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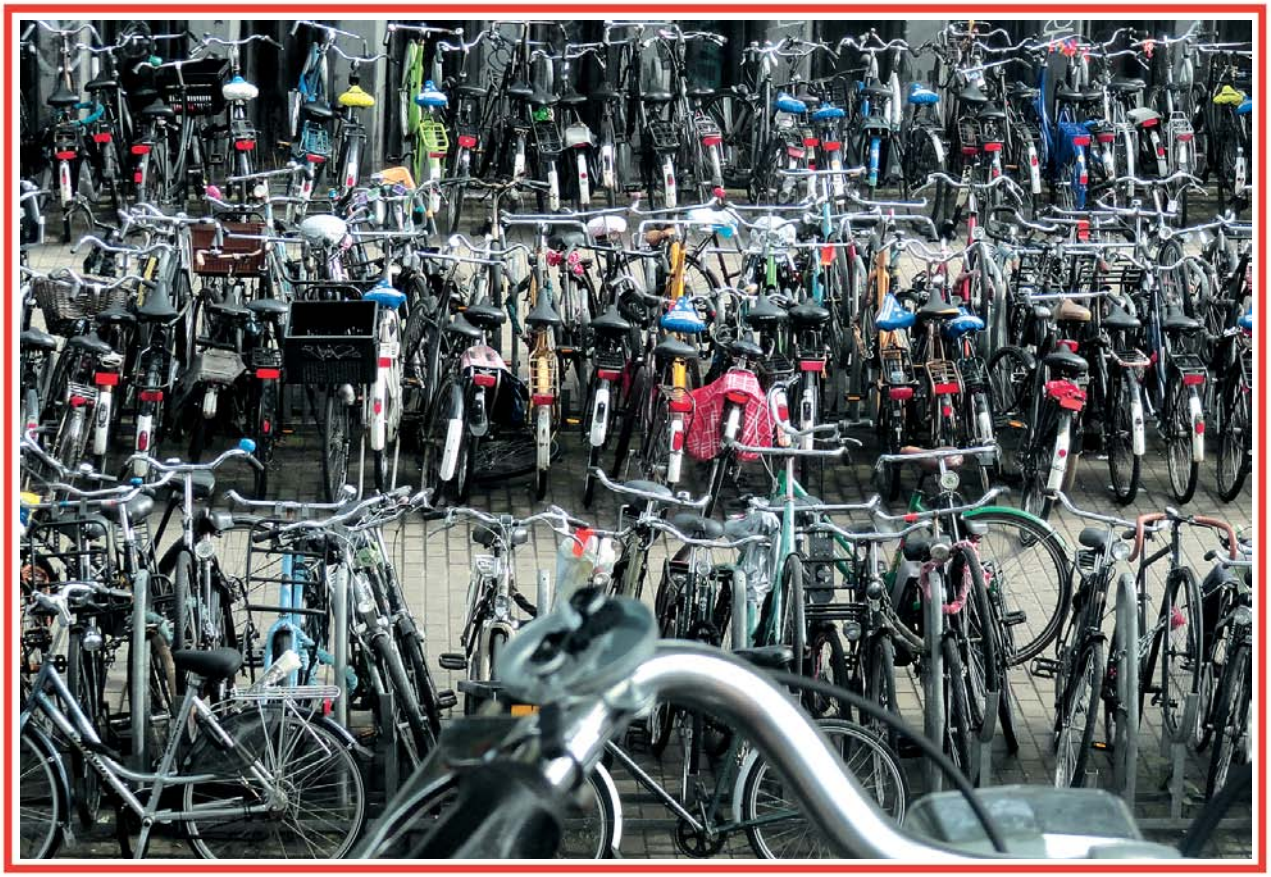

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Pregledni članak / Review article

Trauma srca (tamponada srca-perikarda)
Cardiac Trauma (cardiac-pericardium tamponade)

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SAŽETAK: Prikazani su najčešći uzroci traume srca s posebnim osvrtom i definicijom nepenetrantne — tupe i penetrantne — oštre ozljede, obje česte u tijeku traume prsnog koša. Opisane su tamponada srca i kontuzija miokarda. Navedeni su simptomi, klinička slika, patomorfološka-patofiziološka zbivanja oba entiteta. Ukazano je na važnost brze intervencije na mjestu nesreće, incidenta, osobito kod penetrantne traume srca. Istaknuti su značenje prehospitalne skrbi za pacijenta kao i potreba visoke stručnosti ekipe hitne medicinske pomoći uz primjenu transtorakalnog ehokardiografskog pregleda na mjestu incidenta. Naglašena je potreba da se uz ehokardiografiju primijeni i terapijska perikardiocenteza kao važan zahvat na mjestu incidenta, ali s velikim oprezom u pojedinoj penetrantnoj ozljedi srca, u cilju sprječavanja razvitka tamponade srca. Istaknute su dijagnostičke mogućnosti instrumentalnih pretraga srca i prsnog koša u hospitalnom razdoblju, u ocjeni osobito tupe — nepenetrantne traume srca.

KLJUČNE RIJEČI: trauma srca, tamponada perikarda, transtorakalna ehokardiografija, terapijska perikardiocenteza.

SUMMARY: The most common causes of cardiac trauma, with special regard to nonpenetrating — blunt and penetrating — sharp injuries, frequent in the course of thoracal injury, and their definitions are presented. Symptoms, clinical course and patomorphologic-pathophysiological events in cardiac tamponade and myocardial contusion are described. The importance of rapid intervention at the spot, especially in penetrating cardiac trauma is stressed. Special significance is given to prehospital care and accordingly the need for highly educated teams of first aid with the application of transthoracic echocardiography on the spot of the incident as diagnostic method. Beside echocardiography, a need for careful application of therapeutic pericardiocentesis as urgent intervention as an important procedure at the place of accident with the aim of prevention of fatal outcome due to pericardial tamponade is strongly pointed. Diagnostic possibilities of instrumental heart and thorax check-ups during hospital stay, especially in evaluation of blunt — nonpenetrating cardiac trauma is described.

KEYWORDS: cardiac trauma, pericardial tamponade, transthoracic echocardiogragraphy, therapeutic cardiocentesis.

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Uvod

Ovaj je pregled potaknut epidemijom prometnih nesreća motornim vozilima u Hrvatskoj s traumom prsnog koša i srca te učestalim smrtnim ishodom kod nekih sportova kod kojih postoji i trauma prsnog koša, pa time i mogućnost traume srca. Povećana učestalost traume srca je češća u našim društveno-gospodarskim uvjetima života još uvijek i primjenom hladnog oružja. Ova problematika se ne može zanemariti obzirom na učestalost posjedovanja vatrenog oružja budući to predstavlja potencijalni pojedinačni izvor penetrantnih srčanih ozljeda sa smrtnim ishodom.

Smatra se da je oko 25% svih traumatskih ozljeda prsnog koša koje završavaju smrtno uzrokovano upravo oštećenjem srca[1]. Statistički podaci pokazuju da je najčešće zahvaćena desna klijetka (DV; u 35%), a potom slijede lijeva kljetka (LV; u 25%), desna pretklijetka (DA; u 33%) te lijeva pretklijetka (LA; u 14%)[1]. Drugi statistički podaci iznose incidenciju oštećenja desnog dijela srca kod traume srca od

Introduction

This review has been prompted by an epidemic of car accidents in Croatia with thoracic and cardiac trauma and frequent fatal outcome in some sports associated with thoracic trauma, and thus the possibility of cardiac trauma. An increased incidence of cardiac trauma is more common in our socio-economic living conditions still due to using cold weapons. This problem can not be ignored considering the prevalence of possession of firearms which is a potential individual source of penetrating cardiac injuries with fatal outcome.

The exact cause of about 25% of all thoracic traumas with deadly outcome is the cardiac injury[1]. Statistical data show that the right ventricle (RV; in 35%) is the most frequently affected, followed by left ventricle (LV; in 25%), the right atrium (RA; in 33%) and the left atrium (LA; in 14%)[1]. Some other statistical data report on the incidence of injury of the right part of the heart in cardiac trauma of 76% and left part of 14.3%[2]. In addition to the cardiac injury, thoracic trauma

76%, a lijevog od 14,3%[2]. Uz oštećenje srca kod traume prsnog koša često je prisutno i oštećenje drugih organskih sustava: pluća, pleure, medijastinuma, traheje, bronha, ezofagusa, rebara, aortne stijenke, kralježnice, što doprinosi nastanku kompleksne simptomatologije te stvara diferencijalno dijagnostičke poteškoće[1,3-5].

Izvješća svjetskih traumatoloških centara osim potrebe neposredne hitne intervencije "na licu mjesta" naglašavaju važnost brze informiranosti i spremnosti ekipe kirurškog centra, što bi trebalo omogućiti učinkovitu hospitalnu intervenciju.

Usprkos neposrednoj pomoći i hitnoj intervenciji na mjestu incidenta, a potom analize te hospitalnog liječenja, traumatsko oštećenje srčanih struktura s tamponadom perikarda i dalje ima visoku incidenciju smrtnosti u prometnim nesrećama — 20 %[6]. Na intervenciju kod penetrantnih ozljeda srca u kirurškim centrima otpada mali broj, svega 0,5% svih kirurških intervencija[5]. Čini se da mnogi pacijenti ne stignu do stručne specijalističke pomoći, a uzrok tome je možda i činjenica da hitna medicinska pomoć na terenu nije opskrbljena adekvatnom aparaturom ili nije u stanju dijagnosticirati i pružiti adekvatnu pomoć. Traume srca — nepenetrantne i penetrantne, u nesrećama s motornim vozilima se javljaju u visokoj zajedničkoj incidenciji od 80% do 90%[6,7]. Nepenetrantne ozljede ne moraju biti odmah smrtonosne, ali se u daljnjem praćenju često kompliciraju lošim ishodom, a smrtnost u duljem posthospitalnom periodu također je visokih 57% do 64%[8].

Definicija i uzroci

Srčana trauma se dijeli na:

• ***nepenetrantnu — tupu povredu srca*** — bez neposredno vidljivog oštećenja (rane, laceracije) na prsnom košu, ali moguće posredno utvrđenim kasnije unutrašnjim oštećenjima na srcu, aorti i ev. drugim organima;

• ***akutnu penetrantnu — oštru povredu srca*** (ranu), uz manju ili veću ranu, razderotinu, laceraciju prsnog koša, koja je neposredno najčešće i vidljiva.

Nepenetrantna povreda srca

Kod tupe traume dolazi do nagnječenja prsnog koša, srca, krvnih žila (ev. i drugih organa) od sile tupog udarca, a što se može dalje komplicirati strukturnim promjenama srca, perikarda, miokarda, srčanih valvula, korda tendineja, papilarnih mišića, rijetko endokarda te pluća, aortne stijenke s disekcijom i s arterijsko-venskim fistulama — nastalim npr. kod rupture sinusa Valsalve aorte s lijevo-desnim shuntom ili lijevo-lijevim shuntom u LA te rijetko shuntom u perikardijsku vreću ili rupturom descendentne aorte na mjestu ligamentum arteriosum Botalli (posljednje zbog akceleracijskih i deceleracijskih sila oko osovine sigurnosnog pojasa u autu). U prvi trenutak djelovanja, blage tupe sile, unesrećeni može biti bez većih smetnji. Stoga, tupa trauma često zahtijeva duže kliničko praćenje i monitoriranje EKG-om, ultrazvukom srca, radiološkim i drugim metodama.

12-kanalni EKG treba snimiti odmah i najmanje 24 sata monitorirati te hospitalno promatrati bolesnika 7 dana i kod pretpostavljeno "lakših kontuzija" te potom činiti povremene kontrolne analize (holter EKG i ultrazvuk srca) koje mogu utvrditi (u kronicitetu) kasne promjene[8,9]. Tupu traumu blažeg intenziteta bolesnik nekad i zaboravi, pogotovo ako su prvi simptomi bili blagi — opća slabost i blaga substernalna

is usually accompanied by an injury of other organ systems: lungs, pleura, mediastinum, trachea, bronchus, esophagus, ribs, aortic wall, spine, contributing to the occurrence of complex symptomatology and causing differential diagnostic difficulties[1,3-5].

Reports of international trauma centers emphasize not only a need for direct emergency intervention "on the spot" but also the importance of timely awareness and preparedness of a surgical center team, which should allow for efficient in-hospital intervention.

Despite direct assistance and emergency intervention on the spot of the incident, followed by the analysis and in-hospital treatment, traumatic injury of cardiac structures with pericardial tamponade still shows a high incidence of deaths in traffic accidents — 20%[6]. There is a small number of interventions in case of penetrating cardiac injuries in surgical centers, only 0.5% of all surgical interventions[5]. It seems that many patients come late for professional specialist assistance, and the reason for this may be the fact that the emergency medical assistance in the field is not equipped with suitable apparatus or is unable to diagnose and provide an appropriate assistance. Cardiac traumas — both non-penetrating and penetrating, in car accidents show a high common incidence from 80% to 90%[6,7]. Non-penetrating injuries may not be immediately fatal, but the further follow-up often reveals complications followed by poor outcome thereby recording a high mortality over a longer post hospital period from 57% to 64%[8].

Definitions and causes

Cardiac trauma is divided in:

• ***non-penetrating — blunt cardiac injury*** — without a direct visible injury (wounds, lacerations) in the chest, but later internal injury of the heart, aorta and any other organs can be indirectly determined;

• ***acute penetrating — sharp cardiac (wound) injury***, with a smaller or larger wound, tear, chest laceration, which is directly usually visible.

Non-penetrating cardiac injury

In case of blunt trauma, contusions of the chest, heart, blood vessels (or any other organs) are caused by blunt force impact, which can further get complicated as a consequence of structural changes to the heart, pericardium, myocardium, heart valves, chordae tendineae, papillary muscles, rarely endocardium and lungs, aortic wall with dissection and arterial-venous fistulas — occurred for instance in case of sinus rupture of the Valsalva aorta with left-right shunt or left-left shunt in LA and rarely shunt in the pericardial sac or rupture of the descending aorta at the point of ligamentum arteriosum Botalli (the latter due to acceleration and deceleration forces around the seat belt shaft in the car). At the first moment of action of mild blunt force, the injured may feel no major problems. Therefore, blunt trauma often requires longer clinical follow-up and monitoring by ECG, echocardiography, radiological and other methods.

12-lead ECG should immediately record and should be monitoring a patient for at least 24 hours in the hospital even in case of presumed "minor contusions" to be followed by periodic follow-up analyses (Holter ECG and echocardiography), which can identify (in the chronicity) late changes[8,9]. Slight intensity blunt trauma will never be forgotten by a patient, especially if the first symptoms were mild — general fatigue and slight substernal pain. However, various

bol. Međutim, u duljem su praćenju često prisutne različite aritmije, pa i ventrikulska tahikardija te smetnje provođenja s pogibeljnim AV blokovima[10]. Rijetke su manifestacije srčane slabosti s globalnim padom kontraktilnosti miokarda, ako nije bilo dokazanog opsežnijeg oštećenja.

Tamponada perikarda je vrlo rijetka u tupoj ozljedi, ali može ipak nastati djelovanjem nepenetrantne sile preko prsnog koša ili preko trbušne šupljine. Češće se javlja u situaciji tupe traume — manji perikardijski izljev s polaganim razvitkom, najčešće kao serozno eksudativna reakcija (ne hematoperikard), autoimunog uzroka nastanka. To su reakcije na minimalno oštećenje perikarda, poput postoperacijskog perikarditisa — perikardiotomički sindrom. Takav perikardijski izljev, obično manjeg volumena, ne ugrožava punjenje DV, a ako polagano dosegne veličinu oko 200 mL može kod bolesnika u naporu izazvati blagu tahikardiju i zaduhu. Povlačenjem eksudata mogu zaostati manje fibrinsko-fibrozne promjene unutar perikarda, bez značajnih hemodinamskiih implikacija (najčešće bez konstrikcije). Iznimno rijetko tupa trauma uzrokuje neposredno naglu smrt, kada kontuzija miokarda dovede do rupture miokarda zbog manje ili veće laceracije stijenke miokarda ili perikarda ili zbog opsežnije disekcije aortne stijenke ili kada se tupi udarac dogodi u tzv. vulnerabilnoj fazi srčane rezolucije.

Iako je manje ugrožavajuća od penetrantne traume, jaka sila i kod takve ozljede može dovesti do oštećenja drugih organa, kao npr. do dijafragmalne hernije zbog nastale razderotine dijafragme s hernijacijom abdominalnog sadržaja u prsni koš i time učiniti pritisak -kompresiju na srčane šupljine, ali i hernijaciju miokarda kroz manju razderotinu perikarda, nastalu tupom silom[4,8]. Jaka tupa sila može preko prsnog koša i trbušne stijenke izazvati rotaciju srca i tzv. "luksaciju" čitavog srca iz njegovog sjedišta. Posljednje promjene treba isključiti u hospitalnom razdoblju, najbolje višeslojnom kompjutoriziranom tomografijom (MSCT).

Uzroci tupe nepenetrantne traume su mnogobrojni, češće samo s posljedičnim nagnječenjem prsnog koša i srca, a rjeđe manjim ili većim rupturama srca i okolnih organa. To se događa u prometnim nesrećama zbog nagle deceleracije, neposredne kontuzije volanom vozila u sternum te u mnogobrojnim kontuzijama prsnog koša i trbuha kod prevrtanja vozila. Čest uzrok kontuzije prsnog koša i srca nadalje je pad s visine na tlo kao ozljeda na radu, namjerni jaki "ubilački" udarci rukom u prsni koš, nenamjerni jaki udarci loptom, sudar dvaju tijela u sportu, a u stočarstvu npr. udarac kopitom životinje u prsni koš, pad kod jahanja životinja, pad s motocikla, bicikla i sl. Kod liječničke reanimacije često se ne može izbjeći manje ili veće iatrogeno nagnječenje miokarda i perikarda, nekad i uz frakturu rebara (što može izazvati i penetrantnu ozljedu). Sljedeći uzroci su zračni udari — zračni "blast" u neposrednoj blizini eksplozije bombe, mine, s kompresijom sternuma i organa na kralježnicu, ev. vodeni "blast" ili druga kompresija toraksa između dviju nestlačivih — metalnih podloga.

Osim deceleracijskih sila kod zaustavljanja dvaju vozila, stvaraju se nekad u nesrećama i kod prevrtanja vozila i jake akceleracijske sile, velike snage, koje mogu dovesti do "fleksije" prsnog koša s manifestacijom sila rastezanja (stretching) i sila rotacije (twisting)1 te time do ozljeda srca i drugih organa u prsištu. Učestale elektrokardioverzije mogu u terapijskim zahvatima biti uzrok mikropromjena na miokardu, edema miokarda, pa i manjih nekroza. Slično vrijedi i za nesretne udare izmjeničnom električnom strujom, a čini se i za udare elektriciteta iz munje (groma). U slučajevima tupe traume srca podatke o jačini miokardne ozljede može se

arrhythmias, including ventricular tachycardia and conduction disorders with fatal AV blocks are usually present over a long follow-up period.[10] Heart failure symptoms are rare with a global decrease in myocardial contractility, if no extensive injury has been proved.

Pericardial tamponade is very rare in the blunt injury, but still may be caused by non-penetrating forces through the chest or abdominal cavity. It occurs more commonly in a situation of blunt trauma — a smaller pericardial effusion with a slow development, usually as a serous exudative reaction (not hemopericardium) of autoimmune etiology. These are the reactions to minimal injury of the pericardium, such as postsurgical pericarditis — postpericardiotomy syndrome. Such a pericardial effusion, usually a smaller pericardial effusion, does not endanger the LV filling, and if it slowly reaches the size of approximately 200 mL it can cause mild tachycardia and dyspnea in the patient in effort. The retreat of exudates may lead to smaller fibrinous-fibrous changes that may remain within the pericardium, without significant hemodynamic implications (usually without constriction). Extremely rare blunt trauma causes a direct sudden death, when myocardial contusion causes myocardial rupture due to a minor or major laceration of the myocardial or pericardial wall due to a more extensive dissection of the aortic wall or when the blunt impact occurs in the so-called vulnerable stage of cardiac resolution.

Although it is less life-threatening than penetrating trauma, a strong force in case of such an injury may cause injury of other organs, such as diaphragmatic hernia as a result of diaphragmatic rupture with herniation of abdominal contents into the chest causing thus pressure on — compression of the cardiac cavities, but also myocardial herniation due to a small pericardial rupture, resulting from a blunt force[4,8]. A strong blunt force can cause rotation of the heart and the so-called "luxation" or the dislocation of the whole heart through the chest and abdominal wall. The last changes need to be excluded in the in-hospital period, best by using multi-layer computed tomography (MSCT).

The causes of blunt non-penetrating trauma are multiple, usually resulting in consequential chest and heart compression and rarely in minor or major ruptures of the heart and surrounding organs. This happens in car accidents as a result of sudden deceleration, direct contusion of the sternum by the steering wheel and numerous contusions of the chest and abdomen in case of a car rollover. A common cause of contusion of the chest and the heart is also a fall from the height onto the ground as an occupational injury, intentional strong "murderous" blows to the chest, unintentional fierce hit by the ball, collision of two bodies in the sport, and in cattle breeding the kick by an animal's hoof in the chest, falling off a riding animal, falling off a motorcycle, bicycle, etc. Minor or major iatrogenic myocardial and pericardial contusion cannot often be avoided in medical resuscitation, sometimes accompanied by fractured ribs (which can cause a penetrating injury). The following causes are air strikes — air "blast" in the immediate vicinity of the explosion of a bomb, mine, with compression of the sternum and organs on the spine, any water "blast" or other compression of the thorax between the two incompressible — metal substrates.

Besides the deceleration forces, when bringing two vehicles to a halt a strong acceleration forces are created, sometimes even in accidents in a case of rollover. Such acceleration forces of high power can lead to "flexion" of the chest with the manifestation of the stretching forces and twisting forces1 and thus to the cardiac injury and injury of other organs in the chest. Frequent electrocardioversions can in therapeutic interventions be the cause of micro changes to the myocardium, myocardial edema and minor necrosis. The same applies to the unfortunate alternating electric current strikes, and probably to lightning strikes and electrical discharge produced by the thunderstorm. In cases of blunt

dobiti određivanjem specifičnih miokardnih enzima i troponina.

Akutna penetrantna povreda srca

Kod akutne penetrantne — oštre ozljede posljedice djelovanja sila se očituju odmah teškim kardiološkim smetnjama i općim teškim stanjem ozlijeđenog, često s hipovolemičkim — uz oligemiju, hemoragičnim šokom (neki kliničari hipovolemički šok nazivaju i "opstruktivnim" — jer je spriječeno normalno punjenje srca u dijastoli uz ev. opstrukciju velikih žila) ili općenito traumatskim šokom, što zahtijeva što hitniju, podrobniju dijagnozu i terapiju. Uzroci takve ozljede s najčešće trenutnim smrtnim ishodom i u mirnodopskim su uvjetima i dalje projektili iz vatrenog oružja, zrna većeg kalibra iz samokresa/pištolja, "magnuma", "beretke" ili više manjih zrna iz oružja za lov "sačmarice"; namjerne ubodne rane hladnim oružjem, nožem; slučajne ozljede oruđem i drugim oštrim predmetima u industriji i proizvodnji. U prometnim nesrećama događaju se veće razderotine, laceracije prsnog koša i prekid kontinuiteta struktura perikarda, miokarda, aorte, oštrim rubovima frakturiranih rebara i sternuma, ozljedom "letećim" oštrim predmetima velikih brzina (akceleracijskih sila) od stakla ili lima te nekad i samim jakim kompresijama (s tlačenjem između sternuma, rebara i kralježnice). Procjenjuje se da je kod takvih događanja incidencija težih lacerirajućih oštećenja srca od oko 20%[3], od kojih polovica završava smrtno. U poljoprivrednim aktivnostima svjedoci smo da je prevrtanje poljoprivrednih strojeva (traktora) gotovo uvijek smrtonosno za vozača. Radi li se pri tome o srčanoj smrti ili drugim uzrocima nije ispitano.

Penetrirajuća trauma srca u civilnom društvu sjeverne Amerike u četvrtini slučajeva (svih penetracija u prsa) i dalje je uzrokovana nožem. U Turskoj je retrospektivnom analizom od 2005. do 2008. god. pokazano da je 5% penetrantnih ozljeda uzrokovano zrnom iz vatrenog oružja, a 95% ubodnih rana hladnim oružjem, oruđem ili drugim[11].

Premještaj (displasman) trbušnih organa u prsni koš i obratno (samog srca prema trbušnoj šupljini) preko rupturirane dijafragme dovodi do hernijacije trbušnih organa i nekad tzv. "luksacije", pomaka srca s nagnječenjem kao kod tupe traume ili/i s posljedičnom laceracijom, rupturom srca — miokarda, perikarda, disrupcijom srčanih valvula, papilarnih mišića, aorte i velikih vena. Ortopedski naziv "luksacija", "iščašenje", izvrnuće iz primarnog položaja srca, kao i "volvulus" (zapletaj) — naziv iz abdominalne hitne kirurgije ovdje iznimno imaju značenje zaokreta srca i velikih žila oko njihove osovine i mogu dovesti do opstrukcije vene kave inferior, velikih arterija i kompresije desne strane srca i medijastinalnih organa[1,12]. Oštećenja su usko povezana i s kompliciranom srčanom rupturom u 28% slučajeva, čija smrtnost je visoka — 67%[13]. Značajna promjena električne osi na EKG-u u tim situacijama (ako je poznat raniji nalaz) suspektna je uvijek na "luksaciju" i premještaj srca.

I u penetrantnoj ozljedi uz laceraciju miokarda, perikarda, može istodobno postojati dodatno oštećenje miokardnih arterija, arteriola te preko ishemije dovesti do sekundarne nekroze i rupture miokarda ili opet neposredno zbog rupture stijenke koronarnih arterija i spomenutih arteriola do hematoperikarda.

Penetrirajuća, prostrijelna i ubodna rana vidljivo oštećuju prednji dio prsnog koša (najčešće na ulazu) te projektilom (nevidljivo) velike žile, aortu, vene, medijastinum i kralježnicu u kojoj se projektil može zaustaviti i prouzrokovati neurološke ispade. Projektil i ubodna rana mogu, međutim, biti

cardiac trauma, the details on the severity of myocardial injury can be obtained by determining specific myocardial enzymes and troponin.

Acute penetrating cardiac injury

In acute penetrating — sharp injury the consequences of the forces are immediately manifested by severe cardiac disorders and severe general condition of the injured, often with hypovolemic — with oligemia, hemorrhagic shock (hypovolemic shock is called "obstructive shock" by some clinicians — because the normal filling of the heart in diastole with potential obstruction of large vessels is prevented) or generally with traumatic shock, which requires an urgent, thorough diagnosis and therapy. The causes of such an injury usually with a deadly outcome are even at peacetime still projectiles from firearms, larger caliber bullets from the rifle/pistol "magnum", "beret" or several smaller bullets from the hunting "shotgun"; deliberate stab wounds by cold weapon, knife; accidental injuries by tools and other sharp objects in the industry and production. In traffic accidents major tears, chest lacerations and a break in the continuity of the pericardial, myocardial, aorta structures which are caused by sharp edges of fractured ribs and sternum, an injury by "flying" high speed sharp objects (acceleration force) of glass or metal, and sometimes the very strong compressions (with compression between the sternum, ribs and spine) occur. It is estimated that the incidence of such events in severe cardiac lacerations is about 20%[3] of which a half of them end up with a fatal outcome. In agricultural activities, we have witnessed that overturning of agricultural machinery (tractors) is almost always fatal for a driver. It has not been studied whether a cardiac death or some other causes were the reason for death.

Penetrating cardiac trauma in the civil society of North America in a quarter of cases (of all penetrations into the chest) is still caused by a knife. In Turkey, a retrospective analysis conducted from 2005 to 2008, showed that 5% of penetrating injuries were caused by bullets from a firearm, and 95% of stab wounds by a cold weapon, tools etc.[11].

The displacement of abdominal organs in the chest and reversely (of the very heart towards the abdominal cavity) via the ruptured diaphragm leads to herniation of abdominal organs and sometimes the so called "luxation", displacement of the heart with contusion as in blunt trauma or/and with consequential laceration, rupture of the heart — myocardium, pericardium, disruption of cardiac valves, papillary muscles, aortic and large veins. Orthopedic term "luxation", "dislocation" from the primary position of the heart, as well as "volvulus" (obstruction) — the name taken from emergency abdominal surgery denote here rotation of the heart and large vessels around their axis and can lead to obstruction of the inferior vena cava, large arteries and compression of the right side of the heart and mediastinal organs[1,12]. The injuries are closely associated with complicated cardiac rupture in 28% of cases, where mortality is high — 67%[13]. Significant changes in the electrical axis in ECG in these situations (if an earlier finding is known) are always suspicious for "luxation" and "dislocation" of the heart.

The penetrating injury along with the myocardial, pericardial laceration can be accompanied by additional injury of myocardial arteries and arterioles causing secondary necrosis and myocardial rupture through ischemia or again directly causing hemopericardium as a consequence of the rupture of the walls of coronary arteries and above mentioned arterioles.

The penetrating, gunshot and stab wounds visibly damage the anterior chest (usually at the entrance) and the missile (invisibly) damage large vessels, aorta, veins, mediastinum, and spine where the missile can stop and cause neurological injuries. The missile and stab wounds, however, can be

usmjereni iz trbušne šupljine u pravcu srca, pa je tada ulazna rana na trbušnoj stijenci, ponekad i sa stražnje strane prsišta u leđima, što zahtijeva detaljan pregled da se rane ne previde. Lacerirajuća povreda srca može se dogoditi i iznutra kod jakih kompresija (bez vidljive ulazne i izlazne rane) te kod nekih dijagnostičkih i terapijskih kardioloških zahvata kao što su: kateterizacije srca, ispitivanja provodnog sustava srca, radiofrekventne ablacije provodnih puteva, postavljanja električnog stimulatora srca, TAVI operacije aortne srčane greške ili rekonstrukcije zalistka arterijskim ili venskim putem (kao npr. kod perkutane mitralne valvuloplastike, plastike trikuspidnog zalistka), biopsije miokarda, za vrijeme koronarografije s postavljanjem stentova ili/i tijekom dilatacije koronarnih arterija.

Patofiziologija i klinička slika tamponade perikarda

Svaki perikardijski sadržaj uz nastalu akutnu oštru traumu srca treba smatrati hematoperikardom dok se ne dokaže suprotno, kao i potencijalnim uzrokom tamponade perikarda[1,3,9,11,24]. Hematoperikard zbog naglog nastanka i ovdje velike količine krvi u perikardijskoj šupljini bez intervencije gotovo uvijek prelazi u tamponadu. Stoga intervenciju, terapijsku perikardiocentezu, treba učiniti što prije, u intervenciji ekipe hitne medicinske pomoći (HMP) na terenu incidenta, osim kod ozbiljne sumnje da je hematoperikard uzrokovan disekcijom aorte, kada je perikardiocenteza kontraindicirana.

Tamponada perikarda se ujedno smatra i ekvivalentom ponajprije penetrantne ozljede srca izvana (iako može nastati i kod nepenetrantne ozljede) koja ne mora biti vidljiva kao rana na površini prsnog koša ili trbuha. Statistički podaci ukazuju da neke ubodne rane hladnim oružjem, uskim vrškom noža ili manje ubodne rane vrškom frakturiranog rebra, ivera sternuma imaju bolju prognozu od rana nastalih vatrenim oružjem. Nastanak tamponade perikarda u prvom slučaju je obično postupniji, polaganiji, a mala rana ili rana uzdužnog rasjeka miokarda i perikarda nekada se stisne, suzi te može i spontano trombozirati. Oštećenje miokarda velikim projektilom dovodi naglo do tamponade velikom količinom hemoperikarda, a ukoliko nema intervencije, često i do brzog smrtnog ishoda.

Na procjeni količine perikardijskog sadržaja neposredno nakon incidenta već su 1999. god. inzistirali japanski autori primjenom ultrazvuka srca i intervencijom[9]. Perikard nije rastezljiv, osim u postupnom povećanju perikardijskog sadržaja (hipotireoza, uremija) kada se može povećati volumen perikardijske vreće sve do 1.500-2.000 mL, bez značajnih simptoma u mirovanju. Ako se perikardijski sadržaj poveća naglo, nekad i 100mL krvi može uzrokovati simptome tamponade.

Naglim povećanjem volumena u perikardijskoj vreći raste intraperikardijski tlak. Kada se tlak u perikardu približi tlaku u DA, funkcija DV je bitno oštećena. Povišeni intraperikardijski tlak ometa nadalje dijastoličko širenje klijetki. To vodi daljem povećanju intrakavitarnog dijastoličkog tlaka i smanjuje punjenje klijetke (u početku više DV, potom i LV), a time se bitno smanjuju udarni i minutni volumen lijeve strane srca i pada sustavni arterijski tlak. Porast intraperikardijskog tlaka je u upravnoj korelaciji i s porastom sustavnog venskog tlaka i tlaka u plućnim venama te posljedično dovodi do spomenutog porasta tlaka u DA, ali i u LA. Zbog porasta sustavnog venskog tlaka i tlaka u plućnim venama, dijastoličkog tlaka u obje komore, dijastoličkog tlaka i u plućnoj

directed from the abdominal cavity in direction of the heart, and then the entry wound in the abdominal wall is sometimes in the posterior chest in the back, which requires a detailed examination to prevent overlooking of the wound. Cardiac laceration can even occur from the inside in case of strong compressions (with no visible entry and exit wound) and in some diagnostic and therapeutic cardiac procedures such as: cardiac catheterization, examining the conduction system of the heart, radiofrequency ablation of conductive pathways, implantation of electrical pacemaker, TAVI procedures on the aortic heart valve defects or arterial or venous valve repair (such as in percutaneous mitral valvuloplasty, plastic procedure on the tricuspid valve), myocardial biopsy, during coronary angiography with stent implantation and/or during the dilation of coronary arteries.

Pathophysiology and clinical course of pericardial tamponade

Each pericardial fluid with sharp cardiac trauma should be considered hemopericardium unless proven otherwise, and also the potential cause of pericardial tamponade[1,3,9,11,24]. Due to its sudden occurrence and here large amounts of blood in the pericardial cavity, hemopericardium develops almost always to tamponade if no intervention is performed. Therefore, the intervention, therapeutic pericardiocentesis should be performed as soon as possible by the emergency medical services (EMS) on the spot of the incident, except in case when reasonably suspecting that hemopericardium is caused by aortic dissection, when pericardiocentesis is contraindicated.

Pericardial tamponade is also considered equivalent primarily to penetrating cardiac injury from the outside (although it can occur in case of non-penetrating injury) that may not be visible as a wound on the surface of the chest or abdomen. The statistical data show that some stab wounds caused by cold weapons, a narrow tip of a knife or minor stab wounds caused by a tip of a fractured rib, body of sternum have a better prognosis than the gunshot wounds. The pericardial tamponade in the first case usually occurs more gradually, slowly, and a minor wound or a longitudinal myocardial or pericardial rupture wound is sometimes squeezed, narrowed and can spontaneously thrombosed. Myocardial injury by a large missile causes a sudden tamponade by a large amount of hemopericardium, and a fatal outcome if no intervention is performed.

The Japanese authors insisted on the assessment of the amount of pericardial fluid immediately after the incident in 1999 by using the heart ultrasound and intervention[9]. Pericardium may not stretch, except in gradual increase in pericardial fluid (hypothyroidism, uremia) when the volume of pericardial sac can increase up to 1,500-2,000 mL without significant symptoms at rest. If the pericardial fluid increases all of a sudden, sometimes 100mL of blood, can cause symptoms of tamponade.

A sudden increase in volume in pericardial sac increases intrapericardial pressure. When the pressure in the pericardium becomes close to the pressure in the RA, RV function is then significantly impaired. Elevated intrapericardial pressure hinders further ventricular diastolic expansion. This leads to a further elevation of intracavitary diastolic pressure and reduces ventricular filling (initially more RV, followed by LV), thus significantly reducing the stroke and minute volume of the left side of the heart whereas the systemic arterial pressure drops. The elevation of the intrapericardial pressure administratively correlates to an elevation of the systemic venous pressure and the pressure in the pulmonary veins consequently leading to the aforementioned elevation of pressure not only in the RA, but also in LA. The elevated systemic venous pressure and pulmonary venous pressure,

arteriji, rastu vrijednosti tlaka u srcu na približno istu razinu: nestaju intrakavitarne i intravaskularne razlike tlaka i nastaje stanje tamponade perikarda s daljnjim padom udarnog volumena, padom arterijskog tlaka i preko cirkulacijskog kolapsa dolazi do kardiogenog šoka, najčešće sa smrtnim ishodom.

Može se zaključiti da tamponadu perikarda patofiziološki karakterizira:

1. povećanje intrakardijskih tlakova uzrokovano naglim povećanjem intraperikardijskog tlaka,

2. ograničeno punjenje srčanih komora u dijastoli,

3. redukcija udarnog i minutnog volumena srca.

Kliničku simptomatologiju tamponade čini u početku jaka prsna bol substernalno te epigastrično (vezana najčešće uz lacerirajuću ozljedu), potom opće teško prostrirajuće stanje s bljedoćom, zaduhom, tahipnejom, tahikardijom, a ponekad u početku i disfagijom, kašljem, promuklošću zbog često jake kompresije pluća, bronha i rekurentnog živca. Na kraju dominira slika šoka.

Fizikalnim pregledom se utvrde tipični znakovi tamponade:

1. sustavna hipotenzija (mali udarni i minutni volumen);

2. distenzija jugularnih vena kao znak nemogućnosti punjenja DV i povišenja tlaka u desnom dijelu srca i venskom sustavu;

3. mukli ili nečujni srčani tonovi (uz tahikardiju) — sve nazvano karakterističnim Beckovim trijasom[14].

Gotovo je uvijek prisutna spomenuta tahikardija zbog kompenzatorne simpatikotonije i kateholaminemije, kao reakcija na pad udarnog volumena i doživljenu traumu; tahipneja (kompresija pluća, bronha, hipoksija), blijedoća kože i sluznica te ev. periferna cijanoza. Perikardijsko trenje kod većeg se izljeva ne čuje. Veći hematoperikard komprimira lijevo plućno krilo, što se perkutorno očituje muklinom, a auskultatorno nečujnim disanjem (Ewartov znak). Inače nema fizikalnih znakova zastoja u plućima što je karakteristično. Arterijski tlak je nizak — oko ili ispod 90 mmHg. Kada bi se mjerio venski tlak u kubitalnoj veni, bio bi povišen.

Može biti prisutan tipičan Kussmaulov znak, koji se očituje smanjenjem distenzije vratnih vena u inspiriju (a koji nije izražen u težoj hipovolemiji) te karakterističan tzv. paradoksni nalaz pulsa, ev. uz pad tlaka. Paradoksni puls je usporenje frekvencije srca u inspiriju (normalno je ubrzanje), a što se teško može klinički ocijeniti u prisutnoj tahipneji. Arterijski tlak mjeren u inspiriju trebao bi pasti također za 15-20 mmHg da se znak prihvati pozitivnim za tamponadu (što neki klinićari također svrstavaju u paradoksnost). Pad tlaka u inspiriju je inače normalno prisutan u zdravih individua ali i u nekim drugim bolestima, pa se sensu stricto ne može taj pad nazvati visoko specifičnim paradoksnim znakom.

Smanjenje distenzije jugularnih vena u inspiriju je znak kratkotrajnog sniženja tlaka u DA i intraperikardijski zbog kratkotrajno nastalog negativnog tlaka u prsnom košu. To omogućuje samo kratkotrajno punjenje DV i kratkotrajno povećanje dimenzija kaviteta DV u inspiriju.

Za tamponadu i oštećenje perikarda nema patognomoničnog EKG znaka, ali se ponekad može utvrditi više značajnih: 1. elevacija ST-spojnice, na vrhu tipično konkavna; 2. električni alternans; 3. niska voltaža amplituda QRS-kompleksa (zbroj amplituda u D1, D2, D3 manje od 15 mm). Posljednji je također neosjetljiv i nespecifičan znak tzv. "kratkog spoja" u putovanju električnog impulsa kroz perikardijski izljev, jer

diastolic blood in the both chambers, diastolic pressure in the pulmonary artery lead to an elevation of pressure values in the heart at approximately the same level: intracavitary and intravascular pressure differences disappear resulting in the condition of pericardial tamponade with a further drop in stroke volume, drop in blood pressure and via circulatory collapse causing cardiogenic shock, often with a fatal outcome.

It can be concluded that pericardial tamponade is pathophysiologically characterized by:

1. elevation of intracardiac pressures caused by sudden elevation of intrapericardial pressure;

2. limited diastolic filling of cardiac chambers;

3. reduction of cardiac stroke and minute volume.

Clinical symptomatology of tamponade is at first manifested as a strong substernal and epigastric chest pain (usually associated with laceration-related injury), followed by the general serious prostrate condition with pallor, dyspnea, tachypnea, tachycardia, and sometimes at the beginning with dysphagia, cough, hoarseness due to frequently severe compression of the lungs, bronchus and recurrent nerve. The manifestation of shock is finally dominant.

Physical examination determines the typical signs of tamponade:

1. systemic hypotension (low stroke and minute volume);

2. jugular vein distension as a sign of a failure of filling RV and rise in pressure in the right side of the heart and venous system,

3. a muffled or inaudible heart sounds (with tachycardia) — all called as characteristic Beck's triad[14].

Tachycardia is almost always present due to compensatory sympathicotonia and catecholamine, in response to the fall in stroke volume and history of trauma: tachypnea (compression of the lungs, bronchi, hypoxia), paleness of skin and mucous membranes, and potential peripheral cyanosis. Pericardial friction is not heard in major effusion. Larger hemopericardium compresses the left pulmonary lobe, which is reflected by dullness to percussion and inaudible breathing auscultatory (Ewart's sign). Otherwise, there are no physical signs of delays in the lungs which is a typical phenomenon. Arterial pressure is low — around or below 90 mmHg. When venous pressure in cubital vein was measured, it would be elevated.

A typical Kussmaul's sign may be present. It is reflected by reducing neck vein distension in inspiration (which is not expressed as more severe hypovolemia) and characteristic paradoxical pulse finding, accompanied by a potential pressure drop. Paradoxical pulse is a slowdown of the heart rate in the inspiration (acceleration is normal), which is difficult to assess clinically in presence of tachypnea. Blood pressure measured in the inspiration should also drop to 15-20 mmHg in order to accept the sign as positive for tamponade (which is classified as paradox by some clinicians). The drop in pressure in the inspiration is otherwise normally present in healthy individuals, but also in other diseases, so sensu stricto this drop can not be called a highly specific paradoxical sign.

Reduction of jugular vein distension in the inspiration is a sign of a short-term drop in pressure in RA and intrapericardially as a result of a negative pressure in the chest. This allows only a slow filling of RV and transitory increase in cavity size of RV in the inspiration.

For pericardial tamponade and injury there is no pathognomonic ECG sign, but sometimes several significant ones can be determined: 1. elevation of the ST-segment at the top typically concave; 2. electrical alternans; 3. low voltage of amplitude of QRS-complex (the sum of the amplitudes in D1, D2, D3 less than 15 mm). The latter is also an insensitive and a nonspecific sign of the so-called "short circuit" in the electrical impulse travel through the pericardial effusion,

postoji i u pretilosti, u pleuralnom izljevu lijevo, nekim kardiomiopatijama, amiloidozi...)[15,16].

Jak porast intraperikardijskog tlaka u tamponadi oštećuje i smanjuje protok u subendokardnom i subepikardnom dijelu miokarda uzrokujući time miokardnu ishemiju, koja se može očitovati u zapisu 12-kanalnog EKG-a kao konveksna elevacija ST-spojnice s pozitivnim ili negativnim T-valom. Depresija ST-spojnice je iznimna. Opisani nalaz ST-spojnice na EKG-u u tamponadi je također nespecifičan. Vrlo su rijetki q- ili QS-zupci i također nisu izraz perikardnog oštećenja u tamponadi, nego subepikardnog oštećenja miokarda, jer i elektrofiziološki visceralni i parijetalni list perikarda i inače normalno ne stvaraju nikakvu razliku električnog potencijala zbog male mase perikarda, da bi je se moglo uopće registrirati[15]. Ruptura miokarda uz tamponadu, ovisno o veličini, može dati sliku nekroze s q- ili QS-zupcima. Razumljivo je, stoga, da i laboratorijski nalazi specifičnih miokardnih enzima i troponina ukazuju samo na dodatno oštećenje miokarda, a ne perikarda[5,15].

Prilikom ehokardiografskog pregleda u tamponadi mogu se utvrditi sljedeći znakovi:

1. povećanje DV u inspiriju s recipročnim smanjenjem LV;

2. kolaps DA u ekspiriju;

3. kolaps DA u sistoli duže od trećine trajanja sistole (osjetljivost 90%, specifičnost 100%);

4. dijastolički kolaps DA i ev. LA, a vrlo rijetko LV;

5. paradoksni pomak iv. septuma u inspiriju prema LV;

6. kolaps DV neposredno nakon zatvaranja pulmonalnog zalistka i otvaranja trikuspidnog, dakle, u ranoj dijastoli;

7. suženje — kolaps izgonskog trakta DV, eksperimentalno osjetljiviji znak čak od kolapsa DV

8. distenzija — dilatacija vene kave inferior (subkostalnim pristupom) bez smanjenja za 50% u inspiriju (što upućuje na povećani srednji tlak u DA iznad 10 mmHg);

9. povećanje protoka u inspiriju, mjereno Doppler metodom, kroz trikuspidno ušće, a smanjenje protoka u inspiriju kroz mitralno ušće i obratno u ekspiriju

10. pristupom transtorakalno-supraklavikulano (iz jugguluma) može se utvrditi stanje arkusa aorte, asc. aorte i proksimalnog dijela desc. aorte te s izvjesnom sigurnošću dokazati ili isključiti disekciju aortne stijenke kao mogući uzrok tamponade[17].

Patomorfologija i klinička slika kontuzije miokarda

Kontuzija miokarda (nagnječenje od udarca) je u većini slučajeva ekvivalent tupe, nepenetrantne traume srca povezane s tupom traumom prsnog koša (ponekad i tupom traumom trbuha)[1,4,8]. Ova trauma srca ovisi o snazi "tupih" sila u djelovanju na prsni koš, ponajprije o učinku tzv. akceleracijskih sila koje djeluju ne samo na površinu prsnog koša, nego time i na površinu srca te na površinu i unutrašnjih srčanih struktura i drugih organa u prsnom košu. Učinak ovisi o mjestu udara, rastežljivosti prsnog koša (dječji ima povećanu rastežljivost, pa je manje smrtnih slučajeva u prometu) i o fazi srčane rezolucije u kojoj se dogodio udarac. Dokazano je na animalnim modelima da nekad i manja sila u kritičnoj fazi srčane rezolucije može izazvati naglu smrt[15,18]. Nema danas standardnih parametara za točnu procjenu veličine, jačine sile i snage tupe traume kod ljudi koja dovodi do kontuzijskog oštećenja, što je razumljivo. Kritičnu fazu srčane rezolucije kod ljudi također je gotovo nemoguće

as it is even present in obesity in the left pleural effusion, some cardiomyopathies, amyloidosis ...)[15,16].

A strong elevation of intrapericardial pressure in the tamponade damages and reduces the flow in the subendocardial and subepicardial part of the myocardium causing thus the myocardial ischemia, which can be manifested in a record of 12-lead ECG as convex elevation of the ST-segment with the positive or negative T-wave. The depression of the ST-segment is exceptional. The described finding of the ST-segment on ECG in the tamponade is also nonspecific. Q or QS waves are very rare and are also not the sign of the pericardial tamponade, but of subendocardial myocardial injury, because the electrophysiological visceral and parietal layer of the pericardium normally make no difference in the electric potential due to a small pericardial mass, so that it could be recorded at all[15]. Myocardial rupture with tamponade, depending on size, can give an image of necrosis with Q-or QS-wave. It is understandable, therefore, that laboratory findings of specific myocardial enzymes and troponin just additionally indicate the injury of the myocardium, not of pericardium[5,15].

When making echocardiographic examination of tamponade the following signs can be determined:

1. elevation of RV in the inspiration with reciprocal reduction in LV;

2. collapse of RA in the expiration;

3. RA collapse in systole longer than a third of the systole duration (sensitivity 90%, specificity 100%);

4. diastolic collapse of RA and potentially LA, very rarely LV;

5. paradoxal shift of iv. septum in the inspiration towards LV;

6. collapse of RV immediately after the closure of pulmonary valve and opening of tricuspid valve, that is, in early diastole;

7. constriction — RV outflow tract collapse, experimentally a sign even more sensitive than the RV collapse

8. distension — inferior vena cava dilatation (by subcostal approach) without reduction by 50% in the inspiration (which indicates an elevated medial pressure in RA above 10 mmHg);

9. an increase in the flow in the inspiration, measured by Doppler method, through the tricuspid orifice, and a decrease in flow in the inspiration through the mitral orifice and reversely in the expiration

10. by transthoracic-supraclavicular approach (from the jugulum) we can determine the condition of aortic arch, ascending aorta and proximal part of descending aorta and can with a certainty prove or exclude the dissection of aortic wall as a possible cause of tamponade[17].

Pathomorfology and clinical course of myocardial contusion

Myocardial contusion (contusion caused by a blow) is in most cases equivalent to blunt, non-penetrating cardiac trauma associated with blunt chest trauma (sometimes even by blunt abdominal trauma)[1,4,8]. The cardiac trauma depends on the strength of "blunt" forces exerted on the chest, primarily on the effect of the so-called acceleration forces exerted not only on the surface of the chest, but consequently also on the surface of the heart and on the surface of internal cardiac structures and other organs in the chest. The effect depends on the site of impact, compliance of the chest (children's chest has increased compliance, so there is fewer number of fatalities in car accidents) and the stage of cardiac resolution in which the impact occurred. It has been proved on animal models that sometimes less force at a critical stage of the cardiac resolution can cause a sudden death[15,18]. Today there are no standard parameters for an accurate assessment of the size, strength of force and power of blunt trauma in people that leads to contusion, which is understandable. The critical stage of the cardiac resolution

odrediti, jer nitko ne nosi holter EKG-aparat u fazi doživljene sile. Ostaje kao jedina točnija procjena snage sile tupe miokardne traume prema histološkom nalazu na autopsiji.

Patomorfološke promjene mogu se histološki utvrditi u obliku blagog edema tkiva miokarda, intramuralne hemoragije, manje ili veće nekroze miokarda koju može slijediti ruptura stijenke[1,4,6,14]. Ruptura miokarda kod tupe traume srca javlja se u oko 0,3%-1,1% (neposredno) traumatiziranih. U duljem promatranju posttraumatskog stanja, nekad i mjesecima ili godinama, događaju se i smrtni ishodi. Mislimo da je teško dokazati uzročnu povezanost nakon dužeg vremena od traume pa je moguće da u studijama (koje navode visoku posthospitalnu smrtnost) nisu dovoljno isključeni svi drugi uzročni faktori?

Pneumoperikard se može javiti poslije tupe traume, komplicirane rupturom, laceracijom perikarda i okolnog plućnog tkiva (dokazuje se MSCT pretragom prsnog koša). Oštećenja koronarnih arterija u tupoj se traumi događaju u oko 2% i to najčešće lijeva prednja silazna aterija, ali i desna koronarna arterija koja je lacerirana desno iza sternuma, dok je cirkumfleksna arterija zahvaćena vrlo rijetko[19-21]. Višežilna koronarna oštećenja su rijetka. Traumatska valvularna disfunkcija s nastankom plućnog edema je također rjeđa[6]. Najčešće je oštećena aortna valvula, slijede mitralna i trikuspidna. Mehanizam nastanka disrupcija kuspisa je nagli porast intrakardijalnog tlaka kod zatvaranja valvule. Uzroci valvularne disfunkcije su rastrgnuće ili izvrnuće, otrgnuće (avulzija) anulusa i najčešće nekoronarnog aortnog kuspisa[6].

Već sam edem miokarda može kompromitirati koronarnu cirkulaciju kompresijom pa se razvije ("sekundarna") ishemija[4,18]. S obzirom da se proces djelovanja tupe sile događa pretežno u miokardu, razumljivo je da se elektrokardiografski može manifestirati kao ishemija ili češće kao infarkt miokarda, koji ima ponekad i zupce nekroze q- ili QS. ST-spojnica u takvim oštećenjima obično je elevirana s konveksitetom na vrhu (kao u infarkta), a T-valovi češće su odmah negativni. ST-spojnica može u nekim odvodima biti i jače denivelirana. Važno je istaknuti da neposredno učinjen EKG s patološkim promjenama identificira rizičnog bolesnika, ali normalan nalaz EKG-a neposredno nakon incidenta nije od pomoći, jer mu je vrijednost negativno prediktivna. Neposredno nakon incidenta, ako je kontuzijska sila bila jaka mogu se utvrditi učestale srčane aritmije u oko 28% tupih ozljeda[8] uz smetnje provođenja. Obično se radi o neopasnim ekstrasistolama, supraventrikulskim tahikardijama, atrijskim ekstrasistolama. Čest je blok desne grane koji u lakšoj ozljedi i nestaje unutar 24 sata, a blok lijeve grane je rijedak. Javljaju se i ventrikulske ekstrasistole i ventrikulska tahikardija, slično kao u ranom postinfarktnom razdoblju, koja kod manjih oštećenja dobro reagira na medikamentnu terapiju (amiodaronom, a rijetko je potrebno dati alternativni lijek — lidokain 100 + 50 mg).

Međutim, ne smije biti iznenađenja za ekipu HMP jer se u ranom razdoblju poslije teške kontuzije javlja i postojana ventrikulska tahikardija (bez pulsa) pa i fibrilacija ventrikula (ritmovi koji se defibriliraju), a koji se javljaju uz srčani arest te se trebaju intenzivno liječiti prema novim smjernicama[22,23]. Nakon tri početne defibrilacije bez uspjeha, preporuča se ordinirati adrenalin 1 mg i.v. (ili intraosealno: humerus, tibia) i ponavljati ga svakih 3-5 minuta. Javlja li se ponovljeno fibrilacija ventrikula treba ordinirati amiodaron 300 mg i.v. u 5% glukozi u bolusu te ev. dodatno još 150 mg amiodarona.

Često se ipak dogodi neuspjeh te se javlja asistolija — stanje bez električne ventrikulske aktivnosti, iako električna aktivnost u ranom razdoblju poslije teške kontuzije javlja i postojana ventrikulska tahikardija (bez pulsa) pa i fibrilacija ventrikula (ritmovi koji se defibriliraju), a koji se javljaju uz srčani arest te se trebaju intenzivno liječiti prema novim smjernicama[22,23]. Nakon tri početne defibrilacije bez uspjeha, preporuča se ordinirati adrenalin 1 mg i.v. (ili intraosealno: humerus, tibia) i ponavljati ga svakih 3-5 minuta. Javlja li se ponovljeno fibrilacija ventrikula treba ordinirati amiodaron 300 mg i.v. u 5% glukozi u bolusu te ev. dodatno još 150 mg amiodarona.

Često se ipak dogodi neuspjeh te se javlja asistolija — stanje bez električne ventrikulske aktivnosti, iako električna aktivnost u

in people is also almost impossible to determine because no one wears Holter ECG monitor in the stage of experienced force. The only accurate assessment of strength of myocardial blunt force trauma force can be made according to the histological findings at autopsy.

Pathomorphological changes can be histologically determined in the form of mild edema of the myocardial tissue, intramural hemorrhage, minor or major myocardial necrosis, which may be followed by rupture of the wall[1,4,6,14]. Myocardial rupture in blunt cardiac trauma occurs in approximately 0.3% - 1.1% of (directly) traumatized persons. Deadly outcomes occur in a longer observation of post-traumatic condition, sometimes lasting for months or years. We think it is difficult to prove a causal connection after a long time since the period of trauma, so it is possible that studies (indicating a high post-hospital mortality) do not sufficiently exclude all other causal factors.

Pneumopericardium may occur after the blunt trauma, being complicated by rupture, laceration of the pericardium and surrounding lung tissue (as proved by MSCT examination of the chest). Damage to the coronary arteries in blunt trauma occurs in about 2%, mostly it is the left anterior descending artery and the right coronary artery which is lacerated on the right side behind the sternum, while the circumflex artery is rarely affected[19-21]. Multi-vessel coronary injuries are rare. Traumatic valvular dysfunction with the development of pulmonary edema is also more rare[6]. Aortic valve, followed by mitral and tricuspid valve are mostly damaged. The mechanism of development of cusp disruptions is a sudden elevation of intracardial pressure when closing the valve. The causes of valvular dysfunction are tear or distortion, avulsion of annulus and usually of non-coronary aortic cusp[6].

The myocardial edema itself may compromise the coronary circulation by compression resulting in the development of ("secondary") ischemia[4,18]. Since the process of exerting blunt force mainly occurs in the myocardium, it is understandable that it can be manifested as ischemia by electrocardiographic leads, or more often as myocardial infarction, whereas q or QS waves sometimes suggest necrosis. The ST-segment in such injuries is usually elevated with the convexity on the top (as in the infarction), and T-waves are often immediately negative. The ST-segment may in some leads be even more denivelated. It is important to point out that recently performed ECG with pathological changes identify a patient at risk, but the normal finding of ECG taken immediately after the incident is of no help, because its value is negatively predictable. Immediately after the incident, if the contusion force was strong, frequent cardiac arrhythmias in around 28% of blunt injuries[8] with the conduction disturbance can be determined. Usually, these are harmless extrasystoles, supraventricular tachycardia, atrial estrasystoles that are concerned. The right bundle branch block which in case of minor injury disappears within 24 hours, while the left bundle branch block is rare. Ventricular extrasystoles and ventricular tachycardia also occur, similar to the early postinfarction period, which in case of minor injuries are well treated by medicamentous therapy (amiodarone, and an alternative medicine — lidocaine 100 + 50 mg is rarely to be administered).

However, the EMS team should be not surprised, because the early period after the severe contusion is followed by the sustained ventricular tachycardia (pulseless), including ventricular fibrillation (rhythms that are defibrillated), which occur along with cardiac arrest and they should be treated intensively according to the new guidelines[22,23]. After three initial defibrillations without success, it is recommended to prescribe epinephrine 1 mg i.v. (or intraoseal: humerus, tibia) which is to be repeated every 3-5 minutes. If the ventricular fibrillation reoccurs, amiodarone 300 mg i.v. in 5% glucose in bolus and additionally 150 mg amiodarone should be prescribed.

tivnost može postojati u vidu P-valova koji nisu uvijek vidljivi na EKG-u. Potrebno je ponovno procjeniti spoj elektroda i ocijeniti nalaz EKG-a. Može postojati asistolija i kod sumnje da se radi pretpostavljeno o tzv. "finoj fibrilaciji ventrikula" (nevidljivoj u EKG zapisu) te se donedavno i u toj situaciji nastavljalo s defibrilacijom. Današnji je stav da se kod asistolije sumnjive na "finu" fibrilaciju ventrikula ne čini ponovo defibrilacija?! Ritmovi koji se ne defibriliraju su dokazana (agonalna) prava asistolija i električna aktivnost bez pulsa (PEA), često zvana elektromehanička disocijacija. Kod asistolije ili razvoja bloka može se pokušati s perkutanom stimulacijom, primjenom torakalnih elektroda ili dakako aplikacijom sa spomenutim adrenalinom. Nove preporuke smatraju da primjena atropina od 3 mg u bolusu nije od velikog učinka (iako ga i nadalje primjenjujemo u pojedinim situacijama kao potentnog vagolitika).

Prema novim stavovima Europskog društva za resuscitaciju[22,23], objavljenim 2010. godine, preživljavanje nakon kardijalnog aresta s asistolijom ili električnom aktivnosti bez pulsa je malo vjerojatno, ako se odmah ne otkriju i ne riješe uzroci (kao što je to ovdje tamponada perikarda). Kod prave asistolije nema koristi od električne stimulacije konsensus je stručnjaka na internacionalnoj razini.

U kontuzijskim oštećenjima srca nisu se smatrale potrebnim druge hospitalne mjere, poput privremenog uvođenja hipotermije 32-34°C, ako bolesnik poslije kardijalnog aresta srca nije bio u komi i nema neurološke ispade. Sadašnja preporuka je da se stanje poslije kardijalnog aresta tretira i hipotermijom. Vrlo je rijetko potrebna mehanička ventilacija uz miorelaksanse i sedaciju, a ekstremno rijetko primjena danas moderne mehaničke potpore srčanožilnom sustavu aparaturom VAD, BIVAD, LVAD, RVAD, LVAS — HEART MTTE II ili dr.

Sva simptomatologija i klinički status ovise o veličini oštećene miokardne mase, koja će dovesti do asistolije i nepopravljivog kardijalnog aresta. Uništenje >50% miokardne mase je vrlo rizično[24]. U kontuzijama prsnog koša više je izvrgnut oštećenju DV, a masa njegova miokarda je manja od mase LV, pa i porast miokradnih specifičnih enzima i troponina, usprkos jakoj sili može stoga biti blag što ne pridonosi ocjeni težine kliničke slike[5].

Tupa trauma prsnog koša s kontuzijom miokarda je statistički češća od penetrantne ozljede, ali čini se da je neposredno za život manje opasna. Često se postavlja pitanje nagle smrti sportaša koji su doživjeli mnoge manje ili veće tupe traume prsnog koša, npr. nogometaša (padovi, sudari, udarci loptom u prsa i sl.), a koji su praktički svi bili prije kardiološki pregledani i nisu imali dokazane uobičajene uzroke nagle srčane smrti. Malobrojno snimani EKG kod kolapsa, odnosno sinkopa nogometaša na terenu ipak ukazuju na malignu ventrikulsku tahikardiju, možda vezanu uz ranije tupe traume? Ako se poslije tupe traume prsnog koša razvije rezistentna hipotenzija usprkos adekvatnoj resuscitaciji hipovolemije i ako nije prisutan drugi evidentni uzrok stanja, treba napraviti dodatnu koronarografiju[21].

Ostale hitne intervencije kod traume srca

Dijagnozu traume srca, osobito penetrantne, trebalo bi utvrditi što prije poslije doživjelog incidenta, jer hitna intervencija kod sumnje na razvitak tamponade perikarda može spasiti život unesrećenika i uvjet je za uspješnu reanimaciju, ako se dogodi kardijalni arest. Očevidna rana, razderotina

However, a failure often occurs, whereas asystole occurs — the state without electrical ventricular activities, although electrical activity may exist in the form of P-waves which are not always visible in the ECG. It is necessary to re-evaluate the connection of electrodes and evaluate the ECG findings. Asystole may exist when suspecting that the so called "fine ventricular fibrillation" (invisible in the ECG record) is concerned and until recently defibrillation continued to be performed in this situation. The today's attitude is that no repeated defibrillation should be performed in case of asystole susceptible for the "fine" ventricular fibrillation. Rhythms that are not defibrillated are proven (agonal) asystole and pulseless electrical activity (PEA), often called electromechanical dissociation. In asystole or development of the block, one can try with percutaneous stimulation, by applying the thoracic electrodes or by administering the above mentioned adrenaline. The new recommendations suggest that the administration of 3 mg atropine in bolus is of a little effect (although we still apply it in certain situations as a potent vagolytic).

According to the new guidelines of the European Resuscitation Council[22,23], published in 2010, the survival after cardiac arrest with asystole or pulseless electrical activity is less likely if causes are not immediately detected and resolved (as it is pericardial tamponade here). In case of a true asystole there is no use of electrical stimulation, which is a consensus of experts at an international level.

In contusion-related cardiac injuries no other in-hospital measures, such as the temporary introduction of hypothermia 32-34°C were considered necessary, if a patient was not in a coma and had no neurological disorders after the cardiac arrest. The current recommendation is that the condition after the cardiac arrest is treated by hypothermia. Mechanical ventilation with myorelaxants and sedation is very rarely required, and the today modern mechanical support to cardiovascular system by apparatus VAD, BIVAD, LVAD, RVAD, LVAS — HEART MTTE II etc. is extremely rarely used.

All the symptoms and clinical status depend on the size of the injured myocardial mass, which will lead to asystole and irreparable cardiac arrest. The destruction of >50% of myocardial mass is very risky[24]. RV is more exposed to injuries in case of chest contusions, while its myocardial mass is lower than that of the LV, so the increase in myocardial specific enzymes and troponins, despite a strong force can therefore be slight which does not contribute to the assessment of severity of clinical course of the disease[5].

Blunt chest trauma with myocardial contusion is statistically more common than penetrating injury, but it seems to be directly less dangerous to life. A frequently asked question is posed in connection with a sudden death of athletes who have experienced many minor or major blunt chest traumas, for instance football players (falls, collisions, blow to the chest by a ball, etc.), who previously underwent cardiac examinations and had no proven common causes of sudden cardiac death. A small number of taken ECGs in case of collapse or syncopes sustained by the players on the playground indicate a malignant ventricular tachycardia, which may be related to the earlier blunt trauma? If the blunt chest trauma is followed by the development of resistant hypotension despite an adequate resuscitation of hypovolemia, and if no other obvious cause of the condition is present, an additional coronary angiography should be performed[21].

Other emergency interventions in cardiac trauma

The diagnosis of the cardiac trauma, particularly penetrating cardiac trauma, should be made as soon as possible after the sustained incident, because the emergency intervention when suspecting the development of pericardial tamponade may save the life of the injured and is the prerequisite for successful resuscitation if cardiac arrest occurs. The appar-

na prsnom košu, već inspekcijom upućuje na vrlo vjerojatnu i razderotinu, ranu srca. Ako se radi o ozljedi vatrenim projektilom potrebno je utvrditi i izlaznu ranu, kako bi se mogao predvidjeti put projektila i oštećenje drugih organa na tom putu te ocijeniti zadržavanje projektila u nekom od organa. Pogodak u samo rebro ili sternum projektilom ili nožem dovodi do rasprsnuća koštanih struktura te upućuje i na laceraciju srca. Procjena stanja pacijenta s takvom ozljedom mora se, dakako, temeljiti na uobičajenom planu zbrinjavanja i algoritmu pristupa za akutne hitne incidente, koji traži reanimaciju označenu akronimom ABCDE — Airway, Breathing, Circulation, Defibrillation odnosno Disability, Expose (osloboditi dišne puteve, procijeniti disanje, primijeniti umjetno disanje, dok se primjena ručne masaže preko donjeg dijela sternuma kod sumnje na tamponadu dakako ne savjetuje, nego dolazi u obzir procjena pulsa, tlaka, cirkulacije, a defibrilaciju u slučaju ventrikulske tahikardije i fibrilacije treba učiniti odmah, ako nema reakcije na medikamentnu terapiju primijenjenu i.v. ili intraosealno[6,22,23]. Više se ne preporuča davanje lijekova intratrahealno zbog slabe resorpcije.

Ljestvica traumatskih oštećenja prsnog koša i srca ima šest stupnjeva i detaljno je opisana u literaturi[24].

Ishod penetrantne i nepenetrantne ozljede ovisi od tri čimbenika: 1. brzina pružanja pomoći na mjestu incidenta; 2. stručnost i opremljenost ekipe HMP; 3. brzina transporta uz neophodno obavještavanje ekipe u kirurškom centru za primitak i intervenciju traumatiziranog[1,5,12,13,18-21,25].

Stanje unesrećenog s penetrantnom ozljedom srca na mjestu nesreće u dijagnostičkom je pogledu složeno. Može biti već prisutan kardiogeni šok s distendiranim jugularnim venama ili /i hipovolemički šok (kada je ta distenzija slabije izražena), a što sve upućuje na brzi razvoj smrtne tamponade perikarda kod vidljive rane na prsnom košu.

Oštećenje projektilom velikog kalibra iz vatrenog oružja ili široke ubodne rane dovode u većini incidenata do trenutne smrti, dok oštećenje projektilom malog kalibra i ubodne rane oštrim, uskim predmetom (frakturirano rebro, dio — iversternuma, vrh noža) mogu se liječiti i spriječiti tamponadu. Kod malog projektila, ulazna rana ne mora biti vidljiva na prvi pogled, jer se kao mala ekhimoza između dva rebra, lako previdi. Upravo takve male, "nevidljive" ulazne rane mogu imati kobne posljedice. EKG zapis u toj situaciji s nastalom tamponadom, daje gotovo uvijek, pa i u malom penetrantnom oštećenju miokarda, sliku perakutne lezije ili ishemije miokarda s eleviranom ST-spojnicom, najčešće konkavnom na samom vrhu elevacije — upravo slično nalazu u prvim satima perakutnog infarkta miokarda, koji inače rijetko viđamo (jer se već u akutnoj fazi infarkta nalazi samo konveksna ST-elevacija). Konkavnost na vrhu elevirane ST-spojnice je suprotna glavnoj el. osi T-vala, koji u početku te male ozljede može biti i pozitivan[26]. Slijedi inverzija T-vala te se takav bolesnik obično smješta u intenzivnu skrb i najčešće liječi kao infarkt miokarda. Manja disrupcija miokarda od manjeg projektila može privremeno, spontano trombozirati. Međutim, na temelju krivo postavljene dijagnoze infarkta bolesniku započinje se liječenje koje dovodi (ovdje s pravom kažemo nažalost) do trombolize već stvorenog tromba na mjestu razderotine i daljnji razvoj tamponade srca te bolesnik umire u intenzivnoj skrbi neutvrđene dijagnoze.

Stoga za točnu procjenu stanja prijeteće tamponade srca, kod penetrantne i nepenetrantne ozljede prsnog koša, liječnik HMP (prema europskim preporukama za reanimaciju) na mjestu incidenta mora imati pri ruci prenosivi ehokardiografski aparat te se njime odmah orijentirati (kao što čini EKG-

ent wound, chest laceration is a sign for a very probable tear and cardiac injury as determined by the examination. In the case of an injury caused by fire missile, it is necessary to determine the entry and exit wound, in order to be able to predict the path of missile and injury of other organs in this path, and assess the retention of the missile in some of the organs. A blow to the rib only or sternum by a missile or a knife leads to bursting of bone structure indicating thus the cardiac laceration. The assessment of the patient's condition with such an injury must, naturally, be based on the usual management plan and algorithm for acute emergency incidents, requiring resuscitation indicated as acronym ABCDE — Airway, Breathing, Circulation, Defibrillation and Disability Expose (free airways, assess breathing, apply artificial respiration, while the use of manual massage over the lower part of the sternum when suspecting tamponade is certainly not advised. However, the evaluation of pulse, blood pressure and circulation will be taken into consideration, while defibrillation is to be performed immediately in case of ventricular tachycardia and fibrillation, if there is no response to medicamentous therapy administered i.v. or intraosseously[6,22,23]. Administration of medicines intratracheally is no longer advisable due to poor absorption.

The scale of traumatic injuries of the chest and heart has six degrees and it is described in the literature[24].

The outcome of penetrating and non-penetrating injury depends on the three factors: 1. promptness in providing assistance on the spot of the incident; 2. expertise and equipment of EMS team; 3. the speed of transport accompanied by providing information to the surgical center about the necessity to admit and manage the traumatized person[1,5,12,13,18-21,25].

The condition of the injured with a penetrative cardiac injury on the spot of an incident is complex in terms of diagnostics. Cardiogenic shock with distended jugular veins and/or hypovolemic shock (when this distension is slightly pronounced) may be present, indicating the rapid development of fatal pericardial tamponade in visible chest wounds.

Damage caused by a large caliber missile from firearms or a wide stab wound in most incidents result in the immediate death, while the damage caused by a small caliber missile and stab wounds caused by a sharp, narrow object (fractured rib, part — body of sternum, tip of a knife) can be treated with prevention of tamponade. In a case of a small missile, the entry wound may not be apparent at a first glance, because it is easily overlooked as a small ecchymosis between the two ribs. Such small, "invisible" entry wounds can have fatal consequences. ECG recording in this situation with the developed tamponade gives almost always, even in a minor penetrative myocardial injury, an image of percutaneous lesion or myocardial ischemia with ST-segment elevation, usually concave at the top of the elevation — similar to a finding in the first hours of percutaneuous myocardial infarction, which we otherwise can rarely see (because already in the acute phase of myocardial infarction we can only see a convex ST-elevation). The concavity at the top of the ST-segment elevation is opposite to the main el. axis of the T-wave, which in case of a minor injury can initially be even positive[26]. It is followed by T-wave inversion, and such a patient is usually referred to the intensive care unit and is often treated as myocardial infarction. Minor myocardial disruption caused by a small missile can be temporarily spontaneously thrombosed. However, should the faulty diagnosis of infarction in the patient be made, the treatment will begin (here we are right to say unfortunately) resulting in a thrombolysis of the already created thrombus at the site of laceration and further development of cardiac tamponade, and the patient dies in the intensive care unit with undetermined diagnosis.

Therefore, for accurate assessment of the condition of life-threatening cardiac tamponade, in case of penetrating and non-penetrating chest trauma, the EMS physician (according to the European guidelines on resuscitation) must at the spot of the incident have portable echocardiography device

om o ritmu i frekvenciji srca) o stanju, količini perikardijskog sadržaja, ali ev. i o laceraciji miokarda, perikarda te stanju srčanih šupljina. Potom slijedi eventualno i terapijski postupak da se pokuša takvog bolesnika s prijetećom ili već izraženom tamponadom perikarda spasiti terapijskom perikardiocentezom koja nije samo zahvat za kardiologa i kardiokirurga nego je u ovim iznimnim slučajevima stručni zadatak za koji treba biti osposobljen liječnik HMP, uz pomoć i asistiranje medicinske sestre ili tehničara.

Medicinska doktrina kaže: "osim u hitnim slučajevima — tamponade perikarda, terapijsku perikardiocentezu, koja je potencijalno i opasna, treba učiniti pod kontrolom ultrazvuka srca u prostoriji za kateterizaciju srca." Na mjestu incidenta nema sobe za kateterizaciju, to može biti doduše dobro opremljeno, adaptirano vozilo HMP, ali je praktičnije, brže, učinkovitije terapijsku perikardiocentezu učiniti neposredno uz ležećeg bolesnika vani, što je dopušteno citiranom doktrinom (i opisano kao uspješno). Ako liječnik HMP utvrdi perikardijski sadržaj koji oblaže miokard iza LV i ispred DV s fenomenom "lelujajućeg" srca ("swinging heart" — srca koje se impresivno klati), a što je u akutnim slučajevima izraz velikog izljeva koji aproksimativno prelazi 1.500 mL, uz pomoć asistenta, koja drži glavu sonde ultrazvuka i "osvjetljava" srce, liječnik bi trebao dužom iglom i većom štrcaljkom 100-200 mL, učiniti punkciju perikarda, pristupom iz subksifoidnog područja, subkostalno lijevo, s usmjerenjem punkcijske igle prema gore i lijevom ramenu, pod kutom od 30 stupnjeva. Poželjno je da se bolesnika postavi u polusjedeći položaj ili u ležeći na desnom boku. Taj zahvat s aspiracijon i 100 mL perikardijskog sadržaja spašava život unesrećenog i omogućuje "kupovanje vremena" za transport do kirurškog centra. Evakuacija i samo 50 mL već dovodi ponekad do olakšanja i često zaustavlja razvoj tamponade.

Drugi problem, koji završava smrtno u danim okolnostima je nastup asistolije kada (pored mogućnosti perkutane stimulacije) u većoj udaljenosti od kirurških centara treba dati prednost, uvođenju privremenog električnog stimulatora srca preko centralnog venskog sustava gornje šuplje vene, vene subklavije ili unutarnje jugularne, vene cefalike. Zahvat treba učiniti također odmah uz ležećeg pacijenta, bez radiološke pomoći (koja se zbog hitnosti uz dobro iskustvo liječnika ne koristi uvijek ni u jedinicama intenzivne skrbi). Implantacija centralnog venskog katetera istim pristupom daje ujedno informaciju o visini centralnog venskog tlaka u šupljinama desnog srca, o ev. hipovolemiji što usmjeruje i određuje daljnju terapiju[27]. Istim venskim pristupom, u vrijeme hospitalizacije u intenzivnoj skrbi, može se implantirati i Swan Ganzov kateter te ga plasirati preko trikuspidnog ušća u plućnu arteriju, s kratkotrajnom opstrukcijom arterije da se izmjeri visina plućnog kapilarnog tlaka koji je jednak tlaku u LA (normalno do 10 mmHg). Time se ujedno dobije procjena stanja miokarda LV, teledijastoličkog tlaka u LV kao izraz teledijastoličkog volumena i kontraktilnosti. Kod tog zahvata postoji mogućnost oštećenja trikuspidnog zalistka te zadnje vrijeme postoje kontroverze o tome poboljšava li preživljavanje.

Ovdje je iznesen moderan pristup tretmanu prijeteće tamponade srca, koji se sprovodi u razvijenim europskim zemljama i traži stručnost i materijalno ulaganje u opremljenost HMP.

on him as to immediately define (as rhythm and heart rate are determined by the ECG) the condition, quantity of pericardial fluid and any myocardial or pericardial lacerations and condition of the heart cavities. This may be followed by therapeutic procedure attempting to save such a patient with life-threatening or already pronounced pericardial tamponade by performing therapeutic pericardiocentesis which is not only an intervention to be performed by a cardiologist and cardiac surgeon, but in these exceptional cases, this is the task that is to be performed by a qualified EMS physician, with the help and assistance of a nurse.

Medical doctrine says, "except in emergency cases — pericardial tamponade, therapeutic pericardiocentesis, which may be dangerous, should be done under heart ultrasound in a room for a heart catheterization." On the spot of the incident there is no room for catheterization, but this may be a well equipped, adjusted EMS vehicle anyway, although it is more convenient, faster, more effective to perform therapeutic pericardiocentesis directly next to the lying patient outside, as permitted by the quoted doctrine (and described as successful). If the EMS physician determines pericardial content coating the myocardium behind the LV and in front of the RV with the phenomenon of "swinging heart" — the heart which impressively swings), which is in acute cases the expression of a large effusion that approximately exceeds 1.500 mL, the physician should with the help of an assistant who keeps the head of the ultrasound probe and "illuminates" the heart, use a longer needle and syringe of 100-200 mL to do the pericardial puncture via the left subxiphoid subcostal region, directing the punctuation needle upwards and left shoulder, at an angle of 30 degrees. It is desirable to place the patient in a semi-sitting position or lying on the right side. This procedure with aspiration and 100 mL of pericardial content will save the life of the injured and allows "buying time" for transportation to the surgical center. The evacuation and only 50 mL, already results in relief and often stops the development of the tamponade.

The second problem resulting in fatal outcome in the given circumstances is the development of asystole when (in addition to a possibility of percutaneous stimulation) at a greater distance from the surgical centers the priority should be given to the introduction of temporary electrical pacemaker via a central venous system of superior vena cava, subclavian vein or internal jugular, cephalic vein. The procedure should be also done immediately with the lying patient, without radiological assistance (which is due to the urgency with the good experience of a physician not always used even in intensive care units). The implantation of central venous catheter by the same approach also gives information on the central venous pressure in the right heart cavities and on any hypovolemia which directs and determines a further treatment[27]. The Swan-Ganz catheter may be implanted and placed by the same venous access at the time of hospitalization in the intensive care unit via the tricuspid orifice into the pulmonary artery, with a short-term obstruction of the artery as to measure the pulmonary capillary pressure that is equal to the pressure in LA (normal up to 10mmHg). This is how we obtain an assessment of the condition of the LV myocardium, telediastolic pressure in the LV as an expression of telediastolic volume and contractility. Regarding this procedure, tricuspid valve may be damaged and recently there are controversies about whether it improves survival.

Here we present a modern approach to the treatment of threatening cardiac tamponade, which is performed in developed countries and requires expertise and material investment in the EMS equipment.

Dijagnostičke metode kod tupe i oštre traume prsnog koša (u hospitalizaciji)

1. Radiološkim pregledom prsnog koša otkriva se pneumotoraks, pneumoperikard, hemotoraks te medijastinalno proširenje zbog hematoma. Konvencionalna snimka i profil prsnog koša ne može prikazati miokardnu kontuziju, valvularno oštećenje, niti dokazati postojanje manjeg perikardijskog sadržaja. Perikardijski izljev tek u količini većoj od 200 mL kod snimanja u ležećem položaju "nalije se" na gornji dio velikih žila i daje sjenu sličnu trapezu. U projekciji stojeći daje "sjenu srca kruškolikog izgleda — praznih pluća".

2. Angiografija koronarnih arterija primjenjuje se rijetko, ako stanje unesrećenog dopušta u nerazjašnjenoj hipotenziji, a u korigiranoj hipovolemiji da se otkrije oštećenje intime, prisutno neposredno poslije traume te u kasnijem tijeku tromboza, okluzija koronarnih arterija, disekcija ili aneurizmatsko proširenje.

3. EKG zapis kod traume, osim aritmija, pokazuje druge nespecifične nalaze ST-segmenta. Nalaz promjena ST-segmenta i T-vala je sličan za perikardno-miokardno oštećenje kod tupe traume nalazu nekih oblika srčanog infarkta, miokardne ishemije, lezije. Kod penetrantne traume prisutni su češće znakovi nekroze q- i QS- zupci.

4. Lijevom i desnom kateterizacijom srca dobiju se detaljne informacije o stanju srčanih valvula, funkciji, intrakardijalni tlakovima Pretraga ne spada u red prvog dijagnostičkog izbora i treba biti dobro indicirana. U velikom hematoperikardu, koji nije tretiran terapijskom perikardiocentezom, niti se ima mogućnosti kiruški intervenirati, već Swan-Ganzovim kateterom, dobiju se informacije o tlakovima desne strane srca.

5. Transtorakalna ehokardiografija (TTE) je visoko osjetljiva i specifična pretraga za otkrivanje i malih količina perikardijskog sadržaja[28]. Nije specifična za diferencijaciju sadržaja — eksudat, transudat (hidroperikard), hemoperikard, hiloperikard (ruptura duktusa toracikusa) i manje je osjetljiva za otkrivanje manjih ruptura, laceracija miokarda i perikarda. Diferencijalna dijagnoza navedenih kvaliteta perikardijskog sadržaja moguća je samo dijagnostičkom perikardiocentezom uz pomoć ultrazvuka i potom dopunskim analizama. Međutim, ta se pretraga (u tu svrhu) rutinski ne primjenjuje. Dijagnostička perikardiocenteza uz pomoć ultrazvuka srca u maloj količini perikardijskog sadržaja inače je visoko rizična, makar je izvodio kardiolog, kardiokirurg (opisan je 2012. godine slučaj bolesnice kod koje je u jednom američkom sveučilišnom centru u dijagnostičkoj perikardiocentezi učinjena perforacija DV, kod malog perikardijalnog sadržaja[25]).

6. Transezofagijska ehokardiografija je osjetljivija metoda od TTE u procjeni nekih parametra, ali u okolnostima prsne traume, zbog čestog oštećenja ezofagusa i kralježnice, nije prikladna za primjenu.

7. Magnetna rezonancija (MR) srca je dobrodošla dijagnostička metoda u mirnom post-traumatskom razdoblju u hospitalizaciji u kirurškom centru radi razjašnjenja atipičnih posttraumatskih prsnih simptoma[29]. U akutnoj fazi traume zbog dugog trajanja je praktički neprimjenjiva. Osjetljivost MR u procjeni stupnja kontuzijskog oštećenja miokarda, s nekrozom ili bez nje, poremećajem kontraktiliteta sa segmentnim ispadanjima, ocjenom hibernacije šireg perinekrotičnog područja miokarda te procjenom vijabilnosti miokarda, visoka je i veća od TTE.

8. Detaljnija procjena kinetike stijenke miokarda, uključujući akineziju, hipokineziju te vijabilnost s visokom senzitivnošću donose nuklearne metode (PET, SPECT).

Diagnostic methods for blunt and sharp chest trauma (in hospitalization)

1. Radiological examination of the chest reveals a pneumothorax, pneumopericardium, hemothorax and mediastinal widening due to hematoma. Conventional image and profile of the chest can not show myocardial contusion, valvular injury, or prove the existence of a minor pericardial fluid. Pericardial effusion only in quantities over 200 mL in case of recording in the lying position "is poured" onto the upper part of the large vessels and a provides a shadow similar to trapeze. In the standing projection it gives a "shadow of the pear-shaped heart — empty lungs".

2. The angiography of the coronary arteries is applied rarely, if the condition of the injured in unclear hypovolemia and corrected hypovolemia allows the detection of the damage to the intima, present immediately after the trauma and in thrombosis in the subsequent course, coronary artery occlusion, dissection or aneurysmal expansion.

3. ECG recording in trauma, except in arrhythmia, shows some other non-specific ST-segment results. The finding of changes to ST-segment and T-wave is for pericardial-myocardial injury in blunt trauma similar to the finding of some forms of cardiac infraction, myocardial ischemia, lesions. Signs of necrosis q-and QS-waves are more often present in penetrating trauma.

4. Left and right heart catheterization gives us some detailed information on the condition of heart valves, function, intracardiac pressures. The examination is not considered to be the first diagnostic choice and should be well indicated. In case of major hemopericardium, which is not treated by therapeutic pericardiocentesis, and which is not to be surgically managed, but where we can use Swan-Ganz catheter, we obtain information on the pressures of the right side of the heart.

5. Transthoracic echocardiography (TTE) is a highly sensitive and a specific test for detecting even small amounts of pericardial fluid[28]. It is not specific for differentiation of the fluid — exudate, transudate (hydropericardium) hemopericardium, chylopericardium (rupture of the ductus toracicus) and is less sensitive for detecting minor ruptures, myocardial and pericardial lacerations. Differential diagnosis of the above indicated qualities of pericardial content can only be made by diagnostic pericardiocentesis under ultrasound guidance followed by additional analyses. However, this test (for this purpose) is not applied routinely. Diagnostic pericardiocentesis is under heart ultrasound guidance in a small quantity of pericardial fluid highly risky, although it is performed by a cardiologist, cardiac surgeon (it was described in 2012 case report of a patient with a small pericardial fluid who in one American university center underwent diagnostic pericardiocentesis resulting in RV perforation[25]).

6. Transesophageal echocardiography is more sensitive method than TTE in the evaluation of some parameters, but in the circumstances of thoracic trauma it is not suitable for use due to frequent damage to the esophagus and spine.

7. Magnetic resonance imaging (MRI) of the heart is a welcome diagnostic method in a quiet post-traumatic period of hospitalization in a surgical center for clarification of atypical post-traumatic thoracic symptoms[29]. It is practically inapplicable in the acute phase of trauma due to the long duration. The sensitivity of MRI in the evaluation of the degree of myocardial injury caused by contusion with necrosis or without it, contractility disorder with segment failure, assessment of hibernation of a wider perinecrotic region of the myocardium and assessment of myocardial viability is high and higher than TTE.

9. MSCT i CT prsnog koša i srca su praktički nezaobilazne metode u hospitalnom razdoblju zbog izvrsne kontrastne rezolucije i kratkog trajanja pregleda. Daju odgovore o ev. zahvaćenosti ostalih organa u prsnom košu, trbuhu, a može se dodatno i točno procijeniti ev. zaostalu količinu hematoperikarda nakon terapijske perikardiocenteze. Metoda otkriva i minimalnu laceraciju miokarda, perikarda — diskontinuitet njegovih granica, manja udubljenja na perikardu, rupturiranu dijafragmu, hernijaciju trbušnih organa u prsni koš i srčanu luksaciju, strangulaciju srčanih struktura i velikih žila, strano tijelo ev. zaustavljen u organima, pneumotoraks, pneumoperikard, pleuralne izljeve, interpoziciju plućnog parenhima između aorte i plućne arterije, između srca i dijafragme ili i DA i izgonskog trakta DV.

Zaključak

Namjera ovog članka bila je ukazati na povećanu incidenciju nastanka tamponade perikarda različite etiologije — zbog penetrantne (oštre) i nepenetrantne (tupe) ozljede srca, danas ipak najčešće kao posljedica "epidemije" prometnih nesreća. Naglašena je potreba pravodobne prehospitalne dijagnostike i intervencije visokostručnog i educiranog medicinskog osoblja, po mogućnosti na mjestu same traume, koja spašava život unesrećenog.

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8. A more detailed assessment of the kinetics of myocardial wall, including akinesia, hypokinesia and viability with high sensitivity is made by nuclear methods (PET, SPECT).

9. MSCT and CT of the chest and heart are practically unavoidable methods in the in-hospital period due to excellent contrast resolution and short duration of the examination. They provide answers about other organs potentially affected in the chest, abdomen, and residual amount of hemopericardium after therapeutic pericardiocentesis is to be additionally accurately assessed. The method detects even minimal laceration of the myocardium and pericardium — discontinuity of its borders, smaller recesses in the pericardium, ruptured diaphragm, herniation of abdominal organs into the chest and cardiac luxation, strangulation of cardiac structures and large vessels, a foreign body potentially stopped in the organs, pneumothorax, pneumopericardium, pleural effusions, interposition of the lung parenchyma between the aorta and pulmonary artery, between the heart and the diaphragm, or both RA and RV outflow tract.

Conclusion

The purpose of this Article was to point to an increased incidence of development of pericardial tamponade of various etiology — caused by penetrating (sharp) and non-penetrating (blunt) cardiac injury, today still usually as a result of "epidemic" of car accidents. The need for prompt pre-hospital diagnosis and intervention by highly qualified and trained medical personnel, preferably on the spot of the trauma, that saves life of an injured person is emphasized.

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Pregledni rad / Review article

Kardiovaskularni učinci oralnih lijekova za liječenje šećerne bolesti tipa 2

Cardiovascular effects of oral medications in the treatment of type 2 diabetes

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SAŽETAK: Šećerna bolest (DM) je u porastu u cijelom svijetu. Više od 90% pacijenata boluje od DM tipa 2. Najeći dio oboljelih od DM tipa 2 liječi se peroralnim lijekovima. Osim snižavanja glikemije lijekovi za liječenje DM mogu imati ili izravne učinke na srčanožilni sustav ili djelovanje na kardiovaskularne čimbenike rizika. Primjena sulfonil urea i tiazolindindiona pobuđuje najviše pozornosti radi potencijalnog negativnog učinka na povećani rizik smrti, odnosno popuštanja srca. S druge strane, navode se povoljni plejotropni i metabolički učinci pioglitazona i metformina. Repaglinid primijenjen s metforminom može povećati kardiovaskularni rizik, iako ima i pozitivno djelovanje na sniženje upalnih citokina. Inhibitori dipeptidil peptidaze 4 ne povećavaju kardiovaskularne rizike i poboljšavaju metaboličke varijable.

KLJUČNE RIJEČI: peroralni hipoglikemici, kardiovaskularni rizici, sulfonil urea, metformin, tiazolidindioni.

SUMMARY: Diabetes mellitus (DM) is in rise worldwide. More than 90% of patients suffer from type 2 DM. The majority of patients suffering from type 2 DM are treated with oral medications. In addition to lowering glycemia, the medications for treatment of DM may either have direct effects on the cardiovascular system or the effects on cardiovascular risk factors. The administration of sulfonylurea and thiazolidinedione attracts the most attention because of the potential negative impact on the increased risk of death or heart failure. On the other hand, better pleiotropic and metabolic effects of pioglitazone and metformin are known. Repaglinide administered with metformin may increase the cardiovascular risk, although it has a positive effect on lowering inflammatory cytokines. Dipeptidyl peptidase-4 inhibitors do not increase cardiovascular risks, and they improve metabolic variables.

KEYWORDS: oral hypoglycemics, cardiovascular risks, sulfonylurea, metformin, thiazolidinediones.

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Uvod

Šećerna bolest (DM) i njezine kronične komplikacije su veliki svjetski zdravstveni problem i u cijelom svijetu su u velikom porastu. Smatra se da trenutno u svijetu 366 milijuna ljudi boluje od DM, a do 2030. godine broj dijabetičara će se povećati na 552 milijuna. Broj oboljelih od DM povećava se u svim državama, a 80% posto svjetske populacije dijabetičara živi u zemljama u razvoju ili novoindustrijaliziranim zemljama[1].

Prevalencija DM u Hrvatskoj u dobnoj skupini između 18-65 godina iznosi 6,1%. Ukupan broj osoba s DM u 2010. godini iznosio je približno 316.000 od čega nešto preko 190.000 bolesnika ima otkrivenu bolest, dok ih je gotovo 123.000 neotkriveno.[2]

U nedavno objavljenom radu[3] vidljivo je da preko 90% pacijenata s DM koji se liječe u Centru za dijabetes Bjelovarsko-bilogorske županije boluje od tipa 2. Daleko najviše pacijenata liječeno je oralnim lijekovima (43%). Oralna sredstva s inzulinom uzima 38% pacijenata, a samo inzulinom bilo je liječeno 15% bolesnika. Prema smjernicama Hrvatskog dija-

Introduction

Diabetes mellitus (DM) and its chronic complications are the major world health problem having a rising trend in the whole world. It is believed that currently 366 millions of people suffer from DM worldwide, and by the year 2030 the number of diabetics will increase to 552 million. The number of patients with DM rises in all countries and 80% percent of the world's population suffering from diabetes live in developing countries or newly industrialized countries.[1]

The prevalence of DM in Croatia in the age group between 18-65 years is 6.1%. The total number of persons suffering from DM in 2010 was approximately 316,000, of whom over 190,000 patients have the disease discovered, while nearly 123,000 have the disease undiscovered.[2]

The recently published paper shows[3] that over 90% of patients with DM treated at the Center for Diabetes in the Bjelovar-Bilogora County suffer from type 2 of DM. The greatest number of patients was treated with oral medications (43%). 38% of patients take oral agents and insulin and 15% of patients were treated only by insulin. According to the guide-

betološkog društva metformin (Glucophage®, Aglurab®, Siofor®, Belformin®, Gluformin®) je odmah uključen, uz promjene životnog stila, u liječenje DM tipa 2[4,5]. Smjernice također navode da se u slučaju nepostizanja ciljeva liječenja nakon 3 do 6 mjeseci (a "dohvatljivost" opće proklamiranih ciljeva liječenja treba individualizirati za svakog pacijenta ponaosob) kao druga linija terapije mogu propisati i sulfonil urea (Diaprel MR®, Gliclada®, Glica®, Amaryl®, Dibiglim®, Diapirid®, Glimepirid PharmaS®, Glibenclamid Genericon®, Glurenorm®), repaglinid (Novonorm®, Reglinid®, Repaglinid PharmaS®), pioglitazon (Pioglitazon Pliva®), inhibitori dipeptidilpeptidase 4 (Januvia®, Galvus®, Trajenta®), blokatori alfa glukoidaze-akarboza (Glucobay®) ili čak GLP-1 analozi (eng. glucagone like peptide 1; Byetta®, Victosa®) koji više ne pripadaju u jeftinu terapiju[5]. Jednako tako u smjernicama se navode kontroverze o kardiovaskularnim rizicima pri primjeni peroralnih lijekova za liječenje šećerne bolesti.[5] To pobuđuje potrebu za racionalnom primjenom tih medikamenata u kardiovaskularnih bolesnika.

Kardiovaskularni događaji pri primjeni sulfonil urea

Kombinacija metformina i sulfonil uree je relativno česta kombinacija u liječenju DM tipa 2. Ovom kombinacijom postiže se sniženje vrijednosti Hba1c za 1,3%.[5] Podaci o povećanoj smrtnosti radi kardiovaskularnih događaja pri primjeni ove kombinacije lijekova su kontroverzni.[5] U talijanskoj opservacijskoj studiji u ispitanika liječenih metforminom i glibenklamidom registrirana je znatno viša stopa smrtnosti (8,7%) u odnosu na skupinu u kojoj je metformin kombiniran s repaglinidom (3,1%), gliklazidom (2,1%) i glimepiridom (0,4%).[6]

S druge strane u kanadskoj studiji *Juurlink i sur* uspoređivani su kardiovaskularni događaji u starijih pacijenata liječenih ili glibenklamidom (starija generacija sulfonil uree, 1.690 pacijenata) odnosno gliklazidom (novija generacija sulfonil uree, 984 pacijenta) tijekom 2 godine. Među starijim pacijentima hospitaliziranima radi akutnog infarkta miokarda ili perkutane koronarne intervencije uporaba glibenklamida u usporedbi s gliklazidom nije bila povezana s povećanim kardiovaskularnim rizicima.[7]

U literaturi se navodi podatak da sulfonil uree inhibirajući kalijeve ATP kanale povećavaju rizik smrti i popuštanja srca u pacijenata s akutnim koronarnim sindromom. Studija *Nagendran i sur* proučavajući baze podataka pacijenata s koronarnim sindromom, nije pronašla povećani rizik od smrti ili zatajivanja srca.[8] Metaanaliza talijanskih autora koja je proučavala velike kardiovaskularne događaje u dijabetičara liječenih sulfonil ureama u 115 studija pronašla je veću incidenciju moždanih udara u pacijenata s DM liječenih sulfonil ureama, no istodobno nije bila registrirana povećana opća incidencija velikih kardiovaskularnih događaja.[9]

Intenzivna kontrola glikemije upotrebom gliklazida u studiji ADVANCE10 uz redukciju Hba1c za 6,5% polučila je 10% smanjenje makro- i mikrovaskularnih događaja i 21% smanjenje broja dijabetičkih nefropatija. Ovaj efekt gliklazida dijelom se pripisuje i njegovim antioksidativnim svojstvima.[10]

Izvješće o 15 studija koje je analiziralo utjecaj sulfonil urea na kardiovaskularne događaje nije registriralo povećanje incidencije kardiovaskularnih događaja.[11]

lines of the Croatian Diabetes Association, metformin (Glucophage®, Aglurab®, Siofor®, Belformin®, Gluformin®) was immediately included in the treatment of type 2 DM, accompanied by changes in a life style.[4,5] The guidelines also suggest that in the case of failure to meet the objectives of treatment after 3-6 months ("reachability" of generally stated goals of treatment should be individualized for each patient), sulfonylurea (Diaprel MR®, Gliclada®, Glica®, Amaryl®, Dibiglim®, Diapirid®, Glimepirid PharmaS®, Glibenclamid Genericon®, Glurenorm®), repaglinid, (Novonorm®, Reglinid®, Repaglinid PharmaS®), pioglitazone (Pioglitazone Pliva®), dipeptidyl peptidase-4 inhibitors (Januvia®, Galvus®, Trajenta®), alpha-glucosidase-inhibitors acarbose (Glucobay®) or even glucagone like peptide-1 analogue (Byetta®, Victosa®) could be prescribed as the second line therapy, drugs that can no longer be inexpensive therapy[5]. Also, the guidelines suggest controversies about the cardiovascular risks in using oral medications for the treatment of diabetes.[5] This urges us to be rational in prescribing these medications to cardiovascular patients.

Cardiovascular events when using sulfonyl urea

The combination of metformin and the sulfonylurea is a relatively common combination in the treatment of type 2 DM. This combination lowers the value of Hba1c by 1.3%.[5] Data on increased mortality for cardiovascular events while administering this combination of drugs is controversial.[5] The Italian observational study in subjects treated with metformin and glibencamide showed a significantly higher mortality rate (8.7%) compared to the group receiving metformin combined with repaglinide (3.1%), gliclazide (2.1%) and glimepiride (0.4%).[6]

The Canadian study by *Juurlink et al.* compared the cardiovascular events in elderly patients treated with either glibencamide (older generation with sulfonylurea, 1,690 patients) or gliclazide (the more recent generation of sulfonylurea, 984 patients) for 2 years' period. Among elderly patients hospitalized for acute myocardial infarction or percutaneous coronary intervention, the administration of glibenclamide compared with gliclazide was not associated with an increased cardiovascular risk.[7]

The literature notes that inhibiting ATP-sensitive potassium channels, sulfonylureas increase the risk of death and heart failure in patients with acute coronary syndrome. The Study Nagendran et al studying a database of patients with coronary syndrome, found no increased risk of death or heart failure.[8] Meta-analysis of the Italian authors that studied major cardiovascular events in diabetic patients treated with sulfonylurea in 115 studies found a higher incidence of strokes in patients with DM treated with sulfonylurea, thereby not recording an increased overall incidence of major cardiovascular events at the same time.[9]

Intensive glycemic control using gliclazide in the study ADVANCE10 with reduction of HbA1c by 6.5% yielded a 10% reduction in macro- and microvascular events and 21% reduction in the number of diabetic nephropathies. This effect of gliclazide is partly attributed to its antioxidant properties.[10]

The report on 15 studies that analyzed the impact of sulfonylurea in cardiovascular events did not record an increase in the incidence of cardiovascular events.[11]

Učinci metformina na miokard u ishemiji

Metformin, lijek iz dugo poznate skupine bigvanida, danas se smatra temeljem medikamentoznog liječenja DM tipa 2. Stoga je u hrvatskim, kao i svim međunarodnim smjernicama za liječenje DM tipa 2 preporučena njegova uporaba odmah nakon otkrivanja bolesti, ravnopravno s promjenama životnog stila i prehrane.[5]

U bolesnika liječenih metforminom, već nakon šest mjeseci liječenja, uočeno je znatno manje makrovaskularnih komplikacija DM kao što su koronarni incidenti, moždani udari ili smrti povezanih s DM.[12] Kao i svaki lijek, metformin ima kontraindikacije. Ne smije se primijeniti u bolesnika s klirensom kreatinina manjim od 60 ml/min, teškim zatajenjem jetre, u alkoholičara, bolesnika s upalom gušterače te svim hipoksičnim stanjima koja uključuju zatajivanje srčane funkcije, zatajenje respiratorne funkcije te teške smetnje periferne cirkulacije (gangrena).[5]

Potencijalni negativni učinak metformina na preraštavanje endotelom stentova koji otpuštaju lijekove nakon koronarne intervencije opisan je u radu *Habib i sur*. Uočeno je da metformin i mTOR (eng. mammalian target of rapamycin) inhibitori (sirolimus) koji se koriste u stentovima koji otpuštaju lijekove imaju suprotne molekularne učinke. To utječe na oporavak endotela nakon koronarne intervencije S6K (eng. ribosomal S6 kinase) ovisnim mehanizmom. Bolesnici koji koriste metformin i dobili su stent s mTOR inhibitorom, potencijalno su u većem riziku od odgođene endotelizacije krvne žile i imaju veći rizik tromboze stenta.[13]

Pretkliničke studije pokazale su da metformin ograničava ishemiju miokarda i djeluje na reperfuziju, neovisno o svom utjecaju na razinu glukoze. Ovaj kardioprotektivni učinak je posredovan aktivacijom RISK (eng. Reperfusion Injury Salvage Kinase) metaboličkog puta i povećanim stvaranjem adenozina.14 Primjena metformina potencijalno može poboljšati ishod kardiovaskularnog događaja čak i u pacijenata koji nemaju DM.[14] Studija na animalnom modelu (štakorima) koji su kronično dobivali 300 mg metformina dnevno pokazala je da primjena metformina pojačava otpornost miokarda na ishemijsku ozljedu, mehanizmom neovisnim o smanjenju glukoze. To pokazuje pozitivan efekt metformina na strukturu mitohondrija koji je posredovan aktivacijom AMPK (eng. AdenosinMonoPhosphate-activated protein kinase) metaboličkog puta.[15] Nalazi studija koji upućuju da metformin ograničava veličinu infarkta miokarda, sugeriraju da pacijenti koji pate od ishemije miokarda mogu imati koristi od primjene metformina, čak iako nemaju DM.[16]

Pioglitazonska kontroverza

Inzulinska rezistencija je temeljni patogenetski poremećaj u DM tipa 2. Poboljšanje inzulinske osjetljivosti može se postići primjenom lijekova koji imaju utjecaj na genetske mehanizme. To su tiazolidindioni (glitazoni)-PPAR-gamma ligandi, na našem tržištu pioglitazon. Glitazoni su aktivatori nuklearnoga transkripcijskog čimbenika (eng. peroxysome proliferator-activated receptor gamma, PPAR-gamma) koji reguliraju transkripciju inzulin odgovornih gena uključenih u kontrolu stvaranja nosača utilizacije glukoze te metabolizma masti. Radi svog mehanizma djelovanja, jedna od najznačajnijih nuspojava pri primjeni glitazona je porast tjelesne težine. Dijelom je to posljedica zadržavanja tekućine, što može imati utjecaja na eventualno zatajivanje srčane funkcije.[5] Kontraindikacije za primjenu pioglitazona su kongestivno zatajivanje srčane funkcije bilo kojeg stupnja (NYHA I-IV),

Effects of metformin on myocardial ischemia

Metformin, a drug from the group of biguanides is today considered to be the basis of pharmacological treatment of type 2 DM. Therefore, it is to be administered immediately after the discovery of the disease accompanied by the changes in the life style and diet as recommended by the Croatian and all international guidelines for the treatment of type 2 DM.[5]

In patients treated with metformin, already after six months' treatment, it was observed a significantly reduced number of DM macrovascular complications, such as coronary incidents, strokes or deaths associated with DM.[12] Like any medicine, metformin has contraindications. It should not be administered to patients with creatinine clearance less than 60 ml/min, with severe liver failure, in alcoholics, patients with pancreatitis and all hypoxic conditions involving heart failure, respiratory failure and severe peripheral vascular disease (gangrene).[5]

Potential adverse effect of metformin on endothelial recovery after placement of drug eluting stents after the coronary intervention is described in the article by *Habib et al.* It was observed that metformin and mTOR (mammalian target of rapamycin) inhibitors (sirolimus) used in drug eluting stents have adverse molecular effects. It affects the endothelial recovery after coronary intervention S6K (ribosomal S6 kinase) dependent mechanism. Patients who take metformin and have the mTOR inhibitor drug-eluting stent are potentially at a higher risk of delayed endothelialization of the blood vessel and are at a higher risk for stent thrombosis.[13]

Preclinical studies have shown that metformin inhibits myocardial ischemia and has effects on reperfusion, regardless of its effect on the blood glucose level. This cardioprotective effect is mediated by activation of RISK (Reperfusion Injury Salvage Kinase) metabolic pathway and increased formation of adenosine.[14] The administration of metformin can potentially improve the outcome of cardiovascular events, even in patients without DM.[14] The study on the animal model (rats) who were chronically receiving 300mg of metformin a day showed that the administration of metformin enhanced the resistance to myocardial ischemic injury by a mechanism independent of the glucose reduction. This shows the positive effect of metformin on the structure of the mitochondria, which is mediated by the activation of AMPK (AdenosinMonoPhosphate-activated protein kinase) of metabolic pathway.[15] The study results indicating that metformin limits the size of myocardial infarction, suggest that the patients suffering from myocardial ischemia can benefit from the administration of metformin, even if they have no DM.[16]

Pioglitazone controversy

Insulin resistance is the underlying pathogenetic disorder in DM type 2. The improvement of insulin sensitivity can be achieved by using drugs that have an impact on the genetic mechanisms. These are the thiazolidinediones (glitazones)-PPAR-gamma ligands, known as pioglitazone on our market. Glitazones are activators of nuclear transcription factor (peroxysome proliferator-activated receptor gamma, PPAR-gamma) that regulate the transcription of genes responsible for insulin involved in the control of formation of glucose utilization carrier and fat metabolism. Due to its mechanism of action, one of the most significant side effects in the use of glitazones is the weight gain. This is partly a consequence of fluid retention, which can have an impact on a potential heart failure.[5] The contraindications to the use of pioglitazone are congestive heart failure of any degree (NYHA class I-IV), liver disease, creatinine clearance <4ml/min, pregnant

bolest jetre, klirens kreatinina <4 ml/min, trudnice i dojilje, dijabetička ketoacidoza, karcinom mokraćnog mjehura aktivan ili u anamnezi, hematurija.[5]

U literaturi se navode i mnogobrojni povoljni plejotropni učinci primjene pioglitazona, poput povoljanog utjecaja na disfunkciju epitela, sniženje arterijskog tlaka, korekcija metabolizma lipida, sniženje razine inflamatornih citokina i protrombotskih čimbenika.[17] I u usporedbi sa metforminom pioglitazon već nakon 16 tjedana primjene pokazuje veće sniženje razine CRP-a, kao i ostalih markera upale, čimbenika trombogeneze i oksidativnog stresa.[18]

Posljedično ovim antiaterogenim učincima pioglitazon reducira stope smrtnosti, infarkt miokarda, moždanog udara.[18] Ovo je naročito važno istaknuti radi usporedbe s rosiglitazonom, lijekom iz iste skupine koji je radi povećanog rizika od zatajivanja srca, infarkta miokarda i ukupne smrtnosti prije nekoliko godina povučen iz uporabe.[19] Metaanaliza kardiovaskularnih učinka jasno razdvaja negativan učinak rosiglitazona na kardiovaskularne događaje u odnosu na pioglitazon koji ne pokazuje takav učinak.[19]

Repaglinid

Repaglinid je trenutno jedini preparat iz skupine analoga sulfonil uree dostupan na hrvatskom tržištu. Može se primijenjivati uz obrok kao monoterapija ili u dvojnoj terapiji uz inhibitore alfa glukozidaze, DPP 4 inhibitore, tiazolidindione i GLP 1 analoge.[5] Međutim, pri istodobnoj primjeni metformina, nije moguće jamčiti da liječenje neće uzrokovati povećanje kardiovaskularnog rizika, naročito u pacijenata oboljelih od koronarne bolesti srca.[5]

Studija *Schramm I sur* objavljena je prije 2 godine i pratila je više od 107.000 oboljelih od DM tipa 2 kroz 9 godina. Prethodni infarkt miokarda imalo je 9.607 pacijenata uključenih u tu studiju. U usporedbi s metforminom primjena starijih sulfonil urea (glibenklamida, glipizida i tolbutamida) bila je povezana s povećanom smrtnošću u pacijenata s i bez prethodnog infarkta miokarda. Uporaba repaglinida i gliklazida u odnosu na metformin nije bila povezana sa većom smrtnošću.[20]

Također, studija provedena u Danskoj na 96 mršavih pacijenata s DM tipa 2 koja je proučavala razinu biljega upale (čimbenik nekroze tumora alfa, plazminogen activator inhibitor 1 antigen, tkivni plazminogen activator antigen, čimbenik von Willebrand, topiva unutarstanična adhezijska molekula, topivi E-selektin) u pacijenata na metforminu, odnosno repaglinidu pronašla je veći pad upalnih parametara odgovornih za disfunkciju endotela u pacijenata liječenih metforminom, u odnosu na pacijente liječene repaglinidom.[21]

Radi ovakvih dvojbenih mišljenja o kardiovaskularnim učincima repaglinida, indikacije za primjenu ovih lijekova moraju biti postavljene prema strožim kriterijima, posebno kod novootkrivenih bolesnika s DM tipa 2 te bolesnika s poznatom koronarnom bolesti srca.[5]

Blokatori dipeptidil peptidaze 4 (DPP 4 inhibitori)

Mogućnošću povećanja razine inkretinskih hormona u cirkulaciji s ciljem smanjenja glukoze u krvi otvara se novo poglavlje u liječenju DM tipa 2. U tu svrhu koriste se GLP 1 analozi i DPP 4 inhibitori. Inhibitori DPP 4 registrirani u Hrvatskoj su sitagliptin, vildagliptin i linagliptin.

and breasting women, diabetic ketoacidosis, bladder cancer being active or a history of bladder cancer, hematuria.[5]

The literature suggests many favorable pleiotropic effects of administration of pioglitazone such as a favorable effect on epithelial dysfunction, lowering of blood pressure, correction of lipid metabolism, lowering of the level of inflammatory cytokines and protrombotic factors.[17] Compared with metformin, already after 16 weeks of administration, pioglitazone showed a greater reduction in the level of CRP, and other inflammation markers, thrombogenecity factors and oxidative stress.[18]

Consequently, due to these antiatherogenic effects, pioglitazone reduces mortality, myocardial infarction and stroke.[18] This is particularly worth noting for the comparison with rosiglitazone, the drug from the same group that was withdrawn from the market a few years ago due to an increased risk of heart failure, myocardial infarction and total mortality.[19] Meta-analysis of cardiovascular effects clearly indicates the negative effect of rosiglitazone on cardiovascular events compared to pioglitazone, which does not have such an effect.[19]

Repaglinide

Repaglinide is currently the only agent from the group of analogs of sulfonylurea available in the Croatian market. It can be administered with a meal as a monotherapy or as a dual therapy with alpha-glucosidase inhibitors, DPP 4 inhibitors, thiazolidinediones and GLP 1 analogs.[5] However, in concomitant administration of metformin, there is no guarantee that the treatment will not cause an increased cardiovascular risk, especially in patients with coronary heart disease.[5]

The study by *Schramm et al* was published 2 years ago and it followed up more than 107,000 patients with DM type 2 throughout a period of 9 years. 9,607 of patients involved in this study had a history of myocardial infarction. Compared to metformin, the administration of some older sulfonylureas (glibenclamide, glipizide and tolbutamide) was associated with increased mortality in patients with and without history of myocardial infarction. The administration of repaglinide and gliclazide compared to metformin was not associated with higher mortality rate.[20]

Also, a study conducted in Denmark on 96 lean patients with type 2 DM, which studied the level of inflammation markers (tumor necrosis factor alpha, plasminogen activator inhibitor 1 antigen, tissue plasminogen activator antigen, von Willebrand factor, soluble intracellular adhesion molecule, soluble E- selectin) in patients taking metformin or repaglinide found a higher decline in inflammatory parameters responsible for endothelial dysfunction in patients treated with metformin compared to patients treated with repaglinide.[21]

As a result of such controversial opinions on cardiovascular effects of repaglinide, the indications for the administration of these drugs must be set according to strict criteria, particularly in newly diagnosed patients with type 2 DM and patients with known coronary heart disease.[5]

Dipeptidyl peptidase 4 inhibitors (DPP 4 inhibitors)

The possibility to increase the level of incretin hormones in the circulation in order to reduce blood glucose opens up a new chapter in the treatment of type 2 DM. For this purpose, we use the GLP 1 analogs and DPP 4 inhibitors. DPP 4

***Table 1**. Doses, contraindications and possible cardiovascular effects of the oral drugs for the treatment of type 2 diabetes mellitus. Beside above listed contraindications, all of the mentioned drugs should not be used in the treatment of diabetic ketoacidosis and during pregnancy and breast-feeding.*

	Doses	Contraindications	Possible cardiovascular effects
Metformin	0,5-3g/daily	Severe renal, cardiac, respiratory failure and liver disfunction, alcoholism, pancreatitis, gangrene	Enhances resistance to myocardial ischemic injury. Concomitant use with mTOR inhibitors probably slows recovery of endothelium after coronary intervention
Pioglitazone	15-30mg/daily	Heart failure of any grade, kidney and liver disfunction, bladder cancer, hematuria	Favorable effect on epithelial dysfunction, decreases blood pressure, decreases markers of inflammation and oxidative stress.
Repaglinide	1,5-16 mg/daily	End stage renal disease, concomitant use of gemfibrozil	Concomitant use of metformin probably increases cardiovascular risk in patients with coronary artery disease. Smaller decrease of inflammatory parameters responsible for the dysfunction of the epithelium compared with metformin.
Sulfonyl ureas: • **gliclazide** • **glimepiride** • **gliquvidone** • **glibenclamide**	Gliclazide 30-120 mg/daily Glimepiride 1-6mg/daily Gliquvidone 15-120 mg/daily Glibenclamide 1,25-14 mg/daily	Gliclazide: severe liver and kidneys disfunction, concomitant use of miconazole Glimepiride: severe renal and liver disfunction Gliquvidone: pancreatic surgery, severe infections, severe liver failure, acute intemittent hepatic porphyria Glibenclamide: pancreatic surgery, severe renal, hepatic, adrenocortical, thyroid and pituitary disfunction	The combination of metformin and glibenclamide increases the risk of cardiovascular events more than metformin in combination with other sulphonylureas. The ambiguous effect on the risk of death and heart failure is mediated by blocking potassium ATP channels. Gliclazide has antioxidant effect.
DPP 4 inhibitors: • **sitagliptin** • **vildagliptin** • **linagliptin**	Sitagliptin 100 mg/daily Vildagliptin 100 mg/daily Linagliptin 5mg/daily	Sitagliptin: pancreatitis, dose adjustment in the case of liver or kidney damage Vildagliptin: heart failure NYHA III-IV, liver disfunction, careful use in the case of severe renal failure Linagliptin: pancreatitis	Reducing the risk of cardiovascular events-class effect.Vildagliptin and sitagliptin enhances cardiac function by preventing cardial mitochondrial disfunction. Stabilization of variability of heart frequency.

Pored svoje uloge u snižavanju glukoze, linagliptin je u životinjskim modelima pokazao sposobnost smanjenja područja miokarda zahvaćenog infarktom.[22] Također, u usporedbi s glimepiridom (sulfonilureom) u pacijenata liječenih linagliptinom zabilježen je značajno manji relativni rizik od kardiovaskularnih događaja, posebno moždanog udara, neovisno o činjenici da linagliptin uzrokuje manje hipoglikemija od sulfoniluree.[23] Meta analiza koja je uključivala 8 studija u trajanju više od 12 tjedana analizirala je kardiovaskularnu smrtnost (fatalni infarkt miokarda, fatalni moždani udar), nefatalni moždani udar, nefatalni infarkt miokarda, nestabilnu anginu pektoris. Stupanj rizika za ove primarne događaje bio je značajno niži uz primjenu linagliptina u usporedbi s placebom i glimepiridom.[23] Ove analize pokazuju da primjena linagliptina ne povećava kardiovaskularne rizike, već vjerojatno polučuje kardiovaskularne dobrobiti u pacijenata s DM tipa 2.[23]

inhibitors registered in Croatia are sitagliptin, vildagliptin and linagliptin.

In addition to its role in lowering glucose, linagliptin tested on animal models proved to be able to reduce the areas of the affected myocardial infarction.[22] Also, compared to glimepiride (sulphonylurea), the patients treated with linagliptin had a significantly lower relative risk of cardiovascular events, particularly stroke, regardless of the fact that linagliptin causes hypoglycemia less than sulfonylureas.[23] A meta-analysis that involved 8 studies lasting more than 12 weeks analyzed cardiovascular mortality (fatal myocardial infarction, fatal stroke), nonfatal stroke, nonfatal myocardial infarction, unstable angina pectoris. The degree of risk of these primary events was significantly lower with the use of linagliptin compared with placebo and glimepiride.[23] These analyses show that the administration of linagliptin does not increase cardiovas-

Sličan kardioprotektivan učinak sitagliptina pokazan je i u izraelskoj studiji iz 2013. godine. Pacijenti sa tipom 2 DM koji su prije velikog kardiovaskularnog događaja dobivali sitagliptin imali su značajno manje hospitalnih komplikacija (postinfarktna angina, ponovni infarkt miokarda, edem pluća, infekcije, zatajenje bubrega) u usporedbi s pacijentima liječenima samo metforminom ili drugim oralnim hipoglikemizantnim sredstvima.[24] Zaključak da primjena sitagliptina ne povećava kardiovaskularne rizike donosi i analiza 25 randomiziranih kliničkih istraživanja.[25] Štoviše u životinjskim modelima je pokazano da i vildagliptin, kao i sitagliptin, imaju podjednaki kardiovaskularni zaštitni učinak.[26] Štakori hranjeni prehranom s visokim udjelom masti, s visokim indeksom tjelesne mase, razinom inzulina u plazmi, povišenim parametrima oksidativnog stresa i dislipidemijom dobivali su vildagliptin i sitagliptin. Osim poboljšanja navedenih metaboličkih parametara zabilježeno je i poboljšanje srčane funkcije, prevenirana je kardijalna mitohondrijalna disfunkcija te stabilizirana varijabilnost srčane frekvencije.[26]

Zaključak

Mnoštvo oralnih lijekova za liječenje DM tipa 2 pokazuje da se u liječenju ove bolesti iskorištava svaki novi, dostupni i prepoznati patofiziološki mehanizam. Ovo mnoštvo molekula svakako osim na razinu glikemije, može imati izravni učinak na srčanožilni sustav ili učinak na čimbenike rizika. Općenito, kontroverze i dvojbe o srčanožilnoj sigurnosti su veće za starije lijekove za oralno liječenje DM tipa 2, posebno iz skupine sulfonil uree. Sulfonil uree iz starije skupine (glibenklamid) bi trebalo izbjegavati, naročito u kombinciji s metforminom, jer se čini da su njihovom uporabom kardiovaskularni rizici u porastu. Dosadašnja istraživanja pokazuju da je pioglitazon siguran lijek, ali kliničkim pregledom treba detektirati pacijente na koja bi se mogla odnositi gore navedena ograničenja upotrebe. Repaglinid je također siguran lijek, iako u pacijenata sa koronarnom bolesti srca ostaju dvojbe o sigurnosti koje bi trebalo razjasniti daljnjim istraživanjima. Studije koje ukazuju na povoljne učinke na metaboličke parametre i endotelnu funkciju čine novije lijekove iz skupine DPP 4 inhibitora atraktivnijim za propisivanje pacijentima s istodobnom kardiovaskularnom problematikom.

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cular risks, but probably confers cardiovascular benefits in patients with DM type 2.[23]

A similar cardioprotective effect of sitagliptin was shown in the 2013 Israeli study. Patients with type 2 DM who received sitagliptin before the major cardiovascular event had significantly fewer hospital complications (postinfarction angina, myocardial reinfarction, pulmonary edema, infections, renal failure) compared to the patients treated only with metformin or other oral hypoglycemic agents.[24] The conclusion that the administration of sitagliptin does not increase cardiovascular risks is reached by the analysis of 25 randomized clinical trials.[25] Moreover, in animal models vildagliptin and sitagliptin also proved to have equal cardiovascular protective effect.[26] Rats on high fat diet, with high body mass index, high insulin levels in plasma, increased parameters of oxidative stress and dyslipidemia received vildagliptin and sitagliptin. In addition to improving these metabolic parameters, the improvement of cardiac function was also recorded. The mitochondrial dysfunction in cardiac disease was prevented and the heart rate variability was stabilized.[26]

Conclusion

A variety of oral medications for the treatment of type 2 DM shows that every new, available and recognizable pathophysiological mechanism is exploited in the treatment of this disease. Such a great number of molecules can certainly have a direct effect on the cardiovascular system or the effect of the risk factors in addition to blood glucose level. Generally, controversies and doubts regarding cardiovascular safety are greater for older medicines for oral treatment of type 2 DM, especially from the group of sulfonylureas. Sulfonylurea from the older group (glibenclamide) should be avoided, particularly in the combination with metformin, because cardiovascular risks seem to be rising as a result of their administration. Previous studies show that pioglitazone is a safe medicine, but clinical examination should detect patients to whom the above limitation of use might relate. Repaglinide is also a safe medicine, although there are still doubts about the safety of this medicine in patients with coronary heart disease which should be clarified by the research to follow. Studies that suggest beneficial effects on metabolic parameters and endothelial function make the more recent medicines from the group of DPP 4 inhibitors more attractive for prescribing to patients with concomitant cardiovascular disorders.

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Prikaz slučaja / Case report

Lutembacherov sindrom: prikaz slučaja

Lutembacher's syndrome: a case report

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SAŽETAK: Lutembacherov sindrom je kombinacija kongenitalnog atrijskog septalnog defekta (ASD) i stečene mitralne stenoze (MS). Prvi put ga je opisao francuski liječnik Lutembacher 1916. godine. Ovaj sindrom je vrlo rijedak i smatra se da mu je incidencija 0.001/10,00000. Hemodinamski efekti ovog sindroma posljedica su relativnog utjecaja težine MS i veličine ASD.

Prikazujemo 54-godišnju pacijenticu kojoj je bio indiciran transtorakalni ehokardiografski pregled (TTE) zbog evaluacije prijašnjeg nalaza srednje teške MS u sklopu progresije zaduhe unatrag mjesec dana. Prije dvije godine prilikom hospitalizacije uslijed srčanog popuštanja, primjenom TTE registrirana je teška MS uz urednu sistoličku funkciju lijeve klijetke. Sada se primjenom TTE i transezofagijske ehokardiografije registrira srednje teška MS te ASD koji nije bio opisan u prijašnjim ultazvučnim nalazima pa je postavljena dijagnoza Lutembacherova sindroma.

Ovaj prikaz slučaja pokazuje kako je ehokardiografija nezaobilazna dijagnostička metoda u otkrivanju mnogih kardioloških entiteta uključujući i ovaj rijetko prisutan sindrom.

KLJUČNE RIJEČI: Lutembacherov sindrom, atrijski septalni defekt, mitralna stenoza, ehokardiografija.

SUMMARY: Lutembacher's syndrome refers to a congenital atrial septal defect (ASD) complicated by aquired mitral stenosis (MS). It was first described by Lutembacher, a French physician, in 1916. This syndrome is a very rare disease, it is found that the incidence of Lutembacher's syndrom is 0.001/10,00000. The hemodynamic effects of this syndrome are a result of the interplay between the relative effects of the ASD and MS.

We present a 54-year-old female referred to hospital for echocardiographic evaluation of previously diagnosed mild MS. She reported progression of dyspnea over the last month. Two years ago, she was admitted to another hospital because of heart failure and transthoracic echocardiography (TTE) revealed moderate MS with perserved left ventricular systolic function. We performed TTE and transesophageal echocardiogram and found severe MS with ASD that was previously unrecognised. The diagnosis of Lutembacher's syndrome was established.

This case demonstrates the presence of this rare disease in our population, but we would also like to stress the importance of the role of echocardiography in identifying many clinical syndromes including this one.

KEYWORDS: Lutembacher"s syndrome, atrial septal defect, mitral stenosis, echocardiography.

CITATION: Cardiol Croat. 2013;8(10-11):352-355.

Prikaz slučaja

Pedesetčetverogodišnja pacijentica s anamnezom preboljele reumatske groznice u djetinjstvu i arterijskom hipertenzijom u nekoliko je navrata hospitalizirana zbog zaduhe u sklopu srčanog zatajivanja. Koronarografijom, učinjenom 4 godine ranije, nije dokazana koronarna bolest srca.

Sada je transtorakalna ehokardiografija (TTE) indicirana zbog pogoršanja zaduhe unazad mjesec dana. Pacijentica je afebrilna, nepravilnih otkucaja srca frekvencije oko 70/min te izmjerenog arterijskog tlaka 100/70 mmHg. Bolesnica je bila tahipnoična, ortopnoična i cijanotična. Auskultatorno se registrira holosistolički šum i dijastoličko bubnjanje u području apeksa. Na okrajinama su prisutni bilateralni edemi s palpabilnim perifernim pulzacijama.

Elektrokardiografski se bilježi atrijska fibrilacija s frekvencijom 70/min. Liječena je beta-blokatorom, diuretikom i oralnom antikoagulantnom terapijom.

Case report

A 54-year-old female with a past medical history of reumatic fever as a child and hypertension was previously hospitalized on several occasions for severe shortness of breath due to heart failure. Left side cardiac catheterisation that was done 4 years ago showed coronary arteries without stenosis.

She was referred to transthoracic echocardiography (TTE) for evaluation of progression of shortness of breath over the last month. On physical examination she was afebrile. Her blood pressure was 100/70 mmHg and pulse was irregular at a rate of 70 beats per minute. The patient was tachypneic, orthopneic and cyanotic. A grade II/IV holosystolic murmur and a diastolic rumble were heard at the cardiac apex. The examination of lower extremities revealed palpable pulses and ankle edema bilaterally.

Electrocardiogram showed atrial fibrilation and chest X-ray revealed signs of pulmonary congestion. She was treated with beta-blockers, diuretics and oral anticoagulant therapy.

Na TTE registrira se zadebljana mitralna valvula s fibrosklerotičnim prednjim zaliskom (**Slika 1**) te posljedičnom teškom mitralnom stenozom (MS) s mitralnom areom od 0,8 cm^2 (**Slika 2**) uz blagu mitralnu insuficijenciju. Maksimalni transvalvularni gradijent u dijastoli je 5 mmHg. Također se transezofagijskom ehokrdografijom (TEE) bilježi atrijski septalni defekt (ASD) tipa ostium secundum promjera 0,5x0,6 cm s areom u 3D prikazu od 0,2-0,3 cm^2 (**Slika 3**), a doplerom se potvrdi lijevo-desni spoj na nivou atrija (**Slika 4**). Postoji i umjerena plućna hipertenzija s maksimalnim tlakom u plućnoj arteriji od 50 mmHg procjenjena temljem doplerskog zapisa mlaza trikuspidne regurgitacije. Sistolička funkcija lijevog i desnog srca su u granicama normale.

Obzirom na nalaz kombinirane reumatske MS i ASD postavlja se dijagnoza Lutembacherovog sindroma.

Transthoracic echocardiography showed thickened mitral valve with fibrosclerotic changed anterior mitral leaflet (**Figure 1**). As a consenquence, there was severe mitral stenosis (MS) with mitral valve area og 0.8 cm^2 and mild mitral regurgitation (**Figure 2**). The diastolic pressure gradient was 5 mmHg. However, an ostium secundum atrial septal defect (ASD) was noted by transeophageal echocardiography (TEE), having diameter of 0.5x0.6 mm, and area of 0.2-0.3 cm^2 (**Figure 3**). Doppler echocardiography showed left to right interatrial shunt (**Figure 4**). Mild pulmonary hypertension with maximal pressure gradient in pulmonary artery of 50mmHg was estimated by using Doppler recording of the tricuspidal regurgitation jet. Left and right ventricular systolic function was normal.

On the basis of the combined finding of rheumatic mitral valve stenosis and a ASD the diagnosis of Lutembacher's syndrome was made.

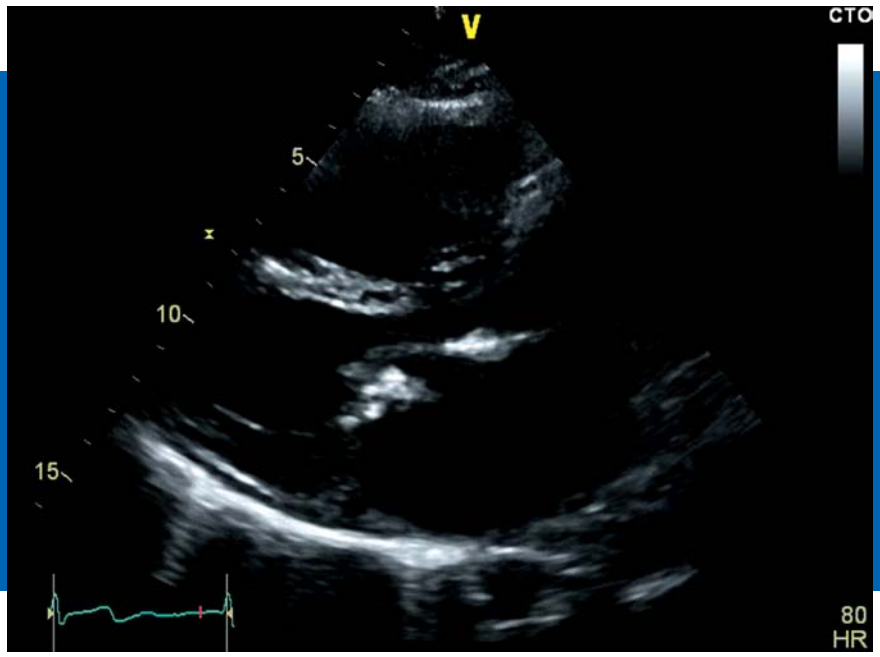

Figure 1. *Two-dimensional transthoracic echocardiography presenting fibrosclerotic mitral valve; long parasternal view.*

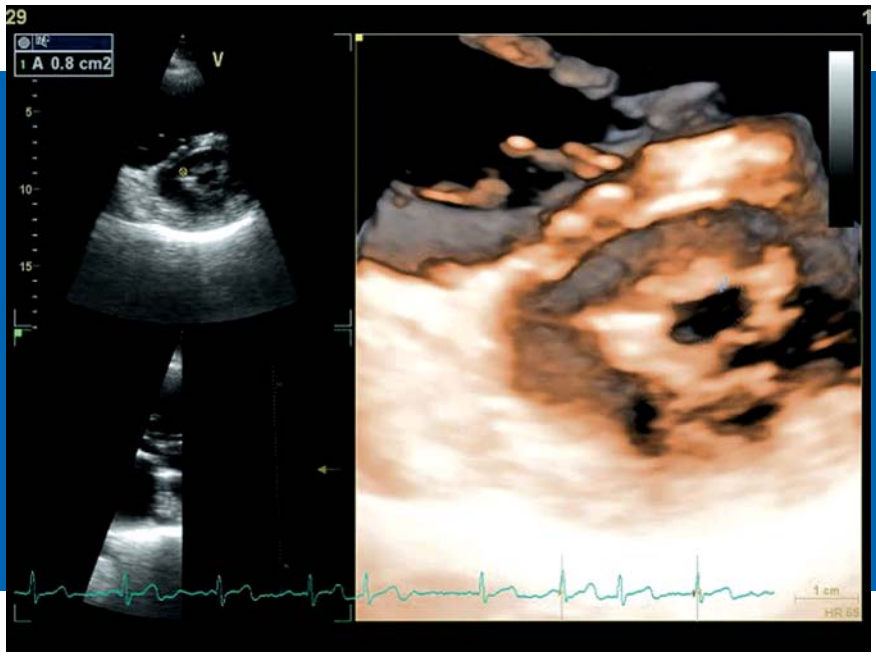

Figure 2. *Stenotic mitral valve orificium obtained by three dimensional transthoracic echocardiography.*

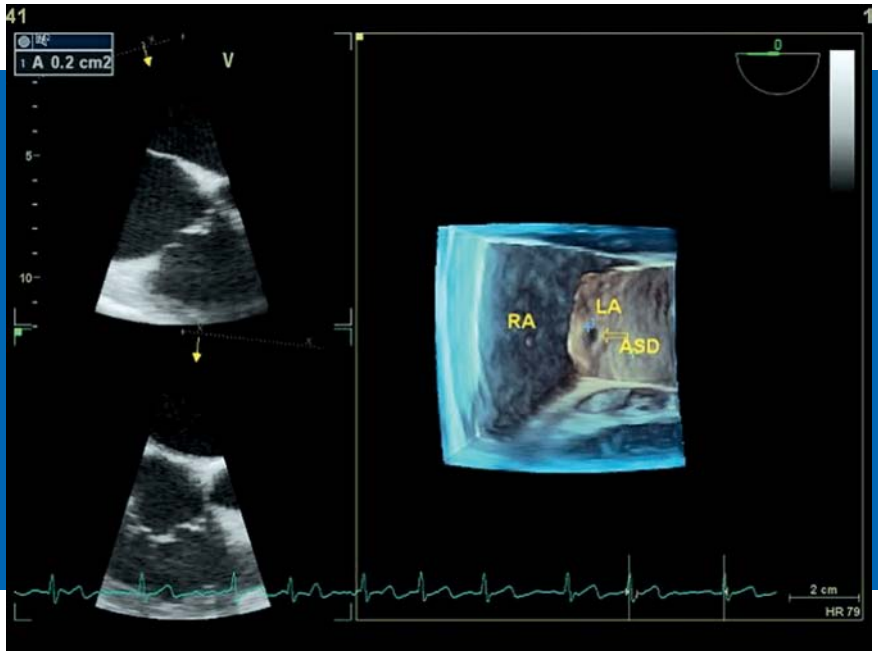

Figure 3. *Three-dimensional transesophageal echocardiography showing atrial septal defect; view from the left atrium.*

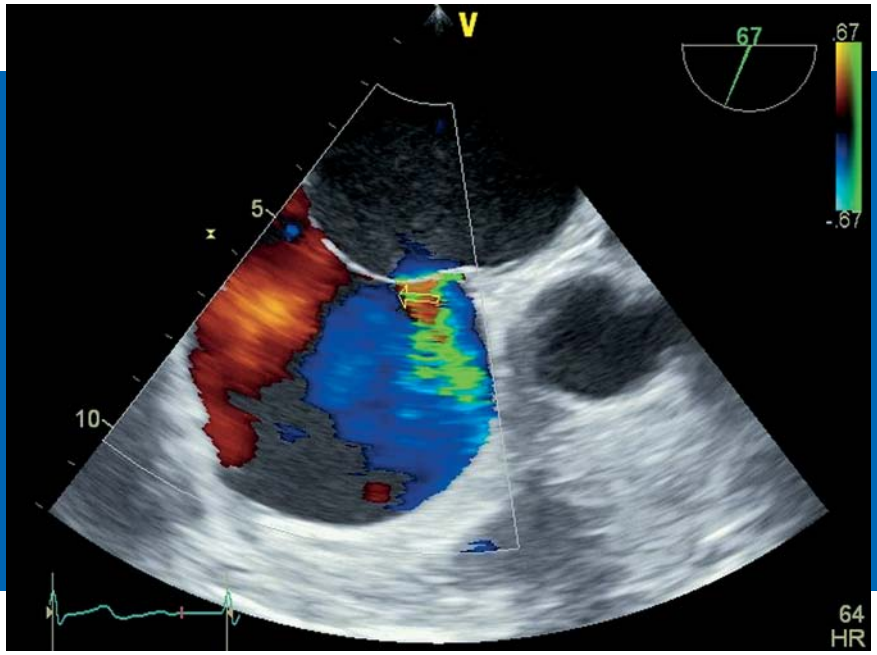

Figure 4. *Two-dimensional transesophageal echocardiography presenting left-right atrial shunt using color Doppler.*

Diskusija

Godine 1916. Lutembacher je prvi opisao kombinaciju kongenitalnog ASD i stečene MS[1]. Incidencija ovog sindroma je vrlo niska i uglavnom se javlja u žena. Incidencija MS u bolesnika s ASD je 4%, a incidencija ASD u bolesnika s MS je 0,6-0,7%[2]. Hemodinamika i sami tijek ovog sindroma ovisi o veličini ASD, težini MS, plućnoj vaskularnoj rezistenciji i prilagodljivom odgovoru desne klijetke. U slučaju teške MS i malog ASD bolesnik se uglavnom klinički prezentira slikom MS. U slučaju kada je ASD veći, kliničkom slikom dominiraju simptomi ASD. Mitralna stenoza povećava lijevo-desni shunt, dok ASD vrši dekompresiju tlačnog opterećenja lijeve pretklijetke. Treba naglasiti da smjer shunta uglavnom ovisi o odgovoru i prilagodljivosti lijeve odnosno desne klijetke. Obično desna klijetka ima bolju mogućnost prilagodbe, stoga u prisustvu MS, krv ide u desnu pretklijetku umjesto u plućne vene te je tako izbjegnuta plućna kongestija. Krajnji rezultat je progresivna dilatacija i zatajivanje desne klijetke

Discussion

In 1916, Lutembacher first described a combination of congenital ASD and acquired MS[1]. The incidence of this condition is very rare and has a predilection for females. The incidence of MS in patients with ASD is 4%, and ASD in patients with MS is 0-6-0.7%[2]. The hemodynamic features and natural history of patients with this syndrome depend on the size of ASD, severity of MS, pulmonary vascular resistence and the compliance of right ventricle. When MS is severe and ASD is small, it usually presents clinically as pure MS. On the contrary, when the ASD is large the signs and symptoms of ASD dominate. MS augments the left to right interatrial shunt, while ASD serves to decompress the left atrium. However, it should be stressed that the direction of blood flow is determined largely by the compliance of left and right ventricles. Normally, the right ventricle is more compliant than the left ventricle. In the presence of MS, blood flows to the right atrium through the ASD instead of going backward

te redukcija toka krvi u lijevu klijetku. Pojava Eisenmengerov sindroma u Lutembacherovu sindromu je izuzetno rijetka zbog prisustva velikog interatrijskog septalnog defekta i visokog tlaka u lijevom atriju zbog MS.

Klinička sumnja na postojanje ovog sindroma trebala bi biti prisutna u bolesnika s anamnezom reumatske vrućice koji imaju ASD i srčano popuštanje.

Uloga ehokardiografije (2D TTE uz obojani Doppler i konvencionalni kontrast, a osobito TTE i TEE 3D prikaz) u dijagnozi ovog sindroma je krucijalna i moguće jedina dijagnostička metoda potrebna prije intervencijske ili kiruške korekcije[3,4]. Prije je kiruška korekcija oba defekta bila jedina opcija u liječenju, ali danas, razvojem medicine i novim intervencijskim mogućnostima, oba ova defekta moguće je korigirati perkutanim transkateterskim pristupom[5-7].

Zaključno, Lutembacherov sindrom je rijetka, kompleksna kongenitalna srčana bolest. Rana dijagnoza te rano invazivno ili operativno liječenje imaju za ove bolesnike dobru prognozu, za razliku od bolesnika kojima je dijagnoza kasno postavljena i koji su razvili srčano popuštanje. Stoga naglašavamo važnost ehokardiografije u ranom otkrivanju ovog rijetkog entiteta, kako bi se pravodobno moglo terapijski djelovati i time poboljšati kvaliteta i duljina trajanja života ovih bolesnika.

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into the pulmonary veins, thus avoiding pulmonary congestion. The final result is the progressive dilatation and failure of the right ventricle and reduced blood flow to the left ventricle. Eisenmenger syndrome is very uncommon in the presence of large ASD and high left atrial pressure because of MS.

Clinical suspicion of Lutembacher's syndrome should be raised by history of rheumatic heart disease, heart failure and ASD.

The role of echocardiography (2D TTE with color Doppler echocardiography, using conventional contrast technique and 3D TTE and TEE) in identifying this syndrome is well documented and it is suggested that this may be the only diagnostic technique needed before interventional or surgical correction[3,4]. Surgical correction has been previously the treatment of choice. However, nowadays, both MS and ASD, are amendable to percutaneous transcatheter intervention[5-7].

In conclusion, Lutembacher's syndrome is rare, complex, congenital heart disease. Early diagnosis and invasive or operative treatment has a good prognostic value but late diagnosis and development of heart failure bears bad prognosis.

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Poseban članak / Special article

Poticanje širenja znanstvenih sadržaja časopisa nacionalnih kardiovaskularnih društava: nova tražilica na web portalu Europskoga kardiološkog društva

Fostering diffusion of scientific contents of National Society Cardiovascular Journals: the new ESC search engine

Fernando Alfonso[1,2*], **Lino Goncalves**[3], **Fausto Pinto** (Editor-in-Chief, *Revista Portuguesa de Cardiologia*)[1], **Adam Timmis** (Editor-in-Chief, *Heart*)[1], **Hugo Ector** (Editor-in-Chief, *Acta Cardiologica*)[1], **Giuseppe Ambrosio**[1], **Panos Vardas** (Editor-in-Chief, *Hellenic Journal of Cardiology*)[1]; On behalf of the Editors' Network European Society of Cardiology Task Force

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Ernst Van der Wall (Editor-in-Chief, *Netherlands Heart Journal*),
Jorgen Videbak (Editor-in-Chief, *Cardiologisk Forum*),
Thomas F Lüscher (Editor-in-Chief, *Cardiovascular Medicine*).

Zajednička inicijativa za istodobnu publikaciju ovog članka uključuje sve zainteresirane časopise nacionalnih kardiovaskularnih društava pri Europskom kardiološkom društvu.
This is a joint simultaneous publication initiative involving all interested National Society Cardiovascular Journals of the European Society of Cardiology.

SAŽETAK: Časopisi nacionalnih kardiovaskularnih društava (NSCJ) pri Europskom kardiološkom društvu (ESC) predstavljaju visokokvalitetne biomedicinske časopise usmjerene na kardiovaskularnih bolesti. Mreža urednika pri ESC donosi uredničke inicijative usmjerene na poboljšanje znanstvene kvalitete i širenje utjecaja NSCJ. Ovaj članak donosi prikaz značaja interneta, elektroničkih izdanja i strategije otvorenog pristupa na znanstveno izdavaštvo. Predložit ćemo novu uredničku inicijativu, temeljenu na novom elektroničkom alatu na portalu ESC, koja može pomoći širenju sadržaja i vidljivosti NSCJ.

KLJUČNE RIJEČI: časopisi, elektronička izdanja, otvoreni pristup, internet.

SUMMARY: European Society of Cardiology (ESC) National Society Cardiovascular Journals (NSCJs) are high-quality biomedical journals focused on cardiovascular diseases. The Editors' Network of the ESC devises editorial initiatives aimed at improving the scientific quality and diffusion of NSCJ. In this article we will discuss on the importance of the Internet, electronic editions and open access strategies on scientific publishing. Finally, we will propose a new editorial initiative based on a novel electronic tool on the ESC web-page that may further help to increase the dissemination of contents and visibility of NSCJs.

KEYWORDS: journals, electronic editions, open access, Internet.

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Časopisi nacionalnih kardiovaskularnih društava (NSCJ) pri Europskom kardiološkom društvu (ESC) su visokokvalitetni biomedicinski časopisi posvećeni objavljivanje izvornih istraživačkih i edukativnih materijala o kardiovaskularnim bolestima.[1-3] Ovi časopisi službeno pripadaju odgovarajućim nacionalnim kardiološkim društvima uključenima u ESC. Mnogi od njih postigli su veliko međunarodno priznanje, uključeni su u najvažnije bibliometrijske baze podataka i postigli su veliki znanstveni utjecaj.[1-5] Neki od NSCJ su u potpunosti na engleskom jeziku te su u cijelosti dostupni u elektroničkom izdanju. Međutim, NSCJ su uglavnom heterogeni, a pojedini časopisi se objavljuju samo na lokalnim jezicima zbog čega su ograničeno dostupni.[1-3]

Glavni cilj biomedicinskih časopisa je objaviti kvalitetne znanstvene informacije. Da bi se postigao ovaj cilj, časopisi bi se trebali natjecati za objavu najboljih istraživanja provedenih u području interesa, pri čemu bi utjecaj časopisa bio glavna pokretačka snaga za privlačenje originalnih znanstvenih članaka.[1-3] Utjecaj časopisa se temelji na vjerodostojnosti, raširenosti i znanstvenom odjeku.[6] Kako bi se osiguralo da je znanstveni proces u potpunosti ispoštovan, časopisi se oslanjaju na sustav recenzije. Ovaj proces ne samo da omogućava urednicima da odaberu najbolji mogući materijal za objavu, nego omogućava čitateljima kvalitetu informacija koja odgovara najvišim znanstvenim standardima. U stvari, proces značajno poboljšava konačnu kvalitetu rukopisa koji će se eventualno objaviti. Nakon što članak definitivno bude prihvaćen za objavu, časopis bi trebao jamčiti ubrzanu objavu i širenje unutar znanstvene zajednice.[1-3]

Mreža urednika pri ESC osigurava jedinstvenu platformu za izradu uredničkih inicijativa usmjerenih na poboljšanje znanstvene kvalitete i pomoć u distribuciji sadržaja NSCJ.[1-5] U članku će se raspravljati o važnosti interneta i elektroničkih izdanja u znanstvenom izdavaštvu, a razmotrit će se sve veća važnost strategija otvorenog pristupa (OP). Posljednje, ali ne manje važno, predložiti će se nova inicijativu temeljenu na novom elektroničkom alatu koji može dodatno pomoći povećati širenje, distribuiranje sadržaja i cjelokupnu vidljivost NSCJ. Ovim alatom koji se nalazi na web portalu ESC treba poticati suradnju među različitim NSCJ te također proširiti dostupnost različitih znanstvenih mjesta te službenih časopisa ESC. Nadajmo se da će ovo pomoći u širenju znanstvenog utjecaja europskih kardiovaskularnih istraživanja.

The National Society Cardiovascular Journals (NSCJs) of the European Society of Cardiology (ESC) are high-quality biomedical journals devoted to publishing original research and educative material on cardiovascular diseases.[1-3] These journals officially belong to the corresponding ESC National Cardiac Societies. Many of them have achieved major international recognition, are included in most important bibliometric databases, and have made major scientific impact.[1-5] Some NSCJs offer full-text English content and are freely available in electronic editions. However, NSCJs are largely heterogeneous and some of them are only published in local languages with a limited visibility.[1-3]

The main goal of biomedical journals is to publish high-quality scientific information. To achieve this goal, journals should compete for the best research carried out in their field, the "prestige" of the journal being the main driver to attract original contributions.[1-3] In turn, a journal's prestige is based on credibility, diffusion and scientific impact.[6] To ensure that the scientific process is fully respected, journals rely in the "peer review" system. This process not only allows the editors to select the best possible material for publication, but also assures the readers that the quality of the information follows the highest scientific standards. In fact, the process significantly improves the final quality of manuscripts eventually published. Once an article is definitely accepted for publication, the journal should guarantee its expedited publication and widespread diffusion among the scientific community.[1-3]

The Editors' Network of the ESC provides a unique platform for devising editorial initiatives aimed to improve the scientific quality, and facilitate diffusion of the contents of NSCJs.[1-5] Herein we will discuss the importance of the Internet and electronic editions in scientific publishing. We will also review the growing relevance of open access (OA) strategies. Last but not least, we will propose a new initiative based on a novel electronic tool that may further help to increase the diffusion, dissemination and overall visibility of NSCJs. This tool, located on the ESC website, should foster collaboration among the different NSCJs and also broaden exposure from diverse scientific sites and ESC official journals. Hopefully, this will help to further expand the scientific impact of European cardiovascular research.

Elektronička izdanja i internet: promjena obrasca u znanstvenom izdavaštvu

Razmjena rezultata najnovijih istraživanja putem recenziranih časopisa ostaje glavno uporište znanstvenog procesa i napretka u znanosti.[1-3] Za uspjeh istraživanja potrebno je da su članci čitani, široko dostupni te su premet debate i da ih citiraju zainteresirani istraživači. U globalnom svijetu znanosti koji se brzo mijenja, časopisi bi trebali osigurati maksimalnu dostupnost i proširenost članaka.[1-3] Doista, većina izdanja su se već preselila u novo mrežno razdoblje gdje je naglasak stavljen na internet i elektronička izdanja.[1-3] Do prije nekoliko godina za čitanje članaka znanstvenici su pretežito koristili tiskana izdanja bilo kao primjerke osobne pretplate ili iz knjižnica.[7] Danas je pretežiti način čitanja članaka preuzimanje digitalne inačice koja se čita izravno na zaslonu ili ispisuje.[7] Čitatelji i istraživači danas aktivno preuzimaju članke klikom na računalu u svom domu ili uredu.[7]

Zanimljivo je napomenuti da internet ne utječe samo da na istraživanja, nego i na kliničku praksu. Danas nerijetko pacijenti preuzimaju medicinske informacije s interneta koje mogu biti predmetom spora u kontaktu s liječnicima, a često se susreću i nepotrebno zabrinuti ili bolesnici s nerealnim očekivanjima. Iako su neki pacijenti zbunjeni, ostali su prekomjerno informirani i traže iscrpna objašnjenja o svojoj dijagnozi, liječenju i prognozi. Radi ispunjenja tih zahtjeva informacije za pacijenta trebaju omogućiti znanstvena, odnosno stručna društva. Stoga, čak bi i svakodnevna klinička praksa trebala uključivati sociokulturalne promjene uzrokovane internetom.

Pristup medicinskim informacijama je revolucionarno promijenjen elektroničkim izdanjima. Također se razvijaju i bibliometrijske baze podataka. *Medline, ISI Web of Science* te u novije vrijeme *Scopus* nude cjelovite online informacije o medicinskoj literaturi.[8-11] *Google Scholar* sve više koriste mnogi istraživači.[8-11] Scopus i naročito Google Scholar dobivaju podatke iz većih izvora podataka, uključujući najrazličitije znanstvene izvore (ne samo publikacije ISI) i stoga nude nešto drugačiju mogućnost na tom području. Zanimljivo, Google Scholar je besplatan te razne studije ukazuju na to da pruža točna pretraživanja i analize podataka koji se malo razlikuju od onih dobivenih od klasičnih bibliometrijskih izvora.[8-11]

Tradicionalno je najčešće korišteni izvor bibliometrijskih podataka *Thomson ISI Web of Knowledge*, posebice *Science Citation Index* i *The Journal Citation Reports* koji pružaju godišnje čimbenike odjeka časopisa. Nedavno su se pojavili i ostali pokazatelji kao što je *SCImago scientific journal rank* ocjena kvalitete znanstvenog časopisa (SJR) i *Eigenfactor* kao alternativni pokazatelji kvalitete časopisa.[8-11] Oni u obzir ne uzimaju samo broj nego i "kvalitetu" ili relevantnost citata određenog članka. Kvantitativno mjerenje publikacija (znanstvena produktivnost) i citatna analize (znanstveni utjecaj) su ključne odrednice znanstvenog uspjeha pojedinih istraživača i institucija, jer izreka "objaviti ili nestati" još uvijek prevladava u većini akademskih okruženja.[8-11] U ovom scenariju, elektronička izdanja i dostupnost na internetu zasigurno imaju ključnu ulogu. Danas kada se neki rad objavi u elektroničkom izdanju na web stranici časopisa, informacije se mogu proširiti brzo u zajednici, a iznimno veliki broj preuzimanja mogao bi biti posljedica mehanizama, poput Matejevog efekta ("Jer svakomu tko ima dat će se još pa će obilovati, a onomu tko nema oduzet će se i ono što ima").[12] Doista je istražen odnos između broja citata postignutog u članku i broja preuzimanja.[13] Brojanjem posje-

Electronic editions and the Internet: a paradigm shift in scientific publishing

Sharing the results of late breaking research through peer-reviewed journals remains the mainstay of the scientific process and progress in science.[1-3] The success of research requires articles to be read, spread, discussed and cited by interested investigators. Therefore, in the fast moving and globalised world of science, journals should ensure maximal accessibility and diffusion of their articles.[1-3] Indeed, most publications have already moved into a new "online era" where the emphasis is placed on the Internet and electronic editions.[1-3] Just a few years ago, scholars did all their reading in paper journal issues obtained as personal copies circulating within their organisations, or by retrieving issues from library archives.[7] Today the predominant reading mode is to download a digital copy and either read it directly on the screen or as a printout.[7] Currently, readers and investigators readily retrieve articles with just a click on their home or office computers.[7]

Interestingly, the Internet not only affects research but also clinical practice. Nowadays, physicians are often approached and challenged by patients who have downloaded medical information from the Internet. Often they face either unnecessarily worried patients or patients with unrealistic expectations. Although some patients are confused, others are overinformed and demand in-depth explanations regarding their diagnosis, management and prognosis. Patient-oriented information should be provided by scientific societies to address these demands. Therefore, even everyday clinical practice should accommodate the sociocultural change induced by the Internet.

Access to medical information has been revolutionised by electronic editions. Likewise, bibliometric databases are also evolving. Medline, the ISI Web of Science and, more recently, Scopus offer comprehensive online information on medical literature.[8-11] In addition, Google Scholar is increasingly used by many investigators.[8-11] Scopus and, especially, Google Scholar obtain data from larger data sources including widely diverse scientific items (not only ISI publications) and therefore offer a slightly different perspective on the field. Interestingly, Google Scholar is free, and various studies suggest that it provides accurate search and data analyses that differ little from those obtained from classical bibliometric sources.[8-11]

Traditionally, the most commonly used source of bibliometric data is the Thomson ISI Web of Knowledge, in particular the Science Citation Index and the Journal Citation Reports, which provide the yearly journal Impact Factors. Recently, other indicators such as SCImago scientific journal rank (SJR) and the Eigenfactor have emerged as alternative indices of a journal's quality.[8-11] These consider not only the number but also the "quality" or relevance of the citations received by a given paper. Quantitative publication metrics (research output) and citation analyses (scientific infiuence) are key determinants of the scientific success of individual investigators and institutions because the "publish or perish" dictum still prevails in most academic settings.[8-11] In this scenario, electronic editions and accessibility on the Internet certainly play a critical role. Nowadays, once a paper is electronically published on a journal website, the information can propagate rapidly in the community, and extremely high downloads could be the result of mechanisms such as the "Matthew effect" (richer get richer).[12] Indeed, the relationship between the number of citations acquired by an article and

ta na web stranici časopisa za neki članak u tjednu nakon njegovog online objavljivanja može se predvidjeti broj citata iz tog članka u narednim godinama.[14] Treba napomenuti da se jedinstveni lokatori resursa (URL; web adresa određenog resursa na internetu) sve više koriste u znanstvenim publikacijama.[15] Citat URL pruža mogućnost izračunavanja objektivnog elektroničkog čimbenika odjeka (eIF) za mjerenje utjecaja na znanstveno publiciranje.[15] Međutim, zabrinutost i dalje izaziva stabilnost URL, što bi trebalo biti zajamčeno od strane odgovorne organizacije jer su URL osjetljivi na tehničke probleme te mogu postati nedostupni ovisno o vremenskom razdoblju.[15]

Internet posebno nudi novi prozor u znanost i pruža nova saznanja o pristupu i korištenju istraživanja.[16] Trenutno se podaci o upotrebi weba mogu dubinski analizirati kako bi se istaknula "mapa znanja". Prema Butleru,[16] kada čitatelji kliknu s jedne stranice na drugu dok pregledavaju online znanstvene časopise, generiraju lanac veza između poveznica za koje oni misle da pripadaju zajedno. Ovi događaji putanje korisnika mogu se analizirati radi mapiranja takvih veza i pružanja snimke interkonekcija između disciplina. Korisničke mape otkrivaju koliko često su se korisnici koji su čitali članak u časopisu A prebacivali na članak u časopisu B tijekom sesije preglednika. Zbrajanjem svih ovih složenih odnosa pomoću algoritama za vizualizaciju mreže, mape se mogu generirati na temelju "udaljenosti" između časopisa i disciplina.[16] Struktura tih mapa je vrlo slična onima koje su stvorene pomoću citatnih podataka: mreža klastera u različitim područjima u kojima časopisi imaju jake veze jedni s drugima, ali manje veze s drugim klasterima. Zanimljivo je da su časopisi u humanističkim i društvenim znanostima puno više istaknuti u tim mapama nego u citatnim mapama.[16] Još jedna ključna razlika između citatnih mapa i korisničkih mapa je da citatne mape samo prikazuju citate istraživača koji objavljuju te zanemaruju utjecaj radova na medicinsku zajednicu koja čita i primjenjuje literaturu u kliničkoj praksi, ali koja rijetko vrši objavljivanja. Citatnim podacima se mogu podcijeniti radovi napisani za kliničku praksu koja su učestalo čitaju, ali se proporcionalno ne citiraju.[16] Osim toga, korisničke mape su bolje ažurirane od citatnih mapa zbog inherentne odgode u objavi, stoga pružaju drugačije vremensko razdoblje znanstvenog procesa. Prema gore navedenom, i korisnički i citatni podaci svaki nude dodatne informacije o utjecaju radova i časopisa na znanstvenu zajednicu.[16]

Elektronička izdanja nude jedinstvene mogućnosti objave i otvaraju nove prostore u znanstvenom komuniciranju.[1-3] Primjerice, ona nude fleksibilan izgled i strukturu za članke, nove formate i mogućnost uključivanja dodatne dokumentacije priložene radu kao medijskog poboljšanja (video, itd.). Značajni dijelovi kao što su metode i dodatni podaci se sada mogu predstaviti kao dodatni materijal bez dodatnog troška. Elektronički sustavi za obradu članaka olakšavaju procese recenzije i objavljivanje.[1-3] Otvorena recenzija ili komentari čitatelja nakon objava mogu biti postavljeni na web stranici časopisa olakšavajući tako interaktivnost te transparentniji i dinamičniji znanstveni proces. Omogućena je statistika o elektroničkim radovima (mjerenje broja preuzimanja i citiranja) zbog interesa čitatelja i istraživača.[17]

Javno dostupni podaci su zagovarani kao sredstvo dodatnog promicanja transparentnosti u istraživanju i otvorenijoj znanosti.[18-20] Online izdanja omogućuju objavljivanje dužih radova bez ekonomskog opterećenja povezanog s troškovima tiskanja. U ovom smislu se zagovara objavljivanje cjelovite anonimizirane baze sirovih (primarnih) podataka.[18-20] Primarnim podacima mogu se koristiti nezavisne analize

the number of downloads has been explored.[13] Hit counts on a journal website for an article during the week after its online publication predict the number of citations of that article in subsequent years.[14] Of note, Uniform Resource Locators (URLs) are being increasingly used in scientific publications.[15] Citation of URLs provides the possibility of calculating an objective electronic Impact Factor (eIF) to measure their impact on scientific research.[15] However, the stability of URLs remains a matter of concern, and this should be guaranteed by the responsible organisation because URLs are vulnerable to technical problems and may become inaccessible in a time-dependent manner.[15]

Notably, the Internet offers a new window into science and provides new insights on access and use of research.[16] Currently, web-usage data can be analysed in depth to outline a "map of knowledge". According to Butler,[16] when readers click from one page to another while looking through online scientific journals, they generate a chain of connections between links they think belong together. These "clickstream events" may be analysed to map such connections and to provide a snapshot of interconnections between disciplines. Usage maps reveal how often users looking at an article in journal A moved on to an article in journal B during a browser session. By aggregating all these complex relationships using network-visualisation algorithms, maps can be generated based on the "distances" between journals and disciplines.[16] The structure of these maps is quite similar to those created using citation data: a network of clusters in different fields within which journals have strong connections with one another but fewer links to other clusters. Interestingly, journals in the humanities and social sciences figure much more prominently in these maps than in citation-based maps.[16] Another key difference between citation- and usage-based maps is that the former only refiect citations by researchers who publish, and ignore the impact of papers on the medical community who read and apply the literature in medical practice but who rarely publish. Citation data may undervalue papers written in practitioner-based fields that are widely read but not cited proportionally.[16] Moreover, usage maps are more up-to-date than citation ones because of the inherent delay in publication, therefore providing a different time slice of the scientific process. Accordingly, both usage and citation data each provide complementary information on the impact of papers and journals on the scientific community.[16]

Electronic editions provide unique publishing possibilities and open up new venues in scientific communication.[1-3] For instance, they offer a fiexible layout and structure for articles, new formats and the possibility of including additional documentation attached to the paper as media enhancements (videos, etc). Important sections such as methods and additional data can be now presented as supplementary material without additional cost. Electronic managing systems facilitate both the processes of peer review and publishing.[1-3] Open peer review and even post-publication readers' comments can be uploaded on the journal website, facilitating interactivity and a more transparent and dynamic scientific process. Finally, statistics on electronic papers (downloads and citation metrics) are offered for the interest of readers and researchers.[17]

Publicly available data are advocated as a means to further promote transparency in research and more open science.[18-20] Online editions allow the publication of longer papers free from the economic burden of print charges. Posting the complete anonymised "raw dataset" has been advocated in

radi potvrđivanja izvornih rezultata, kao i radi povezanih ili novih hipoteza, osobito u kombinaciji s drugim javno dostupnim bazama podataka. S etičkog stajališta, čini se da je neprihvatljivo da dok su pacijenti spremni razmjenjivati podatke o sebi s istražiteljima i sponzorima, istražitelji i sponzori moguće nisu spremni razmjenjivati podatke o istraživanju s drugima. Uspješna je bila već i razmjena podataka među genomskim istražiteljima. Međutim, ova strategija može dovesti do problema kao što su neprimjerene analize, pretraživanje podataka i donošenje neprimjerenih zaključaka.[18-20] Međunarodni odbor urednika medicinskih časopisa je izradio smjernice za pripremu sirovih (primarnih) kliničkih podataka za objavu.[18] Zanimljivo, ovo je bilo povezano s 69%-tnim povećanjem broja citata, neovisno o čimbeniku odjeka časopisa, datumu objave i zemlje podrijetla autora.[20] Korelacija između javno dostupnih podataka i povećanog utjecaja literature može dodatno motivirati istražitelje da razmijene svoje detaljne podatke iz istraživanja.

S druge strane, Web 2.0 se također sve više koristi u području medicine.[21-25] RSS kanali, podcastovi, osobne izdavačke platforme (blogovi), društvene mreže (kao što su Twitter i Facebook) i društveni mediji su predloženi kao inovativni alati za edukaciju i trajnu edukaciju kliničara. Njima se omogućava distribuiranje, razmjena i komentiranje medicinskih informacija.[21-25] Međutim, znanstvena zajednica je manje zainteresirana da ih smatra ekvivalentom tradicionalnim modelima širenja informacija u recenziranim medicinskim časopisima. U tom smislu, neki su predložili da platforme recenzije nakon objave mogu omogućiti potrebnu mjeru zaštite u novom okruženju.[22] Osim toga, intuitivno pregledavanje sadržaja časopisa na pametnim telefonima i na iPad-u omogućuje sve veći broj publikacija (uključujući *European Heart Journal*)[24,25] radi većeg širenja sadržaja.[21] Nadalje, neke Web 2.0 tehnologije olakšavaju suradničko prikupljanje podataka za klinička ispitivanja.[23] *Google Docs*, primjerice, besplatno je dostupan i omogućuje većem broju korisnika da putem mobilnih uređaja unesu podatke o bolesnicima u elektroničke obrasce ispitanika kod multicentričnih ispitivanja.[23]

Konačno, trebamo imati na umu da engleski predstavlja univerzalni (radni) jezik znanosti. To je važno, a napore treba usmjeriti u okviru ESC kako bi se spriječio fenomen Babilonske kule u digitalnom dobu.[1-3] Međutim, time se mogu izazvati veliki problemi i jedinstveni izazovi za istraživače i zemlje koji nisu iz engleskog govornog područja.[26] U stvari, neki NSCJ se objavljuju samo na materinskom jeziku te stoga nisu lako dostupni međunarodnoj znanstvenoj zajednici. Neki NSCJ su odlučili objaviti svoje članke na svojim materinskom jeziku i engleskom jeziku radi obraćanja kako medicinskim djelatnicima, tako i međunarodnim znanstvenicima. Teške pojmove je lakše zapamtiti na materinskom jeziku. Časopisi *Public Library of Science* (PLOS) potiču autore koji ne dolaze iz engleskog govornog područja da dostave inačicu svog članka na svom izvornom jeziku kao popratni materijal.[27] Znanost se ne bi trebala smatrati "akademskom izoliranom kulom" odvojenom od ostatka društva, već bi trebala biti ukorijenjena u društvu kako bi olakšala svoju kulturnu asimilaciju.[27]

Uredničke gledišta o inicijativama otvorenog pristupa znanstvenim informacijama

Internet i elektronička izdanja postavljaju temelj za inicijative otvorenog pristupa znanstvenim informacijama (OP).[28,29] Dvije glavne karakteristike publikacija u OP su: (**1**) svi objavljeni sadržaji su besplatno dostupni putem interneta, (**2**) či-

this regard.[18-20] The raw data can be used to confirm original results by independent analyses and also to explore related or new hypotheses, particularly when combined with other publicly available datasets. From an ethical perspective, it appears unacceptable that, while patients are willing to share data about themselves with investigators and sponsors, the latter may be unwilling to share the trial data with others. Data sharing among genomic investigators has already been successful. However, this strategy may cause concerns such as inappropriate analyses, "data dredging" and drawing inappropriate conclusions.[18-20] The International Committee of Medical Journal Editors has developed guidelines for the preparation of raw clinical data for publication.[18] Interestingly, this practice has been associated with a 69% increase in citations, independently of journal Impact Factor, date of publication and author country of origin.[20] The correlation between publicly available data and increased literature impact may further motivate investigators to share their detailed research data.

On the other hand, Web 2.0 has also been increasingly used in the medical field.[21-25] RSS feeds, podcasts, personal publishing platforms (blogs), social networks (such as Twitter and Facebook) and social media are proposed as innovative tools for educating and updating clinicians. They allow physicians to distribute, share and comment on medical information.[21-25] However, the scientific community is less than eager to regard them as equivalent to the traditional models of information dissemination in peer-reviewed medical journals. In this regard, some have proposed that platforms of post-publication peer review may provide the required safeguard in this new setting.[22] In addition, intuitive browsing of journal content on smartphones and the iPad is being provided by a growing number of publications (including the European Heart Journal)[24,25] to enhance diffusion of contents.[21] Furthermore, some Web 2.0 technologies facilitate collaborative data collection for clinical trials.[23] Google Docs, for instance, is freely available and allows multiple users to enter patient data into electronic case report forms of multicentre trials through mobile devices.[23]

Finally, we should keep in mind that English represents the "lingua franca" of science. This is important, and efforts should be made within the ESC to prevent tower-of-Babel phenomena in the digital era.[1-3] However, this may create major problems and unique challenges for non-English-speaking investigators and countries.[26] In fact, some NSCJs only publish in their mother tongue and are therefore not readily accessible to the international scientific community. Some NSCJs have decided to publish their articles in both their native language and English, to address healthcare professionals and international scholars, respectively. Difficult concepts are easier to remember in the mother tongue. Interestingly, Public Library of Science journals encourage non-English-speaking authors to provide a version of their article in their original language as supporting material.[27] Science should not be considered an 'ivory tower' separated from the rest of society, but rather imbedded in it to facilitate its cultural assimilation.[27]

Some editorial perspectives on "open access" initiatives

The internet and electronic editions set the basis for OA initiatives.[28,29] The two main characteristics of OA publications are: (**1**) all published contents are freely accessible through the Internet; (**2**) readers are given copyright permission as long as authors and publishers receive adequate attribu-

tatelji dobivaju autorsko pravo ako autori i izdavači dobiju adekvatno priznanje.[28] Ovaj model zahtijeva dvije velike promjene iz tradicionalnog pretplatničkog modela. Prvo, OP pomiče financiranje objave s čitatelja (pretplata pojedinaca ili sveučilišta) na autore i istraživače (putem odgovarajućih financijskih organizacija ili akademskih institucija) naknadom za obradu članaka.[28] Drugo, autorsko pravo se više ne koristi kako bi se spriječilo, nego kako bi se stimuliralo republiciranje. Časopisi za koje je potrebna pretplata obično zahtijevaju od autora da prenesu autorska prava na časopis, tako da imaju pravo ograničiti pristup te prijete tužbama zbog povrede prava. Najvažniji časopisi za koje je potrebna pretplata se dijelom financiraju od strane pojedinaca i medicinskih društava, ali uglavnom skupnim e-licenčnim ugovorima između izdavača i sveučilišta ili knjižnica.[28,29] Pojedinačnim elektroničkim člancima se također može pristupiti na osnovi "plati pa čitaj". Čitateljima se naplaćuje naknada na jedan ili drugi, tradicionalan, način, a autorima i istraživačima se naplata vršu kod modela OP.[28,29] Pojedini komercijalni nakladnici naplaćuju autorima naknadu objave kao zamjenu za prihod od pretplate, što znatno ograničava ponovno korištenje. Ove inicijative se ne bi trebale smatrati pravim OP. Neki tradicionalni izdavači su nedavno pokrenuli "hibridne" inicijative gdje je autorima dopušteno (nakon plaćanja naknade) da izrade pojedinačne OP članke.[28,29]

U ranim 90-im godinama prošloga stoljeća, pojedinačni istraživači-volonteri osnivaju pionirske časopise s OP koje pohranjuju na pojedinačnim ili sveučilišnim serverima.[29] Nakon toga, mnogi etablirani časopisi izrađuju svoje članke u OP, nakon usklađivanja usporedne objave digitalnog i tiskanog izdanja. To je osobito slučaj kod službenih časopisa medicinskih društava u zemljama koji nisu u engleskom govornom području u pokušaju da povećaju svoje čitateljstvo i utjecaj.[30] U posljednjih deset godina, novi, formalni časopisi s OP su doživjeli procvat putem naplate troškova za obradu članaka za financiranje publikacija.[29] Zanimljivo, neki veliki izdavači (BioMed Central, PLOS) su specijalizirani za OP.[29] Otvoreni pristup ima dva glavna modaliteta: *zlatni tip* OP (putem izravnog objavljivanja) i *zeleni tip* OP (tradicionalno objavljivanje u časopisima s pretplatom uz paralelnu objavu konačnog rukopisa na webu u OP). Zeleni tip OP isporučuju repozitoriji, dok zlatni tip isporučuju časopisi.[31] Licence se kreću od najotvorenije (CC-BY; dopušta drugima da distribuiraju, remiksiraju, mijenjaju i prerađuju djelo, čak i u komercijalne svrhe, dokle god se navodi autora izvornog djela) do one koja ograničava komercijalnu upotrebu (CC-BY-NC).[31]

Uspješnost slobodnog pristupa prema modelu gdje autor plaća trošak može se dokazati podacima koji pokazuju stalan rast radova objavljenih u časopisima s OP (20% godišnje), kao i brojem časopisa s OP (15% godišnje), koji su ili novi časopisi ili već postojeći koji se prebacuju na ovaj model.[32] Trenutno, 30% svih recenziranih časopisa diljem svijeta su časopisi s OP.[31]

Dobrobit znanosti od OP je ubrzavanje širenja i unosa rezultata istraživanja. Glavna prednost OP je da čitatelji mogu koristiti bilo koji alat web pretraživanje za pristup i pregled literature.[28] Ovi članci su brzo prepoznati, a njihove rezultate stručnjaci lako prikupljaju i o njima raspravljaju.[33] Kao što je već spomenuto, postoje dva glavna OP modaliteta: tip časopisa s OP i tip časopisa sa samostalnim arhiviranjem. Zanimljivo, neke studije ukazuju na to da članci odmah objavljeni kao na stranicama časopisa s OP (zlatni tip) imaju veći utjecaj nego samostalno arhivirani ili na drugi način javno dostupni članci s OP (zeleni tip).[33]

Inicijativama za OP povećava se širenje sadržaja, citiranja i čimbenika odjeka časopisa.[33-35] U prijašnjim studijama je analiziran učinak "online statusa" na čimbenik odjeka biotion.[28] In turn, this model requires two major changes from the traditional subscription-based model. First, OA shifts the financing of publication from readers (subscription fees from individuals or universities) to authors and investigators (through the corresponding funding organisation or academic institutions) by means of article-processing fees.[28] Second, the copyright is no longer used to prevent, but rather to stimulate, republication. Subscription-based journals usually require authors to transfer the copyright to the journal so that they are empowered to restrict access to paying customers and threaten competing publications with infringement lawsuits. Major subscription-based journals are partly financed by individuals and medical societies but mainly by bundled e-license agreements between publishers and universities or librarians.[28,29] Individual electronic articles can also be accessed on a pay-per-view basis. Readers are charged one way or the other in the traditional way, whereas authors and investigators are charged in the OA model.[28,29] Some commercial publishers charge authors a publication fee to substitute for subscription revenue while significantly limiting reuse. These initiatives, however, should not be considered real OA. Some traditional publishers have recently instituted "hybrid" initiatives where authors are allowed (after paying a fee) to make individual articles OA.[28,29]

In the early 90s, pioneer OA journals were founded by individual investigators based on voluntary work and were usually hosted in individual or university servers.[29] Thereafter, many established journals made their articles OA when they implemented their digital editions in parallel with print editions. This was especially the case for official journals of medical societies and in non-English-speaking countries in an attempt to increase their readership and impact.[30] In the last decade, new, formal, OA journals have fiourished using article-processing charges to finance publications.[29] Interestingly, some major publishers (BioMed Central, Public Library of Science) have specialised in OA.[29] OA has two major pathways: "gold" OA (via direct publishing) and "green" OA (traditional publication in subscription-based journals with parallel open posting of the final manuscript on the web). Green OA is delivered by repositories, whereas gold OA is delivered by journals.[31] Licences range from any kind of reuse provided that proper attribution is made (CC-BY) to those that limit commercial use (CC-BY-NC).[31]

The health of the free-access author-pay model can be demonstrated by data showing the steady growth of papers published in OA journals (20% per year) and also in the number of OA journals (15% per year), either as new journals or traditional journals switching to this model.[32] Currently, 30% of all peer-review journals in the world are OA.[31]

OA benefits science by accelerating dissemination and uptake of research findings. A major advantage of OA is that readers can use any web-based research tool to access and review the literature.[28] These articles are quickly recognised and their results are readily picked up and discussed by peers.[33] As already mentioned, there are two main modalities of OA: OA journals and self-archiving. Interestingly, some studies suggest that articles immediately published as OA on the journal site (gold route) have higher impact than self-archived or otherwise openly accessible OA articles (green route).[33]

Overall OA initiatives increase diffusion of content, citations and eventually the Impact Factor of the corresponding journals.[33-35] Early studies analysed the effect of "online status" on the Impact Factor of biomedical journals.[36] They found

medicinskih časopisa.[36] Otkriveno je da omogućen mrežni pristup s cjelovitim tekstom na webu povećava vidljivost časopisa.[36] Također i prisutnost časopisa u indeksu Medline u formi cjelovitog teksta tekst na webu potiče čimbenik odjeka.[37] Ova pristranost objašnjava se tendencijom detaljnog proučavanja dostupnih članaka.[37] Inicijative za OP se također pojavljuju i radi povećanja čimbenika odjeka.[33-35] Neki pak tvrde da taj učinak može dovesti do zabune između otvorenog i elektroničkog pristupa. Ipak, nedavna izvješća ukazuju na to da u većini razvijenih zemalja radovi dobivaju povećani broj citata kada se besplatno postave online, ali dožive dodatni skok kada prvo se pojave online putem komercijalnih izvora.[35] Ovaj efekt se čini obrnutim u siromašnim zemljama gdje je veća vjerojatnost da će članci s besplatnim pristupom biti više citirani.[35] Spomenuti rezultati navode na to da besplatan pristup internetu širi krug onih koji čitaju i koriste znanstvena istraživanja. Prednost principa OP je da se ne pojavljuje pristranost zbog kvalitete, jer su autori samostalno odredili što je OP, jer studije ukazuju da će ova prednost postojati i nakon prilagodbe za mnoge druge potencijalne zbunjujuće čimbenike povezane s uredništvom i kvalitetom istraživanja.[38]

Zanimljivo, randomiziranim ispitivanjem o objavljivanju u OP analizirani su učinci besplatnog pristupa preuzimanja članaka i citiranja.[39] Članci u uvjetima OP evidentirali su znatno više preuzimanja i doprli do šire publike u prvoj godini. Međutim, u ovom istraživanju, članci u OP se nisu citirali češće, kao ni ranije od članaka iz časopisa s pretplatom unutar razdoblja od 3 godine. Predloženo je da bi proces "socijalne stratifikacije", koji čini koncentraciju znanstvenih autora na malom broju vrhunskih istraživačkih sveučilišta s izvrsnim pristupom znanstvenoj literaturi, mogao objasniti ovaj prividni paradoks.[39] Štoviše, ta kontrolirana studija ukazuje na to da pravi korisnik objavljivanja u OP ne može biti znanstvena zajednica, nego stručna zajednica u kliničkoj praksi koja koristi, ali rijetko doprinosi korpusu literature.[39]

Kao što je objašnjeno, nakladnici su trenutno postavili embargo iz ekonomskih razloga. To može biti značajna prepreka za pristup biomedicinskim znanostima. Kao što je već ranije naglašeno, korisnici daju prednost elektroničkom pristupu i često izbjegavaju članke koji nisu elektronički dostupni.[40] U skromnom pokušaju rješavanja tih problema, mnogi časopisi sada nude besplatan pristup svim člancima 6 mjeseci nakon objave, a pozdravljaju objavljivanje članaka kao članaka s OP nakon što autori plate naknadu.

Međutim, tijela za financiranje istraživanja postaju sve razumnija po ovom etičkom pitanju. Mnogi će tvrditi da je neetično koristiti državne poticaje za istraživanja (novac od ljudi), a ne dopustiti znanstvenoj zajednici da ima besplatan pristup rezultatima studije. Za rješavanje takvih pitanja, Berlinskom deklaracijom je predloženo osnivanje OP repozitorija. Svi istraživači koji su primili državne potpore bi trebali dostaviti cijeli tekst rada objavljenog iz njihove studije na *PubMed Central* te također osigurati samoarhiviranje na odgovarajućem fakultetu ili ustanovi za istraživanje. Očito je da časopisi s OP nude atraktivno rješenje za problem ograničenog pristupa rezultatima javno financiranih istraživanja.[41]

Većina zemalja i osnivačkih tijela trenutno poduzimaju daljnje radnje kako bi osigurale OP za javno financirana istraživanja.[41-43] Istraživači su prisiljeni da učine svoj rad javno dostupnim u repozitorijima (zeleni tip) u roku od 12 mjeseci od objave. Ostala tijela čak sugeriraju da bi autori trebali učiniti svoj rad slobodnim jednokratnom naknadom izdavaču (zlatni tip). Jasno, budžeti za istraživanje bi se trebali preraspodijeliti s tim ciljem, iako potrebna logistika i implikacije ove pro-

that providing online access with 'full text on the net' increases the visibility of a journal.[36] In addition, the presence of journals on Medline as 'full text on the net' also boosts their Impact Factor.[37] This bias is explained by the tendency to peruse what is more readily available.[37] OA initiatives also appear to increase the Impact Factor.[33-35] However, some argue that this effect may confound between open and electronic access. Nevertheless, recent reports suggest that, in most developed countries, journal articles receive an increase in citations when they come online freely, but experience an additional jump when they first come online through commercial sources.[35] This effect appears to be reversed in poor countries, where free-access articles are much more likely to be cited.[35] All together, these findings suggest that free internet access widens the circle of those who read and make use of scientific research. In addition, this "OA impact advantage" does not appear to be a "quality bias" from authors self-selecting what to make OA, because some studies suggest that this advance persists after adjustment for many other potential confounders related to the editorial and research quality.[38]

Interestingly, a randomised trial on OA publishing analysed the effects of free access on article downloads and citations.[39] Articles placed in the OA condition received significantly more downloads and reached a broader audience within the first year. However, in this particular study, OA articles were cited no more frequently, nor earlier, than subscription-access articles within 3 years. It was suggested that the process of "social stratification", accounting for a concentration of scientific authors at a small number of elite research universities with excellent access to the scientific literature, might help to explain this apparent paradox.[39] Moreover, this controlled study suggests that the real beneficiaries of OA publishing may not be the research community but rather communities of medical practice that consume, but rarely contribute to, the corpus of literature.[39]

As discussed, embargoes are currently imposed by publishers for economic reasons. This may be a significant barrier to access in biomedical sciences. As previously emphasised, it has been suggested that users favour electronic access and often eschew articles that are not available electronically.[40] In a shy attempt to tackle these problems, many journals now offer free access to all articles 6 months after publication and welcome the publication of articles as OA after a fee is paid by the authors.

However, research funding bodies are becoming increasingly sensible to this ethical issue. Many would argue that it is unethical to use the research grants from government (people's money) and not allow the scientific community to have free access to the results of the study. To address such issues, the Berlin Declaration suggested the establishment of OA repositories. All investigators who have received public grants should submit the full text of the paper published from their study to PubMed Central and also ensure self-archiving at the corresponding university or research institution. Obviously, OA journals provide an attractive solution to the problem of restricted access to results of publicly funded research.[41]

Most countries and founding bodies are currently taking further actions to ensure OA for publicly funded research.[41-43] Researchers are compelled to make their work publicly available in repositories (green road) within 12 months of publication. Other bodies even suggest that authors should make their work free by the publisher upfront (gold road). Clearly, research budgets should be reallocated with this

mjene ostaju predmet o kojem će se nastaviti raspravljati. U srpnju 2012. godine, novu politiku OP je objavila Europska Unija koja je preporučila politike OP za sve države članice.[31,41-43] Nadajmo se da će to će predstavljati pomak u znanstvenom izdavaštvu te da će se time najaviti nova era akademskih otkrića.

Nova tražilica na web portalu Europskoga kardiološkog društva

U posljednjih deset godina, količina dokumenata i edukativnih materijala dostupnih na web portalu ESC je eksponencijalno porasla. Ova situacija korisnicima uzrokuje otežano pronalaženje podataka koji su im potrebni. Postalo je očito da je potrebno sveobuhvatnije rješenje pretraživanja. Iz tog razloga, ESC je odlučio pružiti bolje iskustvo u pretraživanje za posjetitelje web portala.[44] ESC tražilica koristi semantičku analizu kako bi se osigurali najbolji rezultati od upisanih ključnih riječi.[45] Ovaj projekt tražilice ima četiri cilja: **(1)** osigurati ulaznu točku za više izvora podataka (iz jedne ulazne točke korisnik će moći istraživati bogatu ESC bazu podataka sa slajdovima, znanstvene radove, smjernice, sažetke, kliničke slučajeve, novosti i članke iz časopisa ESC); **(2)** predložiti alat kojim se mogu obraditi zahtjevi izraženi prirodnim jezikom na vrlo pristupačan način za korisnike; **(3)** locirati sadržaj kojeg bi inače bilo teško pronaći ili mu pristupiti, stoga omogućuje štednju dragocjenog vremena; **(4)** omogućiti posjetiteljima da intuitivno pronađu sadržaj prema temi ili osobi.

Tijekom 2008. godine odbor ESC pod predsjedanjem Roberta Ferrarija je odlučio podržati razvoj semantičke tražilice koja bi mogla pretražiti informacije na portalu ESC, kao i na internetskim stranicama svih šest udruženja (EHRA, EACVI [prethodno EAE], EAPCI, HFA, EACPR, ACCA). Ova ideja

aim, although the logistics required and the implications of this change remain a matter of ongoing debate. In July 2012, a new OA policy was announced by the European Union that recommended OA policies for all member states.[31,41-43] Hopefully, this will represent a paradigm shift in scientific publishing and will herald a new era of academic discovery.

The ESC search engine

In the last decade, the amount of documents and educational material available on ESC websites has increased exponentially. This situation has led to increasing difficulty for users to find the information they need. It has become obvious that a more comprehensive search solution is necessary. For this reason, the ESC decided to provide a better search experience for ESC site visitors.[44] The ESC search engine uses semantic analysis to provide the best results from the keywords typed in.[45] This search engine project has four goals: **(1)** to provide a single entry point to multiple data sources (in fact, from a single entry point, the user will be able to explore an ESC-rich database of slides, scientific reports, guidelines, abstracts, clinical cases, news and articles from ESC journals); **(2)** to propose a tool that can treat requests expressed in natural language in a very user-friendly way; **(3)** to locate content that would be difficult to find or access otherwise, therefore saving precious time; **(4)** to allow visitors to find content by topic or person in an intuitive way.

In 2008, the ESC Board, chaired by Roberto Ferrari, decided to support the development of a semantic search engine that would be able to search for information on the ESC Central website and also on the websites of all six Associations (EHRA, EACVI [formerly EAE], EAPCI, HFA,

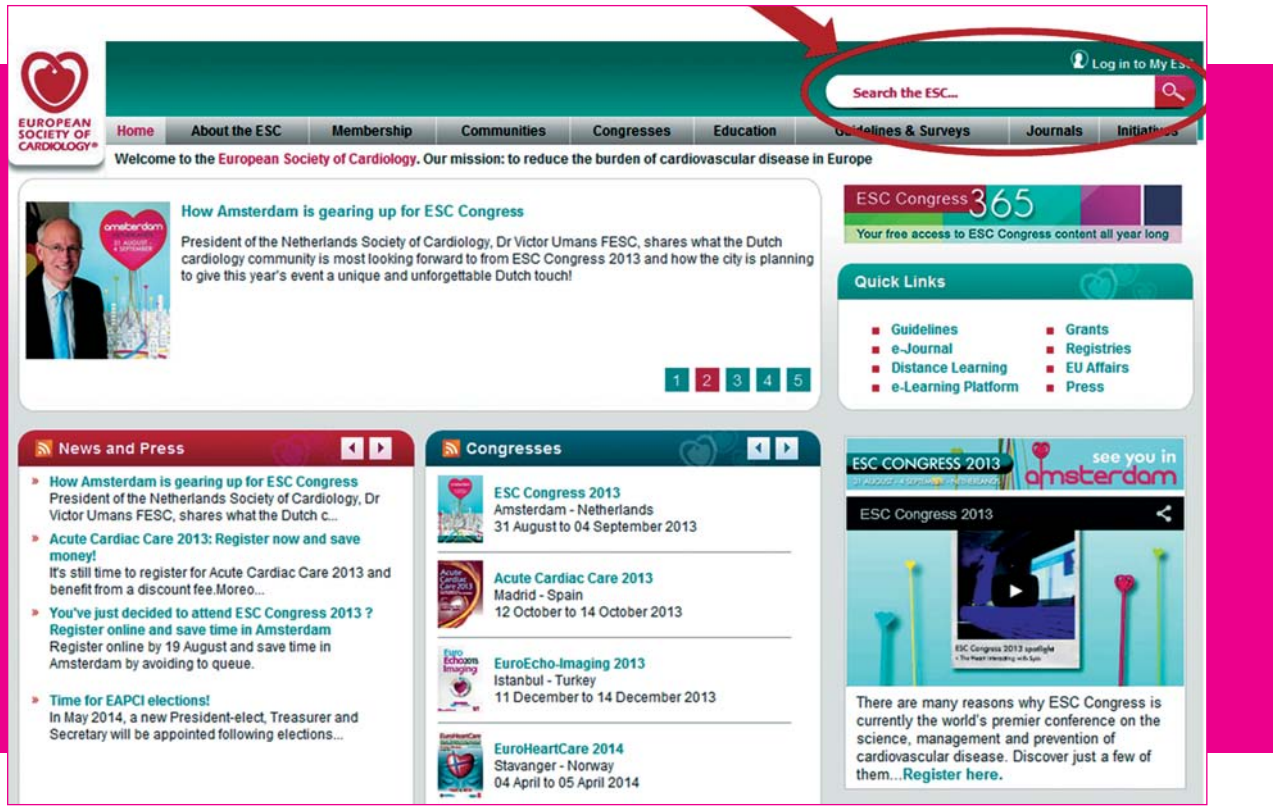

Figure 1. *European Society of Cardiology (ESC) website landing page. The search engine box is located at the top right hand side of the screen (arrow).*

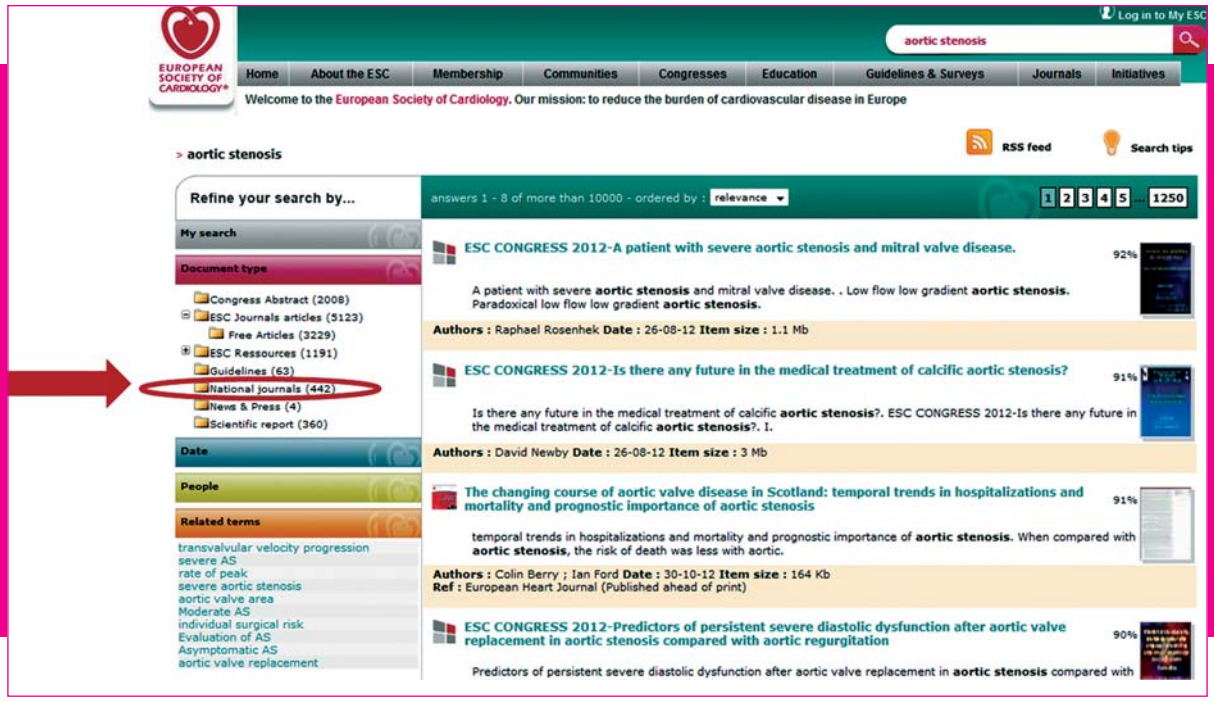

Figure 2. *Results page with relevant information about the documents found. On the left, there is a toolbar with a filtering system to refine the search.*

se temeljila na prethodno prijavljenoj potrebi da se korisniku na brz i jednostavan način osiguraju informacije iz stotine tisuća dokumenata dostupnih na svim ovim web stranicama. Pored toga, ova tražilica ima uvid u sve časopise ESC gdje je moguće dobiti rezultate iz preko 30.000 članaka! Nije iznenađujuće da je ovaj alat veliki uspjeh koji je već druga najposjećenija stranica ESC web stranice sa 49.853 pregleda stranice tijekom listopada i studenoga 2012. godine.[46] Uz pomoć ove tražilice sada je vrlo lako dobiti informacije tako da samo upišete ključne riječi na gornjoj desnoj strani zaslona unutar stranice http://www.escardio.org (**Slika 1**). Rezultat je popis dokumenata u kojima se obrađuje određena tema, a korisnik može odabrati one koje su mu potrebne (**Slika 2**).

Ova stranica s rezultatima sadrži puno informacija i funkcionalnosti. U okviru pregleda dokumenta možete vidjeti kako izgleda dokument (**Slika 2**). Ocjena važnosti dodijeljena ovom dokumentu se također prikazuje u tražilici. Prikazana je i vrsta dokumenta (smjernica, sažetak, slajdovi znanstveno izvješće, novosti, klinički slučaj ili web dokument). Podrijetlo dokumenta se također može lako identificirati na prvi pogled iz malog institucionalnog logotipa koji se također može naći na stranici s rezultatima, upravo ispod ikone koja prikazuje vrstu dokumenta. Također je važno znati dostupnost dokumenta. Simbol lokota se prikazuje kada je za pregled dokumenta potrebna prijava, tako da još uvijek možete vidjeti da resurs postoji, što znači da je njegov pristup samo za članove. Ovaj alat omogućuje da pretraživanje bude obrađeno pomoću filtara lociranih na alatnoj traci s lijeve strane. S ovom trakom korisnik može filtrirati vrstu dokumenta koju je tražio (npr. samo slajdove). Također je moguće filtrirati samo rezultate iz određenog vremenskog razdoblja. Tijekom kongresa, kada se dnevno objavi mnogo sadržaja korisnici mogu filtrirati i odabrati ono što je novo od prethodnog dana, ili samo rezultate gdje je neka osoba citirana. Slične pojmove predlaže tražilica iz ključnih riječi upisanih u zahtjev radi predlaganja drugih srodnih tema koje bi mogle zanimljive. Ako se redovno traži isti pojam korisnik će biti zainteresiran za korištenje funkcije RSS kanala. Svaka stranica

EACPR, ACCA). This idea was based on the previously reported need to provide the user with a quick and easy way of obtaining information from hundreds of thousands of documents available on all these websites. Moreover, this engine is also looking into the ESC journals' family where it is possible to obtain results from more than 30,000 papers! Not surprisingly, this tool is a major success, already being the second most visited page of the ESC website, with 49,853 page views, in October and November of 2012.[46] With the help of this search engine, it is now extremely easy to obtain information by just typing in the keywords on the top right hand side of the screen inside the http://www.escardio.org landing page (**Figure 1**). The result is a list of documents addressing that specific topic, and the user can select the ones required (**Figure 2**).

This results page contains a lot of information and functionalities. Within the document preview, you can see how the document looks (**Figure 2**). The relevance score assigned to this document is also displayed by the search engine. The type of document is also presented (guideline, abstract, slide presentation, scientific report, news, clinical case or a web document). The document origin can also be easily identified at a glance from a small institutional logo that can also be found on the results page, just below the icon showing the type of document. It is also important to know the document's availability. A padlock symbol is displayed when a document is behind a login so that you can still see that the resource exists, meaning that its access is for members only. This tool also allows the search to be refined by using filters located on the toolbar on the left. With this toolbar, the user can filter the type of document looked for (eg, only slides). It is also possible to filter only results from a given time period. During a congress, when a lot of content is published daily, the users can filter for what's new since the previous day, or only the results where a person is cited. Related terms are proposed by the engine from the keywords entered in the request to propose other related topics that could be of interest. If the same term is searched on a regu-

s rezultatom pretraživanja može biti prikazana kao RSS kanal na koju se moguće pretplatiti, a koji pruža redovite najnovije obavijesti o tome što je novog u određenom području.

Vrijeme za uključivanje časopisa nacionalnih kardioloških društava!

Ovaj projekt je već u svojoj poodmakloj fazi, a sada je stiglo vrijeme za ulazak u drugu fazu razvoja kao i uključivanje NSCJ. Odbor ESC pod predsjedanjem Michela Komajde odlučio je podržati razvoj ovog projekta. Mreža urednika pri ESC je također dala entuzijastičan odgovor te je odlučila kontaktirati one NSCJ koje su već objavljeni u elektroničkom obliku i na engleskom jeziku. Neki od njih već imaju značajan čimbenik odjeka. Cilj ove druge faze projekta je povećati vidljivost NSCJ i sukladno tome povećati njihovu čitanost i njihovu razinu referenciranja u drugim međunarodnim časopisima. Osim toga, izvrsno istraživanje koje je provedeno na nacionalnoj razini u mnogim zemljama Europe će postati vidljivo diljem svijeta.

Ovaj novi alat je već dostupan i nakon što upišete ključne riječi, korisnik dobiva dva rezultata: jedan iz dokumenata ESC, a drugi iz NSCJ. Korisnik će paralelno vidjeti oba i lako se premjestiti s jednog rezultata na drugi jednostavnim klikom. Prvi NSCJ su dodani tražilicama, a sada se mogu lako odrediti i odabrati. Prvih pet časopisa su: *Revista Espanola de Cardiologìa, Heart and Blood Vessels* (časopis Kardiološkog društva Srbije), *Hellenic Journal of Cardiology, Egyptian Heart Journal* i *Romanian Journal of Cardiology*. Uskoro će se dodati i *Revista Portuguesa de Cardiologia*. Dogovor je postignut i s Brazilskim kardiološkim društvom, a njegova web stranica sada uključujući ESC tražilicu. Ovo je zanimljiv način da se podigne svijest o ovom vrlo korisnom alatu i omogući brazilskim kardiolozima da imaju bolji pristup znanstvenim resursima. Nema sumnje da će se ovim alatom još više ojačati veze među središta ESC i nacionalnih kardioloških društava, a europska kardiovaskularna znanost će postati vidljivija i dostupnija s bilo kojeg mjesta u svijetu.

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lar basis, the user may be interested in using the RSS feed functionality. Any search result page can be shown as an RSS feed which can be subscribed to, providing regular updates on what's new in the field.

Time to involve the National Cardiac Societies' Journals!

This project is already in its adulthood and the time has now come to enter into a second phase of development and also involve the NSCJs. The ESC Board under Michel Komajda's presidency decided to support the development of this project. The ESC Editors' Network also gave an enthusiastic response and decided to contact those NSCJs that are already published in an electronic format and in English. Some of them already have a significant Impact Factor. The goal of this second phase of the project is to increase the visibility of the NSCJs and, as a consequence, to increase their readership and their level of reference in other international journals. Moreover, the excellent research that is performed at national level in many countries in Europe will become more visible worldwide.

This new tool is already available and, after typing in the keywords, the user gets two results: one from the ESC documents, and a second from the NSCJs. It will be possible for the user to see both in parallel and easily move from one result to the other with a simple click. The first NSCJs have been added to the search results and can now easily be identified and selected. The first five journals are: *Revista Espanola de Cardiologìa, Heart and Blood Vessels* (journal of the Cardiology Society of Serbia), *Hellenic Journal of Cardiology, Egyptian Heart Journal* and *Romanian Journal of Cardiology*. The *Revista Portuguesa de Cardiologia* is soon to be added. An arrangement has been made with the Brazilian Society of Cardiology, and its website is now including our search engine. This is an interesting way to raise awareness about this very useful tool and allow Brazilian cardiologists to have better access to our scientific resources. There is no doubt that providing this tool will strengthen even further the bonds between the ESC Central and the National Cardiac Societies, and European cardiovascular science will become more visible and readily accessible from any place in the world.

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Poseban članak / Special article

Championing cardiovascular health innovation in Europe

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Introduction

The Cardiovascular Round Table (CRT)[1] is an independent forum established by the European Society of Cardiology to facilitate the exchange of scientific knowledge between cardiologists and representatives of the pharmaceutical and medical device industries. Its purpose is to provide a non-commercial environment within which experts can freely discuss future issues in cardiovascular medicine and consider the merits of newdiagnostics and treatment techniques.

The CRT is concerned that a new epidemic of cardiovascular disease (CVD) is gaining ground in Europe as a result of the growing prevalence of metabolic disorders such as obesity and diabetes, and comes at a time when support for innovation in cardiovascular medicine is waning. The epidemic represents a massive challenge in terms of managing avoidable disease and death, but it is also a huge opportunity for EU universities, companies, and healthcare providers to be at the forefront of a global response.

A combination of innovation and prevention education campaigns is clearly needed. Investment to develop new treatments to combat the epidemic is, however, under threat from falling margins, particularly in the pharmaceutical sector. Increased regulation, high development costs, and slow time-to-market are all cited as reasons, and the consequence is a clear shift in R&D focus to other geographical regions and medical areas likely to yield better returns.

This scenario will result in Europe's healthcare systems facing spiralling cost increases, while patients may not receive appropriate diagnosis and treatment. Europe could lose its leading position in cardiovascular-related research, science, and manufacturing just when emerging economies will have most need to pay for innovation.

Without decisive action, the CRT forecasts far-reaching social and economic consequences for Europe as the new epidemic takes hold. Already a major drain on national budgets, the outlook is likely to worsen considerably if left unchecked. Cardiovascular conditions currently account for over 10% of total healthcare expenditure across Europe and cause significant lost productivity through workplace absence. The social impact of disability, hospitalization, informal care arrangements, and premature deaths on family units cannot be measured but will inevitably have a major negative impact.

A sustained period of reduced investment could also precipitate a rapid decline in Europe's cardiovascular innovation and pharmaceutical industry, and lower its scientific and commercial influence. At risk is the major direct and indirect contribution[2] to the European economy, export performance, and employment. Such a scenario would also damage Europe's ability to respond to the inevitable increase in global demand for new CVD treatments, drugs, and techniques. In making these predictions, the CRT does not seek to be alarmist. Its membership enjoys a unique perspective of the challenges to innovation from across the complete cardiovascular spectrum and lifecycle. The CRT's objective in writing this article is to raise the profile of patient needs and ensure that due consideration is given to closing the innovation gap.

While this article does not specifically address prevention education, the CRT firmly endorses the potential forawareness campaigns. These play a major role in influencing the lifestyle choices that lower risk exposure to CVD and metabolic conditions. The power of prevention strategies was well demonstrated by a study[3] of the North Karelia region of Finland in which communications were integrated with primary healthcare alongside collaboration fromthe food industry. Over 25 years, male deaths from CVD reduced by 68%.

Background

Every year, 4.3 million Europeans die[4] from the effects of CVD, while treatment and related costs are estimated at €196 billion/annum. It remains Europe's leading killer despite scientific advances that have arrested — and even reversed — the steep year-on-year mortality increase that used to characterize CVD statistics.[5] By any measure, the global fight against CVD has been very successful. Re-

[†]CRT member organizations are Abbot Vascular, Astra Zeneca, Bayer Healthcare, Boehringer-Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, F.Hoffmann-La Roche, Medtronic, Merck, Novartis Pharma, Pfizer, Philips Medical Systems, Sanofi, Servier International, Siemens, St Jude Medical.

search from the USA[6] has shown that, of the 6-year increase in life expectancy between 1970 and 2000, -65% of the increase — or almost 4 full years — is due to reductions in CVD mortality alone. As positive as this scenario is, CVD remains by far the leading cause of death and the new epidemic has the potential to threaten the advances made to date. The same US research shows that increased life expectancy due to improved cancer therapies is only — 3 months (**Figure 1**).

Many of the advances originated in Europe, the result of sustained R&D innovation and cooperation between academics, cardiologists, scientists, and industry. Notable among them have been the following:

- diagnostic imaging tools including radiology and cardiovascular ultrasound;
- new interventional procedures for arrhythmias and coronary artery disease;
- development and exploitation of drug families including ACE inhibitors, statins, beta-blockers, ARBs, and antithrombotic/thrombolytic agents;
- better understanding of CVD risk factors.

Now, however, Europe is facing a series of emerging trends related to cardiovascular health that could threaten to overwhelm healthcare systems. The rapidly ageing European population is a factor that creates significant problems with many long-term implications. By 2050, the number of people over 50 will rise by 35% and over 85 by 300%. Even if the current rates of diseases in these age groups remain static, many millions more Europeans will suffer from CVD.

There has been a dramatic rise in the detection of cardio-metabolic disorders such as diabetes, while obesity is also a major concern.[7] The International Diabetes Federation reports that over 50 million adults in the EU have diabetes[8] and that this number will grow to 64 million by 2030. Other research suggests that 66% of these will die from heart disease or stroke.[9] Recent work by the Chronic Diseases Collaborating Group[10] asserts that, globally, one in nine adults has a measured body mass index 30 kg/m^2, while the International Association for the Study of Obesity (IASO) states that adult obesity rates in some EU27 countries exceeds 23%.[11] The incidence of atherosclerosis related CVD is expected to accelerate and adverse lifestyle factors such as poor exercise regimes, high fat and sugar diets, and alcohol and tobacco consumption continue to present major risks, especially in the younger population.

Against this backdrop, it is not surprising that an increase in the number of European deaths from CVD and cardio-metabolic disorders is forecast.[12] According to the WHO, CVD and diabetes accounted for over 50% of all global deaths from non-communicable diseases worldwide in 2008 and 30% of all deaths, while the global cost of treatment over the next 20 years has been estimated at a staggering $24 trillion (**Figure 2**).[12]

To illustrate the scale of the epidemic faced by Europe,we can look at forecasts made in the USA. The American Heart Association (AHA) warned in a recent Policy Statement that, by 2030, over 40% of the US population will have at least one form of CVD.[13] This deeply concerning statistic has profound health and socio-economic implications for Europe, and clearly demonstrates a compelling need for R&D to come up with new treatment strategies and products that support those strategies alongside, of course, prevention education.

Having noted the trends, and the difficulties in sustaining improved cardiovascular health levels, cardiologists have identified a number of key areas in which additional R&D is urgently required:

- treatment of chronic and acute heart failure, especially when associated with preserved ejection fraction;
- prevention and treatment of cardio-metabolic diseases;

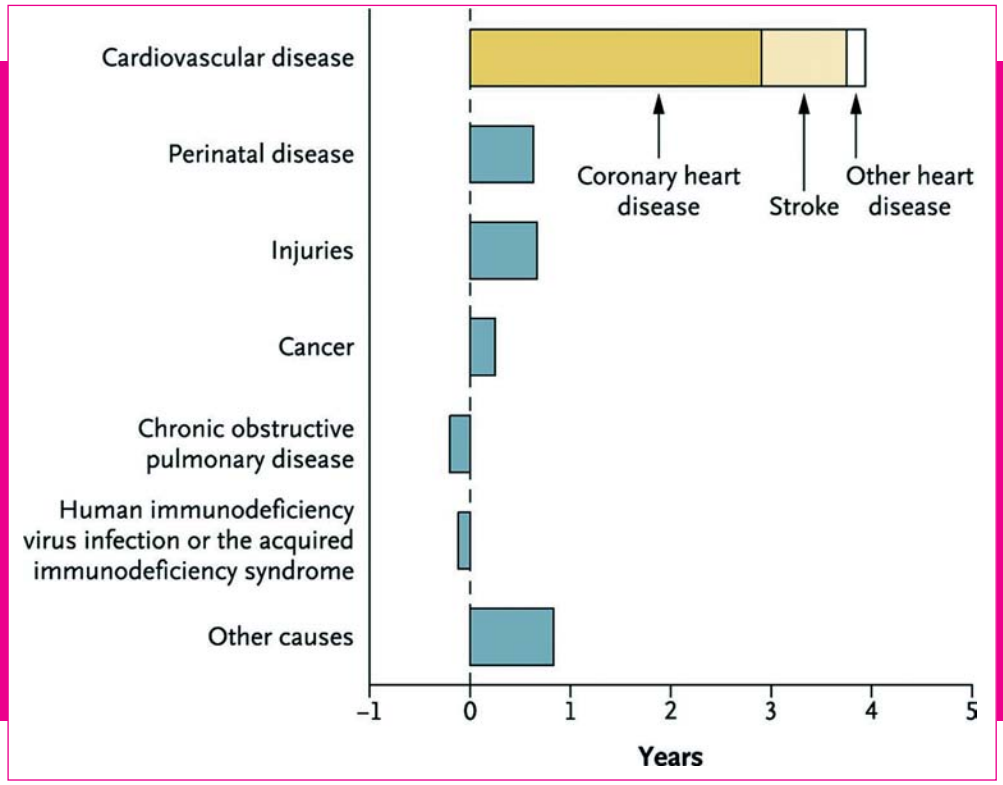

Figure 1. *Cumulative contribution to life expectancy increase, 1970-2000.*

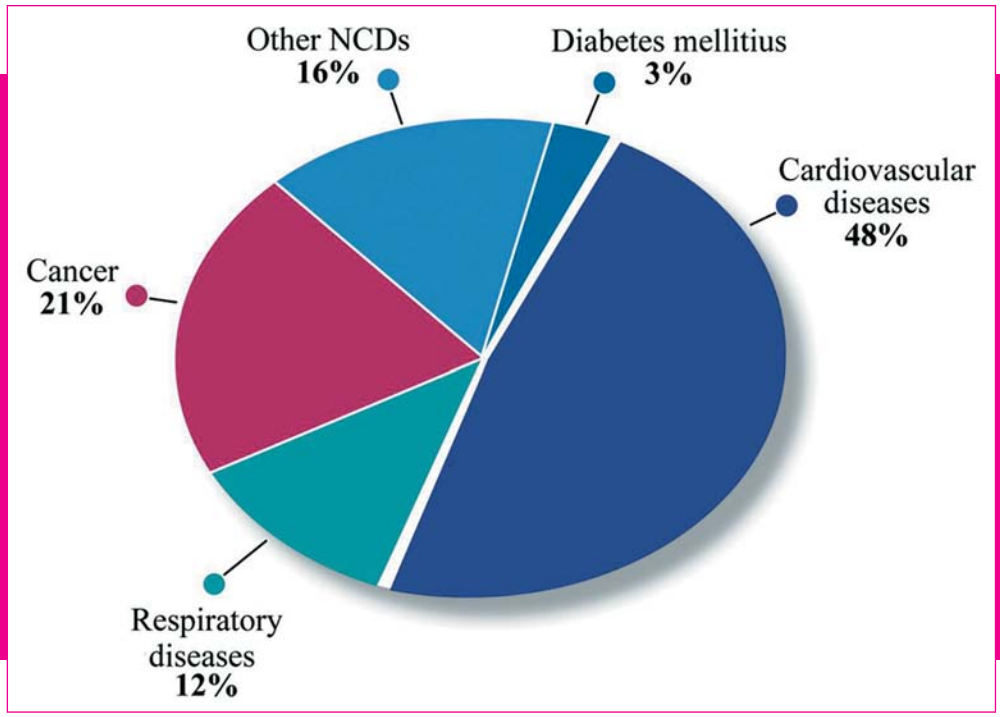

Figure 2. *Global distribution of deaths from non-communicable diseases (NCDs).*

- treatment of arrhythmias, especially related to atrial fibrillation for which there is 25% prevalence in the 80+ population;
- development of more effective and safer anti-thrombotic and antiatheroma drugs.

It is therefore worrying to observe that, when innovation is most needed, and indeed when the likelihood of future export opportunities is highest, R&D activity in Europe appears to be stagnating. The CRT contends that European R&D activity should be an absolute priority at least as long as cardiovascular disorders remain a leading cause of avoidable death.

The innovation landscape

Cardiovascular-related innovation in Europe is characterized by reductions in pharmaceutical R&D productivity and strong evidence that CVD is no longer regarded as a priority area. Research carried out by Thomson Reuters suggests that global pharmaceutical R&D investment has failed to keep pace with sales growth and may have fallen since 2008.[14] Over the period 2000-10, the analysis points to a 20% increase in time-to-market for new drugs with, almost certainly, a consequential increase in development costs. These findings clearly put pressure on those making investment decisions to ensure the best returns (**Figure 3**).

KMR Group, however, takes a different perspective and states that, while global pharmaceutical R&D activity is still rising, it is actually translating into fewer marketable products.[15] Its research indicates that the ratio of new molecular entities (NMEs) at pre-clinical development to those that eventually make it through to product approval has increased from 12:1 (2003-07) to 30:1 (2007-11). This trend is repeated at all stages of development and appears to show a

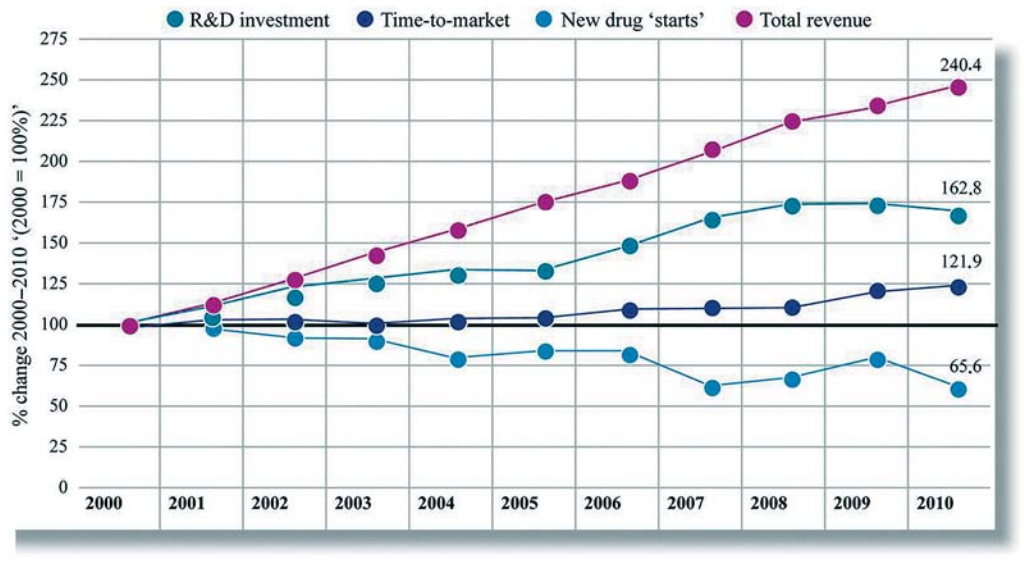

Figure 3. *Changes in pharmaceutical industry productivity 2000-10.*

'kill' policy at the first sign of risk. In terms of cardiovascular innovation, both the WHO and the EU have recognized that R&D activity is insufficient to meet the anticipated need. Yet, analysis by Thomson Reuters[14] (see **Figure 4**) shows that the number of new CVD drug development programmes has dramatically reduced over the last few years and that CVD has not occupied a place in the Top 5 active research areas since 2005.

Europe's R&D investment crisis

The scale of the challenge facing Europe's pharmaceutical companies is shown in recent research[19] by the European Federation of Pharmaceutical Industries Associations (EFPIA). This highlights that out of 5,000 R&D 'starts', just one makes it to product launch while the Economist suggests

Figure 4. *Active research therapeutic areas; 2005-10.*

	2005	2007	2010
Cancer	217	313	312
Infection	76	106	113
Neurological	74	84	85
Gastrointestinal	55	78	66
Endocrine	–	75	57
Cardiovascular	53	–	–

Other research has identified that cardiovascular-related R&D has experienced the biggest contraction in what is a general decline in overall R&D activity.[16] This is reinforced by US data that confirm that, of 2,900 drugs currently in R&D, just 312 are targeted at CVD.[17] Other US research shows the stark contrast between CVD drug development and CVD device development.[18] In the area of valvular heart disease, for instance, there are just two drugs currently in trials, while the pipeline of new devices indicates a total of 20 in trials or awaiting approval (**Figure 5**).

The investment shift onto devices and other medical areas including cancer, infectious diseases, and neurology, although understandable, is nevertheless disturbing given that CVD-related mortality remains the main cause of death, and cardiovascular morbidity is predicted to sharply increase.

that each new drug reaching market will cost an average of €1.3 billion to develop.[20] The decline in European cardiovascular R&D productivity appears more marked than in other jurisdictions. This has been widely attributed to corporate pressure for higher returns on investment (ROI) from development projects in response to rapidly rising development costs driven by changes to European regulatory and clinical trial processes.

In a recent interview, Sir Andrew Witty, Chief Executive of GlaxoSmithKline, highlighted that the European market no longer drives investment decisions in the way it once did.[21] He particularly cited pricing pressure and noted that year-on-year reductions of 6-7% were normal. He added, 'Europe is saying it's not very interested in new products. It doesn't mean we're not going to develop them for Europe but we're

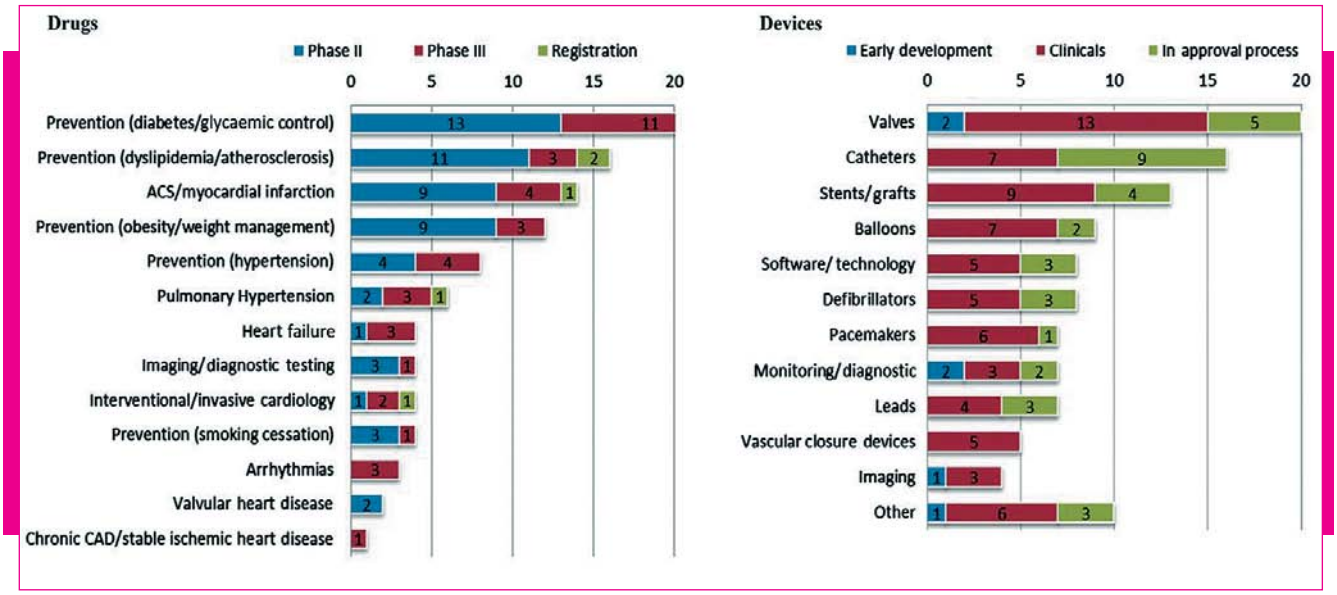

Figure 5. *Pipeline comparison; cardiovascular drugs and devices.*

going to prioritize countries that want to prioritize innovation and that's clearly America, Japan and some of the leading countries in emerging markets.'

European R&D is characterized by high costs due to lengthy timescales and a complex approval process, exacerbated by high wages and operational expenditure.[22] This combination of rising cost and reducing revenues is clearly an unsustainable mix. Although Europe's 2001 Clinical Trials Directive established very high standards of patient safety, it has led to an environment that delays time-to-market and has deterred investment. Analysis shows a 15-25% decrease in the number of clinical trials conducted in Europe between 2007 and 2011.[23] Further evidence of the deteriorating situation is provided by research showing that the number of NME marketing approvals is stagnating.[24]

While reaffirming its total support for patient safety, the CRT welcomes the announcement that the Clinical Trials Directive is to be revised while noting that new procedures will not be ready until at least 2016. It is vital to ensure that overzealous benefit and risk assessments do not delay this important initiative, and that it addresses major imbalances in the scale of patient trials under which oncology drugs can gain approval with far smaller and faster registration programmes than cardiovascular — yet another factor deterring CV-related investment.

Time-to-market is the crucial factor in making investment decisions. With a patent life of 20 years and a typical end-to-end approval process in Europe that can exceed 15 years, there is only a short window to fully exploit intellectual property value. Reducing the process by just 1 year will have profound benefits to ROI and to where R&D investment is committed. The recent closure of mainstream R&D facilities in Europe by companies including Astra Zeneca, Merck, GlaxoSmithKline, Pfizer, and Sanofi is clear evidence of an investment crisis that has to be addressed and a regulatory environment that must be simplified.

Moving beyond the complexity of the regulatory environment, there are other factors which are contributing to the decline in CVD-related innovation in Europe. These include the following:

- Fragmentation on a number of fronts:
  - — each European country imposes unique pricing and reimbursement systems;
  - — research projects by government, academia, scientific bodies, and industry display multiple levels of responsibility;
  - — 'Open' markets encourage cross-border parallel trading.
- Austerity-led cost reduction programmes impact pricing, delay payment terms and increase the commercial risk of supply contracts.
- Costly post-approval regulatory demands affect pharmacovigilance and marketing processes.

Innovation matters

Innovation in Europe flourished because of regulated infrastructure, highly qualified and motivated scientific talent, open markets, and political stability. The European intellect has made significant contributions to techniques and treatments, with many notable achievements.

Innovation matters most, of course, to European patients. Improving the quality of life should, in itself, be the fundamental reason to resolve the innovation gap. However, innovation in cardiovascular R&D also matters to taxpayers. The estimated financial burden of CVD is currently €196 billion annually of which €105 billion is direct healthcare costs, with a further €47 billion assessed as the loss of productivity across the European economy due to sickness and absence and €44 billion as the costs of informal family-based care.

In addition, pharmaceuticals is a strategic industry across Europe. Its economic importance is demonstrated by 2010 estimates[1], which show a trade balance of €70 billion on total exports worth €270 billion, and total employment of 640,000. R&D alone employs 115,000 highly qualified staff, and has an annual budget of €27 billion. This represents 17% of Europe's total business R&D investment across all industrial sectors.

The lack of CVD innovation inevitably has consequences. Shifting the focus of R&D from cardiovascular to other medical areas may well satisfy short-term business imperatives but does nothing to improve CVD morbidity and mortality. Shifting the focus of R&D away from Europe will have a major impact on economic performance, social cohesion, and scientific knowledge.

Despite current concerns, Europe still offers positive advantages as a location for cardiovascular-related R&D:

- established EU-wide processes for quality control and regulatory approval;
- extensive, mobile talent pool including experienced researchers;
- proximity to leading universities with a track record in innovation and fundamental research;
- track record of collaboration between industry and academia;
- access to important data sources;
- EU funding and support for innovation;
- established government research organizations;
- pan-European cooperation.

Recommendations

Stakeholders should urgently come together in a forum to openly discuss the issues raised in this article and allocate actions. As a minimum, the participants should be drawn from the EU, national healthcare authorities, national finance ministries, academia, medical societies, and representatives of the pharmaceutical and medical device industries. The agenda needs to focus on the following:

- to undertake a review of the issues that are driving R&D investment to other jurisdictions;
- to develop and implement a strategic plan that reverses the decline in cardiovascular-related R&D in Europe;
- to simplify the clinical trials environment for new CV drugs and devices;
- to better target EU funding and investment through, for instance, tax incentives and sponsored development programmes;
- to encourage Europe's pharmaceutical industry to develop the necessary drugs;
- to consolidate and extend Europe's proven scientific leadership and successful track record;

- to review patent duration in the context of development timescales and scale of investment;
- to encourage cross-border and cross-discipline collaboration and networking;
- to improve communications between professional cardiovascular and cardio-metabolic communities and the pharmaceutical industry on one side, and patients on the other.

Call to action

The CRT invites:

- EU institutions and national governments to commit to steps that establish a more favourable environment for cardiovascular R&D however it is funded.
- EU institutions and national governments to allocate additional public funding to encourage more cardiovascular R&D programmes and respond to the threat to public health.
- policy makers to measure and analyse the cost of inaction compared with the benefits of a vibrant cardiovascular R&D environment.
- policy makers to investigate and propose forward-looking regulatory measures that balance patient safety with a climate for genuine R&D innovation.
- pharmaceutical companies to review the commercial risk environment relating to cardiovascular R&D and reassess investment decisions in light of the potential epidemic.
- cardiologists and scientists to make concerted efforts to identify further needs in CVD, prioritize them, highlight them, and lobby for pre-emptive funding to address the expected increase in NCDs.

These actions, together with aggressive promotion of prevention strategies including lifestyle factor changes, can address the threat of a cardio-metabolic epidemic in Europe.

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Izvorni znanstveni članak / Original scientific paper

Mortalitet i morbiditet od kardiovaskularnih bolesti

Morbidity and mortality from cardiovascular diseases

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SAŽETAK: Prema podacima Svjetske zdravstvene organizacije kardiovaskularne bolesti (KVB) uzrok su smrti 17,3 milijuna ljudi na razini svijeta, odnosno 30% ukupne smrtnosti, a na razini Europe odgovorne su za 47% svih smrti. U Hrvatskoj su također vodeći uzrok smrti s udjelom od 48,3% u ukupnom mortalitetu 2012. godine. Uzrok su smrti u 54,5% umrlih žena i 42,1% umrlih muškaraca. U bolničkom morbiditetu KVB su godinama na prvom ili drugom mjestu po broju hospitalizacija, izmjenjujući se s malignim bolestima. Stope hospitalizacija za KVB rastu s dobi i više su u muškaraca nego u žena u svim dobnim skupinama. Intenzivniji porast bolničkog morbiditeta počinje u dobi iznad 40 godina, desetak godina ranije od porasta smrtnosti. Posljednjih deset godina uočava se kontinuirani trend smanjenja smrtnosti zbog KVB, što je izraženije za cerebrovaskularne bolesti, nego za ishemijsku bolest srca i to osobito za dob od 0 do 64 godine, no one su i dalje vodeći uzrok smrtnosti i pobola.

KLJUČNE RIJEČI: kardiovaskularne bolesti, mortalitet, morbiditet.

SUMMARY: According to the data provided by World Health Organization, the cardiovascular diseases (CVD) are the cause of death of 17.3 million of people at an international level, or 30% of total mortality, whereas they account for 47% of all deaths at the European level. Even in Croatia, they are the major cause of death, accounting for 48.3% of total mortality in 2012. They are the cause of death of 54.5% of dead women and 42.1% of dead men. In hospital morbidity, CVDs have held the first or second place in the number of hospitalizations for years, alternating with malignant diseases. Hospitalization rates for CVD rise with age and are higher in men than in women in all age groups. Intense rise in hospital morbidity begins at the age of 40, ten years earlier than the rise in mortality. The period of the last ten years shows a continuing downward trend in mortality caused by CVD, which is more pronounced for cerebrovascular diseases, than for ischemic heart disease and especially for the age from 0 to 64, but they are still the major cause of mortality and morbidity.

KEYWORDS: cardiovascular diseases, mortality, morbidity.

CITATION: Cardiol Croat. 2013;8(10-11):373-378.

Kardiovaskularne bolesti — globalni javnozdravstveni problem

Kardiovaskularne bolesti (KVB) su vodeće nezarazne bolesti, odgovorne za gotovo polovinu smrtnosti od nezaraznih bolesti. Prema podacima Svjetske zdravstvene organizacije, 2008. godine KVB su bile uzrok smrti 17,3 milijuna ljudi na razini svijeta (30% sveukupne smrtnosti), od toga, 7,3 milijuna smrti od ishemijskih bolesti srca, a 6,2 milijuna od cerebrovaskularnih bolesti. Više od 3 milijuna tih smrti bilo je u dobi do 60 godina. Udio prijevremenih smrti od KVB varira od 4% u visoko dohodovnim zemljama do 42% u nisko dohodovnim zemljama. Procjenjuje se da će do 2030. godine umirati 23,6 milijuna ljudi zbog KVB[1,2]. Prema Svjetskoj kardiološkoj federaciji KVB su odgovorne za 10% opterećenja bolestima izraženo pokazateljem DALYs (u čiji izračun ulaze izgubljene godine života radi prijevremenog umiranja i godine onesposobljenosti uslijed bolesti) u nisko dohodovnim zemljama i za oko 18% DALYs u visoko dohodovnim zemljama[3]. Pokazatelj izgubljene godine života (YLL) zbog

Cardiovascular disease — a global public health problem

Cardiovascular diseases (CVD) are the major non-communicable diseases accountable for nearly a half of deaths from non-communicable diseases. According to the data of the World Health Organization (WHO), in 2008 the CVDs were the cause of death of 17.3 million of people at an international level (30% of all deaths), of whom 7.3 million of deaths were caused by ischemic heart disease and 6.2 million of deaths were caused by cerebrovascular diseases. More than 3 million of these deaths occurred at the age up to 60 years of age. The frequency of premature deaths from CVDs ranges from 4% in high-income countries to 42% in low-income countries. It is estimated that by the year 2030, some 23.6 million of people will die from CVD[1,2]. According to the World Heart Federation, CVD accounts for 10% of burden of diseases expressed by the indicator DALYs (disability adjusted life years — which includes years of life lost due to premature death and disability due to the disease) in low-income countries, and for about 18% of DALYs in high-income countries[3]. The indicator of years of life lost (YLL)

KVB četiri je puta viši u nisko dohodovnim zemljama te dva puta viši u srednje dohodovnim zemljama nego što je to u visoko dohodovnim zemljama[4].

Na razini Europe KVB su odgovorne za nešto više od 4 milijuna smrti godišnje, odnosno 47% svih smrti (52% smrti u žena i 42% smrti u muškaraca), a u zemljama Europske Unije (EU) odgovorne su za 40% smrti (43% smrti u žena i 36% smrti u muškaraca). Prema podacima europske statistike o KVB one su vodeći uzrok smrti u žena u svim zemljama Europe te u muškaraca također, osim u šest zemalja (Francuska, Izrael, Nizozemska, San Marino, Slovenija i Španjolska). Nešto manje od polovine smrti od KVB uzrokovano je ishemijskim bolestima srca u muškaraca i žena, a oko trećine cerebrovaskularnim bolestima u žena i četvrtine u muškaraca. KVB su i vodeći uzrok smrti u dobi do 65 godina na razini Europe (31% smrti u muškaraca i 26% smrti u žena do 65 godine), dok su u zemljama EU na drugom mjestu s udjelom od 22%, iza novotvorina s 36%. Stope smrtnosti od KVB više su u zemljama srednje i istočne Europe, nego u zemljama zapadne, sjeverne i južne Europe. U većini zemalja sjeverne, zapadne i južne Europe mortalitet, incidencija i letalitet od KVB opadaju zadnjih tridesetak godina, dok u nekim zemljama srednje i istočne Europe još uvijek rastu, a u nekima stagniraju i počinju opadati[5].

Epidemiološki prikaz kardiovaskularnih bolesti u Hrvatskoj

U Hrvatskoj su KVB također vodeći uzrok smrti s udjelom od 48,3% u ukupnom mortalitetu 2012. godine. U 2012. godini umrlo je 24.988 osoba od KVB, a od toga 14.133 žena i 10.855 muškarca. One su uzrok smrti u 54,5% umrlih žena i 42,1% umrlih muškaraca. U dobnoj skupini do 65 godina KVB drugi su uzrok smrtnosti s 2.702 umrlih, odnosno udjelom od 26,6% u mortalitetu te dobne skupine. Na prvom mjestu uzrok smrtnosti u toj dobi su maligne bolesti s 4.056 umrlih, odnosno udjelom od 40,0%[6]. U toj dobnoj skupini KVB uzrok su smrti u 21,7% umrlih žena (650 žena) i 28,7% umrlih muškaraca (2.052 muškaraca), što pokazuje da u mlađoj dobi umire više muškaraca, a starijoj dobi više žena od KVB.

Najčešće dijagnostičke podskupine kao uzrok smrti su ishemijske bolesti srca s udjelom od 22,2% (11.464 umrle osobe) i cerebrovaskularne bolesti s udjelom od 14,1% (7.291 umrlih osoba) u ukupnom mortalitetu, zatim slijede srčana

caused by CVD is four times higher in low-income countries, and two times higher in the middle-income countries than in high-income countries[4].

At the European level, CVD accounts for more than 4 million of deaths on an annual basis, or 47% of all deaths (52% of deaths in women and 42% of deaths in men), and in the European Union (EU) states they account for 40% of deaths (43% of deaths in women and 36% of deaths in men). According to the European statistics on CVD, they are the major cause of deaths in women in all European countries and also in men, except in six countries (France, Israel, Netherlands, San Marino, Slovenia and Spain). Slightly less than a half of the deaths from CVDs are caused by ischemic heart diseases in men and women, about one third of deaths is caused by cerebrovascular diseases in women and one quarter of deaths is caused by cerebrovascular diseases in men. CVDs are the major cause of death up to 65 years of age at the European level (31% of deaths in men and 26% of deaths in women up to 65 years of age), while in the EU states they take the second place with a proportion of 22% being ranked behind the neoplasm with a proportion of 36%. The rates of mortality from CVD are higher in the Central and Eastern European countries than in the western, northern and southern European countries. In the most of the northern, western and southern European countries, mortality, incidence and lethality of CVDs have declined over the past thirty years, and in some central and eastern European countries they are still rising, while in some other countries they stagnate and begin to decline[5].

Epidemiological presentation of cardiovascular diseases in Croatia

Even in Croatia, CVD is the major cause of death, accounting for 48.3% of total mortality in 2012. In 2012, 24,988 persons died of CVD of whom 14,133 women and 10,855 men. They are the cause of death of 54.5% of dead women and 42.1% of dead men. In the age group up to 65 years, CVD is the second cause of mortality with 2,702 deaths, or with a frequency of 26.6% in the mortality of this age group. Malignant diseases with 4,056 dead persons, or with a frequency of 40.0% are ranked the first cause of death in this age group.[6] In this age group CVDs are the cause of death in 21.7% of dead women (650 women) and 28.7% of dead men (2,052 men), which shows that more men die at a younger age and more women die from CVD at an older age.

The most common diagnostic subgroups as the cause of death are ischemic heart diseases with a proportion of

Table 1.
10 leading causes of death and their respective shares — total, Croatia 2012.

Source: *Croatian Central Bureau of Statistics, Croatian National Institute of Public Health.*

ICD-10 CODE	DIAGNOSIS	No	%
I20-I25	Ischaemic heart diseases	11.464	22,17
I60-I69	Cerebrovascular diseases	7.291	14,10
C33-C34	Malignant neoplasms of trachea, bronchus and lung	2.790	5,40
C18-C21	Malignant neoplasms of colon, rectum and anus	2.006	3,88
J40-J47	Chronic lower respiratory diseases	1.656	3,20
I50	Heart failure	1.555	3,01
I10-I15	Hypertensive diseases	1.545	2,99
E10-E14	Diabetes mellitus	1.330	2,57
K70,K73-K74	Chronic liver diseases, fibrosis and cirrhosis	1.084	2,10
C50	Malignant neoplasm of breast	1.048	2,03
First 10 causes		31.769	61,44
Total		31.710	—

insuficijencija s 1.555 umrlih osoba (3,0%) i hipertenzija s 1.545 umrlih (3,0%) (**Tablica 1**).

Analiza smrtnosti prema dobi u muškaraca i žena pokazuje da dobno-specifične stope smrtnosti za KVB rastu s dobi i više su u muškaraca nego u žena u svim dobnim skupinama. Intenzivniji porast smrtnosti počinje u dobi iznad 50 godina[7]. U dobi iznad 65 godina bilježi se 89,2% umrlih od KVB (81,1% muškaraca i 95,4% žena). U dobi 40-64 godina je 10,4% umrlih (18,2% muškaraca i 4,4% žena), u dobi 20-39 godina 0,4% (0,7% muškaraca i 0,2% žena) te u dobi 0-19 godina 0,02% umrlih (0,03% muškaraca i 0,02% žena) (**Tablica 2**). Međutim, u izračunu stope smrtnosti po spolu, veća zastupljenost žena u starijim dobnim skupinama, kao i veći broj umrlih žena, rezultira višom ukupnom stopom smrtnosti od KVB u žena nego u muškaraca[5]. Tako je opća stopa smrtnosti od KVB ukupno iznosila u 2012. godini 585,5/100.000, u žena je stopa smrtnosti bila 639,8/100.000, a u muškaraca 527,3/100.000.

22.7% (11,464 dead persons) and cerebrovascular diseases with a proportion of 14.1% (7,291 dead persons) in total mortality, followed by heart failure, with 1,555 dead persons (3.0%) and hypertension with 1,545 dead persons (3.0%) (**Table 1**).

The analysis of mortality by age in men and women shows that age-specific mortality rates for CVD rise with age and are higher in men than in women in all age groups. An intense rise in mortality begins at the age of 50[7]. 89.2% of persons who died of CVD are recorded to be at the age over 65 (81.1% men and 95.4% women). At the age of 40 to 64 there were 10.4% of dead persons (18.2% of men and 4.4% of women), at the age from 20 to 39 there were 0.4% of dead persons (0.7% for men and 0.2% of women) and at the age from 0 to 19 there were 0.02% of dead persons (0.03% of men and 0.02% of women) (**Table 2**). However, in the calculation of mortality rates by gender, the greater representation of women in the older age groups, as well as the increasing number of dead women results in a higher overall mortality rate from CVD in women than in men[5]. Thus, the overall mortality rate from CVD totaled to 585.5/100,000 in 2012, and the mortality rate was 639.8/100,000 in women and the mortality rater was 527.3/100,000 in men.

Table 2.
Cardiovascular diseases mortality by age and sex in Croatia, 2012.

Age group	Total		Male		Female	
	No.	%	No.	%	No.	%
0-19	6	0,02	3	0,03	3	0,02
20-39	97	0,40	72	0,70	25	0,20
40-64	2.599	10,40	1.977	18,20	622	4,40
65+	22.286	89,20	8.803	81,10	13.483	95,40
Total	**24.988**	**100,0**	**10.855**	**100,0**	**14.133**	**100,0**

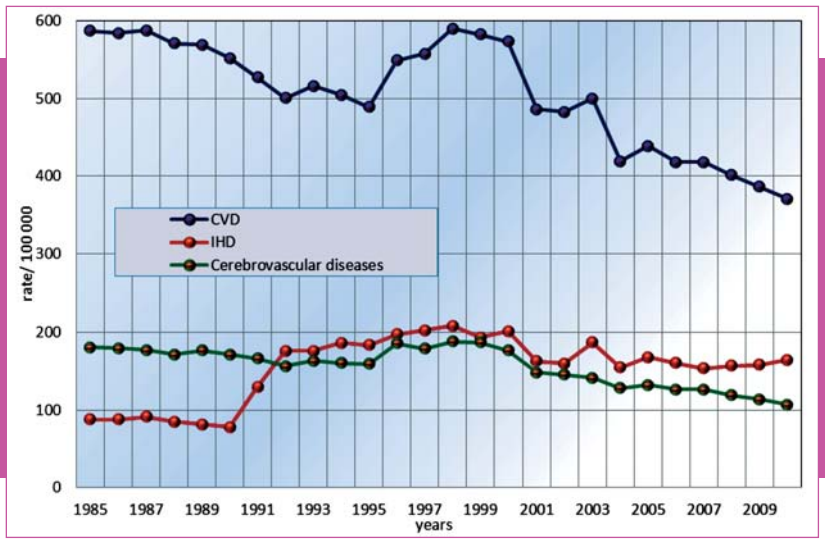
Source: *Croatian Central Bureau of Statistics, Croatian National Institute of Public Health.*

Analizirajući kretanje mortaliteta od KVB uočava se trend smanjenja smrtnosti posljednjih deset godina, što je izraženije za cerebrovaskularne bolesti, nego za ishemijsku bolest srca i to osobito za dob 0-64 godine[8]. Dobno standardizirana stopa smrtnosti od KVB ukupno u Hrvatskoj 2000. godine iznosila je 572,7/100.000, a do 2011. godine pala je na 370,8/100.000, što je pad smrtnosti za 35,6%. Za ishemijsku bolest srca pad smrtnosti u tom razdoblju iznosi 18,3%, a za cerebrovaskularne bolesti 39,4% (**Slika 1**).

Analyzing CVD mortality trends, we have observed the falling mortality trend in the last ten years, which is more pronounced for cerebrovascular diseases than for ischemic heart disease, especially for the age between 0 and 64 years of age[8]. The age standardized mortality rate from CVD in Croatia totaled to 572.7/100,000 in 2000 and by the year 2011, it fell to 370.8/100,000, which is a fall in mortality by 35.6%. For ischemic heart disease, the fall in mortality during this period was 18.3%, and it was 39.4% for cerebrovascular diseases (**Figure 1**).

Figure 1.
Age standardized mortality rates for cardiovascular diseases for all ages in Croatia, 1985-2010.

CVD = cardiovascular diseases, IHD = ishaemic heart disease

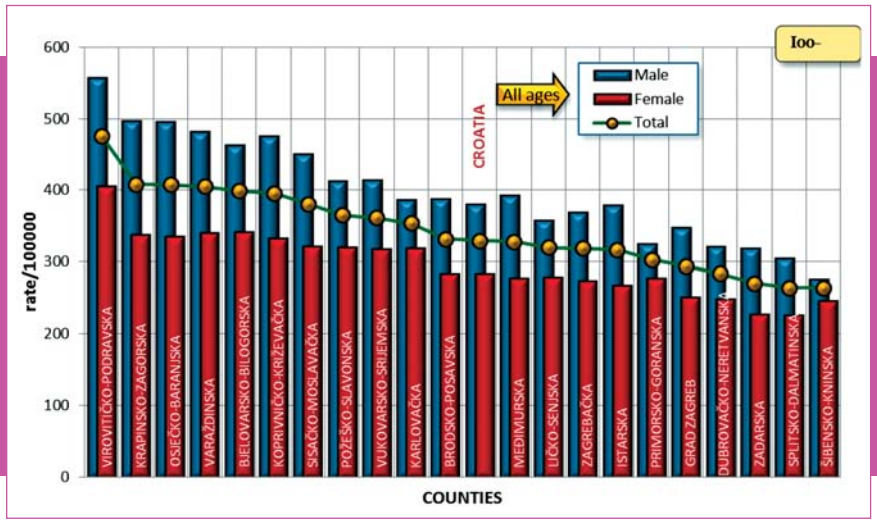


Source: *WHO, Health for All, 2013.*

U dobnoj skupini do 64 godine pad smrtnosti za KVB iznosi 33% u tom razdoblju. Usporedi li se smrtnost od KVB po županijama, dobno-standardizirane stope smrtnosti kreću se u rasponu od najviše 475,4 u Virovitičko-podravskoj županiji do najniže 264,3/100.000 u Šibensko-kninskoj županiji. Uglavnom su stope smrtnosti od KVB više u kontinentalnom dijelu Hrvatske, a niže u priobalnom dijelu Hrvatske, uz izuzetak Grada Zagreba i Međimurske županije koji imaju nižu stopu smrtnosti kao i priobalne županije (**Slika 2**).

In the age group up to 64 years of age, the fall in mortality from CVD is 33% during this period. If we compare the mortality from CVD by counties, the age-standardized mortality rates are in the range of up to 475.4 in the Virovitica-Podravina County of up to the minimum of 264.3/100,000 in the Šibenik-Knin County. Basically the rates of death from CVD are higher in the continental part of Croatia, and lower in the Croatian coastal regions, except for the City of Zagreb and Međimurje County that have the mortality rate as low as in the coastal counties (**Figure 2**).

Figure 2.
Age standardized mortality rates for cardiovascular diseases for all ages in Croatian counties, 2011.



Source: *Croatian Central Bureau of Statistics, Croatian National Institute of Public Health.*

U odnosu na druge europske zemlje Hrvatska sa standardiziranom stopom smrtnosti za KVB od 370,8/100.000 spada među zemlje u Europi koje imaju srednje visoke stope smrtnosti. Prosjek za zemlje EU "stare" članice prije 2004. iznosi 174,6/100.000, za zemlje članice EU koje su pristupile od 2004. godine 428,9/100.000. Susjedna Slovenija ima znatno nižu stopu smrtnosti od kardiovaskularnih bolesti 231,8, a Češka nešto nižu od Hrvatske 344/100.0009. Zemlje Istočne Europe imaju uglavnom više stope smrtnosti od Hrvatske, a zemlje Zapadne i Južne (mediteranske) Europe imaju znatno niže stope smrtnosti od Hrvatske sa stalnim trendom smanjenja.

Compared to the other European countries, Croatia with the standardized mortality rate for CVD of 370.8/100,000 belongs to the countries in Europe that have medium-high mortality rates. The average for the EU "old" member states before the year 2004 is 174.6/100,000, for the EU member states that joined EU after the year 2004 is 428.9/100,000. The neighboring Slovenia has significantly lower mortality rate from cardiovascular diseases, it is 231.8, and the Czech Republic has slightly lower mortality rate than Croatia which is 344/100.0009. The eastern European countries generally have higher rates of mortality than Croatia, and countries of western and southern (Mediterranean) Europe have significantly lower rates of death than Croatia with a continuous downward trend.

Table 3.
Years of life lost (YLL) within age group 1-75 for the leading disease groups on the mortality scale in Croatia, 2011.

Disease group		No. of death	Rate/100 000	YLL
Cardiovascular diseases	**Total**	**24 841**	**579,7**	**67 832,5**
	Male	10 522	509,2	48 522,5
	Female	14 319	645,4	19 310,0
Neoplasms	**Total**	**13 861**	**323,5**	**98 688,0**
	Male	7 973	385,9	60 302,0
	Female	5 888	265,4	38 386,0
Injury	**Total**	**2 767**	**64,6**	**41 788,5**
	Male	1 703	82,4	33 359,5
	Female	1 064	48,0	8 429,0
Diseases of the digestive system	**Total**	**2 314**	**54,0**	**18 385,0**
	Male	1 431	69,3	14 462,5
	Female	883	39,8	3 922,5
Diseases of the respiratoty system	**Total**	**2 052**	**47,9**	**6 332,0**
	Male	1 257	60,8	4 519,5
	Female	795	35,8	1 812,5

Source: *Croatian Central Bureau of Statistics, Croatian National Institute of Public Health.*

Prema broju izgubljenih godina života, pokazatelju prijevremenog umiranja (YLL), KVB su na drugom mjestu iza skupine novotvorina, sa 67.832 izgubljenih godina života te dvostruko većim brojem izgubljenih godina života u muškaraca nego u žena (**Tablica 3**).

U bolničkom morbiditetu KVB su godinama na prvom ili drugom mjestu po broju hospitalizacija, izmjenjujući se s malignim bolestima. U 2011. godini nalazile su se na prvom mjestu po broju hospitalizacija (83.935) s udjelom od 14,2%, od toga su 46,7% hospitalizacije žena i 53,3% hospitalizacije muškaraca. Međutim, analiza prema spolu pokazuje da su u muškaraca KVB na prvom mjestu po broju hospitalizacija s udjelom od 15,5%, a kod žena su na drugom mjestu s udjelom od 12,9%, iza novotvorina čiji je udio 13,7% u ukupnom broju hospitalizacija žena. Ukupna stopa hospitalizacija iznosila je 1.958,9/100.000 stanovnika, u muškaraca 2.165,1/100.000, a u žena 1.766,8/100.000[7]. Analiza bolničkog pobola prema dobi pokazuje da kako u muškaraca tako i žena, stope hospitalizacija za KVB rastu s dobi i više su u muškaraca nego u žena u svim dobnim skupinama. Intenzivniji porast bolničkog pobola počinje u dobi iznad 40 godina. Analizirajući bolnički morbiditet od KVB prema dobi, vidimo da je 62,5% hospitaliziranih u dobi iznad 65 godina (54,8% muškaraca i 71,4% žena). U dobi 35-64 godina je 34,1% hospitaliziranih (41,4% mušaraca i 25,8% žena), u dobi 20-34 godina 2,1% hospitaliziranih (2,2% muškaraca i 1,9% žena) te u dobi 0-19 godina 1,3% hospitaliziranih (1,6% muškaraca i 0,9% žena) (**Tablica 4**). Najčešći uzroci hospitalizacija bile su ishemijska bolest srca s udjelom od 26,5%,(najčešće angina pektoris, infarkt miokarda), podskupina ostali oblici srčane bolesti 26,3% s najčešćom dijagnozom srčane insuficijencije i kardiomiopatije te cerebrovaskularne bolesti s udjelom od 21,5 % u skupini KVB[10].

According to a number of years of life lost which is the indicator of premature mortality (YLL), CVDs take the second place behind the group of neoplasms, with 67,832 years of life lost and twice as many years of life lost in men than in women (**Table 3**).

In hospital morbidity, CVD have held the first or second place in the number of hospitalizations for years, alternating with malignant diseases. In 2011, they took the first place in the number of hospitalizations (83,935) with a proportion of 14.2% of which 46.7% of hospitalizations have been recorded in women and 53.3 % have been recorded in men. However, the analysis by gender shows that CVDs take the first place in men in the number of hospitalizations with a proportion of 15.5%, and among women they take the second place with a proportion of 12.9% followed by neoplasm accounting for 13.7% in the total number of hospitalizations of women. The overall rate of hospitalization was 1,958.9/100,000 inhabitants, in men it was 2,165.1/100,000 and in women it was 1,766.8/100,000[7]. The analysis of hospital morbidity by age shows that both the rates of hospitalization for CVD in men and women rise with age and are higher in men than in women in all age groups. An intense rise in hospital morbidity begins at the age over 40. Analyzing hospital morbidity from CVD by age, we can see that 62.5% of hospitalized patients are aged over 65 (54.8% of men and 71.4% of women). At the age from 35 to 64 there were 34.1% of hospitalized patients (41.4% were men and 25.8% were women), at the age from 20 to 34 there were 2.1% of hospitalized patients (2.2% of men and 1.9% of women) and from the age from 0 to 19 there were 1.3% of hospitalized patients (1.6% of men and 0.9% of women) (**Table 4**). The most common causes of hospitalization were ischemic heart disease with a frequency of 26.5% (usually angina pectoris, myocardial infarction), the subgroup of other forms of cardiac diseases accounting for 26.3% with the most common diagnosis of heart failure and cardiomyopathy and cerebrovascular diseases with a frequency of 21.5% in the group of CVDs[10].

Table 4. *Cardiovascular diseases hospitalizations by age and sex in Croatia, 2011.*

Age group	Total		Male		Female	
	No.	%	No.	%	No.	%
0-19	1.071	1,3	711	1,6	360	0,9
20-34	1.731	2,1	996	2,2	735	1,9
35-64	28 654	34,1	18 526	41,4	10 128	25,8
65+	52 469	62,5	24 500	54,8	27 969	71,4
Unknown	10	0,01	5	0,01	5	0,01
Total	**83 935**	**100,0**	**44 738**	**100,0**	**39 197**	**100,0**

Source: *Croatian National Institute of Public Health.*

Prema broju bolno-opskrbnih dana (broj dana bolničkog liječenja) KVB su na drugom mjestu, iza duševnih bolesti i poremećaja s 864.699 dana bolničkog liječenja, odnosno udjelom od 14%. Vodeće dijagnostičke podskupine unutar grupe KVB prema broju dana bolničkog liječenja su skupina druge srčane bolesti s udjelom od 30,4%, zatim cerebrovaskularne bolesti s udjelom od 26,7%, i ishemijske bolesti srca s udjelom od 22%. Prosječna dužina liječenja za KVB ukupno iznosi 10,3 dana (9,7 za muškarce i 11,0 za žene) i raste s dobi. U dobi 0-19 godina prosječna dužina liječenja je 7,7 dana, a u dobi iznad 65 godina je 11,4 dana i dulja je u žena.

Po broju dijagnoza zabilježenih u općoj/obiteljskoj medicini 2011. godine KVB nalaze se na drugom mjestu s udjelom od 12% iza bolesti dišnog sustava čiji udio je iznosio 15%. Najučestalija dijagnostička podskupina bile su hipertenzivne

According to a number of bed days (the number of days of treatment) the CVDs take the second place, falling behind mental illnesses and disorders with 864,699 days of hospital treatment, or a proportion of 14%. The major diagnostic subgroups within the group of CVDs according to the number of days of hospital treatment are the group of other cardiac diseases with a proportion of 30.4%, followed by cerebrovascular diseases that account for 26.7%, and ischemic heart diseases accounting for 22%. The average length of stay for CVD totals to 10.3 days (9.7 for men and 11.0 for women) and it rises with age. At the age from 0 to 19, the average length of stay was 7.7 days, and at the age over 65 it is 11.4 days and is longer in women.

Judging by the number of diagnoses recorded in the general/family medicine in 2011, the CVDs take the second place

bolesti s udjelom od 57,6% u skupini KVB. Slijedi podskupina druge srčane bolesti (15,7%), ishemijske bolesti (9,8%), bolesti vena (8,1%) te cerebrovaskularne bolesti s udjelom od 4,1% u skupini KVB[11].

Zaključak

Zadnjih desetak godina prisutan je trend smanjenja smrtnosti od KVB u Hrvatskoj, kao što je to već ranije zabilježeno u razvijenim zemljama svijeta, no one su i dalje vodeći uzrok smrtnosti i pobola. Iako u zemljama EU opadaju stope smrtnosti od KVB, raste broj ljudi koji žive s tim bolestima, što je u vezi s dužim očekivanim trajanjem života i boljim preživljenjem ljudi s bolestima srca i krvnih žila, ali i učinkovitijim preventivnim i terapijskim postupcima. Sve to rezultira većom prevalencijom KVB. Imajući u vidu starenje populacije, sveprisutnu globalizaciju i urbanizaciju, socioekonomsku situaciju, visoku prevalencije nekih čimbenika rizika kao što je pretilost i dijabetes, moguće je očekivati sve veće opterećenje KVB, ako se ne poduzmu sveobuhvatne mjere prevencije.

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with a frequency of 12% after respiratory diseases accounting for 15%. The most common diagnostic subgroups were hypertensive diseases with a frequency of 57.6% in the CVD group. They were followed by the subgroup of other cardiac diseases (15.7%), ischemic diseases (9.8%), vascular diseases (8.1%), and cerebrovascular disease with a portion of 4.1 % in the CVD group[11].

Conclusion

During the last ten years have seen a downward trend of mortality from CVDs in Croatia, as it has already been observed in the developed countries internationally, but they are still the major cause of mortality and morbidity. While the rates of mortality decline in the EU countries, the number of people living with such diseases rise. It is associated with better life expectancy and better survival of people with CVDs, but also with more effective preventive and therapeutic procedures. Consequently, we are facing higher prevalence of CVDs. Considering the fact that the population is getting older, considering ubiquitous globalization and urbanization, socio-economic situation, high prevalence of some risk factors such as obesity and diabetes, we can expect a growing burden of CVD, unless some comprehensive preventive measures are taken.

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Suvremeno liječenje arterijske hipertenzije telmisartanom

Contemporary management of hypertension with telmisartan

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SAŽETAK: Telmisartan je dugodjelujući, snažan, vrlo selektivan antagonist AT1 receptora angiotenzina II. Omogućuje precizniju i potpuniju blokadu djelovanja angiotenzina II od ACE inhibitora. Telmisartan je već etabliran kao učinkovit antihipertenzivni lijek s jednokratnim doziranjem koji se primjenjuje kod različitih skupina hipertenzivnih bolesnika. Dobro je podnošljiv i učinkovit antihipertenziv koji nudi potpunu 24-satnu kontrolu arterijskog tlaka čak i u slučaju izostanka doze. Iako je učinkovitost blokatora angiotenzinskih receptora (ARB) potvrđena u različitih tipova bolesnika, telmisartan je trenutno jedini ARB s jasnim dokazima i indikacijom za uporabu za smanjenje rizika od kardiovaskularnih događaja.

KLJUČNE RIJEČI: telmisartan, arterijska hipertenzija, arterijski tlak, antagonisti angiotenzinskih receptora, kardiovaskularne bolesti.

SUMMARY: Telmisartan is long-acting, potent, highly selective angiotensin II subtype 1 (AT1) receptor antagonist. It provides a more specific and complete blockade of the actions of angiotensin II than ACE inhibitors. Telmisartan has already been established as an effective once-daily blood-pressure-lowering drug in different types of patients. It is a well-tolerated and effective antihypertensive therapy, which offers full 24 h control of blood pressure even in the event of a missed dose. Nevertheless that the efficacy of angiotensin receptor blockers (ARBs) in different type of patients were confirmed, telmisartan is currently the only ARB with clear evidence and indication for usage in cardiovascular event risk reduction.

KEYWORDS: telmisartan, hypertension, blood pressure, angiotensin receptor antagonist, cardiovascular disease.

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Renin-angiotenzin sustav ima važnu ulogu u reguliranju kardiovaskularne homeostaze. Angiotenzin II uzrokuje vazokonstrikciju, smanjuje izlučivanje natrija i vode stimuliranjem izlučivanja aldosterona i olakšava simpatičku aktivnost. Svi ovi učinci povećavaju arterijski tlak (AT).

Pojedini blokatori angiotenzinskih receptora (ARB) razlikuju se međusobno u topljivosti lipida, distribuciji, bioraspoloživosti, biotransformaciji, poluživotu plazme i eliminaciji. Svi ovi čimbenici pridonose razlikama u trajanju njihovog djelovanja te utječu na njihove fiziološke rezultate. Telmisartan ima i jedinstvena farmakološka svojstva.[1-3] Vrlo je lipofilan i ima brzu kinetiku propusnosti membrane, što olakšava distribuciju u tkiva. Telmisartan se gotovo u cijelosti razgrađuje u jetri, ne metabolizira se sustavom citokroma P450 i dobro se podnosi kada se koristi u kombinaciji s drugim često korištenim lijekovima. Nije potrebna nikakva prilagodba doze ovisno o spolu, dobi ili bubrežnoj insuficijenciji. Telmisartan se može uzeti neovisno o obroku.[3,4]

Nakon početne brze apsorpcije, telmisartan se polako se eliminira sa prosječnim krajnjim poluživotom eliminacije od približno 24 sata.[5] To je najdulji poluživot među svim ARB do-

The renin-angiotensin system plays an important role in the regulation of cardiovascular homeostasis. Angiotensin II causes vasoconstriction, decreases sodium and water excretion via stimulation of the secretion of aldosterone and facilitates sympathetic activity. All of these effects increase blood pressure.

Differences between angiotensin receptor blockers (ARBs) are responsible for variations in lipid solubility, distribution, bioavailability, biotransformation, plasma half-life and elimination. All of these factors contribute to differences in their duration of action and, therefore, affect their physiological effects. Telmisartan has s unique pharmacological properties.[1-3] It is highly lipophilic and has rapid membrane permeability kinetics. These properties facilitate easy distribution into tissue. Telmisartan is cleared almost entirely by the liver and it is not metabolized by the cytochrome P450 system and is therefore well tolerated when used in combination with other commonly used medications. No dosage adjustment based on gender, age or in case of renal insufficiency is required. Telmisartan can be taken with or without food.[3,4]

After the initial rapid absorption telmisartan is slowly eliminated, with a mean terminal elimination half-life of approximately 24 hours.[5] This is the longest half-life of any of the

stupnim za liječenje arterijske hipertenzije.[3] Korist od dugotrajnog djelovanja telmisartana je očit nakon propuštene doze. Ranojutarnje povišenje vrijednosti AT i 24-satni srednji AT je povezan s oštećenjem ciljnog organa i kardiovaskularnim događajima. Antihipertenzivi bi trebali održavati kontrolu AT, osobito u posljednjih 6 sati intervala doziranja ili ako je doziranje propušteno. Zbog duljeg poluživota, telmisartan pruža neprekidnu i kontinuiranu kontrolu vrijednosti AT. Djelovanje telmisartana preneseno iz prethodne doze nastavlja se i nakon 24-satnog intervala doziranja. Štoviše, telmisartan pruža 48-satnu zaštitu od gubitka kontrole AT usprkos propuštene doze, pruža dodatnu sigurnost za bolesnike koji povremeno moguće zaborave uzeti svoj lijek.[6]

Djelotvornost telmisartana je analizirana je u mnogim kliničkim ispitivanjima u širokom spektru hipertenzivnih bolesnika.[7] Telmisartan do 160 mg jednom dnevno je konstantno smanjivao sistolički arterijski tlak (SAT)u ležećem položaju i dijastolički arterijski tlak (DAT) ($p \geq 0,05$) u većoj mjeri od placeba u najnižoj razini ili tijekom 24-satnog intervala doziranja. Doze iznad 80 mg jednom dnevno nisu rezultirale daljnjim smanjenjem AT u bolesnika s blagom do umjerenom hipertenzijom. Osim placebom kontroliranih ispitivanja, telmisartan je uspoređen s ACE inhibitorima, sartanima, beta-blokatorima i blokatorima kalcijevih kanala. U tim studijama većina bolesnika je liječena od blage do umjerene hipertenzije. Rezultati kliničkih ispitivanja pokazuju da telmisartan obično smanjuje AT nakon prve doze, a postoji postupno povećanje antihipertenzivnog učinka za do 12 tjedana tijekom nastavka liječenja, s najvećim smanjenjem AT koji se dogodi tijekom prva 4 tjedna.[7]

Kao i svi lijekovi iz skupine ARB, telmisartan nema utjecaja na metabolizam bradikinina.[8] Komparativnim kliničkim ispitivanjima s ACE inhibitorima, primjerice s lizinoprilom, pokazalo se usporedivo smanjenje AT. Iako se obje terapije općenito dobro podnose, značajno manji broj liječenih telmisartanom je imao kašalj povezan s lijekovima, u odnosu na lizinopril (3% u odnosu na 7%, $p = 0,018$).[9]

Utjecaj promjene terapije kod bolesnika koji su ranije imali suhi kašalj na ACE inhibitor enalapril u telmisartanu je također pokazao smanjen rizik od kašlja.[10]

Telmisartan je uspoređen s ramiprilom u širokom presjeku bolesnika s povećanim kardiovaskularnim rizikom. U kliničkoj studiji ONTARGET dokazano je da je telmisartan jednako učinkovit kao i ramipril u smanjenju kardiovaskularnih događaja kod različitih skupina rizičnih kardiovaskularnih bolesnika, ali se bolje podnosi.[11]

Telmisartan smanjuje kardiovaskularni rizik ne samo smanjenjem vrijednosti AT, nego i smanjenjem drugih metaboličkih parametara koji imaju blagotvoran učinak na kardiovaskularnu bolest.[12] U terapijskim dozama telmisartan također ima PPAR (peroksisom proliferator aktiviranog receptora) — sposobnost djelovanja, a što se ne može vidjeti s drugim ARB.[3,13] To uzrokuje povoljne učinke na metabolizam glukoze i lipida, a koji bi mogli biti korisni u bolesnika s hipertenzijom i metaboličkim poremećajima.[3,14] Telmisartan je dosad jedini ARB s kliničkim dokazima i indikacijom smanjenja rizika od kardiovaskularnih događaja.[2,15]

U rujnu 2013. Krka se pohvalila svojim ARB portfeljem u Hrvatskoj s novim sartanom, telmisartanom pod nazivom Tolura® u dozama od 40 mg i 80 mg koji pruža fleksibilno i učinkovito liječenje hipertenzije među hrvatskim bolesnicima. Tolura® je indiciran za liječenje hipertenzije i kardiovaskularnu prevenciju — smanjenje kardiovaskularnog pobola u bolesnika s izraženom aterotrombotskom kardiovaskularnom bolešću (anamneza koronarne bolesti srca ili bolesti

ARB available for the treatment of hypertension.[3] The benefit of the long duration of action of telmisartan is apparent after a missed dose. Early morning blood pressure (BP) surge and 24h-mean BP is linked to target-organ damage and cardiovascular events. Antihypertensive agents should sustain BP control, particularly in the last 6 h of the dosing interval or if dosing is missed. Due to its longer half-life, telmisartan provides consistent and sustained control of blood pressure.The activity of telmisartan is carried over from the previous dose and activity persists beyond the 24 h dosing interval. Moreover, telmisartan provides 48 h protection against loss of BP control following a missed dose, providing extra reassurance for patients who might occasionally forget to take their medication.[6]

The efficacy of telmisartan has been evaluated in many clinical trials in broad spectrum of hypertensive patients.[7] Telmisartan up to 160 mg once daily consistently reduced supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) ($p \geq 0.05$) to greater extent than placebo at trough or throughout the 24-hour dosage interval. Dosages above 80 mg once daily did not result in further BP reduction in patients with mild to moderate hypertension In addition to placebo controlled trials, telmisartan has been examined with the ACE inhibitors, the ARBs, the beta-blockers and the calcium channel blockers. In these studies, most patients were treated for mild-to-moderate hypertension. The results of clinical studies show that telmisartan typically reduces BP after the first dose, and there is a gradual increase in its antihypertensive effect for up to 12 weeks during continued treatment, with most of the BP reduction occurring during the first 4 weeks.[7]

Like all ARBs telmisartan has no effect on bradykinin metabolism.[8] Comparative clinical trials with ACE inhibitors, for instance lisinopril showed comparable reduction of BP. Although both treatments were generally well tolerated, significantly fewer patients receiving telmisartan experienced treatment-related cough compared with lisinopril (3% vs. 7%; $p=0.018$).[9]

The impact of switching patients who had previously experienced dry cough with the ACE inhibitor enalapril to telmisartan, also showed reduced risk of cough.[10]

Telmisartan has been compared with ramipril in a broad cross-section of patients at increased cardiovascular risk. In the ONTARGET clinical study it was demonstrated that telmisartan is as effective as ramipril in reducing cardiovascular events in a wide cross-section of at-risk cardiovascular patients, but it was better tolerated.[11]

Telmisartan reduces CV risk not only by reducing the BP, but also by reducing other metabolic parameters which has beneficial effect on CV disease.[12] At the therapeutic doses telmisartan also exerts PPAR (peroxisome proliferator-activated receptor) — activating ability, which cannot be seen with other ARBs.[3,13] This causes favourable effects on glucose and lipid metabolism, which could be benefitial in patients with hypertension and metabolic disturbances.[3,14] Telmisartan is so far the only ARB with clinical evidence and indication of cardiovascular event risk reduction.[2,15]

In September 2013 Krka has complimented its ARBs portfolio in Croatia with a new sartan, telmisartan named Tolura® in dosages of 40 mg and 80mg, providing flexible and effective treatment of hypertension among the Croatian patients. Tolura® is indicated for the treatment of hypertension and cardiovascular prevention — reduction of cardiovascular morbidity in patients with manifest atherothrombotic cardiovascular disease (history of coronary heart disease or pe-

perifernih arterija) ili dijabetesa mellitusa tipa 2 s dokumentiranim oštećenjem ciljnih organa.

ripheral arterial disease) or type 2 diabetes mellitus with documented target organ damage.

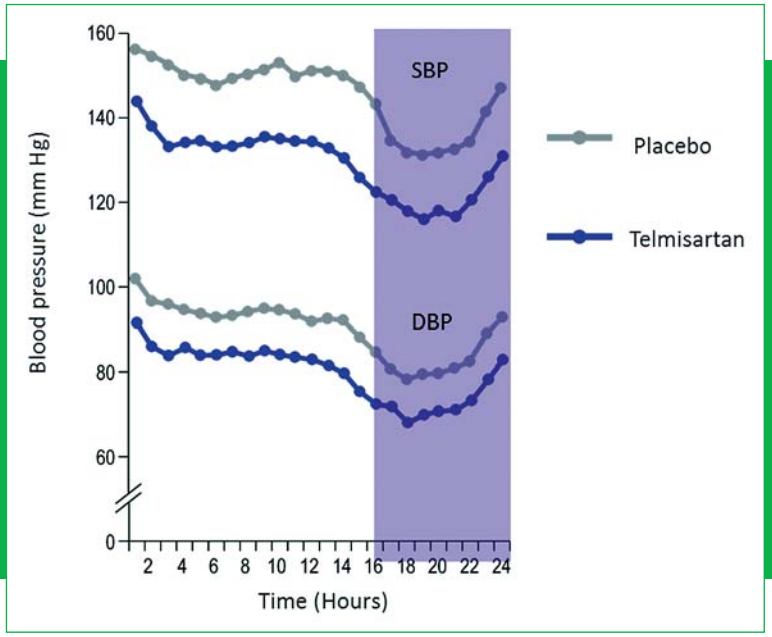

Figure 1.
Mean hourly systolic (SBP) and diastolic (DBP) ambulatory blood pressure after 12 weeks of treatment with telmisartan. Adapted from Lacourciere Y, Lenis J, Orchard J, et al. Blood Pressure. 1998;3:295-302.

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