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Preliminary Communication

ANTIPLATELET THERAPY AFTER CORONARY ARTERY BYPASS GRAFT SURGERY – UNEVENNESS OF DAILY CLINICAL PRACTICE

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SUMMARY – Antiplatelet therapy is an integral part of optimal medicamentous therapy in patients with coronary artery disease. The strategy of antiplatelet/anticoagulant therapy is adjusted (combination of drugs, dosing and duration of therapy) depending on the stage of the disease (acute coronary syndrome with percutaneous coronary intervention, chronic coronary syndrome, or coronary surgical revascularization) and comorbidity of each patient (e.g., atrial fibrillation, left ventricular thrombus, etc.). Guidelines and clinical practice in particular are not uniform and specific regarding dual antiplatelet therapy in patients undergoing coronary artery bypass grafting, especially in the setting of chronic coronary syndrome.

Key words: *Antiplatelet therapy; Coronary artery disease; Coronary artery bypass grafting*

Antiplatelet therapy is an important and integral part of optimal medicamentous therapy in patients with coronary artery disease (CAD), both in acute and in stable, chronic phase of the disease. The estimated number of patients requiring dual antiplatelet therapy (DAPT), consisting of a combination of aspirin and an oral inhibitor of the platelet P2Y12 receptor for adenosine 5'-diphosphate (ADP), is considerable and has increased over time all around the world[1]. There is, however, confusion about the optimal type and duration of DAPT in patients with established CAD, either undergoing coronary revascularization or not. This derives from the apparently conflicting results arising from the available studies and limited evidence on various patient subsets[1]. The strategy of antiplatelet/anticoagulant therapy (combination of drugs, dosing and duration of therapy) is adjusted depending on the stage of the disease (acute coronary syndrome (ACS) with percutaneous coronary intervention (PCI), chronic coronary syndrome (CCS) or coronary surgical revascularization) and comorbidity of each patient (e.g., atrial fibrillation, left ventricular thrombus, etc.).

In patients with ACS treated with coronary stent implantation, DAPT is recommended for 12 months (preferring ticagrelor combined with aspirin)[1]. In patients with stable CAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is recommended for 6 months irrespective of the stent type [class I (class I, strong; class IIa, moderate; class IIb, weak; class III, no benefit/harm), level of evidence A (A, multiple randomized controlled trials (RCTs)/meta-analyses; B, single RCTs/large observational studies; C, expert opinion/small studies)] and DAPT up to 12 months may be

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reasonable (class IIb, level of evidence A)[1]. If treated with drug-coated balloon, DAPT (aspirin plus clopidogrel) should be considered for 6 months (class IIa, level of evidence B) and prolonged up to 12 months in tolerant patients without bleeding complications[1].

Patients with CAD who have comorbidity such as atrial fibrillation, thrombus in the left ventricle or artificial heart valve and need triple therapy (aspirin, P2Y12 inhibitor and oral anticoagulant (OAC)) are at a high risk of bleeding[2]. Assessing ischemic and bleeding risks using validated risk predictors (e.g., CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65-74 years, sex category; ABC, age, biomarkers (growth differentiation factor-15, high-sensitivity cardiac troponin T, hemoglobin) and clinical history; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol) with a focus on modifiable risk factors is one of the strategies to avoid bleeding complications. Triple therapy in patients undergoing PCI should last as short as possible (one month if concerns about bleeding risks are prevailing and up to six months if concerns about ischemic risks are prevailing) and then dual therapy is to be considered (OAC and clopidogrel) for up to twelve months[1]. Non-vitamin-K oral anticoagulant (NOAC) should be considered instead of vitamin K antagonist (VKA), where it can be administered. If patients with CAD are in stable clinical state one year after PCI and therapy with OAC is still indicated, monotherapy only with OAC should be countinued[1]. In patients eligible for coronary artery bypass grafting (CABG), DAPT should be avoided on top of OAC and it is not suggested which antiplatelet agent in addition to OAC should be used[1].

Therefore, in a combined procedure of CABG and heart valve replacement, VKA with one antiplatelet agent is used in daily clinical practice. Unlike the combination of mechanical heart valve and PCI, where guidelines recommend triple therapy as described in previous section, there is no clear recommendation about CABG combined with mechanical heart valve and guidelines suggest that addition of aspirin (75-100 mg) to VKA may be considered in the case of concomitant atherosclerotic disease[3]. In clinical practice, VKA in combination with aspirin is used for up to twelve months and then therapy only with VKA follows. As for biological heart valve, VKA and aspirin is used for three months and then aspirin monotherapy continues.

In case of CABG and left ventricular thrombus, the latest ESC guidelines define 6 months of anticoagulation for the management of left ventricular thrombus, guided by repeated imaging[4].

Guidelines and especially clinical practice are not uniform and specific regarding DAPT in patients scheduled for CABG. The latest guidelines related to antiplatelet therapy after CABG give general recommendation for duration and choice of antiplatelet therapy with relatively strong class of recommendation I or IIa/IIb. Still, the level of evidence in recommendations is mostly C or B, indicating that the foundation of recommendations is based on expert opinion and not on multiple RCTs or meta-analyses[1].

The success of CABG depends mainly on the patency of graft vessels; graft patency has been shown to be closely related to long-term survival after CABG[5]. Platelets play a crucial role in the pathophysiology of graft thrombosis and aspirin is the primary antiplatelet drug that has been shown to improve vein graft patency within the first year after CABG[6]. Aspirin has always been the gold standard to prevent graft occlusion and adverse cardiac events after CABG[7].

Dual antiplatelet therapy was assessed in previous trials but there is no clear evidence regarding utility of DAPT after CABG for preserving graft patency and reducing adverse cardiac events, especially in patients with stable CCS[8].

The latest guidelines recommend the use of DAPT one year after CABG in patients with ACS[1,9], although available evidence is limited to small RCTs and meta-analyses are substudies of larger RTCs. However, the choice between aspirin and which P2Y12 inhibitor to use remains unclear in CABG. The latest review on DAPT and CABG with focus on ACS supports the use of DAPT with aspirin and ticagrelor in patients with ACS after CABG[10].

Furthermore, the latest guidelines note limited evidence on the role of DAPT after CABG in CCS[1,7]. The 2016 ACC/AHA DAPT guideline update provides a class IIb recommendation for 12 months of DAPT to improve saphenous vein graft patency[7]. The 2017 ESC focused update guideline suggests insufficient evidence to generally recommend DAPT post-

operatively to reduce vein graft occlusion in stable CCS patients who underwent CABG, unless concomitant or prior indication overrides[1]. Several studies (RCTs and meta-analyses) have provided conflicting results on the effects of DAPT on graft patency[11-14].

From the experience of the Krapinske Toplice Special Hospital for Medical Rehabilitation, clinical practice regarding antiplatelet therapy after CABG in cardiac surgery centers in Croatia is very inconsistent. Some centers use routine DAPT (aspirin 100 mg + clopidogrel 75 mg) after CABG, others administer aspirin in a 100-150 mg dose. Individual approach is also used where, depending on the results of aggregometry, aspirin in a 100-300 mg dose is administered as monotherapy or in combination with 75 mg clopidogrel.

In conclusion, there is no strong evidence and consequently recommendations based on RCTs or meta-analysis regarding duration and choice of antiplatelet agents after CABG, especially in the setting of CCS. Resistance to antiplatelet drugs and its impact on clinical outcomes (bypass patency, major adverse cardiovascular events such as myocardial infarction, PCI, redo CABG, and cardiac mortality) of patients also requires further investigation. It is reasonable to assume (and meta-analyses of studies consisting of patients with cardiovascular disease suggest) that patients who are resistant to aspirin have a greater risk of clinically important long-term cardiovascular morbidity compared to aspirin sensitive patients[15]. Additional studies are needed in order to define the role of more aggressive antiplatelet therapy post CABG in graft patency and clinical outcome.

Certainly, besides optimal antiplatelet therapy, other variables such as surgeon experience and skill, stage and severity of CAD, long lasting postoperative control of cardiovascular risk factors, degree of reduction of the left ventricular systolic function before CABG and other associated comorbidity (for example, diabetes, chronic renal failure, etc.) have to be taken into consideration when interpreting major adverse cardiovascular and cerebrovascular events and CABG patient outcomes.

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Sažetak

ANTITROMBOCITNA TERAPIJA NAKON AORTOKORONARNOG PREMOŠTENJA – NEUJEDNAČENOST SVAKODNEVNE KLINIČKE PRAKSE

I. Sopek Merkaš, N. Lakušić, K. Fučkar, D. Cerovec i *K. Marić Bešić*

Sastavni dio optimalne medikamentne terapije u bolesnika s koronarnom bolešću je antitrombocitna terapija. Terapija antitrombocitnim te antikoagulantnim lijekovima (kombinacija lijekova, doziranje i trajanje terapije) prilagođava se ovisno o stadiju bolesti (akutni koronarni sindrom s perkutanom koronarnom intervencijom, kronični koronarni sindrom ili kirurška revaskularizacija) i komorbiditetu pojedinog bolesnika (npr. atrijska fibrilacija, tromb lijeve klijetke itd.). Smjernice, a osobito klinička praksa, nisu jedinstvene u pogledu dvojne antitrombocitne terapije u bolesnika koji su podvrgnuti operaciji aortokoronarnog premoštenja, naročito u postavkama kroničnog koronarnog sindroma.

Ključne riječi: *Antitrombocitna terapija; Koronarna bolest; Aortokoronarno premoštenje*