



## Osvrt na stručni skup „Izvršnost hrvatske hipertenzijologije i kardiologije – odabrane teme“

### Overview of the Expert's Meeting “Excellence in Croatian Hypertensiology and Cardiology – Selected Topics”

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U organizaciji Hrvatskoga kardiološkog društva i Hrvatskoga društva za hipertenziju te pod pokroviteljstvom farmaceutske tvrtke Krka-farme d.o.o. održan je 17. ožujka 2018. u Muzeju suvremene umjetnosti u Zagrebu stručni skup pod nazivom „Izvršnost hrvatske kardiologije i hipertenzijologije – odabrane teme“. Voditelji skupa bili su akademik Davor Miličić i prof. dr. sc. Bojan Jelaković.

Prvi blok predavanja koji se bavio neodgovorenim pitanjima o hipertenziji otvorio je prof. Bojan Jelaković i kritički se osvrnuo na posljednje američke smjernice (AHA/ACC) iz 2017. godine. Prema navedenim smjernicama, postavljene su nove granične vrijednosti koje arterijsku hipertenziju definiraju vrijednostima arterijskog tlaka (AT) višim od 130/80 mmHg. Ova se preporuka dominantno temelji na rezultatima studije SPRINT. Profesor Jelaković upozorava da u interpretaciji rezultata navedene studije treba imati na umu metodološki različito mjerenje AT-a u usporedbi s dosadašnjim istraživanjima. Ovdje se AT mjerio automatiziranim tlakomjerom bez nazočnosti liječnika ili medicinske sestre, a u tom se slučaju ovom metodom očekivano mjere vrijednosti AT-a koje su za prosječno 14/8 – 10 mmHg niže nego mjerenjem tlaka uobičajenim načinom pod nadzorom liječnika ili medicinske sestre. Imajući ovu činjenicu u vidu, pretpostavka je da bi vrijednosti AT-a u studiji SPRINT bile za desetak mmHg više da se mjerilo uobičajenom metodom te bi granične vrijednosti za arterijsku hipertenziju ostale 140/90 mmHg kao i do sada. Ako se pak pridržavamo ovih smjernica, AT bi trebalo mjeriti automatiziranim uređajima bez nadzora liječnika. Ove godine na Europskom kongresu o hipertenziji koji će se održati u lipnju u Barceloni bit će predočene nove smjernice Europskog društva za hipertenziju, a prof. Jelaković nagovijestio je da one neće donijeti ovakve radikalne promjene u dijagnostici arterijske hipertenzije. Nakon ovoga, vrlo zanimljivoga predavanja koje nas je podsjetilo da znanstvene

An experts' meeting entitled *The Excellence of Croatian Cardiology and Hypertensionology – Selected Topics*, organized by the Croatian Cardiac Society and the Croatian Society of Hypertension and sponsored by the pharmaceutical company Krka, was held on March 17<sup>th</sup>, 2018 in the Museum of Contemporary Art in Zagreb. The meeting was led by academician Davor Miličić and Prof. Bojan Jelaković.

The first set of lectures, which focused on the unanswered questions in the field of hypertension, was initiated by Prof. Bojan Jelaković, who critically examined the latest American guidelines (AHA/ACC) from 2017. According to the guidelines, new limit values have been set and arterial hypertension is now defined by blood pressure (BP) values larger than 130/80 mmHg. This recommendation is predominantly based on the results of the SPRINT study. Prof. Jelaković warns that when interpreting the results of this study it is necessary to keep in mind a methodologically different measurement of BP in relation to previous research. Blood pressure was measured by an automated BP gauge without the presence of a physician or a nurse, and in such cases this method produces values of arterial pressure which are, on average, 14/8-10 mmHg lower than when measuring pressure using the usual method under the supervision of a physician or a nurse. With that fact in mind, it can be assumed that the values of BP in the SPRINT study would have been approximately 10 mmHg higher if the usual method had been applied, and the limit values for arterial hypertension would have remained at 140/90 mmHg. However, if we follow these guidelines, arterial pressure should be measured by automated devices without the presence of a physician. The new guidelines of the European Society of Hypertension will be presented at this year's European congress on hypertension, which is to be held in June in Barcelona, and Prof. Jelaković suggested they will not bring about such radical

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članke pa tako i smjernice moramo kritički čitati, slijedilo je predavanje o velikom problemu u liječenju kroničnih nezaraznih bolesti pa tako i hipertenzije – ustrajnosti bolesnika u liječenju koje je održala dr. Jelena Kos. Iako na raspolaganju imamo velik broj odličnih antihipertenziva različitih razreda, postotak adekvatno reguliranih hipertoničara poražavajuće je nizak, i u Hrvatskoj i u svijetu, i iznosi oko 20 %. Određeni broj bolesnika nikada i ne počne uzimati preporučenu terapiju, a od onih koji je započnu s odmakom vremena sve manje ih ustraje u uzimanju propisane terapije. Očekivano, ustrajnost pada kako se broj propisanih lijekova povećava, a osim samog broja tableta na ustrajnost utječe i složenost terapijskoga režima, način doziranja lijekova, bolesnikova percepcija uzimanja lijekova kao dodatnog napora itd. Kako bismo povećali ustrajnost bolesnika, trebali bismo, kad god je to moguće, pojednostavniti terapijske preporuke te trajno raditi na edukaciji bolesnika u suradnji s medicinskim sestrama i ljekarnicima. Sve veću ulogu u povećanju ustrajnosti ima i tehnologija, odnosno raznovrsne metode podsjećanja, kao i aplikacije za „pametne telefone“ koje uključuju bolesnika u sam proces liječenja hipertenzije. Dr. Krešimir Đapić predstavio nam je hrvatsku aplikaciju „Moj tlak“ koja je razvijena u suradnji Hrvatskoga društva za hipertenziju i tvrtke Ericsson Nikola Tesla te je sada u pilot-projektu. Aplikacija će korisnicima omogućiti unos i praćenje kretanja vrijednosti AT-a kroz vrijeme, unos lijekova i doza, podsjećati na vrijeme uzimanja tableta, izračunati ukupan kardiovaskularni rizik, a, osim toga, sadržava brojne edukativne materijale te svakodnevno savjet dana. Očekujemo da će i ova aplikacija bolesnicima koji će se njome koristiti pomoći u boljoj regulaciji AT-a. Dr. Josipa Josipović govorila je o hipertenziji u kroničnih bubrežnih bolesnika. U takvih je bolesnika prevalencija arterijske hipertenzije izrazito visoka i iznosi 60 – 90 %. Ciljne vrijednosti AT-a u kroničnoj bubrežnoj bolesti bez albuminurije iznose <140/90mmHg, dok su u kroničnoj bubrežnoj bolesti s albuminurijom <130/80mmHg. Antihipertenzivi prvog izbora u takvih su bolesnika u ranijim stadijima svakako ACE-inhibitori ili blokatori angiotenzinskih AT-1-receptora, a slijede ih diuretici i blokatori kalcijevih kanala. U idućem je predavanju dr. Ana Jelaković iznijela rezultate studije ESH Stroke o sekundarnoj prevenciji moždanoga udara koja se pod pokroviteljstvom Europskoga društva za hipertenziju provodila u više europskih zemalja od 2009. do 2015. godine, a u Hrvatskoj je ona bila glavni istraživač. Moramo naglasiti kako je, prema broju stanovnika, Hrvatska u tu studiju uključila najveći broj ispitanika. Prema rezultatima te studije, u Hrvatskoj je nakon preboljenoga moždanoga udara 42 % bolesnika otpušteno iz bolnice s neadekvatno reguliranim vrijednostima AT-a, a takve vrijednosti perzistiraju i nakon 6 – 36 mjeseci od samog incidenta. Također, unatoč činjenici da je 80 % bolesnika nakon preboljeloga ishemijskoga moždanoga udara otpušteno sa statinom u terapiji, njih 66 % postiže vrijednosti LDL kolesterola niže od 2,6mmol/L, a tek 26 % niže od 1,8 mmol/L. Na ovakve rezultate s neurološkoga stajališta osvrnuo se i prof. dr. sc. Branko Malojčić koji je naglasio važnost rezultata ove studije prema kojima se Hrvatska ne razlikuje znatno od drugih europskih zemalja, ali prema kojima još ima prostora za napredak u regulaciji arterijske hipertenzije i dislipidemije u sekundarnoj prevenciji moždanoga udara.

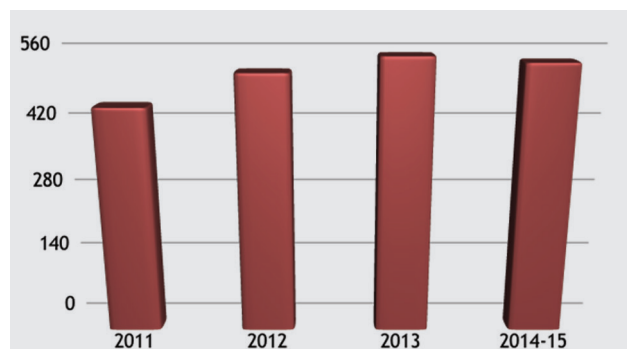
Posljednje predavanje u ovom, hipertenzioškom dijelu bilo je posvećeno mjerenju krutosti velikih krvnih žila. Dr. Tajana Željković Vrkić, koju je kao hipertenzioškinju prepo-

changes in the diagnosis of arterial hypertension. This very interesting presentation, which reminded us of the need to read scientific articles and guidelines with a critical eye, was followed by a lecture on a major problem in the treatment of chronic non-contagious diseases, including hypertension – the perseverance of patients during treatment, held by Dr. Jelena Kos. Although numerous antihypertensive drugs of various classes are available, the percentage of patients suffering from hypertension who adequately regulate their condition is disappointingly low, in Croatia and in the rest of the world, and is approximately 20%. A certain number of patients never even begin their recommended therapies, and the number of those who do take the prescribed medications decreases over time. As expected, perseverance decreases with the increase in the number of prescribed drugs, and apart from the number of pills, perseverance is also affected by the complexity of the therapy, the ways of calculating the dosage of medications, the patient's perception of taking medications as an additional effort, etc. In order to improve a patient's perseverance, we should, whenever possible, simplify the recommendations for the therapy and continually work on the education of patients in cooperation with nurses and pharmacists. An increasingly important role is played by technology and other forms of reminding the patient, such as smartphone applications which include the patient in the process of treating hypertension. Dr. Krešimir Đapić presented *My Pressure*, a Croatian application developed through the cooperation of the Croatian Society of Hypertension and Ericsson Nikola Tesla, which is currently a part of a pilot project. The application will enable users to record and follow changes in BP over time, record medications and dosages, remind patients to take their pills and calculate the total cardiovascular risk, while also containing numerous educational materials and providing daily advice. We expect this application to help patients better regulate their BP. Dr. Josipa Josipović spoke about arterial hypertension in chronic renal patients. In such patients the prevalence of arterial hypertension is extremely high, from 60% to 90%. The target values of BP in chronic kidney disease without albuminuria are <140/90mmHg, while in chronic kidney disease with albuminuria they are <130/80mmHg. Antihypertensive drugs of first choice in such patients in earlier stages are certainly ACE-inhibitors or angiotensin AT-1 receptor blockers, followed by diuretics and calcium channel blockers. In the next lecture, Dr. Ana Jelaković presented the results of the ESH Stroke study on secondary prevention of stroke, which was conducted in several European countries between 2009 and 2015 under the sponsorship of the European Society of Hypertension. Dr. Jelaković was the main researcher on the study conducted in Croatia. It must be pointed out that, according to the number of citizens, Croatia included the largest number of examinees in the study. According to the results of the study, after recovering from a stroke, 42% of patients in Croatia were released from hospitals with inadequately regulated values of BP, and such values persist even after 6-36 months from the event itself. Also, despite the fact that after recovering from an ischemic stroke 80% of patients were discharged with statin therapy, 66% of them reach values of LDL cholesterol lower than 2.6 mmol/L, and only 26% lower than 1.8 mmol/L. These results were examined from a neurological standpoint by Prof. Branko Malojčić, who emphasized their importance and said that, according to them, Croatia does not differ significantly from other European countries, but there is room for

znalo Europsko društvo za hipertenziju kao specijalicu hipertenzije, podsjetila nas je da je krutost arterija pokazatelj oštećenja ciljnih organa i neovisan čimbenik rizika za kardiovaskularni morbiditet i mortalitet. Najčešće se krutost arterija procjenjuje mjerenjem brzine pulsno vala, što je jednostavna, reproducibilna i praktična metoda koja bi trebala biti zastupljenija u kliničkoj praksi. Mjerenje krutosti velikih krvnih žila pridonosi boljoj procjeni ukupnoga kardiovaskularnog rizika i prema recentnim smjernicama i tom se metodom treba koristiti uvijek kada je to moguće.

U nastavku je slijedilo predstavljanje lijeka Co-Dalneva farmaceutske tvrtke Krka-farme d.o.o. Co-Dalneva je fiksna trojna kombinacija perindopрила, amlodipina i indapamida, predstavnika triju najčešćih propisanih skupina antihipertenziva. Dostupnost još jedne fiksne trojne kombinacije na našem tržištu svakako je dobrodošla ako se ima u vidu sve prije rečeno o potrebi bolje regulacije naših hipertoničara, kao i jednostavnijih terapijskih režima sa svrhom poboljšanja ustrajnosti bolesnika.

U kardiološkom dijelu simpozija predstavljena su hrvatska iskustva u pogledu liječenja triju ključnih kardijalnih entiteta – akutnog infarkta miokarda (AIM), aritmija i srčanog zatajivanja. Kad je o infarktu miokarda riječ, valja napomenuti kako je ishemijska bolest srca vodeći pojedinačni uzrok smrti u svijetu pa tako i u Hrvatskoj<sup>1</sup>. Zadnjih desetljeća bilježi se tendencija smanjenja smrtnosti bolesnika s AIM koje je rezultat prije svega napretka u primjeni primarne koronarne perkutane intervencije (pPCI) kao vodećega terapijskog sredstva u liječenju ove skupine bolesnika. Tako ukupni unutarbolnički mortalitet bolesnika liječenih zbog akutnog infarkta miokarda s elevacijom ST-segmenta (STEMI) u europskim zemljama iznosi 3 – 10 %, dok je u skupini bolesnika liječenih pPCI-jem on mnogo niži i iznosi 2,2 – 6,1 %<sup>2</sup>. Mortalitet bolesnika liječenih zbog STEMI-ja u Hrvatskoj nalazi se unutar navedenoga europskog prosjeka i iznosi 4,4 – 6,3 %<sup>3</sup>. Hrvatska je, iako s mnogo ograničenijim financijskim sredstvima u usporedbi s drugim europskim zemljama, od samog početka pratila trendove i osnovala mrežu kardioloških centara primarne koronarne intervencije. Tako se posljednjih godina unutar mreže zbrinjava 540 – 550 bolesnika s akutnim STEMI-jem na milijun stanovnika (**Slika 1**), što svakako našu zemlju svrstava uz bok vodećih europskih zemalja<sup>3</sup>. Zahvaljujući uložnim velikim naporima Radne skupine za akutni koronarni sindrom



**FIGURE 1.** Total number of patients with ST-elevation myocardial infarction in Croatia treated with primary percutaneous coronary intervention per 1 million population per year.

improvement in the regulation of arterial hypertension and dyslipidaemia in secondary prevention of stroke.

The final lecture in this part on hypertensionology was dedicated to measuring the stiffness of major blood vessels. Dr. Tatjana Željковиć Vrkić, who has been recognized as a hypertensionologist by the European Society of Hypertension, reminded us that the stiffness of arteries is a marker of damage in target organs and an independent risk factor for cardiovascular morbidity and mortality. Arterial stiffness is most commonly evaluated by measuring pulse wave velocity, which is a simple, reproducible, and practical method which should be used more in clinical practice. Measuring arterial stiffness contributes to a better evaluation of total cardiovascular risk and, according to recent guidelines, this method should be used whenever possible.

The next part contained a presentation of Co-Dalneva, a medication by the pharmaceutical company Krka. Co-Dalneva is a fixed triple combination of perindopril, amlodipine, and indapamide, a representative of three most commonly prescribed groups of antihypertensives. The availability of another fixed triple combination on our market is certainly welcome if we consider all that has been said on the need for a better regulation of our patients suffering from hypertension, as well as for simpler therapies with the goal of improving patient perseverance.

The cardiological part of the symposium included presentations of Croatian experiences regarding the treatment of three key cardiac entities – acute myocardial infarction, arrhythmia, and heart failure. Regarding myocardial infarction, it is necessary to point out that ischemic heart disease is the leading cause of death in the world, including Croatia<sup>1</sup>. In the last few decades there has been a reduction in the mortality of patients with acute myocardial infarction, which is primarily a result of the advancements in the use of primary percutaneous coronary intervention (pPCI) as a leading form of therapy in the treatment of such patients. Therefore, the total in-hospital mortality of patients treated for acute ST-elevation myocardial infarction (STEMI) in European countries is 3-10%, while in the group of patients with pPCI it is significantly lower and comes to 2.2-6.1%<sup>2</sup>. The mortality of patients treated for STEMI in Croatia is within the aforementioned European average and comes to 4.4-6.3%<sup>3</sup>. Although significantly financially constrained in comparison to other European countries, Croatia has been following trends from the very beginning and has started a network of cardiological centres for primary coronary intervention. In the last few years, 540-550 patients with acute STEMI per million population (**Figure 1**) have been treated within the network, which positions our country alongside leading European countries<sup>3</sup>. As a result of major efforts on the part of the Working Group for Acute Coronary Syndrome and the Working Group for Interventional Cardiology of the Croatian Cardiac Society, a prospective national Registry of invasive and intervention cardiology – STENOS was formed at the end of 2016, enabling direct monitoring of a large amount of data concerning the treatment of patients with acute coronary syndrome in Croatia.

It is certainly necessary to point out that contemporary treatment of patients with acute non-ST segment elevation myocardial infarction (NSTEMI), based on contemporary guidelines, also includes timely and early percutaneous coronary revascularization. Therefore, it is very important to

i Radne skupine za intervencijsku kardiologiju Hrvatskoga kardiološkog društva potkraj 2016. godine formiran je i prospektivni nacionalni Registar invazivne i intervencijske kardiologije – STENOS, koji je omogućio izravno praćenje niza podataka o liječenju bolesnika s akutnim koronarnim sindromom u Hrvatskoj.

Svakako je potrebno napomenuti da i suvremeno zbrinjavanje bolesnika s akutnim infarktom miokarda bez elevacije ST-segmenta (NSTEMI), na temelju suvremenih smjernica, uključuje jednako tako pravodobnu i ranu perkutanu koronarnu revaskularizaciju. Zbog navedenog je napose važno prepoznavanje skupine bolesnika visokog rizika kojima je ovaj oblik liječenja nužno osigurati što ranije (unutar 2 sata od postavljanja dijagnoze) jednako kao što je to slučaj i s bolesnicima sa STEMI-jem bolesnicima. Riječ je o bolesnicima koji su hemodinamski nestabilni, koji imaju kontinuirane i/ili rekurentne stenokardije refraktorne na medikamentnu terapiju, koji su ritmološki ugroženi, imaju znakove srčanog zatajavanja ili mehaničke komplikacije infarkta<sup>4</sup>. Prema takvim bolesnicima nužno je postupati kao da je riječ o bolesnicima sa STEMI-jem te im osigurati žurnu koronarografiju s mogućnošću pPCI-ja.

Neovisno o potrebi daljnjih ulaganja ljudskih i financijskih resursa u razvoj mreže primarne perkutane koronarne intervencije ne smijemo zaboraviti ni na nužnost suvremenoga farmakološkog liječenja. Kako je temelj farmakološkog liječenja ove skupine bolesnika primjena dvojne antiagregacijske terapije (tikagrelor/prasugrel uz acetilsalicilatnu kiselinu), posebno valja naglasiti činjenicu da je bolesnicima sa STEMI-jem u Republici Hrvatskoj dostupno liječenje tikagrelorom bez naknade tijekom 12 mjeseci nakon pPCI-ja, a od 1. ožujka 2018. lijek tikagrelor uključen u Osnovnu listu lijekova Hrvatskog zavoda za zdravstveno osiguranje i za liječenje visokorizičnih bolesnika s NSTEMI-jem. Glede primjene dvojne antiagregacijske terapije, postoje jasne smjernice o vrsti i duljini primjene odgovarajućih lijekova. Iako je tikagrelor uz asetilsalicilatnu kiselinu osnova modernog liječenja, s obzirom na dostupnost i cijenu, klopidogrel je i dalje jedan od najpropisivanijih antiagregacijskih lijekova u svijetu pa tako i u nas. Budući da je klopidogrel lijek koji se tek nakon ulaska u organizam prevodi u aktivni metabolit procesima u jetri, poznat je i opisan njegov oslabljeni učinak u određene skupine bolesnika determiniran oslabljenim procesom aktivacije lijeka. Upravo zbog toga su u kliničku uporabu uvedene laboratorijske metode određivanja stupnja trombocitne aktivnosti u uzorku krvi bolesnika. Napominjemo kako smjernice ne preporučuju rutinsko određivanje reaktivnosti trombocita, odnosno kvantificiranje stupnja inhibicije trombocita uvjetovana primjenom antiagregacijskih lijekova, ali omogućuju primjenu navedenih testova u selekcioniranih bolesnika<sup>5</sup>. Na tom je tragu formiran i projekt Hrvatske zaklade za znanost koji ispituje aktivnost trombocita mjerenjem agregabilnosti krvi u bolesnika liječenih antiagregacijskim lijekovima u različitim indikacijama, a napose onih s AIM. Tako je dosadašnjim istraživanjima u sklopu spomenutog projekta dokazano kako se upravo prilagodbom doze klopidogrela u bolesnika s izmjerenom povišenom ostatnom aktivnošću trombocita uz standardnu dozu klopidogrela mogu poboljšati klinički ishodi, što potvrđuje činjenicu da su u navedenom segmentu potrebna dodatna istraživanja sa svrhom utvrđivanja optimalne strategije liječenja bolesnika s AIM<sup>6</sup>.

identify high-risk patients who must be provided this form of treatment as early as possible (within 2 hours from diagnosis) just like in the case of STEMI patients. Such patients are hemodynamically unstable, have continued and/or recurrent stenocardia refractory to drug treatment, are at arrhythmologic risk, show signs of heart failure or mechanical complications of infarction<sup>4</sup>. Such patients should be treated as though they were patients with STEMI and provide them with an immediate coronarography with the possibility of pPCI.

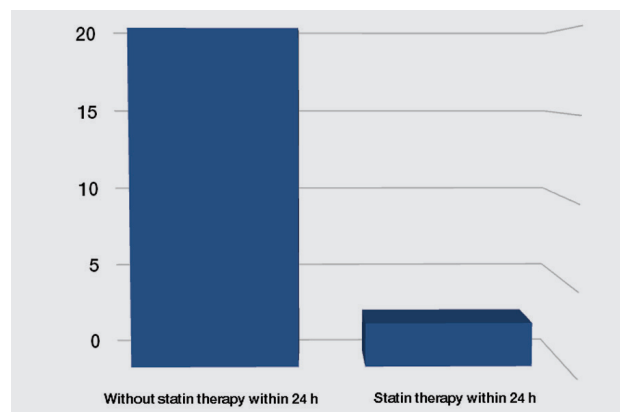
Regardless of the need for further investment of human and financial resources into the development of the network of primary percutaneous coronary intervention, we must not forget the need for modern pharmacological treatment. Since the basis for pharmacological treatment of this group of patients is represented by a dual antiplatelet therapy (ticagrelor/prasugrel with aspirin), it is important to emphasize the fact that in Croatia patients with acute STEMI can receive treatment with ticagrelor without charge during twelve months following pPCI, and from March 1<sup>st</sup>, 2018 ticagrelor has been included on the Basic list of all medication of the Croatian Health Insurance Fund for the treatment of high-risk patients with NSTEMI. There are clear guidelines for the application of a dual antiplatelet therapy regarding the type of medication used and the duration of their usage. Although ticagrelor with aspirin is the basis of modern treatment, due to its availability and price clopidogrel remains one of the most prescribed antiplatelet medications in the world, including Croatia. Since clopidogrel is a drug that transforms into an active metabolite only after entering the body through processes in the liver, its weakened effect in a certain group of patients, determined by a weakened process of drug activation, has been recognized and described. Consequently, laboratory methods for determining the level of thrombocyte activity in a patient's blood sample have been introduced into clinical use. We stress that the guidelines do not recommend a routine determination of thrombocyte reactivity or the quantification of the thrombocyte inhibition level conditioned by the application of anti-aggregational drugs, but they do enable the use of aforementioned tests in selected patients<sup>5</sup>. This was the reason for the creation of a project of the Croatian Science Foundation which tests thrombocyte activity by measuring aggregability in the blood of patients treated with anti-aggregational drugs for a variety of indications, and especially in those with acute myocardial infarction. Research conducted as part of the project has shown that by adjusting clopidogrel dosage in patients with a measured elevated residual thrombocyte activity with a standard clopidogrel dosage can improve clinical outcomes, which is confirmed by the fact that in the aforementioned segment there is a need for additional research with the aim of determining the optimal treatment strategy for patients with acute myocardial infarction<sup>6</sup>.

Apart from antiplatelet therapy, it is also necessary to understand the need for the application of other drugs in the treatment of patients with acute myocardial infarction. Special attention should be paid to statins – drugs which, according to multicentric randomized studies, significantly improve clinical outcomes for this group of patients. We therefore wish to point out one large international and retrospective registry of patients with acute coronary syndrome: ISAC-TC (International Survey of Acute Coronary Syndromes in Transitional Countries). University Hospital Centre Zagreb also participates in this registry as the sole institution from the

Osim antiagregacijske terapije, svakako je nužno poznavanje potrebe primjene i ostalih lijekova u liječenju bolesnika s akutnim infarktomiokarda. Među navedenim posebnu pozornost svakako zaslužuju statini – lijekovi koji, na temelju multicentričnih randomiziranih studija, znatno poboljšavaju kliničke ishode ove skupine bolesnika. U tom segmentu skrećemo pozornost na jedan veliki, međunarodni, retrospektivni registar bolesnika s akutnim koronarnim sindromom: ISACS-TC. U navedenom registru sudjeluje i Klinički bolnički centar (KBC) Zagreb kao jedina ustanova iz Republike Hrvatske. Registar ISACS-TC (*International Survey of Acute Coronary Syndromes in Transitional Countries*) omogućuje praćenje klasičnih demografskih i antropometrijskih podataka, mnoštva kliničkih izmjerenih varijabli te niza podataka o komorbiditetima uvrštenih bolesnika. Tako je naknadnom podanalizom hrvatske skupine bolesnika u tom registru ustanovljeno kako rana primjena statina u bolesnika sa STEMI-jem (unutar 24 h od prijma u bolnicu) znatno smanjuje unutarbolničku smrtnost s obzirom na kasniji početak terapije ovim lijekovima (**Slika 2**). Upravo su navedeni rezultati razlog zbog kojeg će se provesti dodatna analiza svih bolesnika uključenih u spomenuti registar kako bi se testirala ova nadasve zanimljiva hipoteza.

U aritmološkom dijelu simpozija predloženi su rezultati hrvatskih elektrofizioloških centara, s posebnim osvrtom na razvoj nacionalnog ablacijskog programa. Naime, u modernoj su aritmologiji zahvaljujući znatnim tehnološkim napredcima uloženi veliki naponi koji su strategiju liječenja danas najčešće kliničke srčane aritmije – fibrilacije atrija (FA), podigli na razinu visoko sofisticiranoga terapijskog pristupa. Kako je riječ o aritmiji čija se prevalencija u odrasloj populaciji kreće oko 3 % (uz mnogo veću prevalenciju u starijih ljudi, a posebno u bolesnika s poznatom arterijskom hipertenzijom, koronarnom bolesti srca i/ili srčanim zatajivanjem), svaki napredak koji dovodi do uspješnijeg liječenja ovoga kliničkog entiteta ima izravne velike implikacije na svakodnevnu kliničku praksu. Nakon početnih znanstvenih radova koji su dokazali kako FA započinje izbijanjem električnih impulsa u području utoka plućnih vena u lijevi atrij, započeto je s razvojem mnogobrojnih metoda elektrofiziološke ablacije kojima je svrha izolacija plućnih vena i time prekid širenja navedenog električnog izbijanja na tkivo atrijskog miokarda, čime se dokidaju nastanak i održavanje ove aritmije. Na temelju mnogobrojnih studija danas znamo kako je kateterska ablacija FA uspješna metoda očuvanja sinusnog ritma u bolesnika s paroksizmalnom i perzistentnom FA nakon neuspjeha i/ili nepodnošenja antiaritmijske terapije. Štoviše, novije studije upućuju i na znatnu dobit navedenoga invazivnog oblika liječenja kao linije primarnoga terapijskog odabira u bolesnika s paroksizmalnom aritmijom<sup>7</sup>. Ablacijsko liječenje FA u Hrvatskoj ima već dugogodišnju tradiciju uz znatno povećanje broja procedura upravo u zadnje tri godine (**Slika 3**). U navedenom se razdoblju zahvaljujući porastu broja provedenih postupaka, Republika Hrvatska izdignula iznad prosjeka zemalja u regiji te se približila vodećim europskim zemljama (**Slika 4**). Navedeni napredak jedan je od najvažnijih nacionalnih kliničkih kardioloških pomaka u recentnoj medicinskoj povijesti naše zemlje i zasigurno je zalag budućih istovjetnih trendova.

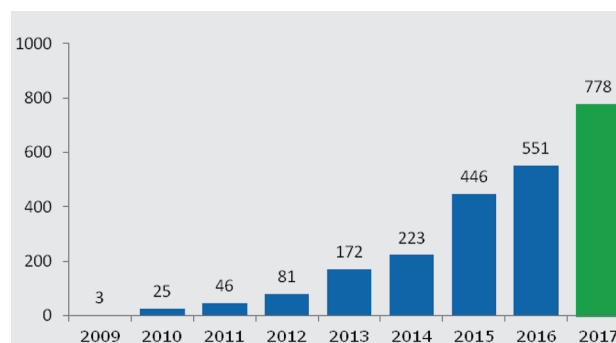
Sindrom srčanog zatajivanja u punom je smislu riječi pošast modernog doba. Riječ je o stanju čija se prevalencija procjenjuje na 1 – 2 % ukupne populacije, dok u skupini osoba



**FIGURE 2. Hospital mortality in Croatian subjects in the International Survey of Acute Coronary Syndromes in Transitional Countries (N=1788) regarding the time of statin administration.**

Republic of Croatia. ISACS-TC registry enables us to follow classic demographic and anthropometric data, numerous measured clinical variables, and a host of data on comorbidities of included patients. A subsequent sub-analysis of a Croatian group of patients in the registry found that an early application of statins in patients with STEMI (within 24 hours from admittance) significantly lowers in-hospital mortality in comparison with a later start of a therapy based on those drugs (**Figure 2**). Those results are the reason why an additional analysis of all patients included in the registry will be carried out with the aim of testing this very interesting hypothesis.

In the part of the symposium focusing on arrhythmia the results of Croatian electrophysiological centres were presented, with a particular look at the development of the national ablation program. Thanks to significant technological improvements, modern arrhythmology has advanced considerably and raised the treatment strategy for atrium fibrillation, today's most common clinical heart arrhythmia, to the level of a highly sophisticated treatment. Since the prevalence of this arrhythmia in adult population is approximately 3% (with significantly greater prevalence in the elderly, and especially in patients with diagnosed arterial hypertension, coronary



**FIGURE 3. Number of atrial fibrillation ablations per year in Croatia.**

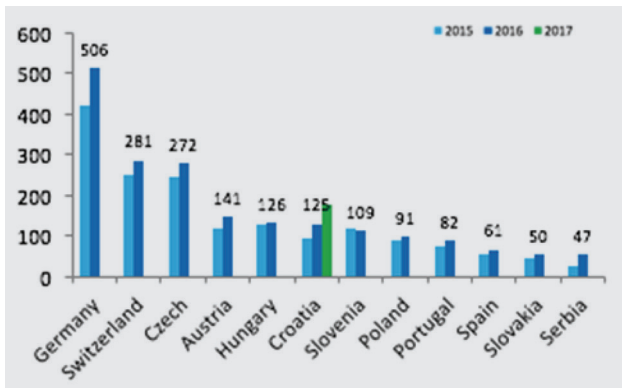


FIGURE 4. Number of atrial fibrillation ablations per year in Europe.

starijih od 70 godina učestalost ovoga kliničkog entiteta prelazi i više od 10%<sup>8</sup>. Posebno je zabrinjavajuća činjenica kako je, unatoč naporima moderne medicine, petogodišnje preživljenje ovakvih bolesnika i dalje nisko te često mnogo lošije od bolesnika s malignim bolestima (Slika 5). Ipak, u zadnjih dvadesetak godina uloženi su veliki znanstveni i tehnološki napori koji su rezultirali aktualno dostupnim raznim sofisticiranim farmakološkim i nefarmakološkim terapijskim rješenjima za liječenje ove vulnerabilne skupine bolesnika. Kad je riječ o ovima, posljednjima, prije svega mislimo na moderne izvantjelesne, kratkoročne jednako kao i ugradbene, dugoročne cirkulacijske potporne crpke. U sferi zbrinjavanja vitalno ugroženih bolesnika s akutnim srčanim zatajivanjem posebno mjesto zauzima kratkoročna potporna crpka koja akutno zamjenjuje i cirkulacijsku i respiracijsku funkciju – V-A ECMO (vensko-arterijski ECMO). U KBC Zagreb program ugradnje uređaja za izvantjelesnu membransku oksigenaciju (engl. *extracorporeal membrane oxygenation*, ECMO) postoji već dulji niz godina. Iako inicijalno primjenjivan tek kao kirurška terapija (tzv. postkardiotomijski ECMO – primjena crpke u neposrednom perioperacijskom postupku za optimiza-

heart disease and/or heart failure), every improvement that leads to a more successful treatment of this clinical entity has great direct implications for everyday clinical practice. After initial scientific articles proved that atrial fibrillation begins with the eruption of electrical impulses in the confluence of pulmonary veins in the left atrium, the development of numerous methods of electrophysiological ablation were initiated with the aim of isolating pulmonary veins and stopping the electrical eruption from spreading to the tissue of atrial myocardia, which interrupts the occurrence and sustention of arrhythmia. On the basis of numerous studies, we now know that catheter ablation of atrial fibrillation is a successful method of preserving sinus rhythm in patients with paroxysmal and persistent atrial fibrillation after an unsuccessful antiarrhythmic therapy. Moreover, new studies show a significant benefit of the invasive form of treatment as a type of primary treatment choice for patients with paroxysmal arrhythmia<sup>7</sup>. Ablation treatment for atrial fibrillation has a longstanding tradition in Croatia, with a significant increase in the number of procedures in the last three years (Figure 3). In that period, due to an increase in the number of performed procedures, Croatia has surpassed the average of other countries in the region and come closer to leading European countries (Figure 4). This advancement represents one of the most significant national clinical cardiological improvements in recent medical history of our country and is surely a sign of similar future trends.

The syndrome of heart failure is certainly an epidemic of modern times. The prevalence of this condition is estimated at 1-2% of total population, while the frequency of this clinical entity among people above the age of 70 surpasses 10%<sup>8</sup>. It is especially worrying that, despite the efforts of modern medicine, the 5-year survival rate of such patients remains low and is often significantly lower than in patients with malign diseases (Figure 5). However, in the last twenty years great scientific and technological efforts have resulted in a variety of currently available sophisticated pharmacological and non-pharmacological treatment options for this vulnerable group of patients. In the case of the

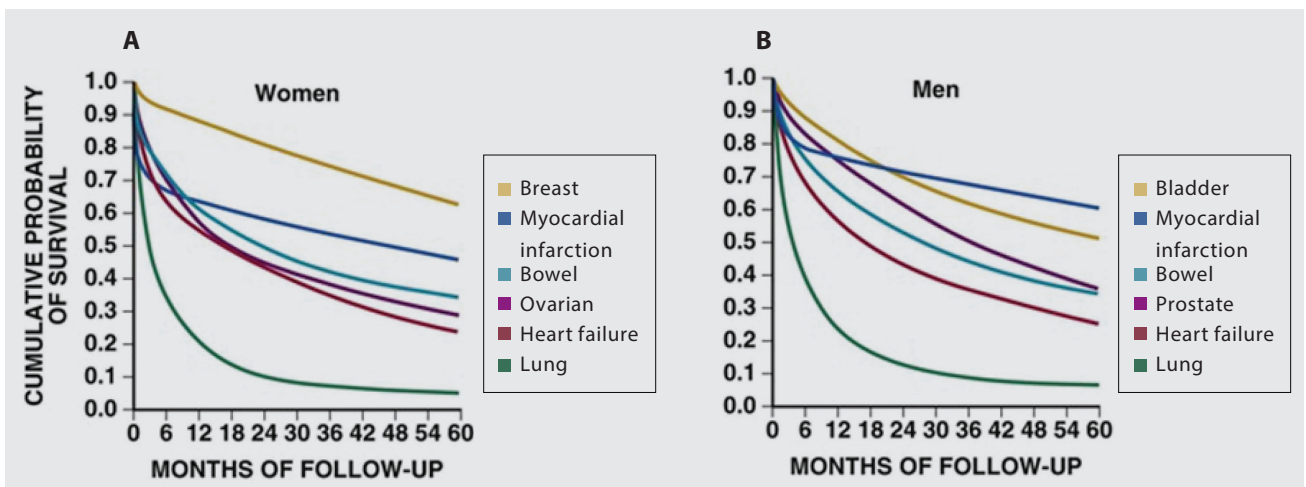
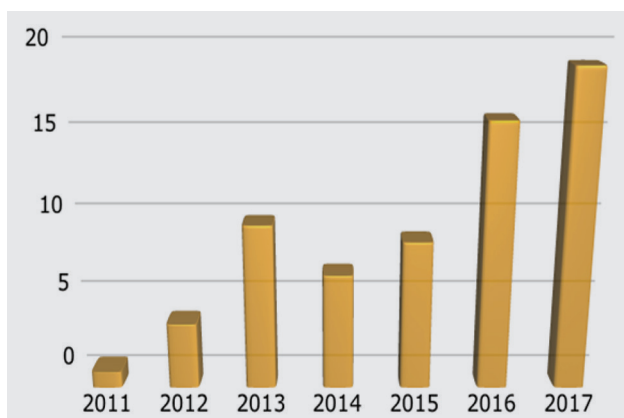


FIGURE 5. 5-year survival of chronic heart failure patients in regard to survival of patients with malignant diseases.

Adapted from: Eur J Heart Fail. 2001 Jun;3(3):315-22.



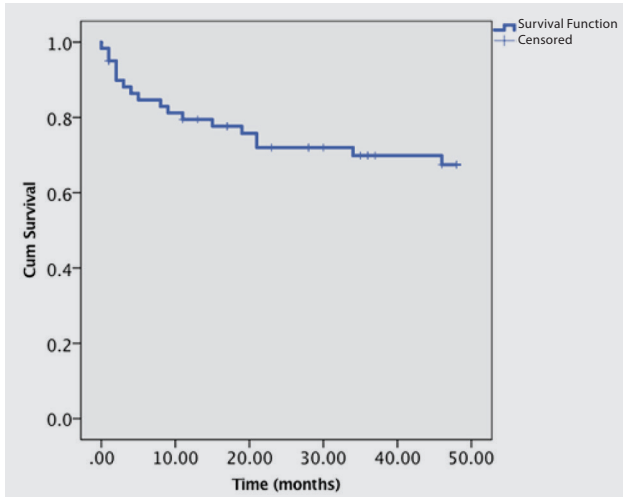
**FIGURE 6. Number of veno-arterial extracorporeal membrane oxygenation implantations in University Hospital Centre Zagreb per year.**

ciju kirurških rezultata) u novije vrijeme učestalo se rabi kao perkutana kardiološka metoda osiguravanja akutne stabilizacije hemodinamskog i/ili respiracijskog stanja bolesnika, najčešće u fazi kardiogenog šoka zbog AIM ili pak akutizacije kroničnoga srčanog popuštanja. Tako je u razdoblju od početka 2011. do kraja 2017. godine u KBC-u Zagreb V-A ECMO uređaj ugrađen ukupno u 66 bolesnika (srednja dob 56,6 godina, 47 muškaraca). U navedenom se razdoblju bilježi kontinuirani porast godišnje stope ugrađenih uređaja (**Slika 6**). Ukupna uspješnost ECMO terapije (definirana kao uspješno skidanje s ECMO uređaja zbog oporavka srčane funkcije, ugradnje dugoročne srčane crpke ili provođenja transplantacijskog liječenja) iznosi 54,5 %. Navedeni rezultati svrstavaju ovaj program kratkoročne cirkulacijske potpore u KBC-u Zagreb uz bok suvremenim inozemnim centrima izvrsnosti koji, na temelju podataka registra ELSO (*Extracorporeal Life Support Organization*) ostvaruju uspješnost ECMO terapije na razini 38-55%<sup>9</sup>. S druge pak strane ugradnja dugoročnih, unutartjelesnih cirkulacijskih potpornih crpki metoda je liječenja terminalnog srčanog popuštanja u bolesnika koji su aktualno, unatoč optimalnoj medikamentnoj terapiji, teško narušenoga funkcijskog stanja, a kandidati su za transplantacijsko liječenje. Također se smatra kako je navedena terapija pogodna opcija za liječenje bolesnika koji nisu kandidati za transplantacijsko liječenje, a koji bez naprednoga nefarmakološkog liječenja imaju izrazito visoku stopu smrtnosti<sup>7</sup>. KBC Zagreb vodeći je hrvatski centar za ugradnju dugoročnih cirkulacijskih crpki za potporu rada lijeve klijetke (engl. left ventricle assist device, LVAD). U razdoblju od 2010. do rujna 2017. godine navedeni su uređaji ugrađeni u ukupno 64 bolesnika, a četverogodišnja stopa preživljenja iznosi 70 % (**Slika 7**). Imajući na umu rezultate iz najvećega svjetskog registra bolesnika LVAD – INTERMACS, koji prijavljuju četverogodišnje preživljenje na razini od 40%, jasno je kako navedeni podatci KBC-a Zagreb govore u prilog vrhunskog pristupa u probiru, pripremi, liječenju i praćenju ove skupine iznimno zahtjevnih bolesnika.

Unatoč iznimnom napretku i razvoju tehnologije ugradbenih srčanih crpki, transplantacija srca i dalje je „zlatni standard“ u liječenju terminalnoga srčanog zatajivanja. Izuzmemo li činjenicu sve većeg manjka donorskih organa, glavni problemi suvremene transplantacijske kardiologije leže u

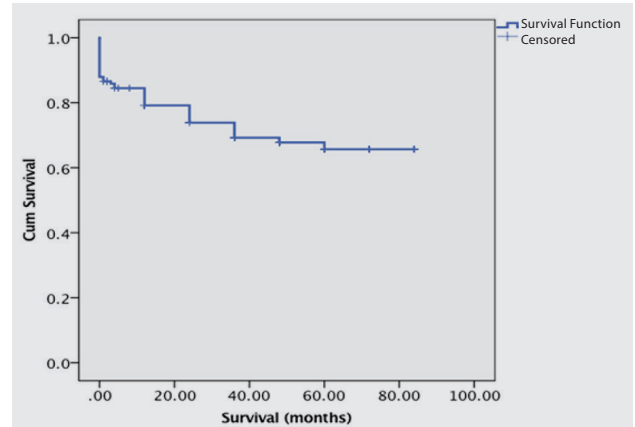
latter, we are primarily referring to modern extracorporeal, short term and implanted, long-term pumps for circulatory support. In the area of treating patients with vital risk and acute heart failure, the short-term support pump V-A-ECMO (veno-arterial extracorporeal membrane oxygenation) that acutely replaces circulatory and respiratory functions is of special importance. At the University Hospital Centre Zagreb, the program for implanting ECMO devices has existed for several years. Although initially used only as surgical therapy (so-called postcardiotomic ECMO – the application of the pump in direct preoperational procedure for the optimization of surgical results), in recent times it is frequently used as a percutaneous cardiological method of ensuring acute stabilization of the hemodynamic and/or respiratory state of the patient, most commonly in the stage of cardiogenic shock following acute myocardial infarction or acute exacerbation of chronic cardiac insufficiency. In the period between the beginning of 2011 and the end of 2017, at the University Hospital Centre Zagreb the V-A-ECMO device was implanted in a total of 66 patients (average age 56.6 years, 47 men). In this period there was a continued increase in the yearly rate of implanted devices (**Figure 6**). The total success rate of the ECMO therapy (defined as a successful removal of the ECMO device due to a recovery in the cardiac function, an implantation of a long-term heart pump, or transplantation therapy) is 54.5%. These results place this program of short-term circulatory support at the University Hospital Centre Zagreb alongside foreign contemporary centres of excellence which, based on data from the ELSO registry (Extracorporeal Life Support Organization) show a success rate of 38-55%<sup>9</sup> for the ECMO therapy. On the other hand, the implantation of long-term, intracorporeal pumps for circulatory support is a method of treating terminal heart deficiency in patients who have, despite optimal medical therapy, acutely damaged functional status and are candidates for transplantation therapy (“bridge to transplantation”). It is also believed that this therapy is a good option in the treatment of patients who are not candidates for transplantation therapy and have a very high rate of mortality without advanced non-pharmacological therapy (“destination therapy”)<sup>7</sup>. University Hospital Centre Zagreb is the leading Croatian centre for the implantation of long-term circulatory pumps that support the left ventricle (LVAD – left ventricle assist device). From 2010 to September 2017, a total of 64 patients received these devices, and the 4-year survival rate is 70% (**Figure 7**). Keeping in mind the results from LVAD – INTERMACS, the world's largest patient registry, which shows the 4-year survival rate of 40%, it is clear that the data from the University Hospital Centre Zagreb represents excellence in the choice, preparation, treatment and monitoring of this group of extremely challenging patients.

Despite remarkable progress and development in the technology of implanted heart pumps, heart transplantation still represents the gold standard in the treatment of terminal heart failure. If we exclude the fact that there are decreasing numbers of donor organs, the main problems of modern heart transplantation lie in immunosuppressant therapy – the limited effectiveness of immunosuppressant drugs and the development of complications after their long-term use. The basis of modern immunosuppressant therapy is the so-called “triple therapy” which includes tacrolimus or cyclosporin, mycophenolic acid, and corticosteroid drugs, and the basis for monitoring after performed transplantation, apart from



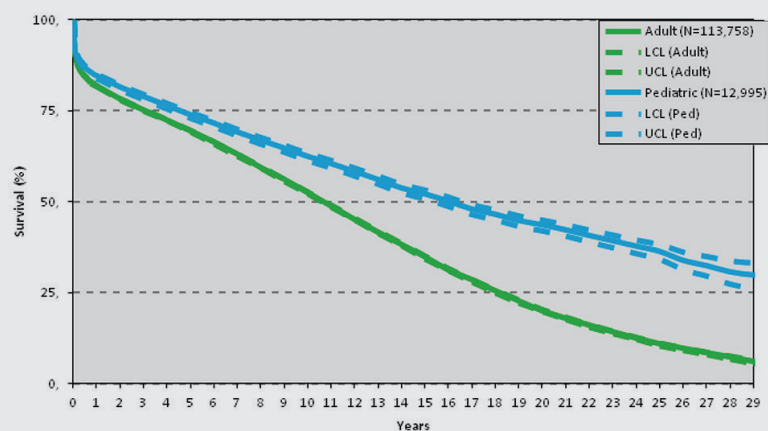
**FIGURE 7. Cumulative survival rates in patients with left ventricle assist device in University Hospital Centre Zagreb.**

imunosupresivnoj terapiji – ograničenoj učinkovitosti imunosupresivnih lijekova te razvoju komplikacija nakon njihove dugoročne primjene. Temelj modernoga imunosupresivnog liječenja čini tzv. trostruka terapija koja uključuje takrolimus ili ciklosporin, mikofenolnu kiselinu te kortikosteroid, a temelj praćenja bolesnika nakon izvedene transplantacije, osim rutinskih kliničkih, laboratorijskih, ehokardiografskih te funkcijskih testova, svakako su redovite endomiokardne biopsije desne klijetke te patohistološka analiza uzorka sa svrhom detekcije staničnog i humoralnog odbačivanja. Na ovakav način liječeni i vođeni bolesnici danas u svijetu ostvaruju i respektabilno petogodišnje preživljenje koje iznosi više od 70% (Slika 8). KBC Zagreb najveći je kardijalni transplantacijski centar u Republici Hrvatskoj u kojemu je prva transplantacija srca učinjena davne, 1988. godine. U godinama koje su uslijedile godišnje je u KBC-u Zagreb prosječno učinjeno 5 transplantacija i tako sve do 2007. godine. Te je godine Republika



**FIGURE 9. Cumulative survival rates in patients after heart transplantation in University Hospital Centre Zagreb.**

routine clinical, laboratory, echocardiographic, and functional testing, are certainly regular endomyocardial biopsies of the right ventricle and pathohistological analysis of samples with the aim of detecting cellular and humoral rejection. With this type of therapy and management, patients today have a respectable 5-year survival rate of over 70% (Figure 8). University Hospital Centre Zagreb is the larger cardiac transplant centre in Croatia, in which the first heart transplantation was performed long ago, in 1988. In the years after that, on average there were 5 transplantations performed each year at University Hospital Centre Zagreb, and this continued until 2007. That year Croatia became a member of Eurotransplant, which had a direct and significant influence on the transplantation program – the same year the number of performed transplantations increased to 11, and continued to rise in the following decade to at least 20 procedures yearly, which places University Hospital Centre Zagreb alongside leading transplantation centres in the world (Figure 9).



**FIGURE 8. Cumulative survival rates in pediatric and adult patients after heart transplantation.**

Adapted from the ISHLT International Registry for Heart and Lung Transplantation; <https://www.isHLT.org/registries/slides.asp?slides=heartLungRegistry>.



Hrvatska postala članicom Eurotransplanta, što je imalo izravan i golem utjecaj na transplantacijski program – već je navedene godine broj učinjenih transplantacija porastao na 11, a u idućem se desetljeću dodatno povećao i održao na barem 20 postupaka godišnje, što KBC Zagreb svrstava uz bok vodećim svjetskim transplantacijskim centrima. I ne samo to, petogodišnje preživljenje bolesnika s transplaciranim srcem u KBC-u Zagreb iznosi 68 %, što je svakako u skladu s rezultatima renomiranih inozemnih centara (**Slika 9**).

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