6	**< 0.001**

Parameter		Total (N = 293)	No hypotension (N = 201)	Hypotension (N = 92)	P
(ng/ml)		2.4 (0.0; 20.9)	1.8 (0.0; 20.9)	3.5 (0.0; 18.1)	
BNP (pg/ml)	(N = 275)	412.6 ± 412.8 283.9 (27.5; 3 129.0)	358.5 ± 396.9 233.3 (30.8; 3 129.0)	524.0 ± 424.5 388.0 (27.5; 2 313.0)	**< 0.001**
Time to reperfusion therapy(in hours)	(N = 292)	6.9 ± 4.2 3.4 (1.0; 24.6)	5.0 ± 4.5 3.3 (1.1; 24.6)	4.9 ± 3.4 3.7 (1.0; 23.0)	0.261
Hypotension therapy	None	-	-	63 (68.5%)	-
	Volumotherapy	-	-	10 (10.9%)	-
	Vasocative agents	-	-	6 (6.5%)	-
	Both	-	-	13 (14.1%)	-
LVEF (%) at discharge	(N = 291)	52.1 ± 10.0 55.0 (25.0; 79.0)	53.3 ± 10.1 55.0 (25.0; 79.0)	49.7 ± 9.5 50.0 (30.0; 70.0)	**0.004**
Length of follow-up (in months)	(N = 293)	20.2 ± 8.1 18.9 (0.7; 34.6)	19.7 ± 8.2 18.7 (0.7; 34.6)	21.1 ± 7.7 19.8 (0.7; 34.5)	0.194

Categorical variables are described by absolute and relative frequencies; mean (± SD) and median (min; max) are shown for continuous variables. P-value of Fisher's exact test and P-value of Mann-Whitney U test are shown for categorical and continuous variables, respectively.

* Multiple localizations are possible.

AMI = acute myocardial infarction, BMI = Body Mass Index, BNP = brain natriuretic peptide, CABG = coronary artery bypass surgery, LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention.

Figure 1

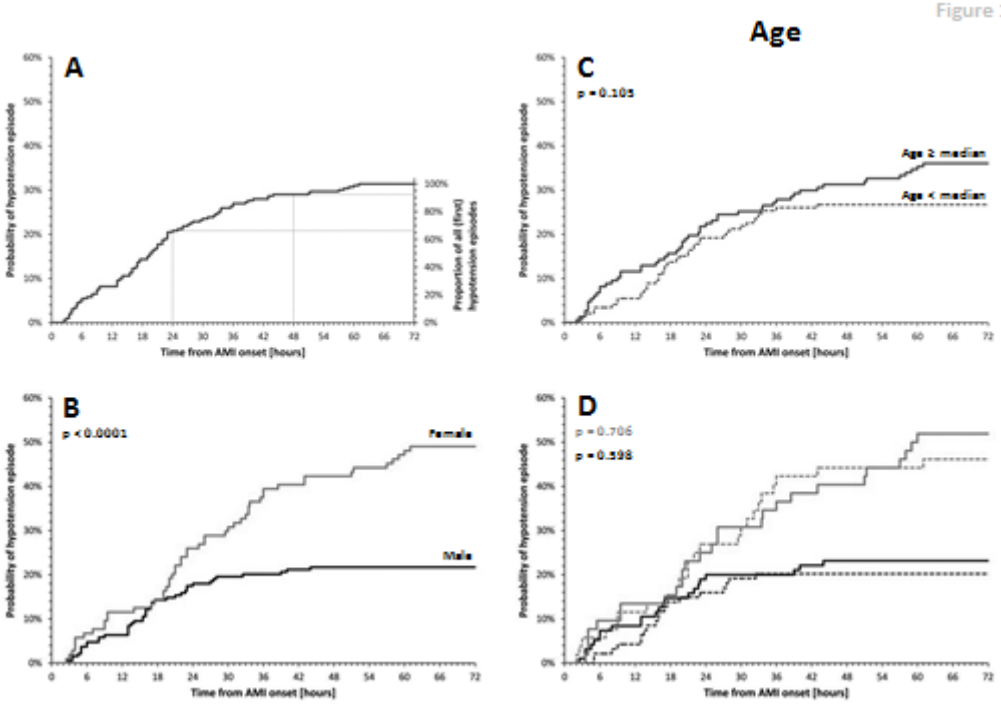


Figure 2

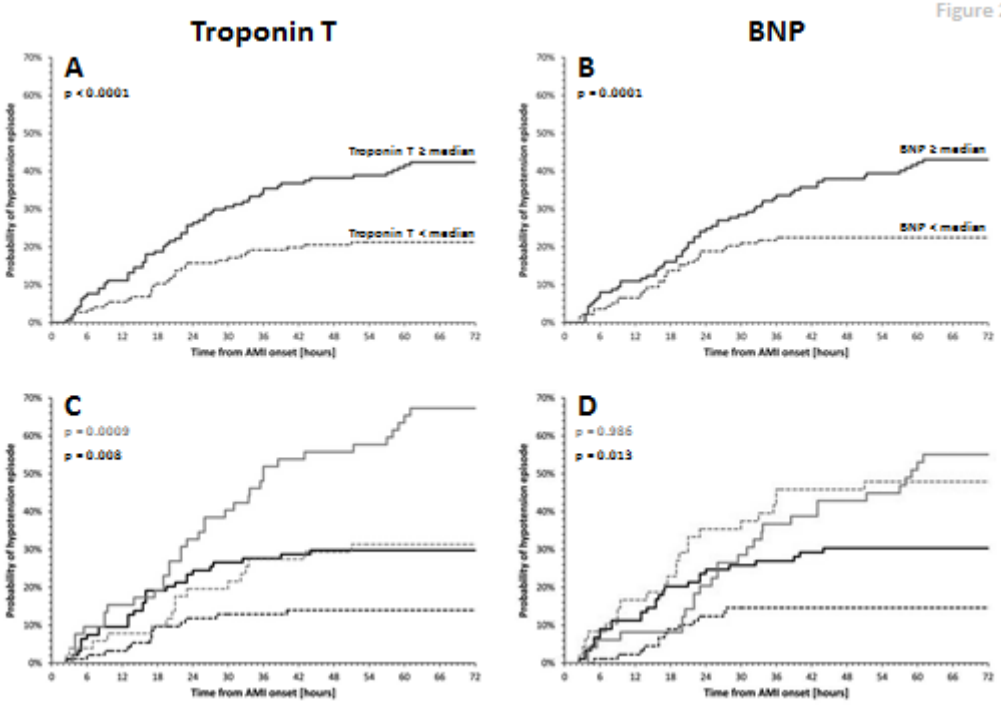


Figure 3

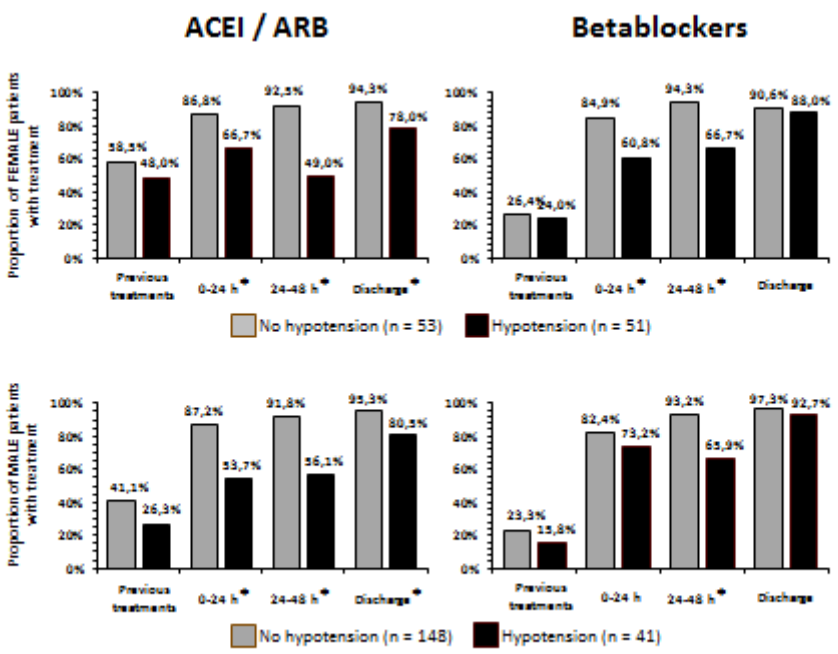
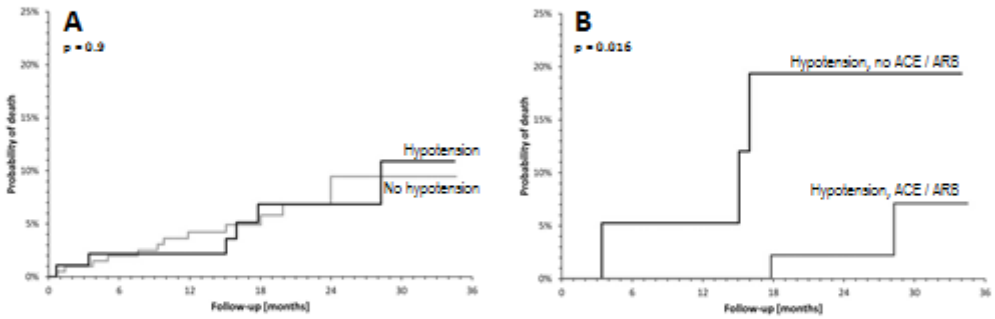


Figure 4



4. Závěr

Současná léčba pacientů se STEMI je při správně volené farmakologické a mechanické strategii velmi sofistikovaná, bezpečná a vysoce efektivní. Primární PCI jako metoda první volby by měla být dostupná co největší části populace, a to bez ohledu na její věk. Stávající technika bude do budoucna pravděpodobně doplněna o morfologické a funkční posouzení infarktových i neinfarktových tepen. Stále větší pozornost pak musí být věnována rizikovým podskupinám pacientů, a to nejen se STEMI, ale i NSTEMI, pacientům s kompletní blokádou pravého raménka Tawarova a po srdeční zástavě, kde časná invazivní diagnostika eventuální revaskularizace může výrazným způsobem zlepšit přežívání i jeho kvalitu. Pozornost je napřena i na praktické zjednodušení selekce pacientů indikovaných k časnému – emergentnímu invazivnímu vyšetření event. revaskularizaci.

5. Seznam literatury úvodu a doprovodných komentářů

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