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Časopis Udruženja kardiologa Srbije

SRCE i krvni sudovi

Heart and Blood Vessels

Journal of the Cardiology Society of Serbia

Volumen 36
Suplement B
2017. godina

Ovaj broj je posvećen Drugom kongresu 34-og ogranka Američkog koledža kardiologije za Srbiju i Republiku Srpsku

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Broj odobrenja ALIMS: 515-08-00174-16-002

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SRCE I KRVNI SUDOVI
HEART AND BLOOD VESSELS

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Srce i krvni sudovi: Časopis Udruženja kardiologa Srbije
Heart and blood vessels: Journal of Cardiology society of Serbia
Editor in-chief Tatjana S. Potpara, Godina 6,
Volumen 36, Suplement B
Beograd, Višegradska 26: Udruženje kardiologa Srbije
2017-Beograd: Newassist doo
Tromesečno-Broj 1 izašao 2011. god.

ISSN 182-4835=Srce i krvni sudovi
COBISS.SR-ID 174253580

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UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI

Volumen 36 Suplement B 2017. godina

Sadržaj

Poštovane koleginice i kolege,
Veliko mi je zadovoljstvo da Vas pozdravim na početku Drugog kongresa 34. Ogranka Američkog koledža kardiologa za Srbiju i Republiku Srpsku, koji će se održati 3-4. marta 2017. godine, u hotelu M "Best Western" u Beogradu.
34. Ogranak Američkog koledža kardiologa za Srbiju i Republiku Srpsku (*ACC Consortium Chapter for Serbia and Republic of Srpska*) je osnovan početkom 2015. godine, a promovisan 15. marta 2015. godine u San Dijegu na 64. kongresu Američkog koledža kardiologa.
Ovaj Ogranak je formiran sa ciljem unapređenja saradnje i povezivanja Američkog koledža kardiologa sa Udruženjem kardiologa Srbije i Udruženjem kardiologa Republike Srpske.
Prvi vidovi ove saradnje su bili realizovani kroz organizaciju zajedničkih sesija na XX Kongresu Udruženja kardiologa Srbije održanom na Zlatiboru oktobra 2015. godine, 65. Kongresu Američkog koledža kardiologa održanom u Čikagu u martu 2016. godine, kao in prošlogodišnjem Prvom kongresu PRACSIS 2016.
Teme Drugog kongresa biće prikaz i analiza najvažnijih preporuka Američkog koledža kardiologa i Evropskog udruženja kardiologa. Predavači i moderatori će biti najistaknutiji kardiolozi Udruženja kardiologa Srbije i Udruženja kardiologa Republike Srpske.

S poštovanjem,
Milan Nedeljkovic
Prof. dr Milan A. Nedeljković
Prvi predsednik 34. Ogranka Američkog koledža kardiologa
za Srbiju i Republiku Srpsku

It is my great pleasure to greet you at the beginning of the Second Congress of the 34th American College of Cardiology Consortium Chapter of Serbia and Republic of Srpska, which will be held on March 3-4, 2017, at Hotel M "Best Western" in Belgrade.
34th Chapter of the American College of Cardiology of Serbia and the Republic of Srpska was founded in early 2015 and was promoted on March 15, 2015 in San Diego at the 64th Congress of the American College of Cardiology. This Chapter was founded with the aim of improving cooperation and connection with the American College of Cardiology, Cardiology Society of Serbia, and Cardiology Society of the Republic of Srpska. The first steps of this cooperation were realized through the organization of joint sessions at the 20th Congress of the Cardiology Society of Serbia that was held on Zlatibor in October 2015, 65th Congress of the American College of Cardiology held in Chicago in March 2016, and during last year's PRACSIS 2016 meeting.
The main topic of this Congress will be the analysis of the most important clinical guidelines of the American College of Cardiology and the European Society of Cardiology. Speakers and moderators will be the most prominent cardiologists of the Cardiology Society of Serbia and the Cardiology Society of Republic of Srpska.

I wish you successful meeting.
Milan Nedeljkovic
Professor Milan A. Nedeljkovic
First president of the 34the ACC Consortium Chapter
of Serbia and Republic of Srpska

Srce i krvni sudovi 2017; 36(S2): 26-32

Review

ACC/AHA Guidelines for Cholesterol Management and Considerations for Newer and Emerging Therapies

Nathan D. Wong PhD, FACC, FAHA, FNLA

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Abstract The American College of Cardiology/American Heart Association in 2013 issued revolutionary guidelines for blood cholesterol management, accompanied by guidelines on cardiovascular risk assessment, lifestyle management, and obesity management. The use of an atherosclerotic cardiovascular disease (ASCVD) risk calculator was the foundation of the risk assessment guideline and the lifestyle management guideline focused on recommending an evidence-based dietary pattern and regular physical activity. The blood cholesterol management guideline identified four groups of patients shown to benefit from moderate or high intensity statin therapy and removed the use of specific low density lipoprotein (LDL)-cholesterol goals due to lack of evidence for specific targets. Rigorous evidence from randomized clinical trials formed the rationale for moderate and high intensity statin therapy. Updated guidance has since provided recommendations for newer non-statin therapies, including cholesterol absorption inhibitors and proprotein convertase subtilisin kexin type 9 (PCSK9) monoclonal antibody (mAb) therapy when additional LDL-C lowering is needed beyond that provided by maximum tolerated statin therapy. Novel RNA interference therapy for PCSK9 synthesis is also currently in development. The recent development and application of PCSK9 mAb therapies have resulted in remarkable reductions in LDL-C beyond statin therapy that are well-tolerated and with promising outcome data demonstrating ASCVD event reductions beyond statin therapy.

Key words: Cholesterol, statins, risk assessment, prevention, cardiovascular disease.

Introduction

In November 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) issued four bold guidelines for atherosclerotic cardiovascular disease (ASCVD) prevention including ones on cardiovascular risk assessment[1], lifestyle management[2], obesity management[3], and blood cholesterol management[4]. These guidelines were based nearly exclusively on higher quality randomized controlled clinical trials or systematic reviews and meta-analyses, and deemphasized the use of expert opinion in their development. They were also designed to answer specific critical questions rather than to address all aspects of a particular topic (e.g, dyslipidemia management). This paper provides an overview of the ACC/AHA Guideline for Blood Cholesterol Management4 including new and emerging non-statin therapies, as well as the supporting role provided by the risk assessment, lifestyle management, and obesity management guidelines. These guidelines form the foundation of practice in preventive cardiology. The evidence and role for cholesterol absorption inhibitor and PCSK9 monoclonal antibody (mAb) therapy, as well as emerging RNA interference therapy for inhibiting PCSK9 synthesis are also discussed.

Cardiovascular risk assessment, lifestyle, and obesity management guidelines as a foundation for preventive cardiology

The foundation of preventive cardiology is an assessment of a patient's global risk for ASCVD for appropriate targeting of the intensity of lipid and other preventive therapies. As early as 1976, former Framingham Heart Study director Dr. William B. Kannel noted that such risk functions provide an "economic and efficient method for identifying persons at high cardiovascular risk who need preventive treatment"[5]. Some 20 years later the ACC Bethesda Conference noted that the intensity of treatment should match a person's risk[6]. In addition, such risk assessment can help communicate to patients their risk of ASCVD and to motivate adherence to lifestyle and other therapies, promoting improved outcomes[7]. The ACC/AHA Cardiovascular Risk Assessment working group[1] developed a new risk calculator based on the broader endpoint of ASCVD (including coronary heart disease [CHD] death, nonfatal myocardial infarction [MI] and fatal and nonfatal stroke). In contrast to many older calculators that have primarily focused on the prediction of CHD events and based on the predominantly Caucasian population of Framingham, Massachusetts, the new Pooled Cohort Risk Calculator was

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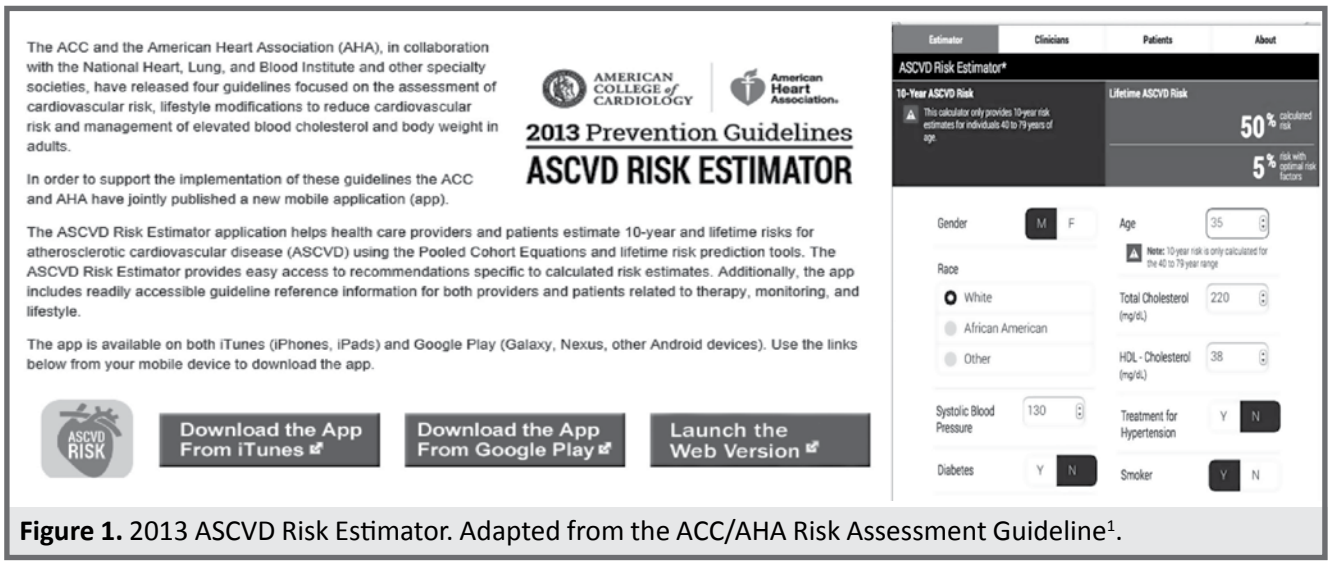

Figure 1. 2013 ASCVD Risk Estimator. Adapted from the ACC/AHA Risk Assessment Guideline[1].

developed from four major cohorts: the Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Coronary Artery Risk Development in Young Adults (CARDIA), and Framingham Original and Offspring Study, which all had at least 10 years of follow-up when developed. It calculates both the 10-year (among those aged 40-74 years) and lifetime ASCVD risk (among those aged 20-59 years) and can be downloaded onto most smartphones, tablets, and computers (Figure 1). When the treatment decision based on initial risk assessment using the Pooled Cohort Risk Calculator, is uncertain, the assessment of other measures (see below in ACC/AHA 2014 Guideline for Cholesterol Management) can be recommended to further inform treatment decision making.

The ACC/AHA Lifestyle Management Guideline[2] recommends for adults who would benefit from LDL-cholesterol or blood pressure (BP) lowering, a dietary pattern focusing on intake of vegetables, fruits, and whole grains, low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts, and limited intake of sweets, sugar-sweetened beverages, and red meats (Class I, level of evidence A recommendation). Such a dietary pattern should also include 5% to 6% calories from saturated fat, with a reduction in calories from trans-fat and no more than 2,400 mg of sodium daily (or a reduction of sodium intake of at least 1,000 mg per day). Moreover, moderate to vigorous aerobic physical activity is recommended 3-4 times per week for ~40 minutes per session. The ACC/AHA/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults[3] provides a key message that only modest weight loss of 3% to 5% of body weight is need to result in clinically meaningful benefits for several cardiometabolic risk factors, including triglycerides, blood glucose, glycated hemoglobin, and development of type 2 diabetes. Importantly, it is advised that overweight and obese individuals participate for at least 6 months in a comprehensive lifestyle program adhering to a reduced calorie diet and increased physical activity as well as high-intensity (≥14 sessions in 6 months) comprehensive weight loss interventions prescribed by a trained professional (e.g., dietitian or exercise physiologist).

ACC/AHA 2014 Guideline for cholesterol management

The recent ACC/AHA cholesterol guideline[4] identified four groups of patients proven from clinical trials to benefit from statin therapy: those with 1) clinical ASCVD, 2) LDL-C ≥190 mg/dl and aged ≥21 years, 3) diabetes and aged 40-75 years with LDL-C 70-189 mg/dl, and 4) primary prevention without diabetes with a ≥7.5% 10-year ASCVD risk, aged 40-75 years, and LDL-C 70-189 mg/dl. Patients in each of these groups are indicated for either moderate intensity statin therapy to reduce LDL-C 30% to <50% or high intensity statin therapy intended to reduce LDL-C ≥50% from baseline. Moreover, in primary prevention, there is also consideration for a moderate intensity statin even in those at lower risk (5 to <7.5% 10-year risk). These intended percentage reductions in LDL-C are now the intended "therapeutic goals" rather than the use of specific LDL-C goals (e.g., <70 mg/dl for very high risk persons) since the guideline committee determined that there was a lack of randomized clinical trial evidence to support titration of drug therapy to specific LDL-C and/or non-HDL-C goals. However, given the wealth of clinical trial data on higher versus lower intensity statin therapy[8], there was strong evidence that the appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit. Therefore, the guideline took the bold step of abandoning specific LDL-C goal levels that have been the principal therapeutic target in lipid management for decades. In addition, there is emphasis on evaluation of net clinical benefit, in which potential harms must be weighed against potential benefits. For example, the ≥7.5% cutpoint for consideration of high intensity statin therapy in primary prevention is consistent with the level of risk where the number needed to treat (NNT) to prevent an ASCVD event is lower (favorable) compared to the number needed to harm (NNH) based on the projected incidence of statin side effects (most of which are incident diabetes, despite its relatively small rate and somewhat arbitrary definition). Net clinical benefit can similarly be demonstrated for a moderate intensity statin when the 10-year ASCVD risk ≥5%.

While the above statin eligible groups indicate where the evidence is clear regarding those who would benefit from statin therapy for ASCVD risk reduction based on the clinical trial data, it is emphasized that these guidelines are not a "point and shoot" approach of prescribing statin therapy exclusively on calculated ASCVD risk, but one that is based on conducting a careful clinician-patient discussion before starting statin therapy, especially in primary prevention. This includes discussing with patients their estimated 10-year ASCVD risk and reviewing other risk factors and strategies for their control, including the potential for benefit from a heart-healthy lifestyle and consideration of referral to a dietitian and/or exercise physiologist. Further, the potential benefit vs. adverse effects of therapy should always be discussed, as well as patient preferences. These are important concepts of shared decision making in which the patient is an equal partner in decisions regarding appropriate care rather than a one-sided "doctor prescribes and tells the patient what to do" approach. Strategies for shared decision making are an important focus of recently released guidance from the ACC/AHA in lipid management[9].

For patients in the statin eligible groups and those not explicitly in these groups (e.g., those aged <40 or >75 with diabetes or candidates for primary prevention) or when the treatment decision is otherwise uncertain (perhaps due to patient and/or provider reluctance or preference), the guideline indicates specific factors that may inform the decision. These include a family history of premature ASCVD, elevated lifetime risk of ASCVD, LDL-C ≥160 mg/dl, hs-CRP ≥2.0 mg/dl, coronary artery calcium score ≥300 or ankle brachial index <0.9. These findings can be used to inform management decisions between the clinician and patient. Finally, while specific LDL-C targets were removed from the ACC/AHA guidelines, this document continues to 1) emphasize adherence to medication and lifestyle and 2) promote assessment of therapeutic response to statin therapy and safety. The latter of course requires monitoring of fasting lipids 4-12 wk after initiating therapy and every 3-12 months thereafter to monitor therapeutic response. Safety laboratory data should be obtained as clinically indicated.

Recommendations for consideration of non-statins

Importantly, the ACC/AHA Cholesterol Guideline indicates that in those at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy (which may be no therapy in a statin intolerant individual), the addition of a non-statin cholesterol lowering drug with proven efficacy may be considered if the ASCVD risk reduction benefits outweigh the potential for adverse effects.[14] Further guidance to this effect is provided by the ACC/AHA 2016 Expert Consensus Decision Pathway on Role for Non-Statin Therapies in LDL-C Lowering[10] as an update to the 2014 guideline statement. This statement notes that non-statin therapies (ezetimibe first, PCSK9 mAb second) may be used in selected high risk patients if at least a 50% LDL-C reduction is not achieved on maximal tolerated statin therapy. These therapies may also serve as alternatives for those with 1) LDL-C <70 mg/dL and ASCVD and other comorbidities, 2) LDL-C ≥190 mg/dl or <100 mg/dl in those with ASCVD without comorbidities, or 3) without ASCVD but LDL-C ≥190 mg/dl. For patients with diabetes (without ASCVD) or in primary prevention patients with 10-year ASCVD risk ≥7.5%, additional therapies may include ezetimibe followed by a bile acid sequestrant if ≥50% LDL-C lowering on maximal statin therapy or LDL-C <100 mg/dl is not achieved. Moreover, the recently released National Lipid Association Recommendations Part II also provide guidance for considering the use of PCSK9 mAb therapy, specifically indicating their use when LDL-C targets of <100 mg/dl in those with ASCVD or <130 mg/dl in those with familial hypercholesterolemia (FH) are not reached[11]. We recently reported from statin-treated U.S. adults in the National Health and Nutrition Examination Survey (NHANES) 2009-2010 showed that only 27% of those with coronary heart disease (CHD) were at LDL-C <70 mg/dL and those not at goal averaged 34 mg/dL above this cutpoint[12]. While it is unclear how many of these persons were on recommended moderate or high-intensity therapy, these data do suggest a significant opportunity for consideration of newer therapies, such as PCSK9 mAb, when reasonable targets cannot be reached.

The Improve-IT trial and implications for cholesterol management

The recent results of the IMPROVE-IT trial[13] in acute coronary syndrome patients with the addition of ezetimibe confirm the value of additional LDL-C lowering with non-statin therapy. Benefits were seen after 7 years of accrual included a significant (albeit modest) 6% relative risk reduction (HR=0.94, p=0.016) and number needed to treat [NNT] of 50 for the primary endpoint of CVD death, myocardial infarction, hospital admission for unstable angina, coronary revascularization, or stroke. Patients in this trial were very high risk randomized shortly (within 10 days) after their ACS and many of the events occurred within the first year of the trial so it is uncertain whether the results can be generalized to lower risk patients. While ezetimibe offers an additional 15-20% LDL-C reduction (on-trial LDL-C in IMPROVE-IT was 53 mg/dl in those receiving ezetimibe vs. 70 mg/dl in the placebo group), those with more severe LDL-C elevations despite statin therapy may need additional therapy beyond ezetimibe.

PCSK9 monoclonal antibody therapy: safety and efficacy

Among the most significant advances in cardiology in the past decade is the development of proprotein convertase subtilisin kexin type 9 (PCSK9) mAb therapy. Alirocumab (Praluent™) and evolocumab (Repatha™) (both fully human mAb) were approved by the US Food and Drug Administration (FDA) in July-August 2015. A third PCSK9 mAb product, bococizumab (RN316) (a humanized mAb product_), however, was discontinued

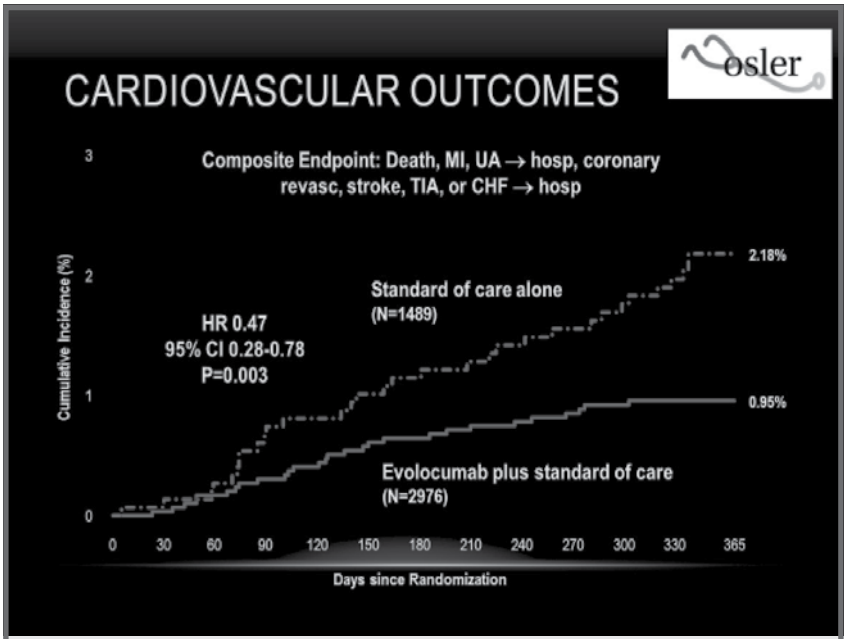

Figure 2. Cumulative incidence of cardiovascular events from two open-label randomized trials (OSLER 1 and OSLER 2) of evolocumab. Kaplan-Meier 1 year event rate. Adapted from Sabatine et al.[17]

from further clinical development in November 2016 due to increase immunogenicity and decreased LDL-C efficacy. PCSK9 is a 692 amino acid mature protein mainly expressed as a secreted protease in the liver, intestines, and kidneys. This molecule forms a complex with the hepatic LDL receptor, which undergoes endocytosis and destruction of the LDL receptor complex. This process reduces the number of LDL receptors available to continue to process LDL, thereby resulting in increased circulating plasma LDL-C particles.[14-15] PCSK9 mAbs bind to PCSK9, which prevents the association of PCSK9 and the LDL receptor. This action inhibits the deleterious effects of PCSK9, maintaining the LDL receptors and promoting continued clearance of LDL particles resulting in lowered LDL-C levels. Multiple phase II and III trials which have examined the efficacy and safety of alirocumab, evolocumab and bococizumab have shown LDL-C reductions averaging 50-60 percent in statin-treated or statin-intolerant patients with or without documented ASCVD. Observed effects on lipid fractions include 25-39% decrease in LDL-C in patients with homozygous FH (HoFH), ~50% reduction in non-HDL-C and apolipoprotein B, and 25% lowering of lipoprotein(a).[15]

Pooled data from relatively short-term safety and efficacy open-label studies were published in spring 2015, providing significant additional insight into safety and preliminary outcomes of treatment of PCSK9 mABs. The Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG-TERM) placebo-controlled trial[16] evaluated 2,341 patients with hyperlipidemia on maximally tolerated statins who were at high risk for CHD (69% with prior CHD and 35% with diabetes). Alirocumab (150 mg biweekly) reduced LDL-C 62% at 24 weeks compared to placebo; mean LDL-C was 48 mg/dL in the alirocumab group compared to 119 mg/dL in placebo patients. Among the alirocumab group, 79% achieved an LDL-C <70 mg/dL at week 24, compared to only 8% in the placebo group. Certain adverse events were higher in the alirocumab group compared to placebo: injection site reactions 5.9 percent vs. 4.2 percent, myalgia 5.4 percent vs. 2.9 percent, neurocognitive events 1.2 percent vs. 0.5 percent, and opthalmologic events 2.9 percent vs. 1.9 percent. Of particular interest, the post-hoc analysis of the composite of cardiovascular events over 78 weeks — including CHD death, myocardial infarction, ischemic stroke and unstable angina requiring hospitalization — showed those in the alirocumab group compared to placebo had a 48% reduced risk of such events (1.7% vs. 3.3%, HR=0.52, 95% CI=0.31-0.60). A similar study of evolocumab (Open-Label Study of Long-Term Evaluation Against LDL-Cholesterol [OSLER])[17] included a pre-specified combined analysis of 4,465 patients who completed one of 12 Phase 2 or 3 studies of evolocumab. These subjects were randomized either to evolocumab 420 mg every 4 weeks plus standard of care vs. standard of care alone in an open-label extension study averaging 11 months. The evolocumab group showed a 61% reduction in LDL-C, from 120 to 48 mg/dL (a 72 mg/dL between-group LDL-C difference) at 12 weeks. There was no difference in the rate of serious adverse events (7.5% in each group). The OSLER study reported a 53% reduction in the incidence of the pre-specified composite endpoint of death, MI, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack and hospitalization for heart failure (0.95 percent vs. 2.18 percent, HR=0.47, 95 percent CI=0.28-0.78). This can be considered a promising outcome in a short time despite a limited number of events (n=60) (Figure 2). Large Phase 3 trials involving >70,000 patients will provide definitive data on reduction in cardiovascular outcomes.

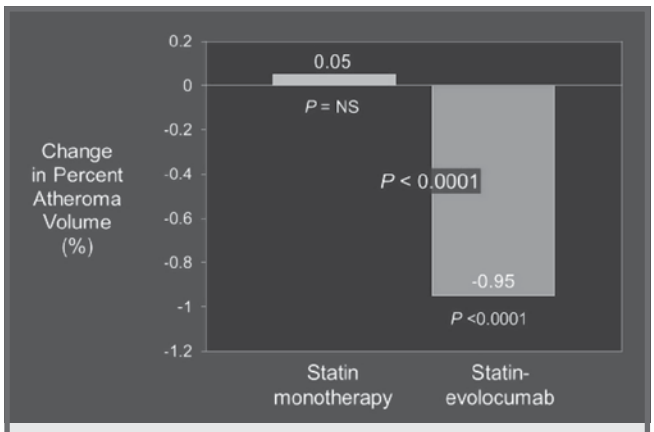

Figure 3. GLAGOV Primary Endpoint: Change in Percent Atheroma Volume. Data adapted from Nicholls et al.[19]

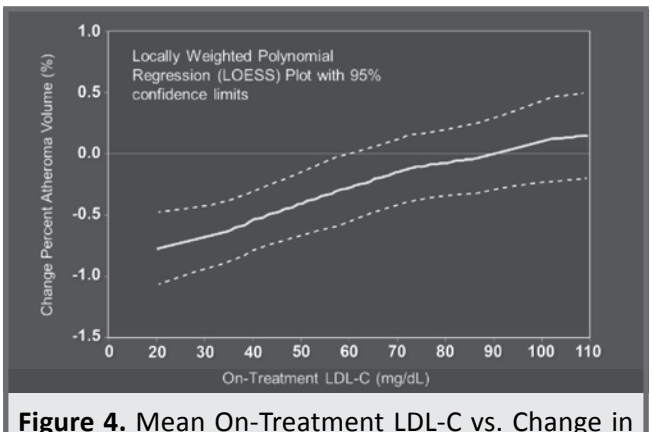

Figure 4. Mean On-Treatment LDL-C vs. Change in Plaque Atheroma Volume from the GLAGOV Study. Data adapted from Nicholls et al.[19]

Most recently, it was announced that the FOURIER trial had met both its primary composite endpoint (including cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina or coronary revascularization) and the even more rigorous key secondary composite endpoint (cardiovascular death, non-fatal MI or non-fatal stroke) and that the important FOURIER substudy, the EBBINGHAUS cognitive function trial, also achieved its primary endpoint, demonstrating that evolocumab was non-inferior to placebo for the effect on cognitive function. The details for both of these studies are due to be released March 2017 at the American College of Cardiology Scientific Sessions.[18]

Impact of combined PCSK9 mAb therapy on regression of atherosclerosis

To assess the impact of PCSK9 inhibitors on ASCVD burden, the GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) multicenter, double-blind, placebo-controlled randomized clinical trial, Nicholls et al.[19] studied 968 patients with angiographic coronary disease, 98% of whom were already on statin therapies. These patients were randomized to a monthly injection of evolocumab (420 mg) or placebo on a background of statin therapy, and examined as the primary endpoint the percent atheroma volume (PAV) over a 84 week treatment period. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels (93.0 vs 36.6 mg/dL; difference, −56.5 mg/dL [95%CI, −59.7 to −53.4]; P <.001). Furthermore, despite a history of prior statin therapy (duration of use not reported), PAV increased 0.05% in those assigned to placebo, compared to a decrease of 0.95% in those assigned to evolocumab; between-group difference of −1.0% [95% CI, −1.8% to −0.64%]; P <.0001) (Figure 3). Moreover, evolocumab induced plaque regression in 64.3% of patients, compared to 47.3% in those on placebo, in addition to statin (p<0.001). In addition, an exploratory pre-specified post hoc analysis showed a linear relationship between achieved LDL-C level and change in PAV with further "regression" in PAV down to LDL-C levels as low as 20 mg/dl, without any evidence of a threshold effect (Figure 4). Finally, MACE occurred in 74 patients (15.3%) on placebo and 59 patients (12.2%) on evolocumab and while not powered to evaluate clinical outcomes, the 20.3% relative and 3.1% absolute risk reduction translates to a very acceptable NNT of 32 in the relatively short 18-month duration trial.

Uses of PCSK9 mAb Therapy

The current indications for both alirocumab and evolocumab, as approved by the US FDA, involve their use as adjuncts to diet and maximally tolerated statin therapy for adults with heterozygous FH or clinical ASCVD who require additional LDL-C lowering[20,21]. Evolocumab is also indicated for such individuals with homozygous FH who require additional LDL-C lowering[21]. There also is an indication for use by adults and adolescents ages ≥12 years with homozygous FH in combination with other lipid-lowering therapies. In Europe, the European Medicines Association[22] approved a broader indication for evolocumab in which usage can be considered for adults with primary hypercholesterolaemia (HeFH and non-familial) or mixed dyslipidemia. It can be an adjunct to diet in combination with a statin or with a statin with other lipid-lowering therapies in patients unable to reach LDL C goals via the maximum tolerated dose of a statin or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contra-indicated. There also is an indication for use by adults and adolescents ages 12 years and older with HoFH in combination with other lipid-lowering therapies. However, both products clearly state in their labeling that the effects on cardiovascular outcomes have not been determined.

The wider inclusion of these therapies in future clinical practice guidelines as well as optimal cost negotiations with payers (given current list pricing of approximately $1200 per month) will be important for accessibility of these agents by patients. It has been recently estimated that annual drug costs per patient would need to be reduced to $4,536 to be cost-effective at the accepted <$100,000 per quality adjusted life year (QALY).[23] Broader indications for PCSK9 mAb therapy may be possible once further data become available in certain patient subgroups, cost-effectiveness is better

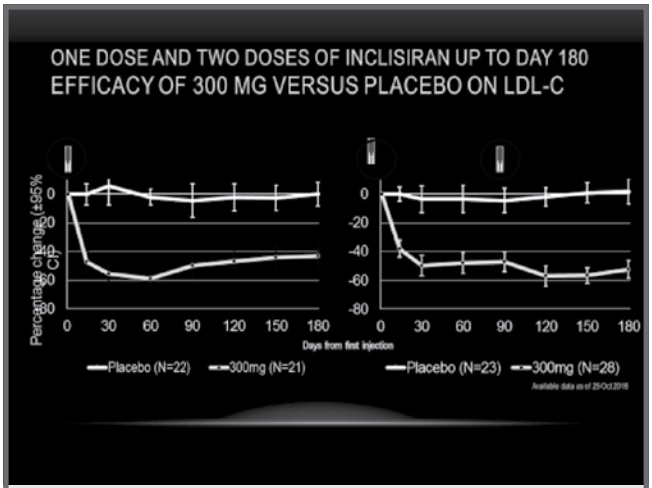

Figure 5. Change in PCSK9 level in single-dose cohorts treated with inclisiran. Data adapted from Fitgerald et al.[24]

documented, and most importantly, an improvement in clinical outcomes has been demonstrated**.** Presently, the use of these PCSK-9 inhibitors require a detailed prior authorization. It is the responsibility of the health care provider to document that the approved indications have been carefully documented in order to limit denials by payers for these expensive newer therapies.

Novel RNA interference therapy for inhibition of PCSK9 synthesis

Administration of 'small interfering RNA' (siRNA) molecules has been recently identified as a novel means to inhibit synthesis of PCSK9 levels, thereby reducing LDL-C levels. These siRNA molecules bind intracellularly to the RNA-induced silencing complex (RISC) enabling it to cleave messenger RNA (mRNA) molecules that encode PCSK9. This cleaved mRNA is degraded and thus not available for protein translation, resulting in decreased levels of PCSK9. Inclisiran (ALN-PCSsc) is a long-acting, subcutaneously delivered, synthetic siRNA directed against PCSK9 that is taken up specifically by hepatocytes. Fitzgerald and colleagues[24] recently demonstrated in a phase 1 trial involving randomization of healthy volunteers to inclisiran or placebo, that a single 300 mg dose of inclisiran was able to reduce the PCSK9 level by 75% and LDL-C levels of 51% for 6 months or longer (Figure 5), with two dosages reducing LDL-C by 57% at 6 months. This product appeared to be very well-tolerated and offers the potential for bi- or tri-annual dosing. Given the positive results, phase 3 outcomes trials are now being planned.

Conclusions

The ACC/AHA Guideline for Blood Cholesterol Management focuses on the identification of four major statin eligible groups and has as its foundation appropriate ASCVD risk assessment for appropriate targeting of therapy in primary prevention. It also promotes appropriate lifestyle and treatment of obesity as the basis of preventive cardiology and lipid management. While many patients will achieve adequate therapeutic response from the prescription of moderate or high intensity statin therapy, some patients, particularly those who cannot tolerate statins or have very high baseline LDL-C (e.g., FH) will require addition of non-statin therapy. The IMPROVE-IT trial provides a potential role for cholesterol absorption inhibitor therapy in combination with a statin in patients with acute coronary syndrome, whereas the remarkable LDL-C lowering achievable by PCSK9 mAb is potentially a valuable approach to further address residual ASCVD risk. Recent data show such therapy can also promote regression of atherosclerosis beyond statin therapy. Confirmation of the utility of PCSK9mAb treatment as a viable strategy to reduce ASCVD residual risk will depend on the results of large scale trials of the unique class of PCSK9 mAb currently in progress (the first of these was recently reported to be positive) as well as further demonstration of cost-effectiveness. Clinical practice guidelines have already adopted PCSK9 mAbs, but they are currently reserved for those at highest risk. Moreover, newer therapies in development, such as mRNA interference therapies targeting PCSK9 may hold further promise in providing more sustained reductions in LDL-C and addressing ASCVD residual risk.

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Srce i krvni sudovi 2017; 36(S2): 33-42

Review

Update in dual antiplatelet therapy in patients with ischemic artery disease

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Abstract Platelet activation and aggregation play a critical role in thrombosis, a fundamental pathophysiologic event responsible for the acute clinical manifestations of atherothrombotic events such as acute coronary syndrome, myocardial infarction, ischemic stroke/transient ischemic attack and peripheral artery disease. Dual antiplatelet therapy (low-dose aspirin plus ADP-P2Y12 receptor blockers) has become the cornerstone of therapy for the management of acute and chronic coronary artery disease and the prevention of ischemic complications associated with percutaneous coronary intervention. The newer ADP-P2Y12 inhibitors, prasugrel and ticagrelor, demonstrated superior ischemic outcomes versus clopidogrel, but there are not recommended in patients with stable coronary artery disease, unless in high-risk situations of elective stenting, such as documented stent thrombosis on clopidogrel or left main stenting. Clopidogrel is still the only ADP-P2Y12 inhibitor agent approved for patients with stable coronary artery disease undergoing percutaneous coronary intervention. The currently guidelines support the use of dual antiplatelet therapy for up to 12 months in patients with acute coronary syndrome with or without ST-segment elevation, irrespective of revascularization strategy or stent type. The recommendations for duration of dual antiplatelet therapy in patients with stable coronary artery disease undergoing percutaneous coronary intervention are 1-12 months after bare-metal stents and 6-12 months after first-generation drug-eluting stents. In a past few years, stent technology has improved and a new-generation drug-eluting stents with a safety profile has been developed. This review is focused on the most recent advances in oral antiplatelet therapy and duration of dual antiplatelet therapy in the era of new-generation drug-eluting stents.

Keywords Antiplatelet, cardiovascular disease, coronary artery disease, stable angina, acute coronary syndrome without ST- segment elevation, ST-segment elevation myocardial infarction, percutaneous coronary intervention, coronary stents.

Introduction

Platelet activation and aggregation play a critical role in thrombosis, a fundamental pathophysiologic event responsible for the acute clinical manifestations of atherothrombotic events such as acute coronary syndrome (ACS), myocardial infarction (MI), ischemic stroke/transient ischemic attack and peripheral artery disease (PAD)[1]. Inhibition of platelet -function by combined use of aspirin (acetylsalicylic acid, ASA) and ADP-P2Y12 receptor blockers is an important strategy for preventing ischemic cardiovascular (CV) events in patients with acute and chronic coronary artery disease (CAD), including those undergoing percutaneous coronary intervention (PCI)[1]. Therefore, dual antiplatelet therapy (DAPT) has become the cornerstone of therapy for the management of acute and chronic CAD and the prevention of ischemic complications associated with PCI[1-2]. However, patients receiving DAPT, especially those with ACS, remain at substantial risk of ischemic CV events because current agents do not interfere with all platelet activation pathways, allowing continued platelet activation via other pathways[1-2]. The currently available adenosine-diphosphate (ADP)-P2Y12 inhibitors are irreversible thienopyridines (clopidogrel and prasugrel) and reversibly binding ticagrelor. The newer ADP-P2Y12 inhibitors, prasugrel and ticagrelor, demonstrated superior ischemic outcomes versus clopidogrel, but increases the risk of both gastrointestinal (GI) and intracranial bleeding[3-7].

Antiplatelet therapy in secondary prevention of cardiovascular disease

The role of aspirin as an antiplatelet agent in the treatment of acute CVD events as well as for secondary prevention of future CVD events has been well established in multiple clinical trials, systematic reviews, and

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Table 1. Randomized controlled trials (RCTs) that evaluated the efficacy and safety of short-term DAPT (3-6 months) versus long-term DAPT (12-24 months) after percutaneous coronary intervention (PCI) with a newer-generation drug-eluting stents (DESs).

RCT	Year	Trial design	Number of patients	Primary Study Endpoint	Outcome
EXCELLENT	2012	6-months *vs*. 12- months DAPT after EES or SES	1443	Cardiac death, MI, or ischemia-driven TVR	Non-inferiority confirmed
RESET	2012	3-months *vs*. 12- months DAPT after ZES	2117	Cardiac death, MI, ST, TVR, or bleeding	Non-inferiority confirmed
OPTIMIZE	2013	3-months *vs*. 12- months DAPT after ZES	3119	Death, MI, stroke, or major bleeding	Non-inferiority confirmed
SECURITY	2014	6-months *vs*. 12- months DAPT after ZES or biolimus A9-eluting stents	1399	Cardiac death, MI, ST, stroke or BARC type 3 or 5 bleeding	Non-inferiority confirmed
ITALIC	2015	6-months *vs*. 24- months DAPT after EES implantation	2031	Death, MI, urgent TVR, stroke, or major bleeding	Non-inferiority confirmed
ISAR-SAFE	2015	6-months *vs*. 12- months DAPT after SES, PES, ZES or EES	4005	Death, MI, ST, stroke, or TIMI major bleeding	Non-inferiority confirmed

DAPT - dual antiplatelet therapy; MI - myocardial infarction; TVR - target vessel revascularization; ST - stent thrombosis; SES - sirolimus-eluting stent; EES - everolimus-eluting stent; ZES - zotarolimus-eluting stent; PES - paclitaxel-eluting stent; BARC - Bleeding Academic Research Consortium.

meta-analyses (8-14). The Antithrombotic Trialists` Collaboration meta-analysis of 16 secondary prevention RCTs with more than 17,000 patients with previous MI, stroke or transient cerebral ischemia demonstrated that aspirin versus control therapy was associated with significant reduction in annual rates of any serious vascular events (OR, 0.81 [95% CI, 0.75-0.81]), non-fatal MI (OR, 0.80 [95% CI, 0.73-0.88]), total stroke (OR, 0.81 [95% CI, 0.71-0.92]) and CV death (OR, 0.83 [95% CI 0.78-0.87]) (13). In another meta-analysis of six RCTs with more than 9,000 patients comparing benefits and risks of low-dose aspirin treatment (50-325 mg daily) for secondary prevention in patients with stable CVD, aspirin was associated with a significant 21% reduction in total CV events (OR, 0.79 [95% CI, 0.72-0.88]), 26% reduction in non-fatal MI (OR, 0.74 [95% CI, 0.60-0.91]), 25% reduction in stroke (OR, 0.75 [95% CI, 0.65-0.87]), and 13% reduction in all-cause mortality (OR, 0.87 [95% CI, 0.76-0.98])[45]. Although there was an increase risk of severe bleeding (especially major extracranial bleeding) in both meta-analyses, the net clinical benefit favored aspirin use in the secondary prevention of CVD events[13-14].

The currently used ADP-P2Y12 inhibitors, irreversible thienopyridines clopidogrel and prasugrel, and reversibly binding ticagrelor, have been administered as an adjunct to aspirin therapy in the management of ACS with or without ST-segment elevation, especially in patients undergoing PCI. Dual antiplatelet therapy given for a period of 12 months is a standard treatment in these patients, based on results from the CURE, PCI-CURE, CREDO, COMMIT, CLARITY-TIMI 28, CURRENT-OASIS-7, TRITON, and PLATO trials[15-23]. Conversely, there are no clinical studies supporting the use of prasugrel and ticagrelor in patients with stable CAD[15].

Clopidogrel is a prodrug which requires cytochrome P450 enzymes (including CYP2C19) in liver for its activation. It successfully replaces the first-generation ADP-P2Y12 inhibitor ticlopidine which has several disadvantages such as bone-marrow depression (usually with neutropenia), rash and diarrhea[24]. Clopidogrel irreversibly inhibits ADP-induced platelet aggregation which is several times stronger than with ticlopidine[24]. However, clopidogrel also has several limitations: 1) only 10-15% of the prodrug converts in the active drug, 2) the inhibition of platelet aggregation is dose-dependent, 3) delayed onset and offset of action, 4) there is a resistance to the drug because of CYP2C19 gene polymorphism in 15-46% of patients, and 5) the drug effect is decreased in interaction with other drugs such as proton-pump inhibitors (except pantroprazole) or non-steroidal anti-inflammatory drugs[1,24]. Only one study compared the efficacy and safety of clopidogrel versus aspirin monotherapy for secondary prevention in patients with recent MI, ischemic stroke or symptomatic PAD[25]. The CAPRIE trial demonstrated that clopidogrel was slightly superior then aspirin in reduction of major CV events (MI, ischemic stroke or CV death) in these patients, with relative-risk reduction of 8.7% in favour of clopidogrel[25]. Aspirin was associated with more, but non-significant rate of major bleedings[25]. Five RCTs showed that DAPT (loading dose of clopidogrel 300 mg, then 75 mg daily + low-dose aspirin 75-325 mg daily) versus aspirin alone significantly reduce the annual risk of total ischemic outcomes events (MI, ischemic stroke or CV death) in these patients[16-20]. Among aforementioned RCTs, only the CURE study showed that DAPT was associated with a significant increase in the rate of TIMI-defined major bleeding (OR, 1.38 [95% CI, 1.13-1.67]), but without significant increase of life-threatening bleeding and/or hemorrhagic stroke (OR, 1.21 [95% CI, 0.95-1.56])[16]. In the CURRENT-OASIS 7 study, a strategy of double-dose clopidogrel (600 mg loading dose on day 1, followed by 150 mg for 6 days, and 75 mg daily thereafter) in addition to low or higher dose aspirin therapy did not further decrease the 30-days-rate of total CV events (MI, ischemic stroke or CV death) compared with standard dose of clopidogrel (300 mg loading dose on day 1 and 75 mg daily thereafter) in ACS patients (OR, 0.94 [95% CI, 0.83-1.06])[21]. However, in the subgroup of ACS patients

who underwent PCI, double-dose clopidogrel therapy was associated with a 32% reduction in the secondary outcome of definite stent thrombosis (OR, 0.68 [95% CI, 0.55-0.85]), with slightly increase in major bleeding (OR, 1.24 [95% CI, 1.05-1.46])[21]. Meta-analysis of 10 studies (7 RCTs, 3 non-randomized) with more than 1,500 patients referred for PCI, showed that high-loading dose of clopidogrel (>300 mg) before PCI reduces the 30-days risk of cardiac death or non-fatal MI compared with 300 mg dose of clopidogrel (OR, 0.54 [95% CI, 0.32-0.90]), without any significant increase in major or minor bleeding[26]. Additionally, in the CURRENT-OASIS 7 study, there was no significant difference between higher-dose (300-325 mg daily) and lower-dose (75-100 mg daily) aspirin with respect to the total ischemic outcomes events (OR, 0.97 [95% CI, 0.86-1.09]) or major bleeding (OR, 0.99 [95% CI, 0.84-1.17])[21].

Yet, previous data suggest that about 25% of patients on clopidogrel therapy are non-responders and the risks of recurrent major ischemic CV events in these patients are 3-fold greater compared with responders (OR, 3.52 [95% CI, 2.39-5.20])[27]. Therefore, alternative strategies were proposed, such as increasing the loading and maintenance doses of clopidogrel,

aimed to achieve a greater, more rapid, and more consistent platelet inhibition. However, such strategies have failed to improve CV outcomes[28-29]. This led to the development of newer ADP-P2Y12 antiplatelet agents that have more rapid and more consistent inhibition of platelet aggregation and improving CV outcomes[27].

Prasugrel is a third-generation thienopyridine that irreversibly inhibits ADP-induced platelet aggregation. It has several advantages over clopidogrel: 1) it has a more rapid onset of antiplatelet effect (within 30 minutes) since 80% of the prodrug converts into the active metabolite by gut enzymes CYP3A during its absorption, 2) it achieves more consistent and 10 times stronger inhibition of ADP-induced platelet aggregation than clopidogrel, 3) the drug metabolism is independent of the hepatic CYP450 enzyme complex which means that its effect does not depend on genetic polymorphism, and 4) the concomitant use of proton-pump inhibitors do not interfere with the drug metabolism[1-2,24]. In the TRITON-TIMI 38 study, 13,608 patients with ACS scheduled for PCI were randomized to receive either clopidogrel 300 mg loading dose followed by 75 mg daily or prasugrel 60 mg loading dose followed by 10 mg daily, in addition to low-dose (75-162 mg daily) aspirin therapy[3]. Patients receiving prasugrel had a significant 19% reduction in total CV events (MI, stroke or CV death) during median follow-up of 14.5 months compared with clopidogrel (OR, 0.81 [95% CI, 0.73-0.90])[30]. In the prasugrel group, there were also a significant 24% reduction in non-fatal MI (OR, 0.76 [95% CI, 0.67-0.85]), 34% reduction in urgent target-vessel revascularization (OR, 0.66 [95% CI, 0.73-0.90]) and 52% reduction in definite or probable stent thrombosis according to the Academic Research Consortium (ARC) definition (OR, 0.48 [95% CI, 0.36-0.64])[3]. The prasugrel efficacy was greater among patients with diabetes (OR, 0.70 [95% CI, 0.58-0.85]) than among patients without diabetes (OR, 0.86 [95% CI, 0.76-0.98])[3]. However, this beneficial effect was associated with an increased risk of non coronary artery bypass graft (CABG)-related TIMI major bleeding (OR, 1.32 [95% CI, 1.03-1.68]), including life-threatening (OR, 1.52 [95% CI, 1.08-2.13]) and fatal bleeding (OR, 4.19 [95% CI, 1.58-11.11])[3]. The study identified three subgroups of ACS patients that had less net clinical benefit or clinical harm with prasugrel: 1) patients with previous history of stroke or transient ischemic attack, 2) elderly $\geq$ 75 years, and 3) patients with a body weight of less than 60 kg[3]. After excluding these three groups of patients who were at higher risk for bleeding, there was a significant reduction in total CV events in prasugrel group of ACS patients compared with clopidogrel group (OR, 0.74 [95% CI, 0.66-0.84]), without a significant difference in the rate of non CABG-related TIMI major bleeding (OR, 1.24 [95% CI, 0.91-1.69])[3]. Therefore, the currently ACC/AHA and ESC guidelines do not recommend prasugrel therapy in ACS patients with: 1) active bleeding, 2) previous stroke or TIA, 3) 75 years or older, and 4) body weight less than 60 kg[30-31].

An additional subanalysis of the TRITON-TIMI 38 study also confirmed that ACS patients with diabetes had a greater net clinical benefit with prasugrel compared with clopidogrel (OR, 0.74 [95% CI, 0.62-0.89]), irrespective to diabetes treatment type (OR, 0.66 [95% CI, 0.47-0.92] for patients on insulin; OR, 0.78 [95% CI, 0.63-0.96] for patients on oral antidiabetic drugs)[32]. A significant 30% reduction in total CV events was seen in diabetics (OR, 0.70 [95% CI, 0.58-0.85), mostly because of a significant 40% reduction in non-fatal MI (OR, 0.60 [95% CI, 0.48-0.76) and 48% reduction in stent thrombosis (OR, 0.52 [95% CI, 0.33-0.84)[32]. Among insulin-treated and non insulin-treated patients with diabetes, a significant reduction in total ischemic outcomes were observed (OR, 0.63 [95% CI, 0.44-0.89] for insulin-treated diabetics; OR, 0.74 [95% CI, 0.59-0.93] for non insulin-treated diabetics)[32]. Although a significant increase in non CABG-related TIMI major bleeding were observed among patients without diabetes (OR, 1.43 [95% CI, 1.07-1.91]), there was no difference in the rate of major bleeding among patients with diabetes (OR, 1.06 [95% CI, 0.66-1.69])[32]. According to this data, this study suggested that prasugrel in addition to aspirin therapy had a greater net clinical benefit for secondary prevention in ACS patients with diabetes (OR, 0.74 [95% CI, 0.62-0.89]) than in those without diabetes (OR, 0.92 [95% CI, 0.82-1.03])[32].

Another subanalysis of the TRITON-TIMI 38 study was performed in 12,844 patients with ACS who received at least one coronary stent (5,743 drug-eluting stent, and 6,461 bare-metal stent)[33]. This study showed that prasugrel compared with clopidogrel reduced the incidence of total ischemic outcomes for overall 19% (OR, 0.81 [95% CI, 0.72-0.90]), CV death for 16% (OR, 0.84 [95% CI, 0.66-1.08]), fatal or non-fatal MI for 24% (OR, 0.76 [95% CI, 0.67-0.86]), and urgent target-vessel revascularization for 32% (OR, 0.68 [95% CI, 0.55-0.84]), irrespective of stent type (OR, 0.80 [95% CI, 0.69-0.93] for bare-metal stent; OR, 0.82 [95% CI, 0.69-0.97] for drug-eluting stent)[33]. Additionally, prasugrel significant-

ly reduced the incidence of stent thrombosis (OR, 0.48 [95% CI, 0.36-0.64]), irrespective of stent type, the ARC definition used, or clinical characteristics[33]. Stent thrombosis was reduced both early (between 0 and 30 days) and late (> 30 days) after stent placement with prasugrel compared with clopidogrel (OR, 0.41 [95% CI, 0.29-0.59] for early stent thrombosis; OR, 0.60 [95% CI, 0.37-0.97] for late stent thrombosis)[33]. In contrary, TRILOGY ACS study evaluated efficacy and safety of prasugrel (10 mg daily) versus clopidogrel (75 mg daily) in addition to aspirin (75-100 mg daily) therapy in patients with unstable angina or MI without ST-segment elevation who did not referred for PCI and who were under the age of 75 years, during median follow-up of 17 months[4]. This study failed to demonstrate the superiority of prasugrel over clopidogrel for reducing total ischemic events (MI, stroke or CV death) in these patients (OR, 0.91 [95% CI, 0.79-1.05]), with similar risks for severe and intracranial bleeding between the two groups[4]. The ACCOAST study compared efficacy and safety of prasugrel as pretreatment at the time of diagnosis or after the coronary angiography if PCI was indicated, in patients with non ST-elevation MI who were scheduled to undergo coronary angiography within 2-48 hours after randomization[34]. Patients were treated with prasugrel (30 mg loading dose) before angiography (pretreatment group) or placebo (control group), and an additional 30 mg of prasugrel was given in the pretreatment group at the time of PCI, and 60 mg of prasugrel was given in the control group at the time of PCI[34]. The rate of total CV events (MI, stroke, CV death and urgent revascularization) through day 7 did not differ significantly between the two groups (OR, 1.02 [95% CI, 0.84-1.25])[34]. However, the rate of all TIMI major bleeding (CABG or non-CABG) through day 7 was increased in the pretreatment group (OR, 1.90 [95% CI, 1.19-3.02])[34]. Bleeding events were predominantly associated with PCI or CABG and occurred early in patients who referred for PCI (OR, 2.69 [95% CI, 1.13-6.40])[34]. The study found that pretreatment with prasugrel in patients with non ST-elevation MI who were scheduled to undergo cardiac catheterization within 48 hours after admission did not reduce the rate of major ischemic events up to 30 days, but increased the rate of major bleeding complications[34].

Ticagrelor is oral, reversible, direct-acting inhibitor of the ADP-P2Y12 platelet receptors that has several advantages over clopidogrel and prasugrel: 1) it does not require metabolic biotransformation for its antiplatelet activity, and 2) it is associated with a rapid onset of action, a greater level of AD-induced platelet inhibition and a more rapid offset of pharmacodynamic action[1,24]. In the PLATO study, 18,624 patients admitted to the hospital within 24 hours after symptom onset, who suffered from ACS with or without ST-segment elevation and referred for cardiac catheterization, were randomized to receive either clopidogrel 300-600 mg loading dose followed by 75 mg daily or ticagrelor 180 mg loading dose followed by a dose of 90 mg twice daily, in addition to low-dose (75-100 mg daily) aspirin therapy[5]. Patients receiving ticagrelor had a significant 16% reduction in total CV events (MI, stroke or CV death) during median follow-up of 12 months compared with clopidogrel (OR, 0.84 [95% CI, 0.77-0.92]). In the ticagrelor group, there were also a significant 16% reduction in non-fatal MI (OR, 0.84 [95% CI, 0.75-0.95]), and 21% reduction in death from vascular causes (OR, 0.79 [95% CI, 0.69-0.91]), but the rate of stroke did not differ significantly between the two treatment groups (OR, 1.17 [95% CI, 0.91-1.52])[5]. Among patients who received a stent during the study, the rate of definite, probable or possible stent thrombosis according to the ARC definition was significantly lower in the ticagrelor group than in the clopidogrel group (OR, 0.77 [95% CI, 0.62-0.95])[5]. There was no significant difference in the rates of TIMI major bleeding (OR, 1.03 [95% CI, 0.93-1.15]), including CABG-related TIMI major bleeding between the two groups (OR, 0.94 [95% CI, 0.82-1.07]), but ticagrelor was associated with a higher rate of non-CABG-related TIMI major bleeding (OR, 1.25 [95% CI, 1.03-1.53]), especially more instances of fatal intracranial and nonintracranial bleeding[5]. Because ticagrelor is structurally similar to adenosine, it may cause dyspnea and/or bradyarrhythmias (including ventricular pauses) that are usually resolved after first month of continued treatment[5,35]. Several subanalyses of the PLATO study confirmed that ticagrelor versus clopidogrel significantly reduced the rates of total ischemic events in ACS patients scheduled either for early invasive strategy (PCI or CABG) (OR, 0.84 [95% CI, 0.75-0.94]) (36), or medical therapy only (OR 0.85 [95% CI, 0.73-1.00]) (37), in ACS patients with chronic kidney disease (OR, 0.77 [95% CI, 0.65-0.90])[38], or with diabetes (OR, 0.80 [95% CI, 0.70-0.91])[39], with similar rates of total major bleeding in all aforementioned substudies.

Meta-analysis of four RCTs with more than 31,000 patients who suffered from ACS without ST-Elevation MI (NSTE-ACS) showed that newer oral ADP-P2Y12 inhibitors (prasugrel or ticagrelor) significantly decreased major ischemic CV events (MI, stroke or CV death) by 13% compared with clopidogrel (OR, 0.87 [95% CI, 0.80-0.95])[7]. Newer oral ADP-P2Y12 inhibitor also significantly reduced MI (OR, 0.85 [95% CI, 0.75-0.96]) with a trend towards reduction of CV death (OR, 0.89 [95% CI, 0.71-1.01]) and without significant difference in the rate of stroke (OR, 0.96 [95% CI, 0.78-1.18])[7]. This results were similar when stratified by prasugrel versus ticagrelor for all primary and secondary end point ($p_{interaction}>0.05$). Newer ADP-P2Y12 inhibitors showed a significant increase in non-CABG-related TIMI major bleeding (OR, 1.27 [95% CI, 1.07-1.5]) and in TIMI major or minor bleeding (OR, 1.20 [95% CI, 1.02-1.42]) compared with clopidogrel[7]. This results were similar when stratified by prasugrel versus ticagrelor for TIMI major bleeding ($p_{interaction}>0.05$), but not for TIMI major and minor bleeding ($p_{interaction}<0.05$) which was significantly increased with prasugrel[7]. Two additional meta-analyses demonstrated that newer ADP-P2Y12 inhibitors compared with clopidogrel had a stronger anti-ischemic effect in patients with ST-Elevation MI (STEMI) than in NSTE-ACS patients, with a 16-23% reduction in total CV events, 19-25% in non-fatal MI, 33-36% in stent thrombosis, 19% reduction in CV mortality, and 22-23% reduction in all-cause mor-

tality[40-41]. Contrary to NSTE-ACS patients, both meta-analyses showed similar stroke and TIMI major bleeding rates between newer ADP-P2Y12 group and clopidogrel group among STEMI[7,40-41].

Prasugrel and ticagrelor in addition to low-dose aspirin therapy in secondary CVD prevention appear to be more effective for a reduction in major ischemic CV events compared with clopidogrel. The ESC guidelines support using ticagrelor and prasugrel over clopidogrel in NSTE-ACS and STEMI patients (Class of Recommendation I, Level of Evidence B)[30,42-43]. The AHA/ACC guidelines provide a similar level of recommendation for all oral ADP-P2Y12 inhibitors (Class of Recommendation I, Level of Evidence B)[31,44-45]. Clopidogrel is still the only ADP-P2Y12 inhibitor agent approved for patients with stable CAD undergoing PCI (Class of Recommendation I, Level of Evidence A)[46]. Prasugrel and ticagrelor are not recommended in patients with stable CAD, unless in high-risk situations of elective stenting, such as documented stent thrombosis on clopidogrel or left main stenting (Class of Recommendation IIb, Level of Evidence C)[46].

Duration of dual antiplatelet therapy in patients with ischemic heart disease

According to previous RCTs[3,5,16-18], the currently ACC/AHA and ESC guidelines support the use of DAPT for up to 12 months in patients with ASC with or without ST-segment elevation, irrespective of revascularization strategy or stent type[30-31,42-45]. In patients with stable CAD, DAPT is recommended only after elective PCI[46-47]. The CHARISMA trial did not show the superiority of DAPT over aspirin monotherapy in reduction of major CV events (MI, stroke, or CV death) among patients with previously documented CAD, PAD or CVD[48]. This trial showed that DAPT (clopidogrel 75 mg/d in combination with low-dose aspirin75-100 mg/d) was not significantly more effective than aspirin alone (75-100 mg/d) in reducing the rate of total CV events (MI, stroke, or CV death) among these patients (OR, 0.88 [95% CI, 0.77-0.998])[48]. Contrary, this study suggested that DAPT was associated with a significant increase in the rate of GUSTO-defined moderate bleeding (OR, 1.62 [1.27–2.08]), especially in patients with documented CAD, PAD or CVD[48].

The recommendations for duration of DAPT in patients with stable CAD undergoing PCI are 1-12 months after bare-metal stents (BMS) and 6-12 months after first-generation drug-eluting stents (sirolimus-eluting stents [SES] and paclitaxel-eluting stents [PES])[46-47]. Both SIRIUS and TAXUS-IV trials demonstrated that PCI with first-generation drug-eluting stents (DES) compared to BMS has a significant reductions of in-stent restenosis, target-lesion revascularization (TLR) and target-vessel revascularization (TVR)[49-50]. However, observational BASKET-LATE trial suggested that the discontinuation of ADP-P2Y12 inhibitor 6 to 18 months after PCI leads to a 2- to 3-fold higher rates of delayed stent thrombosis and thrombosis-related events, such as MI or death, in DES-treated patients compared with BMS-treated patients[51]. This was explained by delayed endothelialization of DES. Therefore, the Food and Drug Administration (FDA) recommended a minimum duration of 12 months of DAPT after first-generation DES implantation (52).

Two recent RCTs, DAPT study and the PEGASUS-TIMI 54 trial, evaluated the efficacy and safety of DAPT therapy beyond 12 months[53-54]. In the DAPT study, 12 months after treatment with standard ADP-P2Y12 thienopyridine drugs (clopidogrel or prasugrel) and low-dose aspirin (75-162 mg daily), patients who had undergone PCI with a first- or new-generation DESs were randomly assigned to continue receiving thienopyridine treatment or to receive placebo for another 18 months in addition to aspirin[53]. The longer-DAPT duration (beyond 12 months after DES placement) compared with standard-DAPT duration (up to 12 months) was associated with a significant reduction in the rates of definite or probable stent thrombosis according to ARC definitions (OR, 0.29 [95% CI, 0.17-0.48]), major CV events (MI, stroke or death) (OR, 0.71 [95% CI, 0.17-0.48]), and non-fatal MI alone (OR, 0.47 [95% CI, 0.37-0.61]), between 12 and 30 months after PCI, irrespective of the specific thienopyridine drugs used and stent type[53]. The efficacy of longer-DAPT duration was even greater in patients presented with MI compared with those presented without MI (OR, 0.27 [95% CI, 0.13-0.57] for stent thrombosis; OR, 0.56 [95% CI, 0.42-0.76] for major CV events; OR, 0.42 [95% CI, 0.29-0.62] for non-fatal MI)[55]. The rate of moderate or severe bleeding was significantly higher in the longer-DAPT duration group compared with standard-DAPT duration group (OR, 1.61 [95% CI, 1.21-2.16])[53]. In addition, the rate of all-cause mortality was unexpectedly higher in the longer-DAPT duration group (OR, 1.36 [95% CI, 1.00-1.85]), mainly due to a higher rate of non-CV death (OR, 2.23 [95% CI, 1.32-3.78]), but the underlying reasons for this remains unclear[53]. In the PEGASUS-TIMI 54 trial, patients with a history of MI in the previous 1 to 3 years, were randomly assigned to continue receiving ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo, for a median of 33 months, in addition to low-dose aspirin (75-150 mg daily[54]. The study found that the use of both ticagrelor dose compared with aspirin alone beyond 12 months significantly reduced the risk of major CV events (OR, 0.85 [95% CI, 0.75-0.96] for 90 mg of ticagrelor; OR, 0.84 [95% CI, 0.74-0.95] for 60 mg of ticagrelor), MI (OR, 0.81 [95% CI, 0.69-0.95] for 90 mg of ticagrelor; OR, 0.84 [95% CI, 0.72-0.98] for 60 mg of ticagrelor), and stroke (OR, 0.82 [95% CI, 0.63-1.07] for 90 mg of ticagrelor; OR, 0.75 [95% CI, 0.57-0.98] for 60 mg of ticagrelor)[54]. The rate of TIMI-defined major bleeding was higher with the two ticagrelor doses than with placebo (OR, 2.69 [95% CI, 1.96-3.70] for 90 mg of ticagrelor; OR, 2.32 [95% CI, 1.68-3.21] for 60 mg of ticagrelor), with a significantly higher rates of bleeding leading to transfusion and bleeding leading to discontinuation of the drug[54]. The PEGASUS-TIMI 54 trial did not demonstrate an increase in all-cause mortality in ticagrelor 90 mg twice daily group (OR, 1.00 [95% CI, 0.86-1.16] for 90 mg of ticagrelor), but rather a trend towards improved all-cause mortality in the ticagrelor 60 mg twice daily group (OR, 0.89 [95% CI, 0.76-1.04])[54]. Thus, the results of DAPT study and PEGASUS-TIMI 54

trial suggest longer-DAPT duration with more potent ADP-P2Y12 inhibitors without interruption in selected patients with high risk for ischemic CV events and lower risk for bleeding may be an option[2].

The PRODIGY trial investigated the efficacy of short-DAPT duration compared to longer-DAPT duration in patients with stable CAD or ACS after PCI[56]. In this trial, patients were randomly assign to receive up to 6 or 24 months of clopidogrel therapy (75mg daily) in addition to low-dose aspirin (80-325 mg daily) after PCI with BMS or DES (zotarolimus-eluting, paclitaxel-eluting or everolimus-eluting stents)[56]. This study showed that the extended use of DAPT, for up to 24 months, was not significantly more effective than a 6-months DAPT duration in reducing the cumulative risk of major CV events (OR, 0.98 [95% CI, 0.74-1.29]), and the individual risk of all-cause mortality (OR, 1.00 [95% CI, 0.72-1.40]), MI (OR, 1.06 [95% CI, 0.69-1.63]), cerebrovascular accident (OR, 0.60, [95% CI, 0.29-1.23]) or delayed definite or probable stent thrombosis according to ARC definition (OR, 1.15 [95% CI, 0.55-2.41]) type[56]. On the other hand, the prolonged use of DAPT was associated with a significant 62% greater risk of TIMI-defined major bleeding (OR, 0.38, [95% CI, 0.15-0.97]), including events that required medical or surgical treatment, red blood cell transfusion, and life-threatening events[56]. An additional subanalysis of the PRODIGY trial demonstrated similar rate of ischemic CV events between 24-months and 6-months DAPT duration in both ACS (OR, 0.94 [95% CI, 0.69-1.27]) and stable CAD patients (OR, 1.59 [95% CI, 0.77-3.27]), while bleeding risk was significantly higher in the long-term DAPT arm in both groups[57]. Long-term DAPT compared with short-term DAPT was associated with a 75% increase of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding in ACS patients (OR, 0.75 [95% CI, 1.11–2.74]), and a 5-fold increase in stable CAD patients (OR, 5.37 [95% CI 1.84–15.74])[57]. The net adverse cardiac events (NACE), consisting of the death, MI, cerebrovascular accident, or BARC 2, 3, or 5 type of bleeding, was significantly increased in the 24-month DAPT duration in stable CAD patients (OR, 2.5 [95% CI 1.35–4.69]), but not in the ACS patients (OR, 1.15 [95% CI 0.88–1.50])[57]. The study pointed out that prolonged use of DAPT after PCI may have a greater efficacy with a lower bleeding risk in ACS patients because of its higher platelet reactivity, while doubled the bleeding risk in patients with stable CAD[57]. Three other RCTs (DES-LATE, ARCTIC-Interruption, and OPTIDUAL trial) confirmed that DAPT duration beyond 1 year after DES implantation in patients with ACS or stable CAD was not superior in the reduction of ischemic CV events, while the rate of major and minor bleeding was increased[58-60].

Additionally, in a past few years, stent technology has improved and a new-generation DESs with a safety profile has been developed[61]. Six RCTs evaluated efficacy and safety of short-term DAPT (3-6 months) versus standard- and long-term DAPT (12-24 months) after PCI with newer-generation DESs. The EXCELLENT, RESET, OPTIMIZE, SECURITY, ITALIC, and ISAR-SAFE trials showed that the use of DAPT up to 6 months was safe and not inferior to the standard- and long-term DAPT for the reduction in ischemic CV events (62-67). Several meta-analyses which included RCTs evaluating the short- (<6 months) and long-term DAPT (>12 months) after implantation of newer-generation DESs concluded that extension of DAPT beyond 6 months increased the risk of bleeding without reducing the risk of all-cause mortality, cardiac death, non-fatal MI, cerebrovascular accident, or stent thrombosis[68-75]. The meta-analysis by Giustino et al. found that short-term DAPT was associated with significantly higher rate of stent thrombosis (OR, 1.71 [95% CI, 1.26-2.32]), but its effect on stent thrombosis was attenuated with the use of newer-generation DESs (OR, 1.54 [95% CI, 0.96-2.47]) compared with the use of first-generation DESs (OR, 3.94 [95% CI, 2.20-7.05])[74]. In contrast to this findings, a meta-analysis by Udell et al. evaluated the use of long-term DAPT in patients with prior MI and demonstrated a significant 22% reduction in ischemic CV events (OR, 0.78 [95% CI, 0.67–0.90]), 25% in cardiac death (OR, 0.85 [95% CI, 0.74–0.98]), 30% in non-fatal MI (OR, 0.70 [95% CI, 0.55–0.88]), 29% in stroke (OR, 0.81 [95% CI, 0.68–0.97]), and 50% in definite or probable stent thrombosis according to ARC definition (OR, 0.50 [95% CI, 0.28–0.89])[76]. There was a significant increase in the risk of major bleeding (OR, 1.73 [95% CI, 1.19–2.50]), but not fatal bleeding (OR, 0.91 [95% CI, 0.53–1.58]), with no excess of non-CV causes of death (OR, 1.03 [95% CI, 0.86–1.23])[76]. Previous trials and meta-analyses suggest that long-term DAPT is best used in patients who are at the highest risk of subsequent ischemic CV events, such as those with an ACS in the preceding 3 years and those who are at low risk for bleeding events[77]. Furthermore, the long-term DAPT should be avoided in patients with stable CAD who are at lower risk for subsequent ischemic CV events, such as those with stable angina, elective PCI with a newer-generation DESs, no previous history of ACS, and high bleeding risk (elderly patients and those with diabetes or chronic kidney disease)[77]. It should be pointed out that the use of DAPT beyond 1 year after PCI must be individualized; however, it remains difficult to predict which patients will have the greatest net clinical benefit from prolonged DAPT due to a lack of standardized risk-benefit algorithm[77]. Regarding this issue, a new risk score (the „DAPT score“) has been developed (78-79). This score, which derived from the DAPT study, may be useful in assessing the benefit and risk of prolonged DAPT (>12 months) in patients treated with PCI (78-79). The score incorporates several factors with the respective weighting points (WP) for benefit/risk calculation of DAPT score: patient age (WP for <65 years = 0; WP for 65-74 years = 1; WP for $\geq$75 years = -2), cigarette smoking (WP = 1), diabetes (WP = 1), MI at presentation or earlier (WP = 1 for each), prior PCI (WP = 1), stent type (WP for paclitaxel-eluting stent = 1; WP for other DES or BMS = 0), stent diameter <3 mm (WP = 1), vein graft PCI (WP = 2), and congestive heart failure or left ventricular ejection fraction <30% (WP = 2) (78-79). The benefit/risk ratio of prolonged DAPT in patients with a high DAPT score ($\geq$2) may be favorable because it reduces both ischemic and bleeding events when compared with short-term DAPT[78-79]. Conversely, in patients with a low

DAPT score (<2), benefit/risk ratio of prolonged DAPT is not favorable due to increased bleeding risk without a reduction in ischemic events[78-79].

Taking into account the available data, the current 2016 ACC/AHA Guideline Focused Update addresses specific recommendations on duration of DAPT in patients with stable CAD or ACS after implantations of newer-generation DESs[80-81]:

I Recommendations for DAPT duration in patients with stable CAD treated with PCI:

a. In patients with stable CAD treated with DAPT, ADP-P2Y12 inhibitor (clopidogrel) should be given for a minimum of 1 month after BMS implantation (Class of Recommendation I; Level of Evidence A), and for at least 6 months after DES implantation (Class of Recommendation I; Level of Evidence B-R),

b. In patients with stable CAD after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with ADP-P2Y12 inhibitor (clopidogrel) for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable (Class of Recommendation IIb; Level of Evidence A),

c. In patients with stable CAD treated with DAPT after DES implantation who are at high risk of severe bleeding complication (eg, treatment with oral anticoagulant therapy), discontinuation of ADP-P2Y12 inhibitor therapy after 3 months may be reasonable (Class of Recommendation IIb; Level of Evidence C-LD),

d. In patients with stable CAD without prior history of ACS, PCI, or recent (within 12 months) coronary artery bypass grafting (CABG), DAPT treatment is not beneficial over aspirin monotherapy (Class of Recommendation III; Level of Evidence B-R).

II Recommendations for DAPT duration in patients with ACS treated with PCI or medical therapy alone:

a. In patients with ACS (NSTE-ACS or STEMI) after PCI with BMS or DES implantation, or medical therapy alone, DAPT with ADP-P2Y12 inhibitor should be given for at least 12 months (Class of Recommendation I; Level of Evidence B-R). The current 2016 ACC/AHA guideline support the use of ticagrelor over clopidogrel in patients with ACS, irrespective of the treatment type (Class of Recommendation IIa; Level of Evidence B-R). Prasugrel is recommended over clopidogrel in ACS patients only after PCI unless they are at high risk for bleeding complications, 75 years or older, who have body weight <60 kg and do not have a history of stroke or TIA (Class of Recommendation IIa; Level of Evidence B-R).

b. In patients with ACS (NSTE-ACS or STEMI) treated with PCI or with medical therapy alone, who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable (Class of Recommendation IIb; Level of Evidence A),

c. In patients with ACS treated with DAPT after DES implantation who are at high risk of severe bleeding complication, or develop significant overt bleeding, discontinuation of ADP-P2Y12 inhibitor therapy after 6 months may be reasonable (Class of Recommendation IIb; Level of Evidence C-LD).

In patients after elective or primary PCI who subsequently undergo CABG, DAPT with ADP-P2Y12 inhibitor should be resumed postoperatively so that DAPT continues until the recommended duration of therapy is completed (Class of Recommendation I; Level of Evidence C)[81]. In patients with stable CAD, DAPT with clopidogrel initiated early postoperatively for 12 months after CABG may be reasonable to improve vein graft patency (Class of Recommendation IIb; Level of Evidence B-NR)[81].

Elective noncardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation (Class of Recommendation I; Level of Evidence B-NR)[81]. It should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively (Class of Recommendation III; Level of Evidence B-NR)[81]. In patients after PCI who must undergo elective noncardiac surgery that mandate the discontinuation of DAPT, it is recommended that aspirin be continued if possible and the ADP-P2Y12 inhibitor be restarted as soon as possible after surgery (Class of Recommendation I; Level of Evidence C-EO).

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Srce i krvni sudovi 2017; 36(S2): 43-45

Commentary

Comparison between US and European Guidelines on Cardiovascular Primary Prevention

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Abstract European Society of Cardiology guidelines on primary prevention of cardiovascular diseases were published in 2016. Those guidelines are to some extent different from current set of American College of Cardiology/American Heart Association guidelines dealing with primary prevention. Both United States and European guidelines agree that primary prevention of cardiovascular diseases is essential. Guidelines ask for individual risk calculation and agree that LDL-cholesterol is directly related to cardiovascular disease morbidity and mortality and should be adequately treated. However, there is substantial difference in risk estimation and treatment strategies in patients without established cardiovascular disease. The purpose of this short review is to underline similarities and especially difference between current primary prevention guidelines in United States and Europe, and to address advantages and disadvantages of each of these strategies.

Introduction

European Society of Cardiology (ESC) released recently new version of guidelines on cardiovascular (CV) disease prevention in order to further decrease CV morbidity and mortality in Europe[1]. In 2013 American Colleague of Cardiology/American Heart Association (ACC/AHA) has published three different papers dealing with CV prevention: assessment of CV risk (2), lifestyle modification to reduce CV risk[3] and the third paper on treatment of high cholesterol levels[4].

Risk estimation

The initial approach of risk management is to establish individual risk for CV events and to start optimal treatment (life style changes with or without pharmacological treatment) based on this calculation. Both, in European and American, guidelines high risk patients are considered as those with established CV disease, diabetes and familial hypercholesterolemia. ESC guidelines consider patients with chronic kidney disease as being (very) high risk patients, whereas in ACC/AHA guidelines CKD patients are not discussed at all. Those high risk patients, according to all available data, require strict risk factor control in order to avoid further adverse events and disease progression.

In all other patients risk should be assessed using global risk calculator. From 2003, ESC guidelines use SCORE charts to calculate individual 10 years risk of first fatal CV event. SCORE charts are based on huge European dataset of more than 200000 patients that have been externally validated[5] for low risk and high risk countries (such as Serbia). Fatal CV events are defined as death due to coronary artery disease, stroke and abdominal aneurism. CV risk is calculated based on the age, gender, smoking status and levels of total cholesterol or total/HDL cholesterol ratio and systolic blood pressure[1]. US guidelines recommend Pooled Cohort Studies Equation (PCSE) (based on the results of 4 cohorts) for the calculation of CV risk using similar variables as SCORE with addition of race, HDL cholesterol, treatments of hypertension and diabetes[2]. However, the major difference between two guidelines is that US guideline uses 10 years risk of any first CV event rather than fatal CV event. From epidemiological point of view it doesn't seem appropriate to use the end point of natural history of the disease as a target for primary prevention as in ESC guidelines. The authors of the guidelines should keep in mind that practitioners in their every-day work want to prevent the disease and not only the death from the disease. Also, in many European countries mortality from CV diseases is decreasing so the SCORE-based treatment (especially statin use) might be omitted in spite of high CV disease morbidity[6]. The authors of ESC guidelines used mortality rather than morbidity deliberately. There were several reasons for this decision: Death is completely reproducible hard endpoint event that is not variable and dependent upon various definitions, diagnostic criteria and diagnostic tests like myocardial infarction; it is obvious that increased risk of CV death is related to increased risk of non-fatal events. The SCORE data indicate that the total CV event risk is about three times higher than risk of CV

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death in men, four times higher in women and less than three times in older persons in whom first event tend to be more frequently fatal[7].Third, using only fatal events enable easy recalibration of the model if needed. The other reason for the use of CV death in SCORE lies in the fact that model is based on old cohorts from 1972 to 1991 year, with death certificates being the most consistent data source at that time.

The second important limitation of ESC guidelines is that SCORE risk is applicable only in age range from 40 to 65 years. The intention was to avoid overtreatment of older subjects due to the high impact of age on overall risk assessment, even though other risk factors are reasonable low in those patients. Based on US guidelines almost to all subjects older than 70 years, according to risk calculator moderate to high-intensity treatment should be prescribed. However, those physicians who advocate for ESC guidelines approach should keep in mind that only 18% of all fatal CV events in apparently healthy people occur in the age group of 40-65 years[8]. Contemporary ESC guidelines do not contain an information how to treat elderly people without apparent CV disease, although it is known that some preventive measures can postpone morbidity and mortality in this age group.

The use of different risk calculators SCORE vs. PCSE as it has been shown previously results in different risk estimation[9]. Obviously US risk calculator by assessing both fatal and nonfatal events results in higher estimation of risk. According to US guidelines patients with 10 years risk of 7.5% for first fatal or non-fatal event are considered to be high risk patients and require intense risk factor management, including statins. However, the 10 years risk of 7.5% corresponds to a 2.5% risk of CV death in next 10 years in the SCORE model that is considered as moderate risk. The recent analysis of Multi-Ethnic Study of Atherosclerosis demonstrated that US risk score overestimates risk of endpoints by 78%(10). From practical point of view the most important question is how this risk estimation affects primary prevention of CV morbidity and mortality.

Consequences of different risk calculation models

The first consequence of ACC/AHA guidelines acceptance is significant increase in statin use. Consistent data including two recent meta-analysis, showed beneficial effect of statin use in primary prevention on CV morbidity and mortality[11,12]. So the question is not whether statins should be used in persons without established disease, rather to identify adequate patients who will benefit most from statin use. It is estimated that adherence to American guidelines would dramatically increase the number of patients eligible for statin treatment, with 12.8 million of new statin users in USA[13]. This number is primarily related to increased statin use among older adults (over 70 years) without CV disease (i.e. in the group of patients in whom the data on mortality reduction with statin are not so definite). Recently, on 7229 individuals free of CV disease, aged 45-75 years, examined between 1997 and 2008. for the Rotterdam study was shown that need for statin treatment is significantly higher when using US instead of ESC guidelines. The ACC/AHA recommends statin in 4284 (58%) participants, while ESC guidelines recommend it in 2399 participants (33%), with huge overlapping by 95.8% with American guidelines. In majority of cases with difference between two guidelines statin treatment is suggested by US guidelines, whereas is inappropriate by ESC guidelines. However, there is small group of patients (0.8%) at very high risk who are eligible by ESC, but not ACC/AHA guidelines. Those are patients with chronic kidney disease and significantly reduced renal function, as well as patients with heart failure who are not mentioned in US guidelines at all14.

Higher prescription of statin according to US guidelines would have two important effects. First, it would increase cost of treatment, that is an issue especially important for countries with low income (such as Serbia). Second, such a broad use of statin in primary prevention would increase statin related side effects, especially among older subjects. These adverse effects include myopathy (with potentially fatal rhabdomyolysis) and liver damage. A much more important adverse effect is increase in new cases of diabetes mellitus, that has been estimated to range from 9-13% of new cases of diabetes with prolonged statin treatment[15-17]. Importantly, it has been shown that new occurrence of diabetes is dose dependent adverse effect[18].

The other crucial difference between US and ESC guidelines is that last issue of US guidelines doesn't define therapeutical goal for LDL-cholesterol. According to calculated risk patient should be offered moderate of intensive statin treatment. This approach is not something that practitioners are used to. In majority of cases doctors start treatment with lower statin dose with further adjustment based on LDL-cholesterol levels. As opposite, ACC/AHA guidelines may unintendedly result in „fire and forget" approach, with prescribing appropriate dose but without further follow up. It has been clearly shown that this approach leads to worse adherence of patients and worse CV outcome due to lesser degree of cholesterol reduction[19] . Adherence to life-long statin treatment is per se a problem, since 50% of all patients with prescribed statin and 75% of those who were prescribed statin for primary prevention stop taking the drug within one year of treatment initiation[20].

It should be clearly stated that US guidelines recommend assessment of therapeutic response and possible side effects 4 to 12 weeks after the beginning of treatment and every 3 to 12 months thereafter[4]. However it remains unclear what doctor should do with such information if the goal of treatment is not define. One should be aware, that this approach may cause problem for general practitioners when in need to treat hypercholesterolemia and to communicate risk to the patients. It is of note that current prevention guidelines from both sides of Atlantic ocean are not designated only for cardiologist but even more to general practitioners, who seeks for easy to use and clear guidelines in order to facilitate every day practice.

Conclusion

Both US and ESC guidelines have some advantages in disadvantages as discussed earlier. Before some consensus between associations is made, it seems prudent to promote application of European guidelines in Serbia. SCORE risk estimation despite of certain limitations is based on European population, similar to ours, although the best approach would be recalibration of the SCORE model according to national CV mortality statistics. The basic principles of risk estimation and patient treatment as recommended by ESC guidelines are more acceptable for our medical practitioners especially in terms of clear goals of treatment. Also, adherence to US guidelines would significantly increase the costs of treatment due to increase statin prescription.

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Srce i krvni sudovi 2017; 36(S2): 46-47

Commentary

Comparative analysis of ESC 2016 guidelines and ACC/AHA/HFSA 2016 guidelines about the importance of angiotensin receptor neprilysin inhibitor (ARNI) in the treatment of patients with systolic heart failure

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The 2016 contemporary Guidelines of European Society of Cardiology for diagnostics and treatment of acute and chronic heart failure recommends that the treatment of heart failure with reduced systolic function should be started with ACE inhibitors and beta blockers1. It is necessary to titrate the dosage of these medicaments and increase it gradually to the level of those in great randomized clinical studies that proved to be efficient in mortality reduction in patients with systolic heart failure. Guidelines from 2016 are not different in this matter from those given by previous guidelines for heart failure of European Society of Cardiology. If, beside the treatment with optimal dosages of ACE inhibitors (blockers of angiotensin receptors in patients intolerant to ACE inhibitors) and beta-blockers, a patient with a reduced systolic function and ejection fraction of 35% or less still shows symptoms and signs of heart failure, it is necessary to add the antagonist of mineral corticoid receptors.

If a patient still shows symptoms and signs of heart failure even after full ACE inhibitors therapy (blockers of angiotensin receptors in patients intolerant to ACE inhibitors), beta blockers and antagonists of mineral corticoid receptors, it is necessary to consider the next step in the treatment. One of the therapeutic options is replacing ACE inhibitors (blockers of angiotensin receptors in patients who are intolerant to ACE inhibitors) with an inhibitor of angiotensin receptor – neprilysin (ARNI). A new composite medicament consists of blockers of angiotensin receptors valsartan and neprilysin inhibitor sacubitril. If QRS duration of the electrocardiogram is 130 msec or more a resynchronization therapy may be considered. If patients still have a heart rate over SF 70/min even after therapy with beta blockers with optimal dosage (maximum tolerated dosage), the addition of ivabradine to the therapeutic list should be considered.

From the initiation of treatment of patients with heart failure diuretics are used optionally, as a symptomatic treatment for congestion. It is important to consider the indication for ICD implantation in a primary or secondary prevention of sudden cardiac death.

The 2016 contemporary Guidelines of European Society of Cardiology suggest replacement of ACE inhibitors (blockers of angiotensin receptors in patients intolerant to ACE inhibitors) with an inhibitor angiotensin receptor–neprilysin (ARNI) as a possible therapeutic procedure. The objective is to increase efficiency in the treatment of patients with systolic heart failure and the improvement of patient`s prognosis. ACE inhibitors reduce the mortality of patients with systolic heart failure by 18%, blockers of angiotensin receptors showed to be slightly less effective in the reduction of mortality by 15%. Beta blockers presented better results in the reduction of mortality by 34%, antagonists of mineral corticoid receptors 25% and ICD implementation 26%.

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure raised ARNI inhibitor to a higher level in the therapeutic algorithm and suggested it as a starting option in the treatment of patients as an alternative therapy for ACE inhibitors (a blocker of angiotensin receptors in patients intolerant to ACE inhibitors)[2,3]. The contemporary American guidelines suggest ARNI inhibitors as a starting option in the treatment of patients with heart failure and reduced ejection fraction below 40% (class I level of evidence B), together with beta blockers and antagonists of mineral corticoid receptors. ARNI inhibitor reduces the mortality of patients with systolic heart failure by 38%. The conceptual principle of the conventional therapy by ACE inhibitors (blockers of angiotensin receptors in patients intolerant to ACE inhibitors) beta blockers and antagonists of mineral corticoid receptors was the blockage of excessive neurohumoral activation in chronic heart failure. Apart from this conceptual principle ARNI inhibitor (blockers angiotensin receptor valsartan) includes stimulation and intensifying of adaptive mechanisms in heart failure through increasing the concentration of endogen vasoactive peptides (neprilysin inhibitor sacubitril). The levels of natriuretic peptides and bradykinin are increased by the blockage of neprilysin receptors. In this way, the adaptive mechanisms of heart failure are stimulated with the final result in vasodilatation, the reduction of progression in myocardium fibrosis, the reduction of salt retention and the reduction of excessive neurohumoral activation as well.

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Composite drug ARNI inhibitor contains the blockers of angiotensin receptors valsartan and the inhibitor of neprilysin receptor sacubitril. This composite medicament was tested in PARADIGM-HF study, in III clinical phase, on over 8000 patients[4]. Patients were randomized on ARNI inhibitor with the dosage of 200 mg twice a day and on enalapril of 10 mg twice a day. ARNI inhibitor showed improvement in patient`s prognosis and the reduction of cardiovascular mortality by 20% compared to enalapril, in recommended dosage by the guidelines for the treatment of heart failure. The overall mortality in patients was reduced by 18 % by using ARNI inhibitor.

European recommendations differ from those of American guidelines regarding introduction of ARNI inhibitor in later phases of the therapeutic algorithm, after previous standard ACE inhibitor therapy (blockers of angiotensin receptors in patients intolerant to ACE inhibitors), beta blockers and antagonists of mineral corticoid receptors. The reason for a more reserved approach in the 2016 Guidelines of European Society of Cardiology for diagnostics and treatment of acute and chronic heart failure is a need for accumulation of experience from a more extensive clinical practice especially regarded side effects. ARNI inhibitor showed in PARADIGM-HF trial a slightly higher incidence of angioedema, without statistical significance. The suggestion of European guidelines is to check the usage of the new drug before it is recommended widely and the treatment of patients with systolic heart failure. The intention of European recommendations is also to check the efficacy of ARNI inhibitor in the group of patients with a less impaired left ventricle systolic function. Although ARNI inhibitor has not revealed any adverse clinical effects on cognitive functions, it has been noticed that in some patients an increase of beta-amyloid peptide can occur in cerebrospinal liquor. The suggestion of European guidelines is to check additionally in practice the effects of the new drug on cognitive functions before its wider usage as a drug for the initiation of systolic heart failure treatment.

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Srce i krvni sudovi2017; 36(S2): 48-52

Commentary

Cardiooncology - cancer treatments and cardiovascular toxicity

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Abstract During Second Congress of the 34th American College of cardiology consortium chapter of Serbia and Republic of Srpska, PRactical aspects and comparative analysis of ACC/AHA and ESC guidelines In Serbia 2017 (PRACSIS 2017) in collaboration with the Project and Campaign "25 by25" Of World Heart Federation, Cardiooncology session- treatment of malignant tumors and cardiovascular toxicity was held. The 2016 ESC Position paper on cancer treatments and cardiovascular toxicity developed under the auspice of the ESC Committee for Practice Guidelines were then presented illustrated with our examples from everyday practice. Further in the text below we present parts of this Guidelines with presentation of our cases and comments from the expert.

Cardiovascular complications of cancer therapy (pathophysiology)

Treatment of malignant diseases by applying conventional radiotherapy, chemotherapy, as well as the so-called, innovative drugs from the group of monoclonal antibodies and small molecules, has led to significant progress in terms of prognosis of patients with hemato-oncological diseases. However, more complex therapeutic approaches have led to the emergence of increased morbidity and mortality rates related to adverse effects of applying different chemotherapy agents.1,2 Cardiovascular diseases (CVD) are considered to be more frequent adverse events as the result of cardiac toxicity of chemotherapy and radiotherapy with concomitant presence of risk factors that predispose their formation.3

Cardiovascular complications occur after treatment of malignant tumors, divided into nine major groups, namely[4]:

1. Myocardial dysfunction and heart failure
2. Coronary artery disease
3. Valvular disease
4. Arrhythmias, especially those with QT prolongation
5. Arterial hypertension
6. Thromboembolic disease
7. Peripheral vascular disease and stroke
8. Pulmonary hypertension
9. Pericardial complications

Myocardial dysfunction and heart failure that is applied termin cardiotoxicity are the most common cardiovascular complications of treatment of malignant disease, and the cause of the increase in morbidity and mortality rates. Cardiotoxicity may be manifested immediately after drug administration, or months or years later. Predicting the degree of cardiovascular damage is very important, because patients receive prolonged polychemotherapy, often combined with radiotherapy.

The dysfunction of the left ventricle (LV) and heart failure are common, so the monitoring of patients in whom they appear is necessary. For example, patients treated for aggressive non Hodgkin lymphoma have the incidence of heart failure, which is 17% after 5 years of treatment of malignant disease.[5]

Drugs that are most commonly responsible for this complication are anthracycline cytostatics, which also represent unique agents in the treatment of hematologic malignancies and solid tumors. They can cause the progressive myocardial remodeling, as a late complication of early myocyte damage and can lead to late cardiomyopathy, but on the other side, the effects can be transient. The most common pathophysiological mechanism for anthracycline – induced cardiotoxicity is a result of hypotheses of oxidative stress with the generation of reactive oxygen species and the process of lipid peroxidation of the cell membrane of cardiomyocytes.[6,7]

The degree of cardiotoxicity is connected with the cumulative dose of the drug, for example, in the case of doxorubicin 400mg/m^2, the incidence of heart failure is 5%, which is growing exponentially and the amounts to as much as 48%, when a cumulative dose of drug is 700 mg/m^2.[8]

According to the time of onset, anthracycline cardiotoxicity may be: acute, early and late. Acute toxicity occurs in <1% of the patients immediately after infusion of the drug, and is usually reversible. Most common is the phenomenon of supraventricular arrhythmias, transient LV dysfunction and ECG changes. Acute toxicity reflects damage to cardiomyocytes and can evolve into early or late cardiotoxicity.[4] Unfortunately, it can not be determined with certainty whether it is reversible or

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progressive cardiac toxicity, but still an increase in serum biomarkers (troponin, BNP, NT-proBNP) can identify patients who are candidates for long-term myocardial damage. Early toxic effects on the myocardium usually occur within the first year of treatment, while late appear after several years.[9,10] Risk factors for anthracycline cardiotoxicity include: cumulative dose, dosing regimen (fast infusion with rapid peak serum concentration vs. long-term infusion of the drug), existing cardiac co-morbidities, arterial hypertension, concomitant use of other chemotherapeutics, mediastinal radiation, age > 65 years, female gender, renal failure.[4,11]

Other conventional cytotoxic drugs that can lead to myocardial dysfunction and heart failure are cyclophosphamide and ifosfamide - in high doses, as alkylating agents, cisplatin, and antitubular cytostatic agents: paclitaxel and docetaxel.

Immunotherapy with monoclonal antibodies and target molecules from the group of tyrosine kinase inhibitors (TKI) and other molecular signaling pathways inhibitors, despite of significant progress in the treatment of malignancies, was exhibited a degree of toxicity on various organs and tissues, including cardiotoxicity.

An example of such effects is drugs that act in the HER2 (human epidermal growth factor receptor 2) signaling pathway, as antibodies (trastuzumab) or as TKI, such as lapatinib, that are used in the treatment of breast cancer in combination with chemotherapy.

The cumulative incidence of composite cardiac dysfunction when trastuzumab is used in combination with anthracyclines was 6.2% and 20.1% after 1 and 5 year respectively.[4,12]

Also, the inhibition of other signaling pathways such as VEGF (vascular endothelial growth factor), by monoclonal antibodies (bevacizumab, ramucirumab), or drugs from the group of TKI to VEGF receptor inhibitors (sunitinib, sorafenib, cabozatinib, etc), may cause cardiotoxicity, when that drugs are used in the treatment of breast tumors, particularly in combination with anthracyclines.[4]

Small molecules, BCR-ABL kinase inhibitors (imatinib, dasatinib, nilotinib, etc) drugs for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors, may also lead to the occurrence of cardiac toxicity, as well as the proteasome inhibitors (bortezomib, carfilzomib) which are used in the treatment of multiple myeloma, as well as certain refractory lymphomas.[4]

Radiotherapy of the mediastinum and breast by applying high doses (> 30 Gy) and using the broader field of radiation (> involved field) also potentially cardiotoxic, especially when combined with anthracyclines.[4]

Coronary artery disease (CAD) as type of myocardial ischemia, myocardial infarction, arrhythmia caused by ischemia, can also be a consequence of chemotherapeutic attack. Mechanisms of CAD can arise due to myocardial ischemia, and range from direct vasospastic effects to endothelial lesions and acute arterial thrombosis, and finally may cause the long-term changes in the metabolism of lipids and consequent arteriosclerosis.

Previous mediastinal and breast radiotherapy may precipitate the effect of previously administered drugs to damaged coronary arteries, especially in correlation with the larger applied dose.

Fluoropyrimidines, like 5-fluorouracil (5-FU), and its oral form capecitabine may cause coronary vasospasm by various mechanisms, whereas cisplatin and anti-VEGF agents (monoclonal antibodies and small molecules), may lead to arterial thrombosis.[4,13]

As for the valve diseases, cytostatic agents can not damaged them directly, but radiation therapy can, in approximately 10% of cases, in terms of the fibrosis and calcification of the aortic root, aortic valve cusps, mitral valve annulus and the base and mid portions of the mitral valve leaflets, particularly at doses > 30 Gy.[4,14]

Cardiac arrhythmias can be diagnosed at 16-36% of patients with malignancies, which are: sinus tachycardia, bradyarrhythmias or tachyarrhythmias, and conduction defects which can be life-threatening.[4,15] Certain cytotoxic agents, such as arsenic trioksid, doxorubicin, histone deacetylase inhibitors and TKI, can cause QT prolongation, which can be a prelude to torsade de pointes as a life-threatening condition. Also, ventricular arrhythmia may occur with prolongation of the QT interval as part of chronic toxicity due to the application of chemotherapy and radiotherapy. Prolongation of the QT interval can appear due to electrolyte dysbalance, metabolic disorders, and usage of antibiotics, antifungal drugs, antipsychotics, and constitutional factors of patients with preexisting co-morbidities.

Arterial hypertension is often preexisting comorbid condition, but appearance of new hypertension during treatment can usually induce therapy with VEGF inhibitors, steroids and hormonal drugs such as erythropoietin.

Thromboembolic disease can be often caused by a variety of pathways, including procoagulant, antifibrinolytic and pro-aggregation, through the release of pro-inflammatory and pro-angiogenesis cytokines, as well as through the interaction of blood cells and vascular endothelium by means of adhesive molecules.

Arterial thrombosis is rare and occurs in about 1% of patients, while venous thrombosis is present in about 20% of hospitalized patients with malignancy, which is unfortunately often unrecognized. Various clinical factors are associated with venous thromboembolism in patients with malignant diseases and are defined as: factors related to the tumor (type and histopathological type of malignant disease, clinical stage of disease), factors related to the patient (demographic factors, co-morbidities, previous history of thromboembolism, performance status), as well as factors related to the therapeutic approach (major surgery, chemotherapy, hormonal therapy, hospitalizations, transfusions, presence of central venous catheter).[16]

Peripheral vascular disease in terms of severe atherosclerosis or non-atherosclerotic peripheral arterial disease of the lower limbs may occur in over 30% of patients on therapy with TKI[4], while the risk of stroke doubles in patients who previously had radiotherapy of neck, head and mediastinum.[17]

Pulmonary hypertension is a rare but serious complication that can occur in patients treated with second-generation TKI, such as dasatinib, which can cause severe precapillary pulmonary hypertension, and in patients who underwent hematopoietic stem cell trans-

plantation.[4] Also, cyclophosphamide and other alkylating cytostatics may cause pulmonary veno-occlusive disease.

Based on the foregoing, it follows that it is essential to define the basic risk of cardiac toxicity of each patient with a malignancy that will be treated with chemotherapy with the possible application of radiotherapy. In this regard, after assessing comorbid status, it is necessary to take into account the cumulative dose of anthracycline cytostatics in particular, a combination of drugs that are precipitating adverse effect, the prevention of venous thromboembolism with low molecular weight heparin (LMWH), and by optimizing doses and fields of radiation therapy.

Therapeutic options for prevention of myocardial dysfunction caused by malignant tumor therapy

These Guidelines[4] are given in order to prevent myocardial dysfunction caused by the treatment of malignant tumor.

Patients with high prior risk for cardiovascular disease (CVD) and were previously treated with the therapy that included anthracyclines, or the risk factor for CVD were poorly controlled the strict control of these risk factors is necessary together with the preventive use of cardioprotective drugs.

If the patient has heart failure (HF) or significant left ventricular (LV) dysfunction before the initiation of treatment, cardiooncological team should decide between the following options: non-cardiotoxic hemotherapy, dose reduction, and/or the use of cardioprotective drugs (beta blockers, ACE inhibitors, aldosterone antagonists, dexraroxan) (Table 1).[4] Cardioprotection should be initiated also in the cases of elevations of troponin during a high dose anthracyclines therapy. If during therapy course LV EF decrease ensues, treatment according to HF guidelines should be initiated.[18] However, there is no evidence to guide specific cardioprotection if early signs of subclinical myocardial dysfunction are detected during echocardiography-based GLS surveillance.[19,20] Cancer patients presenting with clinical HF during or following chemotherapy should be treated according to current ESC guidelines for HF,[21] the therapy is discontinued, and if therapy continuation is considered, patients should be put on beta blocker and ACE inhibitors. Also, during cancer treatment a healthy lifestyle is recommended (smoking cessation, healthy eating habits, body weight control, and regular moderate exercise, etc).

Having in mind that chemotherapy, as well as malignancies, increases a risk for venous thromboembolism (VTE), anticoagulation therapy with low molecular weight heparin (LMWH) is recommended.[22,23]

Strategies for attenuation of complications related to use of specific agents

For attenuating **anthracycline** toxicity, there is a possibility to use less cardiotoxic drugs, the reduction in the cumulative dose; use of continuous infusions to decrease peak plasma levels in adult patients.

Table 1. Strategies to reduce chemotherapy-induced cardiotoxicity[4].

Chemotherapy drug	Potential cardioprotective measure
All chemotherapy	Identify and treat cardiovascular risk factors
Drugs	Treat comorbidities (CAD, HF, PAD, HTN)
	QTc prolongation and torsade de pointes: - Avoid QT prolonging drugs - Manage electrolyte abnormalities - Minimize cardiac irradiation
Anthracyclines and Analogues	Limit cumulative dose (mg/m2): - Daunorubicin <800 - Doxorubicin <360 - Epirubicin <720 - Mitoxantrone <160 - Idarubicin <150
	Altered delivery systems (liposomal doxorubicin) or continuous infusions
	Dexrazoxane as an alternative
	ACE-Is or ARBs
	Beta blockers
	Statins
	Aerobic exercise
Trastuzumab	ACE-Is
	Beta blockers

Co-administration of **anthracyclines and trastuzumab** markedly increases the incidence of HF, but cardiotoxicity can be reduced significantly by introducing a drug-free interval between the two agents. The National Cancer Research Institute[24] recommends that if LVEF decreases to 45% or 10 percentage points from baseline to a value between 45% and 49%, trastuzumab should be interrupted and ACE inhibitors should be started; trastuzumab may be reinitiated if the LVEF is restored to 49%. If the decrease occurs despite ACE inhibitor therapy, the patient should be referred to a cardio-oncologist.

Patients treated with **pyrimidine analogues** frequently present angina pectoris, ischaemia-related ECG abnormalities, arrhythmias and myocardial infarction, even in patients with normal coronary arteries. In cancer patients with pre-existing CAD receiving drugs that may produce myocardial ischaemia, aggressive control of CAD risk factors is necessary.

VEGF signaling pathway inhibitors can cause blood pressure elevation, so close blood pressure monitoring and treatment is recommended.

Heart-sparing **radiotherapy** techniques should be oriented towards lowering the dose of radiation and the cardiac volume exposed using modern techniques based on 3D treatment planning (CT and MRI). Despite these measures, irradiation of the heart is unavoidable when the target volume is close, such as in left breast cancer and some cases of Hodgkin lymphoma.

Long-term surveillance programmes for cancer survivors

Over the past decade, the population of patients surviving for long periods after the diagnosis and treatment of cancer has substantially increased together with the risk of CVD development. It is imperative to raise awareness of possible cardiac disease among these patients. Patients should be informed of their increased risk of CVD at the outset of their Cancer treatment and should be advised and supported to make appropriate lifestyle modifications. They should also be instructed to promptly report early signs and symptoms of CVD.

Cardiovascular complications include myocardial dysfunction, vascular disease and valvular heart disease (VHD).

Both paediatric and adult survivors of anthracycline-based chemotherapy have a lifelong risk for the development of LV dysfunction and HF. The time lapse between treatment and the development of HF can be very long, longer than 10 years. Thus, periodic screening with cardiac imaging and biomarkers, such as BNP, should be considered, particularly in those patients who demonstrated reversible LV dysfunction during cancer treatment.[25] Task Force recommendation is to continue HF therapy indefinitely unless normal systolic LV function remains stable after cessation of HF therapy and no further cancer therapy is planned. Trastuzumab-induced cardiac dysfunction is frequently reversible, cessation of HF treatment after normalization of LVEF may be considered for these patients.[26]

Having in mind that high percent of cardiovascular disease is 'silent' screening for ischaemic heart disease is a recommended for patients with cancer who received mediastinal radiation.[27] This screening should start 5 years after irradiation treatment and repeat it every 5 years. Owing to the increased risk of stroke in patients with previous neck irradiation, ultrasound scanning of carotid arteries to rule out the presence of subclinical atherosclerosis could be included for a comprehensive cerebrovascular risk assessment.

Radiation-induced VHD occurs late after mediastinal radiotherapy, with a median time to diagnosis of 22 years.[28] For asymptomatic patients, the EACVI/ASE consensus document recommends a screening transthoracic echocardiogram (sometimes TEE, 3D ultra-sound and CMR in patients with suboptimal TTE) at 10 years post-radiation and serial exams every 5 years thereafter. The European Association of Cardiovascular Imaging and the American Society of Echocardiography (EACVI/ASE) recommend a focused yearly history and physical examination with echocardiography in symptomatic patients.[29]

Conclusion

The advances in Oncology treatments have brought an increase in long-term survivors.

The primary success was achieved using aggressive protocols with nonspecific, toxic drugs that have brought great consequences on cardiovascular health. On the other hand, the advances in cardiological diagnostic procedures and therapy enabled a great number of patients to be treated for malignancies and to perceive overall cardiovascular risk in these treatments.

A close collaboration between oncologists and cardiologists is necessary as well as formation of cardiac-oncology centres, with well-structured service that includes several healthcare professionals (nurses, doctors, cardiologists, imaging specialists, oncologists, etc.) with expertise in this field.

The role of Cardiologist includes a careful initial evaluation before starting potentially cardiotoxic chemotherapy and optimal control of pre-existing cardiovascular risk factors, followed by ongoing cardiac safety monitoring for early signs of cardiovascular toxicity and timely implementation of preventive or therapeutic measures. Oncologists and haematologists are faced with uncertainty over whether to disqualify or qualify a patient from treatment that might be lifesaving, due to baseline CVD.

One of the most important unresolved issues is the choice between a primary vs. secondary prevention strategy (only relevant in patients at highest cardiovascular risk or when using therapy with a high cardiotoxic potential.) There is a lack of evidence on sensitivity of serial assessment of LVEF. Several circulating biomarkers (troponin I, BNP or NT-proBNP) have shown sensitivity for the early detection of myocardial dysfunction.

In order to better identify patients that would benefit from either primary or secondary prevention there is a need to consider several factors: defining the most reliable cardiac monitoring approach, evaluating the rate of subclinical LV dysfunction and its transition to overt HF, determining the clinical effect and outcome (in terms of morbidity and mortality) after cancer therapy.

This approach could provide data that would allow the construction of true evidence-based strategies and open a new era in cardio-oncology.

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Srce i krvni sudovi 2017; 36(S2): 53-54

Case Report

Combined cardiopulmonary-stress echocardiography testing in discovering latent HFpEF

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Heart failure with preserved ejection fraction (HFPEF) has overtaken heart failure in the setting of reduced ejection fraction (HFREF; also known as systolic heart failure) as the most common form of HF and now comprises more than 50% of all patients with HF[1-2]. Still, the recognition of HFPEF can be difficult due to the multiple confounding co-morbidities that can impair exercise capacity and mimic the signs and symptoms of HF[3]. Thus, the clinician's ability to make early diagnoses and timely initiate therapeutic interventions is often limited.

Here, we present a case in whom we through the combined cardiopulmonary and exercise stress-echocardiography testing (CPET-ESE) discovered masked/latent HFpEF.

A 50 year old man came to our lab for CPET testing due to the exercise-induced chest pain and dyspnea, which began to be occurring during his regular work in the last few months. Symptoms usually stoped after rest. He has been taking medications for hypertension (HTA) and hyperlipoproteinaemia (HLP) and had chronic left bundle branch block (LBBB). His physical exam was unremarkable. Echocardiogram at rest revealed signs of left ventricular (LV) hypertrophy with normal regional contractility and normal systolic function. Mitral inflow pattern showed impaired relaxation of LV, but with normal LV filling pressures; E/E' at rest was 6,5 (figure 1). Based on symptoms patient' reported and echocardiography results at rest, we decided to check the possible existence of ischemic heart disease, as well as to check the systolic/diastolic function of the heart. Thus, we have performed CPET-ESE testing on semi-supine ergobicycle, using Ramp 15 protocol. We used the tissue Doppler imaging measurements (E') and mitral inflow early wave measurement (E) both at rest and at maximal effort during the combined ESE-CPX test for identification of the diastolic dysfunction and increased LV filling pressure.

Patient performed test for 12 minutes and achieved workload of 114 watts when he stopped due to the dyspnea. He had not reported any chest pain during or after the test. The echocardiography analysis during and after the test showed no changes in regional LV contractility or wall motion abnormalities. However, his peak oxygen consumption (VO_2 peak) was lower than expected for his age and sex, and his ventilatory efficiency (VE/VCO_2 slope) was mildly impaired (class II), figure 2. Importantly, stress-echocardiogaphy revealed significant increase in LV filling pressure during exercise (E/E' was 16), while mitral inflow pattern pointed to restrictive LV filling; figure 3. Results of the combined CPET-ESE test pointed to the existence of HFpEF with no signs of ischemic heart disease.

Discussion

The value of ESE in identifying ischemic heart disease in patients with chest pain during exercise is well known

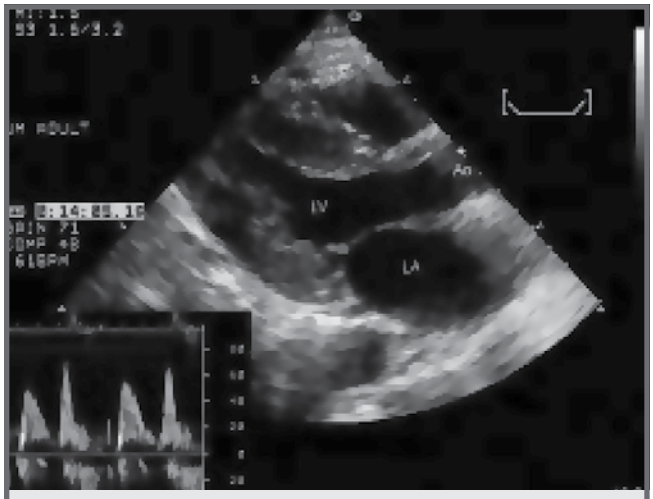

Figure 1. LV of the patient and mitral inflow pattern at rest.

	pred.	rest	AT	Max.Load	max/pred.	AT/Ref
Time ..... h:mm:ss	-	0:01:10	0:11:00	0:12:00	-	-
Load ..... W	178	98	100	114	64%	56%
VO2 ..... l/min	**2,45**	**0,37**	**1,31**	**1,43**	**58%**	**53%**
VO2/kg ..... ml/kg/min	28,5	4,3	15,2	16,7	58%	53%
VCO2 ..... l/min	2,70	0,31	1,15	1,42	53%	43%
RER	**-**	**0,83**	**0,88**	**0,99**	**-**	**-**
Circulation						
HR 1/min	**148**	**64**	**109**	**112**	**76%**	**74%**
O2 pulse ..... ml/beat	**17,9**	**5,8**	**12,0**	**12,8**	**71%**	**67%**
BPsys ..... mmHg	-	176	174	202	-	-
BPdia ..... mmHg	-	100	114	108	-	-
Ventilation						
VE ..... l/min	84,58	13,51	39,43	50,56	60%	47%
VT l	2,66	0,68	1,24	1,45	54%	47%
f-ergo 1/min	29	20	32	35	122%	111%
BR ..... %	**-**	**84**	**53**	**40**	**-**	**-**
VD/VT	-	0,41	0,28	0,25	-	-

Figure 2. The results of CPET in analyzed patient.

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(4). On the other hand, it has been only recently shown that combined CPET-ESE test is a feasible and reliable test can identify patients with masked HFpEF (5). Traditional echocardiographic parameters have been insensitive for the HFpEF diagnosis because they have tried to identify patients with dyspnea during exercise using only resting diagnostic criteria. So, ESE can mimic physiological condition to monitor at the same time diastolic function and LV filling pressure with Doppler echocardiography and symptoms by CPET[6-7]. The only prespecified criteria for the HFpEF diagnosis was a ratio of a Doppler early mitral flow (E wave) and tissue Doppler imaging of early mitral annulus movement (E') at peak exercise greater than 15[8]. However, concomitant analysis of cardiopulmonary functional capacity can improve the specificity of changes in E/E' and can help in avoiding the overreliance on a single echocardiographic measurement during ESE.

Therefore, our decision to perform CPET-ESE test seemed reasonable having in mind patient' symptoms. And the results of the test confirmed that our decision was the right one. Both, suboptimal increase in VO_2 peak and significant increase in E/E' demonstrated that patient has HFpEF. In addition, it has been shown that HFpEF patients have the lower peak VO_2, the lower peak $PetCO_2$ values, and the higher VE/VCO_2 slope, which was also the case with our patient[9-10]. And the normal electrocardiogram and wall motion during and after exercise, together with the absence of chest pain, showed us that ischemic heart disease was not the cause for a increase in LV filling pressure and subsequent HFpEF. Many other mechanism, including cardiac, vascular and metabolic factors (4 u guazzi), may contribute to observed reduction in exercise capacity in our patient. Nevertheless, their net result has been demonstrated during CPET with lower VO2 peak and increase in VE/VCO_2 slope.

Conclusion

In conclusion, to date, there is no approved therapy for HFpEF patients that reduces their high risk for serious adverse events. To improve their outcome, a deeper understanding of the subpopulations

that fit under the HFpEF syndrom, and more specific test that can reliably identify these patients are needed. The combined ESE-CPET test has shown to be just that; a feasible and reliable test that can identify patients with masked HFpEF. The opportunity for early recognition could open a new window for future research to find a successful therapy for these patients.

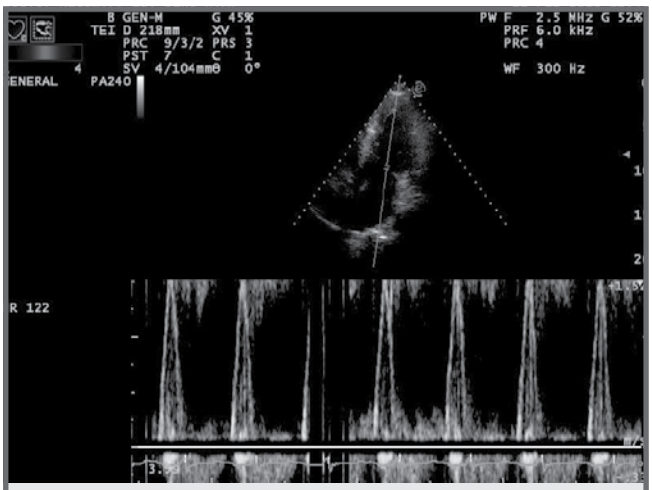

Figure 3. Patient' mitral inflow pattern at peak exercise.

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Srce i krvni sudovi 2017; 36(S2): 55-58

Case Report

Lipid management in young adult with familial hypercholesterolemia

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Familial hypercholesterolemia (FH) is an autosomal dominant genetic lipid metabolism disorder, characterized by high levels of serum cholesterol, particularly the high values of fractions of low density lipoprotein (LDL-c), an accelerated process of atherosclerosis (AS), and premature cardiovascular disease (CVD). Since moderately elevated cholesterol levels are the characteristic of modern day people living inhighly developed countries, it should be noted that 1 in 500 people worldwide suffers from the heterozygous form of FH (heFH). The homozygous form (hoFH) is rarer, occurring in 1 out of a million cases (with greatly elevated serum LDL values and cardiovascular disease in their childhood).

The worldwide epidemiological data show that 10 million people suffer from FH (predominantly the heFH form):

- 200.000 of these prematurely die of coronary heart disease (CHD);
- 80% of heFE patients remain undiagnosed;
- 84% of heFE patients do not take lipid-lowering drugs.

Cardiovascular mortality of individuals with FH aged 20 to 39 years is almost a hundred times greater than that in the general population[1,2,3].

Our country does not have the prevalence data for this disease and the introduction of new guidelines for early detection, screening, diagnosis, and early therapy is essential for the clinical practice in order to prevent the disease complications.

S.D., a patient aged 43 years, was referred for a specialist examination complaining of the feeling of pressure in the chest on exertion. In his personal anamnesis, the patients reported normal blood pressure values, smoking of around 20 cigarettes a day for 15 years, being aware of his elevated lipid levels since his 38 years of age. In the familial history, in his male lineage, there were family members with elevated lipid levels in the blood. His father died suddenly in his 52nd year of life. On first examination, very high cholesterol levels were found in our patient. Table 1 presents the lipid status in the period from 2009 to 2015. In the beginning, 20 mg atorvastatin was prescribed, which was taken regularly for only a few months, and in 2011 the patient ceased to take the therapy altogether, in spite of his doctor's recommendations and dysregulated lipid levels.

The patient came for a new examination on November 3, 2015, complaining of mediastinal pain and rapid fatigue, with the blood pressure value 110/80 mmHg, heart rate (HR) of 75/min, weight 95 kg, height 178 cm, BMI 30, and waist size 105 cm. Notable findings were then the arcus cornealis (Figure 1), ECG sinus rhythm, heart rate (HR) 75/min. Figure 2 depicts his ECG.

Due to progressive dispnea and more common chest pain, complete non-invasive and invasive diagnostic work-up was made.

Color Doppler sonography of the carotid arteries (CDS) was done at the end of 2015, demonstratingintima-media thickness(IMT) of 1,0 mm and *stenosis bulbi lat. dex.*of 43% and *lat. sin.* 36%.

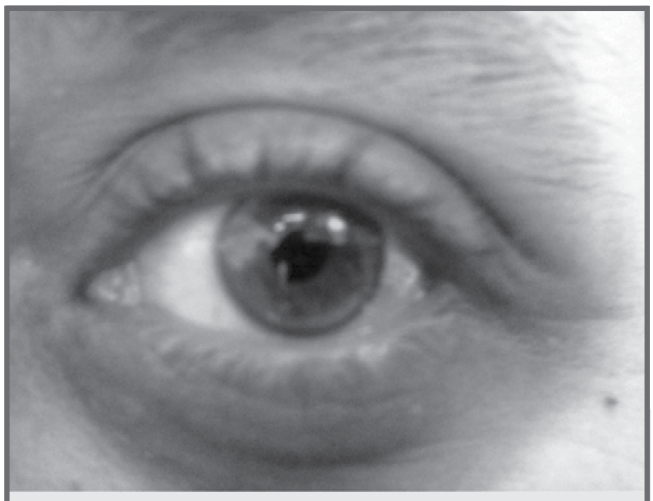

Figure 1. Arcus cornealis.

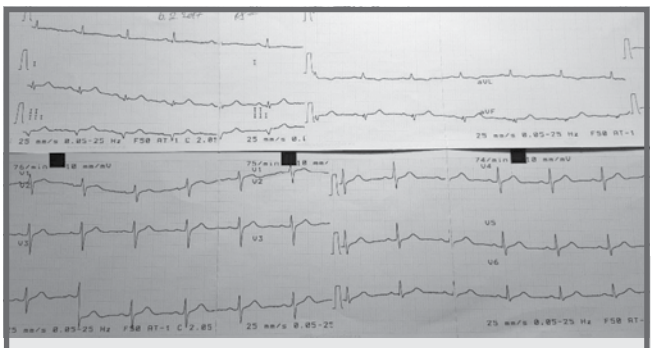

Figure 2. Electrocardiogram of the patient.

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Table 1. Lipid management in young adults with FH –a laboratory analysis

	1.4.2010	1.10.2010	5.3.2011	3.11.2015
Glucose	5.27	5.69	6.08	5.25
TC (mmol/l)	16.64	9.6	10.99	15.15
LDL-C (mmol/l)	13.9		7.61	
HDL-C (mmol/l)	2.1		2.08	
TG (mmol/l)	2.91	1.4	1.62	3.1
Body mass index	28.5	28.8		29.4
Smoking status	Yes	No	No	No
Therapy	Atorva-statin 20 mg	Not regularly taken	Stopped	Rosuva-statin 40 and Fibrate
Status		Exercise test nega-tive for ischemia	Exercise test nega-tive for ischemia	Angina pectoris

TC: Total Cholesterol; LDL-C: Low-denisty lipoprotein-cholesterol; HDL-cholesterol: High-density lipoprotein-cholesterol; TG: Triglycerides.

After the examination, stress echocardiography (on physical exertion) was made, revealing the following: there were no regional disorders while in rest; with the maximum load of 75W and heart rate of 140/min, a discrete deterioration of the lateral wall kinetics to hypokinesia was found. Cardiac imaging with multislice computed tomography (MSCT) was required and done on December 3, 2015, showing the following: Agatstone Calcium Score: 282; left anterior descending (LAD) score: 251; circumflex artery branches (LCx): 4; right coronary artery (RCA): 19. Coronarogram (Figure 3): calcified plaques in the LAD, localized in the proximal portion of the artery, associated with significant, up to 85% stenoses. There was an occlusion of the right coronary artery from itsorigin, with distal supply most probably from the colaterals.

On December 25, 2016 coronarography was performed, demonstrating LAD occluded medially, ACx medially 80% stenosed, and RCA ostial occlusion (Fig.4.) Surgical revascularization was required for LAD, ACx, and possibly alternatively PCI CTO LAD and PCI ACx.

On January 11, 2016, surgical revascularization was done – a coronary artery bypass grafting (CABG)-LAD-LIMA, OM2 and ACDx av graft. The intervention took place without complications.

In mid-January 2017, control examinations were done and the patient's general condition was without complaints. Postsurgical exercise test results were as follows: IV level, Bruce protocol, 9,22 min, TA 130/90 – 200/90 mmHg, SF 93 – 155/min; monitor: without ischemia. The laboratory tests of January 30, 2017 were

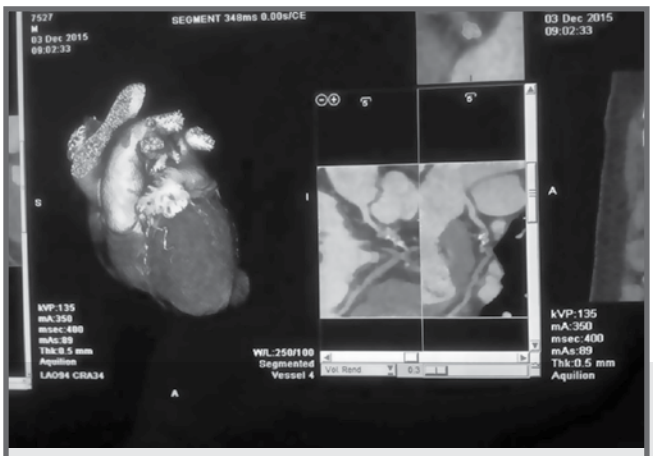

Figure 3. Multislice computed tomography of the coronary arteries.

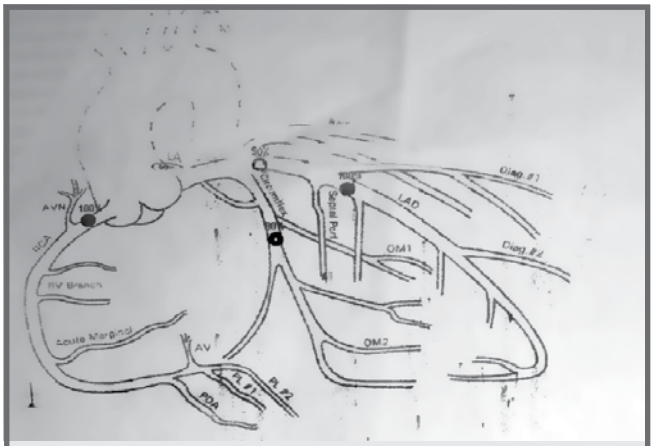

Figure 4. Coronary angiography finding.

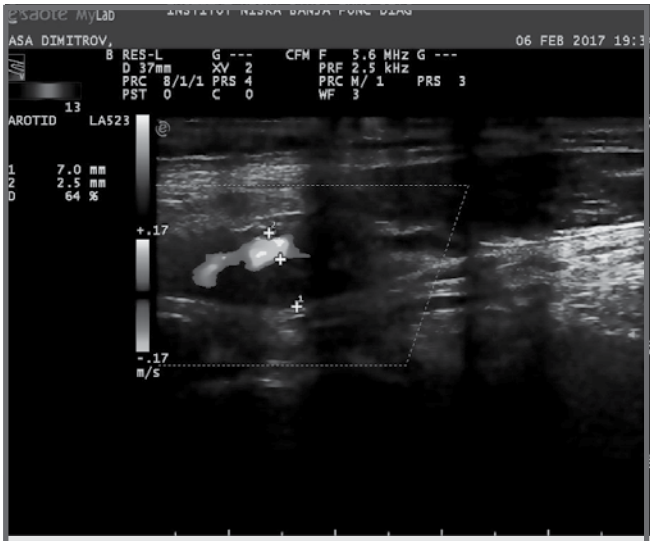

Figure 5. Color Doppler sonography scan of the carotid artery.

as follows: Gly 6,0 mmol/L; Chol 7,99; LDL 5,89;HDL 1,58; Tri 1,15; Creat 77; AU 293; AST 119; ALT 20. Carotid color Doppler sonography of Fabruary 6, 2017 demonstrated stenosis bulbi ACC lat sin 64% (Figure 5).

The therapy prescribed at that time was Rosuvastatin 40 mg; Ezetimib 10 mg, Nebivolol 5 mg; Clopidogrel 75 mg; ASA 100 mg ; and Ramipril 5 mg.

Discussion

The case of a younger adult male with heterozigous form of FH is here reported. The diagnosis of FH was not made on the occasion of first examination back in 2009, although the findings suggested probable FH. A complete diagnostic work-up of the complications of the underlying disease was done shortly after that, and the patient was successully operated. However, an underlying disease such as FH requires early detection and adequate therapy in order to prevent accelerated atherosclerosis. Diagnosed early and properly treated, the risk for CAD may be dramatically reduced, with some studies suggesting even a normal life expectancy[4].

Even the early laboratory findings, with very high LDL cholesterol values (13.9 mmol/l), suggested the need for screening and rapid diagnosis of FH. Such a screening aims at recognizing the index cases, i.e. the individuals with[4]:

- total serum cholesterol ≥8 mmol/L in adult patients (≥6 mmol/L for children), or in an adult family member;
- premature CV disease in the examinee or his family member;
- sudden cardiac death of a family member.

After the screening, the fulfillment of the criteria for FH should be established for a given patient.

The Dutch Lipid Clinic Network(DLCN) formulated in 1998 the criteria – scores – for the diagnosis of FH, approved by the World Health Organization (WHO) and European Atherosclerosis Society (EAS), contained as well in the 2016 guidelines for dyslipidemia treatment[5,4].

The diagnostic criteria were divided into:

- Clinical – arcus cornealis in the corneal margin; xanthomas of the extensor tendons, skin, and pathognomonic xanthomas of the Achilles tendon[6]; peripheral vascular disease (claudication disorders); cardiovascular disease in the family;
- Biochemical – increased serum LDL-C, TC: 7.5-12.9 mmol/L in heFH, and 15.5.-25.8 mmol/L in hoFH; usually normal triglyceride levels, and elevated triglyceride levels do not exclude FH (other potential causes of hypertriglyceridemia should be sought for – interactions with other genes, alcoholism, obesity, diabetes).

In addition to the above criteria, familial history should be analyzed as well (cardiovascular diseases in close family members, familial cases sudden cardiac death) and the responsible gene mutation should be proven.

The diagnosis of FH is definite if the score is >8 points; probable if the score is 6-8 points; and possible if the score is 3-5 points. Our patient had 13 points at the first visit in 2009, and 15 at the examination in 2015. Although a statin was immediately prescribed (20 mg atorvastatin), the patient did not take it regularly, so that the finding in December 2015 practically reflected the natural course of FH. In his 43 years of age, the patient had his two coronary vessels occluded, a severe stenosis in the third vessel, and significant changes in the carotid arteries. Until surgical revascularization intervention, the patient took the maximum rosuvastatin dose (40 mg).

After surgery, 40 mg rosuvastatin therapy was continued, but since the target values (LDL-C <1.8 mmol/l) could not be achieved, a combination approach with ezetimibe was recommended.

According to the 2016 recommendations, FH patients should be treated with intense-dose statin(s), often with the combinations containing ezetimibe (Class of recommendation I, level of evidence C). The treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered in FH patients with CVD or with other factors putting them at very high-risk for CHD, such as other CV risk factors, family history, high Lp(a) or statin intolerance[4].

According to the ACC-AHA Blood Cholesterol Guideline 2013[7], FH with LDL-C >190 mg/dL (>4.92 mmol/l)– In many cases, individuals with FH cannot to achieve an LDL–C goal of <100 mg/dL (<2.59 mmol/l). For example, an individual with FH may only achieve an LDL–C of 120 mg/dL (<3.1 mmol/l) despite the use of three cholesterol-lowering drugs. Although this patient may have fallen short of the 100 mg/dL (<2.59 mmol/l) goal, they have decreased their LDL–C by >50% (starting from an untreated LDL–C level of ~325-400 mg/dL(~8.41-10.36 mmol/l). These patients are not treatment failures, as observational data have shown significant reductions in ASCVD events without achieving specific LDL–C targets. This is an area where observational data support the recommended approach (ACC-AHA guidelines)[7].

In addition to this recommended therapy, „sketching" the family tree of a patient in question is essential in the sense of further evaluation of his close family members. In cases of possible or definite FH diagnosis, a cascade screening should be considered – the LDL level measurements among the family members, as well as genetic testing of the individual in question and his family in order to reveal a possible gene mutation. FH is a monogenic disease caused by a loss of function mutations in the *LDLR* or *apoB* genes, or a gain of function mutation in the *PCSK9* gene; 95% of FH cases are caused by mutations in *LDLR*[4].

Although there are no precise data about the prevalence of heterozigous FH, the disease is not rare and its rate is probably within the range reported for other European countries (according to the latest data, 1/250 adult persons). Early detection of the disease, statins and other antilipid drugs introduced as early as possible, and screening of close family members are essential in the prevention of early atherosclerosis and coronary artery disease (CAD).

Conclusion

In summary, FH is a high prevalence genetic disease, associated with very high CV risk in all ages, not difficult to diagnose (based on clinical findings, scores, genetic testing) and a disease the early identification and management of which is essentialin theprevention of premature CV events.

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Srce i krvni sudovi 2017; 36(S2): 59-61

Case Report

Oral anticoagulant therapy for stroke prevention in patients with atrial fibrillation and recent major bleeding event

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A 76-year old female patient was referred to our hospital for consultation regarding further treatment for permanent atrial fibrillation (AF) of unknown duration, accidentally detected 2.5 years ago at a routine follow-up visit for her hypertension. Upon the documentation of AF, the patient was prescribed a vitamin K antagonist (VKA) warfarin.

The patient reported a history of hypertension, diabetes mellitus, rheumatoid arthritis, cigarette smoking and recent hospitalization for gastrointestinal bleeding. Her medical records also revealed a mild-to-moderate chronic kidney disease with a creatinine clearance (CrCl) of 48mL/min and labile International Normalized Ration (INR) values, ranging from 1.4 up to 4.5. Five weeks ago, she was discharged from local hospital where she was treated for a major upper gastrointestinal bleeding with transient drop in haemoglobin value from 125g/l to 92g/l. Endoscopic gastrointestinal tract examination performed at admission to the local hospital revealed a diffuse erosive gastritis with multiple gastric mucosal erosions, two small ulcerations and active bleeding. Her INR at admission was 4.2. The patient was treated with gastroprotective therapy (a proton pump inhibitor) and received a transfusion (two doses of packed red cells). Warfarin was discontinued. Several weeks before the bleeding event, the patient experienced an exacerbation of her rheumatoid arthritis and started with regular daily intake of a non-steroidal anti-inflammatory drug until the admission to hospital

At discharge, the patient was prescribed most of her pre-admission medication (that is, a beta-blocker, angiotensin converting enzyme inhibitor (ACEi), dihydropyridine calcium channel blocker, thiazide diuretic, proton pump inhibitor and oral antidiabetic drug), but not oral anticoagulant therapy.

On admission to our hospital, the patient had no particular complaints. Physical examination revealed normal finding, except for the irregular heart rhythm. Heart rate was 82bpm, systolic blood pressure was 140mmHg and diastolic blood pressure was 80mmHg. Electrocardiographic recording revealed atrial fibrillation with ventricular rate of 80bpm. Blood testing showed a haemoglobin value of 121g/l and slightly elevated serum creatinine (CrCl was 50mL/min), whilst other blood tests were within normal limits, including her blood glucose level and HBA1c (5.6%). Transthoracic echocardiographic examination revealed a dilated left atrium (51mm) with moderate functional mitral regurgitation, normal left ventricular end-diastolic and end-systolic diameters (50 and 36mm, respectively), normal left ventricular ejection fraction (LVEF 56%) and mild concentric LV hypertrophy (posterior and septal wall thickness was 12-13mm). The right heart cavities and pericardium were within normal range.

Stroke and bleeding risk assessment revealed that our patient had a high stroke risk, as measured by a CHA_2DS_2-VASc score of 5. However, her risk of OAC-related bleeding was also increased, as measured by a HAS-BLED score of 4 (a history of prior bleeding, labile INRs, elderly and concomitant use of non-steroidal anti-inflammatory drugs). Follow-up gastrointestinal endoscopic examination showed that most of the gastric mucosal lesions have healed or near-healed. The patient was prescribed a non-vitamin K oral anticoagulant (NOAC) and advised to avoid the use of non-steroidal anti-inflammatory drugs or aspirin. At 6 months post discharge the patient was doing well, her haemoglobin was 126g/l, and CrCl was 50mL/min.

Discussion

Cardioembolic ischemic stroke is a deleterious complication of AF, associated with significantly greater mortality or permanent disability in comparison to stroke from other causes[1]. Thromboembolic events associated with AF can be effectively reduced using either NOACs or well-controlled VKAs[2]. However, in each patient with AF, the benefit of stroke reduction must be balanced against the risk of bleeding related to the use of oral anticoagulant therapy[3,4].

Our patient has a CHA_2DS_2-VASc score of 5 and is at high risk of stroke or systemic embolism. However, her bleeding risk is also high (a HAS-BLED score of 4) and she suffered a recent major bleeding event during the treatment with a VKA. Indeed, major or clinically relevant gastrointestinal bleeding is a serious medical condition,

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especially in elderly patients with multiple comorbidities. It has been estimated that the annual risk of gastrointestinal bleeding in such AF patients not taking any antithrombotic therapy ranges between 0.3% and 0.5%[5]. In comparison to placebo, warfarin has been associated with a 3-fold greater risk of gastrointestinal bleeding, whilst concomitant use of warfarin and aspirin doubled the risk compared to monotherapy with warfarin[5]. In a meta-analysis of 43 randomized controlled trials comparing NOACs to standard care in different indications for oral anticoagulant therapy in a total of 151578 patients, the overall risk of gastrointestinal bleeding in patients taking NOACs was increased (Odds Ratio [OR] 1.45; 95% Confidence Interval [CI], 1.07–1.97), but there was a substantial heterogeneity amongst the trials. With respect to the indication for oral anticoagulant therapy, the risk of gastrointestinal bleeding was the highest among patients treated for arterial thrombosis (i.e., acute coronary syndrome), in whom NOACs were given concomitantly with other antithrombotic drugs (OR 5.21; 95% CI, 2.58–10.53), intermediate in patients with venous thrombosis (OR 1.59; 95% CI, 1.03–2.44) or AF (OR 1.21; 95% CI, 0.91–1.61) and the lowest in patients with orthopedic surgery (OR 0.78; 95% CI, 0.31–1.96)[6].

In a meta-analysis of the landmark NOACs trials of stroke prevention in patients with non-valvular AF[2], the use of NOACs (taken altogether) has been associated with increased risk of gastrointestinal bleeding in comparison to adjusted-dose warfarin (Relative Risk [RR] 1.25; 95%CI, 1.01-1.55, p=0.043)[2]. However, the difference was driven by the increased risk of gastrointestinal bleeding with the use of dabigatran 150mg-dose, rivaroxaban or edoxaban 60mg-dose, whilst the use of dabigatran 110mg-dose or apixaban 5mg-dose was associated with comparable gastrointestinal bleeding event rates as was the use of adjusted-dose warfarin[2,7].

Importantly, antithrombotic drugs such as aspirin or thienopyridines (e.g., clopidogrel), or non-steroidal anti-inflammatory drugs may cause a direct gastrointestinal mucosal damage, whilst oral anticoagulants can only facilitate bleeding from the pre-existing gastrointestinal lesions[8,9]. Although previous gastrointestinal bleeding event is a risk factor for future bleeding events in AF patients taking oral anticoagulant therapy[10], prior gastrointestinal bleeding is not an absolute contraindication for long-term oral anticoagulant therapy, especially in AF patients at high risk of stroke or systemic embolism[11]. Indeed, it has been shown that permanent discontinuation of warfarin post gastrointestinal bleeding was associated with increased rates of stroke and death in AF patients[12]. However, the timing of oral anticoagulant therapy restart is of key importance to avoid unnecessary complications. Hence, the exact timing of oral anticoagulant therapy restarting should be guided by the cause and severity of gastrointestinal bleeding and the patient's stroke risk level. Once the haemostasis post excision of a gastrointestinal tumour has been achieved or healing of the gastrointestinal mucosa has been confirmed, oral anticoagulant therapy can be safely restarted. However, in patients with multiple gastrointestinal angiectasias, the increased risk of gastrointestinal bleeding will remain[13].

Importantly, the decision to use oral anticoagulant therapy for thromboprophylaxis in AF requires the assessment of bleeding risk associated with the use of oral anticoagulants. Elevated HAS-BLED score itself should not be the reason to deny oral anticoagulant therapy, but should flag-up the patients at higher bleeding risk for regular, more intense clinical follow-up upon identifying and addressing the modifiable bleeding risk factors. Although the latest European Society of Cardiology (ESC) Guidelines on the management of AF do not formally recommend the use of HAS-BLED or other bleeding risk scores for the assessment of bleeding risk in AF patients in whom the use of oral anticoagulant therapy is considered, the correction of modifiable bleeding risk is strongly recommended[11]. Hypertension is a component of the HAS-BLED score, but scores 1 point only if uncontrolled (that is, if the systolic blood pressure persists above 160mmHg despite treatment). Thus, our patient has a well-controlled blood pressure. Her age and a history of prior bleeding event cannot be modified, but the use of non-steroidal anti-inflammatory drug can (and has been corrected). Since her INRs were labile, she could be advised to continue a VKA with a strict INR monitoring and strict diet modification, or she could be prescribed a NOAC.

Which of the two choices would be adequate for our patient? Her SAMe-TT_2R_2 score (see Table 1)[14] is >2 (that is, female sex, tobacco us [renal insufficiency is of moderate severity, hence not encountered in the score calculation]), thus predicting that she is not likely to do well on warfarin[15]. Indeed, her INRs were labile, and she ultimately suffered a major gastrointestinal bleeding during concomitant use of non-steroidal anti-inflammatory medication. According to her SAMe-TT_2R_2 score value of >2, the patient should have been prescribed a NOAC from the beginning.

When choosing a specific NOAC for our patient, her individual risk profile should be the principal driver of the ultimate medication choice. In particular, our patient is >75 years old, has a moderate renal failure, diabetes mellitus and a history of recent gastrointestinal

Table 1. The SAMe-TT_2R_2 score[14].

	Clinical parameter	Points
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history*	1
T	Treatment (interacting drugs, e.g., amiodarone)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2
Max. points		8

*More than two of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease.

bleeding. In the landmark NOACs trials in AF, the use of dabigatran 110mg twice daily, apixaban 5mg twice daily or edoxaban lower-dose regimen (30mg or 15mg once daily) was associated with comparable risk of major or clinically relevant gastrointestinal bleeding relative to warfarin[7]. Edoxaban is not approved in Serbia, which narrows the choice to either dabigatran 110mg twice daily or apixaban 5mg twice daily.

Importantly, a sub-analysis of the RE-LY study of dabigatran for stroke prevention in non-valvular AF compared with adjusted-dose warfarin revealed a significant interaction between the treatment and age. In brief, whilst in patients younger than 75 years dabigatran 110mg twice daily was safer than warfarin in terms of major bleeding, in those ≥75 years old the risk of major *extracranial* (mostly gastrointestinal) bleeding was similar with dabigatran 110mg twice daily and with warfarin[16]. In addition, dabigatran is mostly eliminated via the kidneys (approximately 80% of the ingested dose) and elderly patients with long-standing hypertension and diabetes mellitus may be prone to rapid, unpredictable decline in renal function exposing the patient to increased risk of bleeding related to the use of dabigatran. In contrast, apixaban has been shown to be even more beneficial (that is, safer) in patients with mildly or moderately reduced renal function than in those with normal kidney function with respect to the reduction of major bleeding risk[17]. In our patient, the benefit with apixaban may be slightly attenuated by the interaction of apixaban safety with the presence of diabetes mellitus (the reduction in major bleeding risk with apixaban relative to warfarin was less pronounced in diabetic compared to non-diabetic patients in a sub-analysis of the ARISTOTLE trial)[18], but apixaban was still at least as safe as warfarin in terms of the risk of major bleeding events.

Finally, a non-pharmacological option for AF-related stroke prevention using percutaneous transcatheter left atrial appendage occlusion might be considered. However, more data are needed to better define the role of such treatment for stroke prevention in AF and, presently, such treatments most likely should not be used outside the randomized clinical trial setting. Indeed, the latest ESC AF guidelines recommend that the left atrial appendage occlusion may be considered for stroke prevention in AF patients with contraindications for long-term anticoagulant treatment such as, for example, a previous life-threatening bleed without reversible cause (Class of recommendation IIb, Level of evidence B). However, our patient had neither a life-threatening bleeding nor an irreversible cause of bleeding. Indeed, at 6 months post discharge, our patient was doing well on a NOAC.

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Srce i krvni sudovi 2017; 36(S2): 62-64

Case Report

Non-Hodgkin lymphoma diffuse large B cell- Case report of therapy related cardiotoxicity with review of European Society of Cardiology Guidelines from 2016

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During the last few decades a great progress in treatment of Non-Hodgkin lymphoma (NHL) has been achieved. Irrespectively of clinical stage on disease presentation, in more than 50% of patients would be expected to live more than five years if they were diagnosed with one of the two commonest NHL subtypes, diffuse large B cell (DLBCL) and follicular lymphoma which together represent about 2/3 of all NHL patients[1-3]. Numerous clinical trials signifficantly contributed towards achieving these favorable treatment results by identifying R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) regimen as the "gold" standard of care1-3. Besides these two most frequent NHL subtypes, CHOP with or without rituximabom is also treatment of choice in most others, rare subtypes of NHL[4].

Contemporary recommendations for diagnosis and treatment of NHL very precisely define mandatory diagnostic procedures before, during and after treatment, as well as the approach which depends on clinical stage and the other important risk factors such as agse[4-6]. However, in spite of many decades ago observed potential cardiotoxicity of doxorubicin which is the backbone of CHOP chemotherapy, those recommendations do not provide accurate enough guidelines for initial cardiological assessment regarding the safety of doxorubicin administration, follow up after the treatment and possible prevention of cardiac damage. Still, contemporary recommendations for treatment of NHL define maimal doses and it is not supposed the cumulative dose of doxorubicin to be more than 400 mg/m^2.

In April 2016., a patient 64 years went to his regional hospital due to worsening of dry cough which has been present for one year and, the appearance of breathlessness and fatigue. On chest X-ray mediastinal tumor and right sided pleural effusion had been observed and the patient was referred for cardiac ultrasound (US) and chest CT scan. The cardiac US showed left vetricle (LV) of normal dimmensions, mild hypocontractile apical region of lateral and front wall, with ejekction fraction (EF) of 55%; mitral regurgitation 1+, pericardial effusion with 15 mm fibrin deposits arround right atrium and abnormal movement of free right atrial wall. On the MDCT scan emphisematous changes were found in lungs, as well as moderate right sided pleural effusion with compressive atelectasis of surrounding lung parenchyma, enlarged lymph nodes - in anterior mediastinum 18mm, paratracheal 12mm, subcarineal 30mm, pericardial 21mm, right hilar conglomerate lymph node mass 72x45mm, right tracheobronchial 35mm, in the hilum of the spleen conglomerate lymph node masses 57mm i 60x64mm, few single lymph nodes up to 24 mm. Lung function test revealed moderate pulmonary obstruction.

The patient had been referred to Clinic for Hematology of Clinical Centre of Serbia. On presentation no new complains except already mentioned, on physical examination no peripheral lymphadenopathy or hepatosplenomegaly, chest ausculatation revealed absent breath sound on the base of the right lung with normal cardiac findings. Laboratory investigations revealed normal full blood count, raised level of inflammatory markers with ESR 20 mm/1.h., CRP 6.8 mg/l, fibrinogen 4.3 g/l, and among the other findings elevated β2-microglobulin 3.33 mg/l, AST 86 U/l, ALT 144 U/l, LDH 382 U/l. ECG – no abnormal findings. Virology testing – HCV+. In 1985 he was treated due to pulmonary tuberculosis, since two and half years ago he has been treated for rheumatoid arthritis with methotrexate and prednisone, smoker 50 years. He had been referred for transbronchial needle biopsy of mediastinal tumor, afterwards on that specimen pathjologists diagnosed NHL DLBCL. Also, thoracocentesis had been performed with evacuation 1500 ml of serohemorrhagic fluid and afterwards the cytological findings were in line with primary diagnosis. No bone marrow infiltration was found on bone marrow biopsiy specimen.

The treattment had been commenced with CHOP regimen, and after obtaining consent from infectologist, he was subsequently treated with R-CHOP regimen. Following 1 cycle of CHOP and 3 cycles of R-CHOP with good tolerance without any complain and stable laboratory investigations including liver function tests, the interim CT scans had been performed on which were present mediastinal lymph nodes up to 10mm, in the hilum of the spleen 29x19mm, along greater curvature of stomach 25x23mm. Since the partial remission was achieved, for patient it was decided to receive additional four cycles of R-CHOP.

Five days after completion of eight cycle of R-CHOP the patient was admitted due to dry cough and fatigue.

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Physical examination findings were normal. Chest x-ray revealed shadow in basal parts of the right lung. Laboratory investtigations – except mild elevated transaminases there were also elevated ferritin 1546.2 ng/ml and, NTproBNP 7477 pg/ml. ECG – no abnormal findings. After commencement of antibiotics the patient had become better, he did not accept further examinations including cardiac US and he left the Clinic on third day.

Seven days after the discharge from the Clinic the cardiac US was performed and rexealed drop of LVEF on 40% with enargement of the LV. Two weeks after the discharge he was admitted in the Emergency Centre of Clinicial Centre of Serbia due to severe breathlesnsess, swelling of his legs and low urine output. On physical examination the chest auscultation revealed diminished breath sounds on the bases of both lungs along with inspiratory crackles, rhythmic cardiac activity, heart sounds diminished, mild apical and parasternal on left side systolic murmurs, hypotension 70/50 mmHg, HR 75/min, bilateral pretibial edema. ECG: sinus rhythm, reduced voltage in standard leads, incomplete right band branch block, micro s in D2, D3 and aVF, QS in V2-V3, negative T in V4-V6, s in D1. Laboratory investigations revealed BUN 11,2 mmol/l, creatinine 123 μmol/l, BNP 2694 pg/ml, hs troponine T 160 pg/ml, LDH 581 U/l, mild elevation of ttransaminases, CRP, D-dimer. The cardiac US visualised enlarged keft ventricle (6.7/6.3cm) globally hypocontractile, septum thin and akinetic as well as posterior wall, other parts hypokinetic, total LVEF 15%, no morphological changes on mitral valve, mitral regurgitation 3+, tricuspidal regurgitation 2-3+, enlarged right atrium, right ventricle enlarged 3.4cm. On chest X-ray findings were consistent with pneumonia, consolidated lung parenchyma in right middle and lower lung field and in left middle field, bilateral pleural effusion, size and shape of cardiac silhouette aorticomyopathic. After initial treatment the patient's condition was slightly improved, however on fifth day of hospitalization the patient complained on cough an severe breaathlessness, while prominent findings were orthodyspnea, cyanosis and auscultory findings consistent with pulmonary edema. Soon after that respiratory arrest occurred followed by heart rate decrease up to asystolia. The patient was rescued, intubated, supported by mechanical ventilation with restoring of spontaneus circulation but due to hypotension dual inotropic support was commenced. Next day after the cardiac arrest reoccurred the patient was again rescued with restored spontaneus circulation. Due to suspected pulmonary embolization on heart US and vital indication, the patient received thrombolytic therapy. Despite the treatment the patient remained hypotensive, anuric, in cardiogenic shock with signs of progressive multiorgan failure. Few hours afterwards the cardiac arrest reoccurred, but in spite of undertaken measures and prolonged resuscitation the spontaneus circulation was not restored, resulting in lethal outcome.

Discussion

Cardiac toxicity which is presented as heart failure after doxorubicin treatment represent rare, but potentially very severe treatment complication, since it can cause irreversible cardiac damage and has an impact on treatment outcome and prognosis[7]. The cardiotoxicity of anthracyclines may be acute, early or late[8-10]. Acute toxicity occurs in less than 1% of patients, immediately after infusion and it is usually transient, presented as supravetricular arrhythmia, left ventricle dysfunction, ECG changes. Early and late cardiotoxicity of antracyclines manifest themselves as heart failure with progressive decline of LVEF. Early toxicity occurs within first yerar after treatment, while late effects occur after several years.

In retrospective analysis in oncological trials, a dose dependent increase in incidence of anthracycline cardiotoxicity was observed[11]. Thus, after lifetime doxorubicine cumulative dose of 400 mg/m^2 the incidence of left ventricle dysfunction was up to 5%, while at cumulative dose of 700 mg/m^2 it may reach 48%. Beside that, the elderly patients were identified as vulnerable group since heart failure after treatment with anthracyclines occurs in up to 10% older than 65 years. Moreover, as risk factors for poor outcome were also identified pre-exising cardiac disease, hypertension, concomitant application of others potentially cardiotoxic chemotherapeutical drugs, anthracycline treatment in childhood[11-13]. Also, it was observed that early detection of decrease in LVEF and starting the treatment resulted in good functional recovery[14]. Hence, in contemporary clinical trials it remains a challenge to define optimal balance between treatment efficacy and potential treatment related toxicity, as well as optimal follow up algorithm. In that sense, the guidelines by European Society of Cardiology (ESC) represent an important step towards these aims[15].

Beside that in these guidelines by ESC Comittee for Practice Guidelines are defined risk factors as mentioned above, they also provide the recommendations for frequency of US assessments and further treatment based on these findings. Thus, in patients without risk factors and normal US findings with LVEF more than 50% before the treatment, it is recommended to perform US assessment after 200 mg/m^2 of doxorubicin, after completion of treatment, one year after and five years after the treatment. In patients with risk factors or decreased LVEF it is recommended to consider the possibility of omitting anthracyclines, the use of cardioprotective drugs, as well as more frequent US assessments. If there was a decrease in EF of 10% or more and the findings are in limits of normal, repeated assessment in short time during the treatment or immediately after is recommended. If the US findings are not within the limtis of normal, the commencement of treatment with ACE inhibitor (or angiotensin receptor blocker) combined with β-blocker if not contraindicated is recommended. This drug combination is given to patients with symptomatic heart failure or asymptomatic cardiac dysfunction. Measurement of at least one cardiac biomarker (high-sensitivity troponin I or T, or natriuretic peptide) may be considered before commencement of treatment, as well as measurement of troponin I with each cycle of therapy. Although so far it was not demonstrated that this strategy contribute in prevention or improvement of longer-term toxicity events, it can be useful

for identification of high risk patients who may benefit from preventive treatment. Still, it has to be pointed out that the way and frequency of follow up is defined by expert consensus based on retrospective data and this approach must be validated in prospective trials.

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Srce i krvni sudovi 2017; 36(S2): 65-66

Case Report

Coronary and valvular disease in patient treated for Hodgkin lymphoma

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For many cancers, chest radiation remains an important component of the treatment regimen. Till recent it was believed that the heart is radioresistant and that it can be damaged only with high doses of radiation >30Gy. However it is proved that chest radiation can induce coronary artery disease, valvular heart disease, pericardial disease, conduction system abnormalities, and myocardial fibrosis.1,2

Risk factors for radiation heart disease are radiation of anterior or left lateral thorax, high cumulative dose of radiaton (>30 Gy), younger patients (<50 years), high daily radiation dose (>2Gy), tumor localized in the region of neck or heart, lack of shielding, concomitant chemotherapy (with antracyclines), and presence of conventional risk factors for cardiovasular diseases (diabetes, smoking, overweight, hypertension, high blood lipids, and already present cardiac disease).[1]

Female patient, 43 years of age, was admitted to Clinical center of Serbia complaining of anginal pain, occasionally at night.The pain was accompanied by dysponoea. She begun to feel chest discomfort since she was 40 years of age. She had no convencional risk factors for cardiovasular diseases. When she was 30 years old she was treated with chemotherapy and radiotherapy for Hodgkin lymphoma. Several previous years she was hospitalized twice because of congestive heart failure. She was treated with beta blockers, ACE inhibitors (ACEI), diuretics. Beause of losing weight PET scan was conducted and accumulation of RF in left tonsil described. It was the same finding as two years ago. Haematological consilium stated that here were no contraindications for application of antiplatelet therapy or operative treatment.

At admission objective findings were almost normal except mild systolic murmur at heart apex. Blood pressure was 120⁄80mmHg.

Figure 1 shows her ECG.

Echocardiogrphic measures were: left ventricle enddiastolic dimension (LV EDD) 5.8cm left ventricle endsystolic dimension (LV ESD) 3.7cm LV EF 65%, good regional kinetics of walls, left atrium (LA) 4.7cm, right ventricle (RV) 2.0cm, SPRV 45mmHg. Aortic valve seemed normal, aortic regurgitation was 2+. Mitral leaflets were with moderate fibrotic changes, moderately calcified annulus mitral regurgitation 3+; tricuspid regurgitation 2+.

Coronary arteriography: left main stenosis 65%, proximal right artery stenosis 65%. cifkumflex artery without stenosis.

Patient was reffered to another center and refused performing cardiac surgery. In our clinic she was again presented to cardio-surgical consilium. It was decided that revascularisation should be done, but no intervention on heart valves.

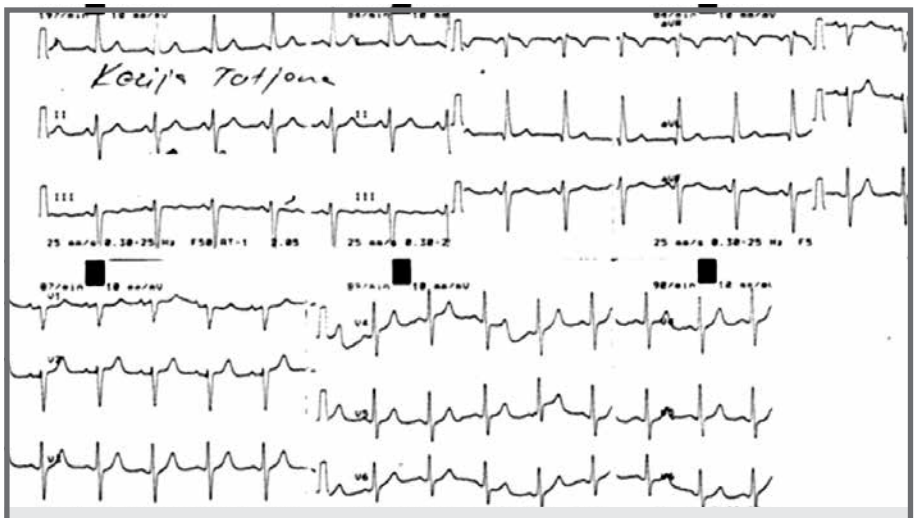

Figure 1. ECG at admittance

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Aortocoronary bypass grafting was performed with two venous grafts. (Ao-LAD, Ao-RCA). Patient died after three years because of heart failure.

Discussion

Cardiovascular diseases (after secondary malignancies) are the most important secondary cause of mortality after radiotherapy of lymphoma.[3] Pericardium is most often damaged, and it is manifested as acute pericardial effusion. Microvascular damage and high capillary permeability can lead to pericardial adhesions and constrictive pericarditis. Microvascular damage that reduces capillary net as well as macrovascular damage (radiation induced accelerated aterosclerosis), lead to myocardial ischaemia and progressive fibrosis. Incidence of coronary disease is 10.4% - 12.0% and restenosis after percutaneous coronary intervention is 85.7%.[4] In radioinduced atherosclerosis intimal proliferation of fibrous tissue produces lumen narrowing. Histologicaly, there is overlap and it is difficult to distinguish radioinduced coronary artery disease. However medial layer is more destroyed and adventitious layer is more thickened and fibrotic in radioinduced heart disease. Patients who already have coronary athroscleotic disease are particularly vulnerable. Average time interval to coronary disease is 82 months after radiation.

Damage to endothelium of valve leaflets lead to their fibrosis, thickening, and calcification. Incidence of clinicaly significant valvular disease is 6% - 40% after radiation. Disease is progressive. Lesions induce valvular insuficiency more often than stenosis. Although valves on right side of the heart are closer to chest surfice, left heart valves are damaged first, asumabbly because higher pressures in the systemic circulation.[5,6] Radition induced heart disease in patients with lymhoma typically manifests 15-20 years after treatment and younger patients are more prone to it. Survivors of Hodgkin lymphoma have a four- to seven-fold increased risk of CAD compared with the general population and a cumulative incidence of CVD up to 50% 40 years after treatment. Based on these data, it appears appropriate to screen regularly for cardiac diseases patients who received radiation therapy, starting 10–15 years after the initial cancer treatment and continuing lifelong.[1]

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Srce i krvni sudovi 2017; 36(S2): 67-68

Case Report

Late manifestation of heart failure in pregnant woman who was treated in the adolescent period for Hodgkin lymphoma

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Cardiovascular diseases are the leading cause of mortality in patients who were treated in childhood with chemotherapy and radiation therapy.1 The survival rate improved over the past decades in pediatric oncology patients2 and the follow-up is strongly suggested in those individuals.3,4 The maternal risk from the cardiovascular toxicity is unknown.5

We present a case of a 32-year old pregnant woman who is in the 26 gestational week who was admitted to the intensive care unit because she had symptoms and signs of heart failure. For the last five days she has bronchopneumonia. We learned from her previous history that she was treated with six cures of ABVD when she was 16 years old because of Hodgkin lymphoma and also with radiation therapy for three more years, with unknown dosage. She is on therapy with levothyroxine, she has hypothyroidism and polycystic ovaries. On the admission she is afebrile, her heart rate is regular 110 beat per minute with mild systolic murmur, hypertensive 160/90 mmHg. She has swelling of the right hand. The chest X-ray revealed bilaterally large pleural effusion. Echocardiography showed an enlarged left ventricle with impaired ejection function (LVEF) 30%, moderate aortic and mitral regurgitation and a small pericardial effusion. Fetal echocardiography registered 140 beat per minute of the fetuses heart. Laboratory analysis showed increased serum blood urea, hipoproteinaemia with hypoalbuminemia, increased white blood count with neutrophilia. The NTproBMB level was highly elevated. She was monitored via central venous catheter and the pleural effusion was bilaterally drained. The arterial line was provided via the femoral artery and the diuresis was measured all the time. There was an elevated central venous pressure (CVP 13 mmHg) and elevated capillary wedge pressure (PCWP 23 mmHg) with decreased cardiac index (CI 3,4 l/min/m2) – all these pointed to heart failure. Thyroid gland hormones were in normal referent values. In 24 hour urine there were proteins 2,7g. Beside antibiotics, according to the Guidelines, the therapy for the heart failure and hypertension was administered. She was taking the following: Methyldopa a 250mg 3 x 1 tbl., Nifedipin a 20mg 2 x 1 tbl., Bisoprolol a 2,5mg 1 x 1 amp., Furosemid a 20mg 3 x I i.v. tbl., Spironolakton a 25mg 1 x 1, Inf. Urapidil up to 20 mcg/min inf. Nitroglicerin up to 40 mcg/min, amp. Levofloxacin a 750mg i.v.

There were no signs of improvement and hemodynamic parameters worsened until the fourth hospitalization day: CVP was 16 mmHg, PCWP was 29 mmHg and CI worsened to 2,7 l/min/m2. That day fetal echo did not registered the baby´s heart beats. An urgent Cesarian section was carried out by a team of gynecologists, cardiologists and cardiac surgeons after witch the medication therapy was continued, ACE inhibitors were introduced. After the delivery symptoms and signs of heart failure improved, her blood pressure normalized. The parameters which were followed up by central venous catheter normalized and she was dismissed from the hospital on the 16th day. The last check-up was done by her cardiologist 2 years later; according his report her blood pressure is normal on propranolol and her LVEF is 60%.

Discussion

There are not much published cases on pregnant women who had lymphoma in their childhood. Pre-eclampsia and dilated cardiomyopathy in pregnant women treated previously in adolescent period of Hodgkin lymphoma- as far as we know- is a scare literature data. Is the cardio toxicity effect of the chemotherapy with the radiation side by side made her hypothyreotic and such an endocrinologic disbalance - which worsened by hypertension in pregnancy- are all interacted and lead this women into such clinical entity with dilated cardiomyopathy? We belive, that the pregnancy is not the only important risk factor in this case, but it is the case of late manifestation of the heart failure which can be explained by the cardio toxicity and radiation effect of the adolescent Hodgkin therapy which was not taken seriously and was not followed up regularly during all these years. The ABVD protocol which contains Adriamycin- which she was treated with 15 years ago- can have a late manifestation of heart failure, after a period of time. The pediatric population is in high risk of adriamycin cardio toxicity and it is known, that the late chemother-

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apy effect in some lymphomas can be expected seven or even more years after the administration of the chemotherapy.[6] The radiation affects all structural and functional components of the heart including pericardium, myocardium, heart valves, conduction system and coronary arteries[7,8], so valvular regurgitation and left ventricular enlargement can be explained, and even should have been expected in our patient. In this case among other risk factors for the heart failure were: femal sex, hypotension, adolescent period when the chemo- and radiation therapy were administered.[9] The radiation therapy can harm the thyroid gland which manifests as hypotireosis. In this case, the hypertension has its etiology deeply based not only in pregnancy but with her previous hemo- and radiation therapy which probably affected the thyroid gland, too. The risk from acute heart failure even in individuals with subclinical form who were treated with adriamycin in the adolescent age will be increased during pregnancy, due to the hypervolemic stage. Pregnancy could be a potential trigger for symptoms and signs of heart failure in such patients, so these individuals should have been followed up regularly during the pregnancy, even the echocardiography is within normal limits. Unfortunately, our patient had no cardiology consultation after the oncology treatment was over.[10] Today, there are many non-invasive imaging modalities for the diagnoses and the follow-up of the cardio toxicity effect after the oncology treatment. The simplest and most important is echocardiography with its serial check-ups. It is the most widely used method with for the estimation of the morphology and function of the heart with parameters as EFLV and global longitudinal strain. Biomarkers are also in focus of interest of the field of cardiac oncology.[13,14] Before, and during the pregnancy the thyroid hormone levels should be perfectly normalized. Hypertension should be followed up before, during and after the pregnancy.[11,12]

Cardiac oncology is a multidisciplinary branch of the internal medicine which is important for the increasing number of oncology patients with cardiovascular complications. It is important not only for the prevention or during the treatment but it has its important role in the follow-up especially in the young patients, even without obvious cardiovascular complications. Cardiac oncologists will have an important advisory role in the pregnancy care system.[15] According to this case and previous study reports, there are cumulating evidence that in patients who suffered cancer and were treated by chemo and radiation therapy in their childhood, should undergo lifelong screening examinations to prevent cardiovascular morbidity and mortality.[9]

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Srce i krvni sudovi 2017; 36(S2): 69-70

Case Report

HER2 + Breast cancer – Case cardiotoxicity of trastuzumab therapy

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In recent decades, malignant diseases, represent a bigger and bigger problem of human population, and thus the challenge for scientists, researchers and clinicians worldwide. A special place occupies breast cancer, by far the leader in terms of number of cancer patients, and after death in the female population. 20-25% of all breast cancers characterized by HER2 positivity.

HER2 receptor belongs to a family of receptors for growth factors, which has a total of 4 (four) and are marked by HER 1-4. HER2 receptor by its structure is a glycoprotein, which is located in the normal epithelial cells. Encoded by a gene localized on chromosome 17. HER2 positive breast cancers are characterized by amplification of the HER2 gene or overexpression of the HER2 protein (receptor) on the cell surface. In most cases, both of these phenomena are simultaneous. In the modern therapeutic approach, HER2 positive breast cancer, the use of biological (immune) therapy based on humanized monoclonal antibody trastuzumab, occupies a central place. The mechanism of action of trastuzumab is based on a blockade of the HER2 receptor and there by prevention of the action of human epidermal growth factors on the growth and proliferation of tumor cells. It is applied after the anthracycline chemotherapy, in combination with taxanes, and also as mono agens. Proven is the most important side effect of trastuzumab cardiotoxicity. It manifests itself mainly as a reversible decrease contractile ability of the left ventricle. In rare cases takes irreversible character and manifested the symptoms and signs of dilated cardiomyopathy. In order to achieve the main objective of striking a balance between achieving the established therapeutic target and spotting the cardiotoxic effects, it is necessary to constantly bear in mind the contemporary guides and recommendations leading European cardiology and oncology associations (ESC ESMO), the algorithm monitoring, primarily based on echocardiography parameters. This approach allows the therapist, timely and appropriate response, including the use of cardioprotective therapy based on angiotensin converting enzyme inhibitors or angiotensin receptor blockers and beta blockers application.

In March 2004, patient aged 48 years, made a self-examinations due to observed changes in the left breast. Less than two months earlier the patient noticed the change, but wasn't immediately reported to the doctor after she noticed an increase in the change of node. Then, she asked for help in the Institute for Oncology and Radiology of Serbia in Belgrade. From anamnesis we get the information that pacient has premenopausal irregular menstrual cycles, with the denial of the personal history of cardiovascular disease and does not use any cardiac medications or other therapies.

Once fully implemented diagnostic diagnosis is cancer of the left breast with the HP findings: CDI gl. mammae GR II II NG hormone positive and HER2-positive tumor. Based on the consultative decisions therapy course was as follows: radical mastectomy left, after that, in the context of adjuvant treatment was carried out 6 cycles of FAC HT, postoperative RT left hemothorax, and less than 5 years of adjuvant hormone therapy Nolvadex. After completion of adjuvant treatment, the patient is converted to the regime of regular check-ups. In May 2009, as part of routine monitoring was performed MSCT thorax in which disease progression was measured by type of meta changes in the lung with mediastinal lymphadenopathy. The patient was shown to a specialist consultant to implement systemic chemotherapy Taxol + W-s.Herceptin. Initial echo of the heart, which was conducted before starting the application herceptin, left ventricular ejection fraction (LVEF) was identified as 65%. After three months of application of this therapy, the control was done. Echocardiogram showed LVEF 54%, which meant a drop in the value of an LVEF> 15% compared to baseline. The therapist decided to carry out a break of 4 weeks without the use of Herceptin and s. W-taxol times. After that, a new control was made; echocardiogram showed an insignificant increase in LVEF, which now stands at 55%, but with the subjective symptoms by an unusual type of fatigue and shortness of breath. Introduced cardioprotective therapy ACE inhibitors and beta blockers with strict monitoring of blood pressure values, potential contraindications for the use of cardioprotective therapy. HT System with Herceptin has been suspended until further notice for new 4 weeks. At the next control echocardiogram showed a marked increase in the LVEF, i.d. it was 60%. Continue the implementation of systemic HT W-Taxol with Herceptin. Achieved therapeutic response with

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oncologic aspect was complete regression of lesions in the lungs and in the meantime the patient HT taxane ended with 20 cycles, while still ongoing system maintenance therapy with Herceptin (so far received 100 cycles). The aforementioned therapeutic response is maintained with good subjective submission and with regular echocardiographic controls. Until now no note of significant changes in LV voliens or LVEF were found.

Discussion

In recent decades, the use of biological therapies in the treatment of HER2 positive breast cancer has a leading role.

It is based primarily on the use of monoclonal antibody, trastuzumab, as in adjuvant approach, and in the treatment of metastatic HER2 + breast cancer. The most important side effect of trastuzumab is cardiotoxicity. In most cases it is manifested by a reversible decrease in contractile function of the left ventricle. Much less cardiotoxicity of trastuzumab takes irreversible character and manifests as dilate cardiomyopathy. This applies primarily to high-risk patients: older than 65 years, positive family and personal history of cardiovascular diseases, previously receiving anthracycline HT.

The main task of the therapist, is to detect signs of potential cardiotoxicity of trastuzumab and adequate response. That's the most important echocardiographic monitoring that is carried out according to a specific algorithm, in accordance with the guides and recommendations of European cardiology and oncology associations. Trastuzumab therapy is carried out in three-week intervals at which it is monitorinig echocardiography initially, and then every three months after receiving the therapy. Upon completion of the same, echocardiographic controls could be done on 6 months and yearly. It is especially important for LVEF. Decrease value of LVEF of 15% or more compared to baseline, and 10% or more between the two measurements, implies the need for break in the application of trastuzumab 3-4 weeks and then re-check. If there is a recovery, the treatment could be continued according to the protocol. If there is no recovery, or possibly on the eve of an LVEF value decrease or signs and symptoms of heart failure, introduced cardioprotective therapy, ACE inhibitors or beta blockers along with continued break in the application of trastuzumab and a new echo checking. Respect for algorithm monitoring in accordance with tiered guides and recommendations, but also with appropriate modifications, the best way to ensure a balance between therapeutic efficacy and potential toxicity of treatment.

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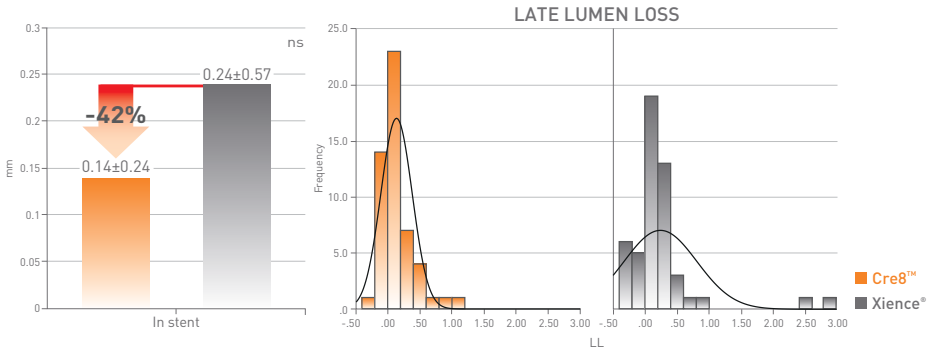

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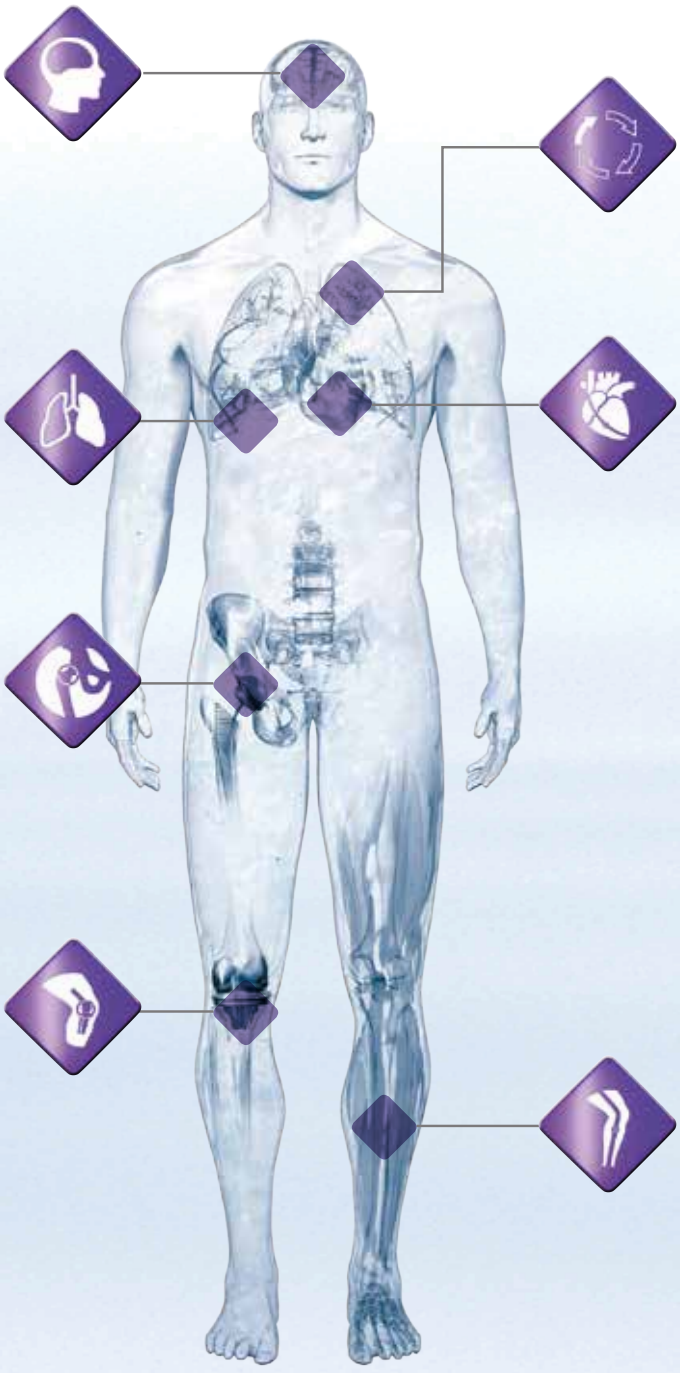

Najpropisivaniji NOAK u svetu, 18 miliona pacijenata* u 5 indikacija[16-20]

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▼ Ovaj lek je pod dodatnim praćenjem. Time se omogućava brzo otkrivanje novih bezbednosnih informacija. Zdravstveni radnici treba da prijave svaku sumnju na neželjene reakcije na ovaj lek.

*Ukupan broj pacijenata u svetu, od datuma prve registracije leka do decembra 2015.

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