

Intervencijska kardiologija u 2012. godini: usporedba svjetskih i hrvatskih trendova

Interventional cardiology in 2012: comparability of Croatia with international trends

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SAŽETAK: Intervencijska kardiologija jedno je od najbrže rastućih područja današnje medicinske znanosti, a tehnološka i farmakološka otkrića unutar tog područja unazad samo nekoliko godina dovela su do značajnih promjena u liječenju i prognozi bolesnika sa srčanožilnim bolestima. Prvenstveno je uloga intervencijske kardiologije u poboljšanju ishoda liječenja najjasnije vidljiva u akutnom koronarnom sindromu, a uspješne mreže primarne perkutane koronarne intervencije u akutnom infarktu miokarda predstavljaju jedno od najvećih dostignuća moderne kardiologije, a možda i medicine uopće. Dok je uloga intervencijske kardiologije u akutnoj koronarnoj bolesti jasna, stabilna koronarna bolest srca i dalje ostaje predmet javne rasprave te predmet brojnih istraživanja. Nove tehnologije i materijali u liječenju koronarne bolesti srca od 2012. postaju dostupne diljem svijeta, pa tako i u Hrvatskoj, a njihova implementacija isključivo ovisi o financijskim okolnostima. Novi antitrombocitni i antiagregacijski lijekovi također su predmet istraživanja, a sve u potrazi za (poželjno) jednim lijekom koji će u kardiovaskularnoj intervenciji imati najbolji omjer učinkovitosti i sigurnosti. Ova godina bila je i godina punog zamaha intervencijskog liječenja strukturne bolesti srca, napose aortne stenozе i mitralne regurgitacije, a kardioembolizacija, arterijska hipertenzija i periferna vaskularna bolest također postaju sve šire "igralište" za intervencijske kardiologe. U ovom preglednom članku prikazali smo sve te moderne trendove u intervencijskoj kardiologiji protekle godine u svijetu i usporedili ih sa stanjem u Hrvatskoj.

KLJUČNE RIJEČI: koronarna bolest srca, intervencijska kardiologija, akutni koronarni sindrom, stent.

ABSTRACT: Interventional cardiology has become among the fastest growing areas in clinical medicine, thanks to technological and pharmacological discoveries over the last few years, which brought important advancements in treatment and overall prognosis of patients with cardiovascular diseases. Benefits of primary interventional treatments became particularly evident in management of acute coronary syndrome, especially in circumstances of organized network of primary percutaneous coronary interventions, which represented a crucial step in development of modern era in cardiology, or even medicine. On the other hand, interventional management of chronic ischemic heart disease recently came to greater focus of attention as the issue of professional challenge, due to exceedingly grown number of investigations. New technologies and devices for treatment of coronary artery disease have become available in 2012 in the world market, as well as in Croatia. However, their implementation for the most depends on availability of financial resources. Further efforts were made around research on novel antiplatelet and antiaggregation drugs, with an aim to develop the agent that would preferably exert greater efficiency, within more favorable safety profile. This was the year in which interventional treatment extended on the structural heart diseases as well particularly due to increase in treatment of aortic stenosis and mitral regurgitation, whilst cardioembolization, arterial hypertension and peripheral vascular disease become ever more attractive "battlefield" for interventional cardiologists. In this review article, we have presented all those modern trends in interventional cardiology in the past year at an international level and compared them to the situation in Croatia.

KEYWORDS: coronary heart disease, interventional cardiology, acute coronary syndrome.

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Uvod

Napredak perkutane intervencije na koronarnim arterijama u akutnom infarktu miokarda (AIM) doveo je u cijelom svijetu do značajnog smanjenja mortaliteta tih bolesnika i trenutno predstavlja najzorniji primjer važne uloge intervencijske kardiologije u tijeku i ishodu akutne koronarne bolesti. Trend smanjenja mortaliteta od AIM primijećen je i u Hrvatskoj, što je i objavljeno u zadnjem izvješću Državnog zavoda za statistiku gdje kardiovaskularne bolesti (KVB) po prvi put imaju manje od 50% udjela u smrtnosti i pobolu među cijelim stanovništvom, a smrtnost od AIM po prvi put je manja od smrtnosti od cerebrovaskularnih bolesti¹. S obzirom da u posljednjih nekoliko godina nije bilo ozbiljnije javne kampanje primarne prevencije KVB, a da su pušenje, debljina i dalje značajan javnozdravstveni problem, takvi rezultati najvjerojatnije su izravna posljedica razvoja nacionalne mreže primarne perkutane koornarne intervencije (PCI) u akutnom infarktu sa ST elevacijom (STEMI) osnovane u suradnji Radne skupine za akutni koronarni sindrom, Radne skupine za intervencijsku kardiologiju Hrvatskog kardiološkog društva i Ministarstva zdravstva Republike Hrvatske 2005. godine, o čemu je nedavno pisano u ovom časopisu². To dokazuju i izvješća suradnih ustanova, gdje je smrtnost od AIM u bolnicama sjeverozapadne Hrvatske prije uvođenja mreže bila 15-20%, a sada je 7-8% i prvenstveno se odnosi na stariju populaciju teško bolesnih pacijenata koji ranije nisu bili upućivani na PCI³. Trenutno nacionalna mreža pokriva više od 70% državnog teritorija s više od 2.500 bolesnika sa STEMI diljem zemlje na godišnjoj razini⁴. Brojka liječenih bolesnika povećava se značajno svake godine, a tijekom 2013. godine očekuje se i potpuna pokrivenost teritorija nakon uključivanja intervencijskih centara u zapadnoj Slavoniji i Dubrovačko-neretvanskoj županiji. Naravno, porast broja liječenih na više od 3.000 bolesnika u sklopu mreže, uz stalno povećanje broja dokaza o potrebi što ranije intervencije u akutnom koronarnom sindromu bez ST elevacije (NSTEMI-ACS)⁵, postat će dodatno opterećenje za već opterećene proračune ustanova koje su nosioci intervencijske djelatnosti u mreži, što će se vrlo vjerojatno odraziti na usporeni razvoj ostalih modernih dostignuća intervencijske kardiologije u Hrvatskoj. Također je potrebno posebno izdvojiti problem vrednovanja rada invazivnih kardiologa, koji se često izjednačava s ostalom rutinskom dijagnostikom no, još od prve PCI koju je 1977. god. u Zurichu učinio Andreas Gruentzig, posve je jasno da se radi o neusporedivim razlikama. To će neminovno dovesti do manjka invazivnih kardiologa te posebice suradnog osoblja. Suradno osoblje zajedno s operaterima radi u stresnom okruženju intervencijskih i elektrofizioloških kardioloških laboratorija, u direktnom snopu štetnog RTG zračenja⁶, s obvezama ostalog svakodnevnog rada u liječenju, njezi i dijagnostici u modernoj kardiologiji, što zasigurno odbija buduće kadrove od moguće karijere u intervencijskoj kardiologiji.

Perkutane koronarne intervencije i stabilna koronarna bolest srca

Iako je indikacija i korist primarne PCI u akutnom koronarnom sindromu (AKS) neupitna i poduprta nizom visokovrijednih dokaza, PCI u stabilnoj koronarnoj bolesti srca (KBS) i dalje ostaje predmet velike rasprave koja se vodi između predstavnika intervencijske kardiologije, kardiokirurgije, ali i neinvazivne kardiologije. Nakon objave rezultata COURAGE ispitivanja 2007. god. koje je kod randomiziranih 2287

Introduction

The progress of percutaneous intervention of coronary arteries in acute myocardial infarction (AMI) has led to a substantial reduction of mortality of these patients worldwide. It currently represents the best example of an important role of interventional cardiology in the improvement of outcomes in management of acute coronary syndrome (ACS). Such a trend of reducing mortality from AMI has been observed in Croatia, as published in the latest report by the State Bureau of Statistics, where for the first time it was recorded that cardiovascular diseases (CVD) had a frequency of less than 50% in the mortality and morbidity in the entire population, while mortality from AMI was for the first time lower than the mortality from cerebrovascular diseases¹. Given that over the last few years there has not been a serious public campaign on primary prevention of CVD, and that smoking and obesity still remain a significant public health problem, such results are most likely a direct consequence of the development of the national network of primary percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction with (STEMI) established in cooperation of the Working Group (WG) for the acute coronary syndrome of the Croatian Cardiac Society (CCS), the WG for interventional cardiology of the CCS and the Ministry of Health of the Republic of Croatia in 2005 which topic was discussed in this journal recently². This is evidenced by the reports of cooperating institutions, where the mortality from AMI in the Croatian hospital centres from Northwest region before the introduction of the network was 15-20%, and now it accounts for 7-8%, and it primarily relates to elderly patients with several comorbidities who have not been previously referred for PCI³. Currently, the national acute-PCI network covers more than 70% of the national territory with more than 2,500 STEMI patients treated across the country on an annual basis⁴. The number of treated patients is increasing significantly every year and during the year 2013, we expect full coverage of the national territory after involving the intervention centers in Western Slavonia and the Dubrovnik-Neretva County. The increase in the number of treated patients to more than 3,000 per year, in cooperation with growing evidence on benefits of earliest PCI intervention in management of the non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS)⁵, will inevitably become an additional burden for overstretched financial budgets of institutions that carry out of the interventional activity in the network. One could reasonably expect the slowdown in overall network development, particularly in concern to introducing of novel technologies and devices for interventional cardiology in Croatia. Pointing out the problem of mis-evaluated professional engagement of invasive cardiologists, which is often represented as equal with other routine and non-invasive diagnostics, although this is a well established fact since the first PCI was performed in Zurich in 1977 by Andreas Gruentzig. This will inevitably lead to a shortage of invasive cardiology and particularly cooperative staff. Cumulative effects of dynamics will inevitably lead to a shortages in material, equipment and personnel enrolled in invasive cardiology, particularly the assistant staff. The assistant staff along with the surgeons work in the stressful environment of catheterization and electrophysiology cardiology labs, exposed to X-ray⁶, with being obligated to perform their daily routine participation in the ward work, medical care and diagnostics, which cumulatively leads to lessened interest for career in interventional cardiology in future generations.

Percutaneous coronary interventions and stable coronary heart disease

Although the indications and benefit of primary PCI in acute coronary syndrome (ACS) is unquestionable and supported by a series of high-quality evidence, position of PCI in chro-

bolesnika od probranih gotovo 30.000 zaključilo kako nema značajnih razlika u važnim srčanim kliničkim ishodima između optimalne konzervativne terapije i PCI s optimalnom konzervativnom terapijom, očekivalo se smanjenje trenda porasta broja PCI u bolesnika sa stabilnom KBS⁷. Međutim, svakodnevna praksa u zemljama zapadne Europe i Sjedinjenim Američkim Državama koje imaju razvijene sustavne baze podataka o koronarnim intervencijama nisu pokazale smanjenje PCI u stabilnoj bolesti unazad ovih 5 godina, s oko 45% bolesnika sa stabilnom KBS koji su liječeni s PCI nakon objavljivanja COURAGE studije što je gotovo identično stanju prije objave studije. Također zanimljiv je podatak iz američkih registara kako samo 30% bolesnika sa stabilnom bolešću kod kojih se učini PCI imaju neki od testova koronarne rezerve učinjen prije intervencije⁸. U Hrvatskoj nije moguće analizirati paralelno takve podatke zbog nepostojanja nacionalnog registra, ali podatci iz pojedinih intervensijskih centara prezentirani na nacionalnim i međunarodnim kongresima pokazuju kako je test opterećenja na pokretnom sagu gotovo rutinski u procjeni potrebe upućivanja bolesnika na koronarografiju i PCI. Stoga, u nekim bogatijim zemljama popularno pitanje o suvišnim i neprimjerenim intervencijama u stabilnih bolesnika, u Hrvatskoj se ne čini toliko aktualnim, pogotovo ako se uzme u obzir uloženi napor cijele intervensijske zajednice u rješavanju problema AKS. Naime, u Hrvatskoj postotak intervencija u bolesnika s AKS konstantno raste, a broj intervencija u bolesnika sa stabilnom bolesti stagnira.

Implantacija koronarnih stentova u stabilnoj KBS zasigurno je jedna od najkontroverznijih tema u liječenju KBS danas. Uz medikamentoznu terapiju, kardiokirurgiju i implantaciju stenta, potpuno novi koncepti poput balona obloženih lijekom ("drug eluting" ili "drug coated balloons" — DEB) u liječenju restenoze stenta, ali i de novo koronarnih lezija postaju od 2012. godine sve aktualniji u raspravama o različitim modalitetima liječenja bolesnika sa stabilnom KBS. Za sada je "samo DEB" koncept uglavnom korišten u liječenju restenoze običnog ili lijekom obloženog stenta, a postoje i podatci o superiornosti DEB s neobaveznom implantacijom običnog stenta nad implantacijom stenta obloženog lijekom u malim koronarnim arterijama čiji je dijametar manji od 2,8 mm⁹. U literaturi se sve više ponovno spominje, uz balon dilataciju i korištenje DEB, tzv "spot-stenting", tj. "provisional" postavljanja stentova samo na mjestu većih disekcija i suženja odgovornih za koronarnu ishemiju¹⁰. Također, mora se napomenuti i razvoj biorazgradivog vaskularnog stenta (BVS), koji zapravo predstavlja privremenu potporicu koronarnoj arteriji načinjenu od razgradive plastične mase. Koronarna arterija bi nakon njegove razgradnje trebala razviti pozitivnu remodelaciju te se tim konceptom želi pitanje restenoze svesti na minimum, uz minimalni rizik tromboze¹¹. BVS je 2012. godine službeno registriran i na tržištu Hrvatske, ali je zbog visoke cijene do sada implantiran samo simboličan broj. Međutim, nove tehnike nalažu nove randomizirane studije, a u stabilnoj KBS mišljenja smo da bi odluku o modalitetu revaskularizacije i daljnjeg liječenja (PCI, kardiokirurgija ili samo lijekovi) svakako trebalo prepustiti "heart teamu" (invazivni i neinvazivni kardiolozi i kardiokirurzi). Na taj način osiguralo bi se bolje pridržavanje smjernica i postizanje optimalnih rezultata, što je dokazano i za invazivne centre manjeg volumena i one bez kardiokirurgije¹², napose u rizičnim skupinama bolesnika sa šećernom bolešću.

nic coronary heart disease (CHD) still remains the subject of great debate among various subspecialties (interventional cardiology, cardiac surgery and noninvasive cardiology). Following the publication of the results of the COURAGE trial in 2007, that included randomization of 2,287 patients from primer pool of 30,000 patients, there were no significant differences reported in major adverse events rates between the optimal conservative therapy vs. PCI, and one would expect that the number of PCIs in patients with chronic CHD will start to fall⁷. However, reports from the countries of Western Europe and the United States of America with well organized systematic database monitoring of coronary interventions showed a trend of remained number of PCI in the management of chronic CHD over the last 5 years. Reported frequency of 45% of patients with chronic CHD who were treated with PCI following the publication of the COURAGE trial was almost identical to the situation prior to the publication. It is interesting to note that only 30% of patients with stable angina pectoris that underwent PCI had any of the coronary flow reserve tests prior to the intervention⁸ in reports from North American registries. It is impossible to make comparison or analyze similar set of data from Croatia due to the lack of a national registry. Nevertheless, the data from intervention centers which were presented at meetings of professional societies showed that the exercise tolerance test on treadmill is almost as a rule performed prior to coronary angiography and PCI. Burning issue in concern to underscored the use of interventional diagnostics and potentially unnecessary interventions in developed countries luckily does not seem to be the challenging issue in Croatia, especially on the bases of limited resources for total budget covering the interventions. In particular, the share of patients with primer PCI interventions in Croatia continuously grows, whilst the number of interventions for chronic heart disease stagnates.

Interventional treatment in stable CHD is certainly one of the most controversial issue in the management of CHD nowadays. In addition to conservative medical therapy, coronary bypass surgery and stent implantation, the brand new concepts like the drug-coated balloon ("drug eluting" or "drug coated balloons" — DEB) for the treatment of in-stent restenosis, and de novo coronary lesions. For the time being, "only DEB" concept has been tested for the treatment of bare metal stent or drug eluting stent restenosis, and there is data about the superiority of DEB with an option for bare metal stent implantation over drug eluting stent implantation in small calibre coronary arteries with a diameter 2.8 mm or less⁹. In addition to balloon dilation and the use of DEB, the so-called "spot-stenting" or "provisional" stenting reported in the literature offered the concept of intervention solely to culprits of major dissections and narrowing responsible for symptoms of coronary ischemia¹⁰. One must not disregard the concept of bioabsorbable vascular stent (BVS), which represents a provisional made from absorbable material placed in the coronary artery. Following its absorption, coronary artery is expected to develop ameliorative remodeling, in order to decrease the potential for developing the restenosis or thrombosis to a minimum¹¹. In 2012 BVS was officially registered in the Croatian market, but due to relative high price, only a low number of them have been implanted. However, all of these techniques require prospective randomized studies. In consideration to chronic CHD, we share an opinion that the modality of revascularization treatment (PCI, cardiac surgery or medications only) should certainly be left to "heart team" (invasive and non-invasive cardiologists and cardiac surgeons). Team approach should ensure better adherence to guidelines and optimal treatment, which has been proved in some low-volume centers without invasive cardiac surgery¹², especially in high-risk groups of patients with diabetes.

Stentovi obloženi lijekom

Sumnje u vezi implantacije stentova obloženih lijekom (*drug eluting stentovi* — DES) i povećanog rizika stent-tromboze nastale objavom rezultata nekih velikih svjetskih registara tijekom 2006. i 2007. potpuno su, u korist DES, razrješene razvojem treće generacije DES i objavom rezultata registara i randomiziranih studija u kojim su korišteni takvi materijali za liječenje bolesnika sa stabilnom KBS i bolesnika s AKS¹³. Dapače, u novim smjernicama Europskog kardiološkog društva (ESC) za liječenje STEMI, DES je po prvi put dobio razinu preporuke IIa (“trebalo bi koristiti”) uz najvišu razinu dokaza A ukoliko nema jasnih kontraindikacija za dugotrajno uzimanje dvojne antiagregacijske terapije¹⁴. Smjernice istog društva za revaskularizaciju miokarda iz 2010. god. daju prednost DES prilikom intervencijskog zahvata u bolesnika sa šećernom bolesti s razinom preporuke I (“svakako koristiti”) uz razinu dokaza A¹⁵. Udjeli DES među implantiranim materijalom u zapadnim zemljama danas se kreću između 65% (Njemačka) i 90% (Švicarska), uz relativno visoke udjele od 35% do 40% i u zemljama koje imaju socioekonomske prilike slične Hrvatskoj. Ponovno, s obzirom na nedostatak nacionalnog registra teško je govoriti o točnom udjelu DES u Hrvatskoj, ali sudeći prema sažecima prikazanim na nacionalnim i svjetskim skupovima u većini centara (pogotovo u velikim centrima s velikim udjelom bolesnika liječenim u sklopu mreže pPCI) ona je ispod 10%. Uvjerljivi dokazi o značajnom smanjenju broja ponovljenih revaskularizacija i boljem dugoročnom kliničkom ishodu u određenih skupina bolesnika liječenih s DES (šećerna bolest, bifurkacijske lezije, duge lezije na uskim koronarnim arterijama, glavno deblu ili aortoostijalne lezije što zajedno zasigurno premašuje više od trećine svih bolesnika kojima se učini PCI) morali bi dovesti do određenih promjena u financiranju elektivnih i akutnih intervencijskih zahvata u Hrvatskoj, što bi omogućilo povećanje udjela bolesnika liječenih s DES kojima je to zaista potrebno.

Antitrombotična i antikoagulacijska terapija

Uspjeh koronarne intervencije i implantacije različitih materijala u akutnoj ili kroničnoj koronarnoj bolesti zasigurno jedan dio duguje i antitrombotičnoj i antikoagulacijskoj terapiji. Protekla godina donijela je mnoštvo novih preporuka i promjena u antitrombotičnoj terapiji u intervencijskoj kardiologiji koje su za sada zaobišle Hrvatsku, gdje je klopidogrel, sa dokazanim problemom rezistencije, za sada jedini dostupni peroralni antitrombotični lijek široke primjene, uz naravno neizostavnu acetylsalicylic acid i prevaziđeni ticlopidin. Napredak je najbrži u antitrombotičnoj terapiji i prednosti primjene ticagrelora u AKS, neovisno o invazivnoj ili neinvazivnoj strategiji liječenja, objavljene u PLATO istraživanju i zadnjim smjernicama ESC za liječenje STEMI¹⁴. Ticagrelor u trenutku pisanja ovog članka u Hrvatskoj još nije službeno dostupan, a kada i postane zasigurno će početna iskustva s tim lijekom u nas biti rijetka s obzirom na njegovu visoku cijenu. Prasugrel, antitrombotični lijek vrlo popularan u zemljama srednje Europe nakon objave rezultata TRITON studije koja je pokazala njegovu superiornost učinkovitosti nad klopidogrelom u invazivnom liječenju AKS, no uz nešto veći broj krvarenja¹⁶ također nije dostupan u Hrvatskoj.

Antikoagulacijska terapija u AKS nudi sve veću lepezu lijekova koji djeluju na različitim razinama koagulacijske kaskade i koji se ekstenzivno ispituju u različitim randomiziranim istraživanjima. Trenutno se ispituje efikasnost i sigurnost otamixabana, apixabana i rivaroksabana¹⁷⁻¹⁹ u invazivnom

Drug eluting stents

Doubts regarding drug eluting stents (DES) implantation and increased risk of stent thrombosis raised by the results published by some major global registries in 2006 and 2007 were completely eliminated in favour of DES by the development of the third generation of DES and results published by registries and randomized studies which included patients with chronic CHD and patients with ACS¹³. On the contrary, in the new guidelines of the European Society of Cardiology (ESC) for the treatment of STEMI, DES was for the first time assigned the level IIa recommendation (“should be used”) with the highest level of evidence A, as well if there were no clear contraindications to the long-term use of dual antiplatelet therapy¹⁴. The 2010 Guidelines evidently prefer DES for interventional revascularisation in diabetic patients with recommendation grade I (“definitely to be used”) and level of evidence A¹⁵. The frequency of DES among the implanted stents in Western countries today range between 65% (Germany) and 90% (Switzerland), and a relatively high frequency of 35% to 40% in countries with socio-economic circumstances similar to Croatia. Given the lack of a national registry, it is hard to estimate the exact share of DES in Croatia. Indirect appraisal gained through reports from major Croatian centers presented at professional symposiums and conferences (especially for the high-volume centers with a large portion of patients treated within the pPCI network) is estimated to be below the 10%. Reported significant reduction in rates of re-vascularization and long-term profile of major adverse events for groups of patients with complex lesions is in favour of DES use (diabetes, bifurcation lesions, long lesions in the narrow coronary arteries, the left main or aorto-ostial lesions which is estimated to be represented in more than one third of patients undergoing PCI). The necessary changes in the reimbursement of elective and acute interventional program in Croatia would allow an increase in the number of patients treated with DES, on the basis of substantial long term benefits offered.

Antiplatelet and anticoagulant therapy

The effectiveness of coronary interventions and implantation of various materials in the acute or chronic CHD is in part connected with the use of antiplatelet and anticoagulant therapy. During the past year a lot of new recommendations and changes were issued in antiplatelet therapy in interventional cardiology that have not been applied in Croatia so far, where clopidogrel, with proven resistance problem is for the time being the only available oral antiplatelet drug. Its wide administration is usually accompanied with aspirin, whilst ticlopidine is rarely used due to and unfavorable side-effect profile. The most important recent improvement of antiplatelet therapy include the use of ticagrelor in ACS, regardless of invasive or noninvasive treatment strategy, as published in the PLATO trial and the latest ESC guidelines for the treatment of STEMI¹⁴. Ticagrelor is not yet available in Croatia, and when it becomes officially available, the initial experience will be limited due to its relative high price. Prasugrel, an antiplatelet drug that became widely used in the Central Europe following the results of the TRITON study which showed its advanced efficacy over clopidogrel for the invasive treatment of ACS, however burdened by increased prevalence of bleedings¹⁶. The later is also not available in Croatia.

Increasing number of drugs from anticoagulants, that mediates different steps of coagulation cascade group is being tested in prospective randomized studies and used for treatment of ACS. Currently, the efficacy and safety of otamix-

liječenju AKS, dok su još uvijek najrašireniji i najistraživaniji te u smjernicama jedino i preporučeni nefrakcionirani heparin, bivaluridin, enoksaparin i fondaparinux¹⁴. Bivaluridin u Hrvatskoj nije dostupan tako da većina intervencijskih kardiologa intervencije u STEMI i u stabilnoj KBS radi uz nefrakcionirani heparin, a intervencije u NSTEMI-ACS uz enoksaparin ili fondaparinux s dodatkom nefrakcioniranog heparina, a rjeđe samo uz nefrakcionirani heparin. Antikoagulacijski lijek sa savršenim odnosom učinkovitosti (manje ugruška) i sigurnosti (manje krvarenja) u AKS još uvijek se traži, iako u većini takvih studija dobri glavni ishodi visokorizičnih bolesnika uglavnom su ovisili o vremenu upućivanja na PCI.

Nove tehnike prikaza koronarne cirkulacije

Jasno je kako obična dvodimenzionalna koronarna angiografija ima određenih ograničenja u prepoznavanju težine i proširenosti KBS, pogotovo na razini glavnog debla lijeve koronarne arterije, u bifurkacijama i u difuznoj višežilnoj bolesti. Razvoj intravaskularnog ultrazvuka (IVUS) i analize rezerve frakcijskog protoka specijalnom koronarnom žicom koja mjeri tlak ispred i ispod stenozе (FFR) uvelike je pomogao intervencijskim kardiolozima u donošenju ispravnih odluka u liječenju podskupina koronarnih bolesnika. S kompleksnim lezijama Upravo objavljena studija FAME-2, nastavak poznate FAME studije kojom je dokazana superiornost FFR-om vođene intervencije u bolesnika s višežilnom bolesti u odnosu na klasičnu angiografiju, pokazala je kako je FFR-om vođena PCI dovela do značajnog smanjenja potrebe urgentne revaskularizacije u inače stabilnih bolesnika²⁰. Mora se napomenuti kako su bolesnici u FAME-2 studiji randomizirani nakon što je svima učinjen FFR, za razliku od FAME studije gdje su bili randomizirani prije invazivne procedure. Posljedično tome, u FAME-2 neki su bolesnici s višežilnom bolesti od kojih je bar jedna bila angiografski i/ili FFR-om značajna dospjeli u skupinu medikamentozno liječenih, a kako te podatke nije moguće zaslijepiti određena pristranost prema potrebi za PCI od strane bolesnika i operatera zasigurno je postojala. Ipak, mora se zaključiti kako FAME i FAME-2 dokazuju vrijednost funkcionalne procjene značajnosti stenozе koronarne arterije, opravdavajući uporabu te tehnologije u bolesnika s višežilnom stabilnom KBS, koju treba dodatno poticati. U Hrvatskoj postoje mogućnost mjerenja FFR u većini kateterizacijskih laboratorija, ali je u kliničkoj praksi primjena ograničena zbog visoke cijene.

Strukturna bolest srca i periferne vaskularne intervencije

Premda je ranije smatrana isključivo "igralištem" KBS, intervencijska kardiologija danas svoj predmet interesa pomiče sve više s koronarne na strukturnu bolest srca. Taj trend toliko je izražen da današnji svjetski veliki intervencijske kardiologije koronarnu intervenciju vide kao blijeđe polje, a u prvi plan stavljaju transkatetersku implantaciju aortne valvule (TAVI), perkutanu reparaciju insuficijentnog mitralnog zaliska (MitraClip) i implantaciju okludera i uređaja za zaštitu od embolije (Amplatzer uređaj, Parachute, Watchmann i drugi). U Hrvatskoj se tek razvija TAVI program u 3 intervencijska centra (Klinička bolnica Dubrava Zagreb, Specijalna bolnica Magdalena Krapinske Toplice i Klinički bolnički centar Zagreb), dok ostali navedeni oblici, osim liječenja otvorenog foramena ovale, za sada nisu dostupni.

ban, apixaban and rivaroxaban¹⁷⁻¹⁹ in invasive treatment of ACS is being tested, while unfractionated heparin, bivaluridin, enoxaparin and fondaparinux are still the most common and most investigated medications and the only medications recommended in the guidelines¹⁴. Bivaluridin is still not available in Croatia, so the majority of interventional procedures are performed with concomitant use of unfractionated heparin for interventions in acute STEMI, as well as for and stable chronic CHD. The use of enoxaparin or fondaparinux as an add-on to of unfractionated heparin is reserved in Croatia for interventions in NSTEMI-ACS, apart from very infrequent use of unfractionated heparin, as a single therapeutic approach. Anticoagulant medication with favorable ratio of efficiency (less clots) to safety profile (less bleeding) is still not available for interventional treatment, although most of the studies reported that treatment success rate of high-risk patients depends mainly on the time of referral to invasive treatment.

New techniques of coronary circulation imaging

Evidence exists that the conventional two-dimensional coronary angiography is at some instances limited for recognizing the true risk of CHD, especially in concern to lesions of the left main coronary artery, bifurcational lesions and diffusely outspread multi-vessel disease. The introduction of novel diagnostic tools as intravascular ultrasound (IVUS) or fractional flow reserve (FFR) through specially equipped guidewire that detects the ratio of intracoronary pressure flow from upstream and distal to atherosclerotic stenosis has greatly helped the interventional cardiologists to make right decisions on treatment of subgroups of patients with CHD. Later technology offered reproducible objectivity for decisions of interventional strategies of those patients with multi-vessel disease and other complex lesions. The recently published FAME-2 study, the continuation of the well-known FAME study reported on superiority of FFR-guided intervention in patients with multi-vessel disease compared to conventional angiography. The use of FFR-guided PCI offered a significant reduction in a number of repeated revascularizations²⁰. One must underline the fact that the patients in the FAME-2 study were randomized in the course after the FFR assessment, apart from the FAME study which randomization was done prior to invasive procedure. Consequently, some of patients from FAME-2, that had multi-vessel disease with at least one clinically significant culprit lesion according to conventional PCI and/or FFR had the great deal of chance to be stratified to arm of conservative pharmacological treatments, due to loss of double-blinding by the operators and the patients. Despite the differences, both the FAME and FAME-2 proved the clinical value of functional evaluation of CHD significance, laying the ground for recommendation on need to foster the use of this technology in patients with multi-vessel stable CHD. Most of the centers from Croatia are sufficiently technically equipped for the use of FFR, however availability is scarce due to a high cost of such devices.

Structural heart disease and peripheral vascular interventions

Once considered exclusively to be the "battle-field" of CHD, the interventional cardiology today extended its interest beyond the coronary circulation. This trend is so pronounced that interventional cardiologists started to see the coronary intervention as a fading field, in relation to the novel techniques as transcatheter aortic valve implantation (TAVI), percutaneous mitral valve repair (using MitraClip), occluder and implantation of embolic protection devices or occluders for

Osim strukturne bolesti srca, intervencijska kardiologija sve više zadire u vaskularne procedure, pogotovo perifernu vaskularnu bolest donjih udova ispod razine koljena te karotidne i intracerebralne stenozе. Vrijedi napomenuti i razvoj intervencijskog liječenja refraktorne arterijske hipertenzije perkutanom denervacijom renalnih arterija uz pomoć specijalnog katetera ili pak balona, u čemu u Hrvatskoj postoje početna "revijalna" iskustva, a ponovno zbog visoke cijene procedure.

Program transkateterske implantacije umjetnog aortnog zaliska u Hrvatskoj

U osnovi TAVI program liječenja uznapredovale aortne stenozе sastoji se od tri elementa. Ključni elementi TAVI sustava su bioprostetična valvula, zatim sustav temeljem kojeg se ista pozicionira u željenu poziciju (projekcija aortne valvule) i kateter kroz koji se to sve dostavlja najčešće veličine 18 french (oko 6 mm). Trenutno većinu svjetskog i hrvatskog tržišta drže dva proizvođača, Medtronic CoreValve sustav i Edwards Sapien XT sustav, a u pripremi su i varijante od drugih proizvođača (Direct Flow od Medical-a, Sadra Lotus od Boston Scientific-a, St Jude Medical Portico, ali i dr.). S obzirom da su dva inicijalno navedena zastupljeni na hrvatskom tržištu, ovaj članak će se primarno baviti njima.

Medtronic CoreValve sustav sastoji se od bioprostetične valvule koja se sama širi (eng. "self-expandable") nakon što se pozicionira na mjestu projekcije aortnog zaliska. Pristup do aortnog zaliska većinom se izvodi preko femoralne arterije, ali često se koriste i ostali vaskularni pristupi (transaksilarni, transaortalni, transsubklavijski, transapikalni itd.). Osnovni kostur Medtronicovog zaliska sastoji se od nitinolne strukture koja je prekrivena specifično obrađenim svinjskim perikardom. Edwardsov sustav se sastoji od bioprostetičnog zaliska čiju jezgru čini nehrđajući čelik (strukturnalno zapravo se radi o stentu) koji se pozicionira i širi uz pomoć balona koji se napuhuje pod kontrolom operatera. Ono što je bitno naglasiti, prema do sada dostupnim podacima, u odnosu na preživljenje nema razlike između dva navedena sustava, s time da je ipak primijećena veća incidencija poremećaja atrioventrikulske (AV) kondukcije koji su zahtijevali implantaciju trajnog elektrostimulatora kod Medtronic CoreValve sustava.

Revolucija za TAVI započela je objavom rezultata PARTNER studije koji su nedvojbeno dokazali korisnost liječenja TAVI metodom, no povijest transkateterske implantacije aortnog zaliska je nešto starija. Naime, transkateterski sustav razvijen je 2002. god. od strane prof. Alain Cribirera iz Rouena, Francuska, ali je tek objavom značajnog preživljenja kod bolesnika s teškom aortnom stenozom koji su liječeni TAVI sustavom od strane prof. Martin Leona²¹ doživio pravu renesansu i to na način da je u potpunosti istisnuo KBS kao primarni interes intervencijske kardiologije. No, TAVI sustav nije bez mana. Osnovni nedostaci TAVI sustava su: paravalvularna regurgitacija (eng. "paravalvular leak"), mogućnost razvoja periproceduralnog moždanog udara, poremećaji AV kondukcije (iatrogeni totalni AV blok), kao i još uvijek nepoznata trajnost implantirane valvule²².

intracardial shunts (Amplatzer device, Parachute, Watchmann etc.) in the foreground. The TAVI program has so far applied in 3 intervention centers from Croatia (Dubrava University Hospital Zagreb, Specialized Hospital Magdalena Krapinske Toplice and University Hospital Center Zagreb). Apart from the treatment of patent foramen ovale other named types of interventional treatment of structural heart disease are not available at the moment in Croatia. In addition to structural heart disease, the interventional cardiology increasingly engages in vascular procedures, especially peripheral artery disease of the lower limbs below the knee level, as well as the carotid and intracranial arterial stenoses. We should disregard the development of interventional treatment for refractory arterial hypertension by percutaneous denervation of renal arteries using the special catheter or a balloon, whereas this system has only been demonstrated in small series of patients, without systematic availability in Croatia, again because of increased costs of the procedure.

Transcatheter aortic valve implantation program in Croatia

Basically the TAVI program of treatment of advanced aortic stenosis consists of three elements. The key structural elements of the TAVI system are the bioprosthetic valve, the guiding system according to which is properly positioned during placement (projection of aortic valve) and a delivering catheter for the system through, most commonly sized 18 french (about 6 mm). Currently the two devices are available and used in most of the procedures taken in Croatia, namely, the Medtronic CoreValve System and Edwards Sapien XT system, while variants by other manufacturers (Direct Flow from Medical, the Sadra Lotus from Boston Scientific, St Jude Medical Portico, and etc.) are being prepared. Given that the two initially mentioned products are represented in the Croatian market, this article will primarily address them.

Medtronic CoreValve system consists of self expandable bioprosthetic valve after it is positioned at the place of the projected aortic valve position. The access to aortic valve is mainly accomplished over the femoral artery, however other sites are also available (transaxillary, transaortic, trans-subclavian, transapical etc.). Basic structure of the Medtronic valve consists of nitinol structure that is covered by technically processed bovine pericardium. The Edwards system consists of a bioprosthetic valve with core made from stainless steel (structurally resembling the stent) that is positioned and expanded by using a balloon that is inflated by an operator. According to present experience with the devices, in relation to the survival there is no difference between the two above mentioned systems, whereas higher incidence of AV conduction abnormalities that required implantation of permanent pacemaker, was observed with use of the Medtronic CoreValve System.

The revolution for TAVI started following the results of the PARTNER study, which undoubtedly proved the benefits of the treatment, although the history of transcatheter aortic valve implantation concept has been known for some time now. Specifically, transcatheter system was developed in 2002 by Prof. Alain Cribirera from Rouen, France, but only following the publication of a significant survival of patients with severe aortic stenosis who were treated by TAVI system by prof. Martin Leona²¹ it experienced a real renaissance in a way that it completely superseded CHD as a primary interest in interventional cardiology. However, the TAVI system is not faultless. The main disadvantages of the TAVI system are: paravalvular leakage, the incidence of periprocedural stroke, AV conduction abnormalities (iatrogenic total AV block), as well as still unknown clinical durability of the implanted valve²².

Stanje u Hrvatskoj — iskustvo Kliničke bolnice Dubrava

U Hrvatskoj, kako je već spomenuto, za sada tri centra imaju aktivni TAVI program, a do današnjeg dana implantirano je ukupno 48 valvula transfemoralnim pristupom, a jedna valvula transaortnim pristupom. U KB Dubrava TAVI program odvija se pod nadzorom "heart teama" koji sačinjavaju kardiokirurg, kardiolog i anesteziolog. Individualno se razmatra svaki pacijent, vrsta vaskularnog pristupa i sustava koji će se implantirati, zatim sama procedura i zbrinjavanje mogućih periproceduralnih komplikacija. U izboru vaskularnog pristupa ključan je stupanj aterosklerotske bolesti, tortuozitet krvnih žila, kalcifikacije i širina žile (>6mm).

Tijekom 2011. i prve polovice 2012. god. na KB Dubrava obrađeno je 25 bolesnika s teškom aortnom stenozom koji su klasificirani kao visokorizični za klasičan zahvat. Nakon obrade 18 je prihvaćeno za TAVI program. Svi su zahvati izvedeni transfemoralnim pristupom, u općoj anesteziji. U 13 bolesnika je implantirana Medtronic CoreValve, a u 5 Edwards Sapien XT. Prosječna dob bolesnika je bila 79,8 godina, uz očekivani mortalitet po EuroScore $17,8 \pm 11,8\%$ te STS $22,6 \pm 11,6\%$. Uspjeh TAVI procedura iznosio je 94%. Tijekom praćenja od šest mjeseci jedan bolesnik je preminuo kao posljedica upale pluća četiri mjeseca nakon implantacije valvule. Od velikih komplikacija u prvih 30 dana jedan je bolesnik imao moždani udar (s potpunim opravkom), jedan je imao plućnu emboliju, a kod dva bolesnika je zbog totalnog AV bloka implantiran trajni elektrostimulator. Svi bolesnici imaju značajno kliničko poboljšanje, uz zanemariv postotak klinički značajne paravalvularne regurgitacije, što odgovara i svjetskim rezultatima²³. Napominjemo kako je zadnjih mjeseci implantirano još pet valvula transfemoralno i jedna transaortnom tehnikom, zbog nemogućnosti perifernog pristupa, svi uz stopostotni uspjeh, bez komplikacija. KB Dubrava je vodeći centar u Hrvatskoj po broju implantacija, ali obzirom da se program razvija gotovo dvije godine, broj od ukupno 24 bolesnika svakako je nedostatan za potpuniju analizu.

TAVI program dostupan je bolesnicima i u Hrvatskoj, no uz značajna ograničenja koja su prvenstveno vezana uz cijenu takvog zahvata. Ključna je uloga tzv. "heart teama" koji će pažljivo razmotriti indikaciju i odlučiti je li bolesnik kandidat za navedenu proceduru.

Zaključak

Intervencijska kardiologija značajno je napredovala unazad nekoliko godina te je nakon dosezanja (po nekima) vrhunca u razvoju liječenja akutne i kronične koronarne bolesti vrlo uspješno prešla u mnoga druga polja kardiovaskularne medicine razvojem tehnologija kao što su TAVI, MitraClip ili kardioembolička zaštita. Ipak, stalna rasprava o liječenju stabilne KBS različitim strategijama, uz razvoj novih tehnoloških i molekularnih koncepata (DEB, BVS, matične stanice, modulacija upalnog odgovora) te stalne napore u dodatnom poboljšanju učinkovitosti i sigurnosti liječenja AKS, koronarnu bolest još uvijek čini zanimljivom intervencijskoj javnosti. Sličan trend zahvaća i našu zemlju, međutim, zbog proračunskog manjka u intervencijskoj kardiologiji i dalje je nedopustivo nizak postotak primjene DES, a o eventualnoj primjeni novih tehnologija i materijala ne može se u ovom trenutku niti govoriti. Velik problem predstavlja izostanak primjene smjernicama preporučenih novih antitrombotičkih lijekova. TAVI program je uspješno započet, no za daljnje

Circumstances in Croatia — experiences from the Dubrava University Hospital, Zagreb

In Croatia, at the moment the three centers have the active TAVI program, and to date a total of 48 valves have been implanted by applying transfemoral approach, and one valve has been implanted by applying transaortic approach. In the Dubrava University Hospital the TAVI program is performed under the guidance of the "heart team" that includes a cardiac surgeon, cardiologist and anesthesiologist, with patient based individualized approach that ought to increase the effectiveness of procedure and timely management of periprocedural complications. Assessment of atherosclerotic disease is a crucial step in selection of the optimal vascular approach, including the degree of atherosclerosis, tortuosity of blood vessels, calcification and vessel width (> 6mm) as the most important factors.

During 2011 and the first half of 2012, 25 patients were been selected for TAVI treatment in Dubrava University Hospital. All patients had severe aortic stenosis and were burdened with increased perioperative risk due to comorbidities. Finally, 18 were included and TAVI was performed. All procedures were performed by applying transfemoral approach under general anesthesia. Medtronic CoreValve was implanted in 13 patients, while Edwards Sapien XT was implanted in 5 patients. The average age of patients was 79.8, with expected mortality according to EuroScore $17.8 \pm 11.8\%$ and STS $22.6 \pm 11.6\%$. The TAVI procedure was successful in 94% of implantations. During the initial 6 months' follow-up, one patient died due to pneumonia (4 months after the valve implantation). Regarding some other complications during the first 30 days' time, one patient suffered from cerebrovascular stroke (with complete clinical recovery), one suffered from pulmonary embolism and two patients underwent the implantation of permanent pacemaker due to development of complete AV block. All patients have a significant clinical improvement of symptoms, with a negligible percentage of significant perivalvular leakage, which was comparable with leading centers from developed countries²³. Additional 5 valves were implanted in the last couple of months over the transfemoral approach and one valve was implanted by transaortic approach, due to characteristics of peripheral arterial access, all with 100% success, and with no major complications. The total number of implantations in the Dubrava University Hospital is in the greatest considering single centre from Croatia, but bearing in the mind the fact that the program is available for nearly two years, the total number of 24 patients is relatively insufficient for reproducible conclusions.

The TAVI treatment is available to Croatian patients, but with significant limitations primarily related to the cost of such a procedure. The role of the "heart team" is crucial for the success of implantation and this team carefully uses individualized approach to patient, outweighing the benefits and risks prior making the treatment decision.

Conclusion

Interventional cardiology demonstrated indeed crucial advancements over the last few years, after reaching the top-most development in treatment of acute and chronic coronary artery disease it began successfully to be applied in many other fields of cardiovascular medicine by developing the technologies such as TAVI, MitraClip or cardioembolic protection. However, the constant debate about the treatment of chronic CHD by applying different strategies, accompanied by the development of new technologic and molecular concepts (DEB, BVS, stem cells, modulation of an inflammatory response), and continuous efforts in further

normalno funkcioniranje timova, trebalo bi godišnji broj implantacija održati dostatnim za održavanje kontinuiteta i kvalitete rada. Potrebna je pomoć cjelokupne kardiološke zajednice za održavanje dosadašnjih zavidnih rezultata u rješavanju AKS, ali i za daljnji razvoj intervencijske kardiologije prvenstveno u skladu sa smjernicama kojih se moramo pridržavati, ali i u primjeni novih tehnologija liječenja koronarne i strukturne bolesti srca koje moramo usvajati.

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improvement of efficacy and safety of ACS treatment, makes the CHD still an interesting issue for the society of interventional cardiologists. Similar trend is seen in Croatia as well; however, the limited budgets for interventional cardiology still causes unacceptably low percentage of DES's usage, while the introduction of new emerging technologies and devices could not be established at the time being. Significant issue is related also with a limited use of the new generations of antiplatelets and anticoagulants recommended by the guidelines. The TAVI program has been successfully initiated, but in order to sustain or keep the quality of treatment, a number of implantations should be increased sufficiently. Assistance of overall cardiology community is necessary in order to maintain the present enviable results in managing ACS and also for the prosperous development of interventional cardiology mainly in accordance with the guidelines, but also in regard to using new technologies of treatment of coronary and structural heart disease that we must adopt.

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