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Antiplatelet Therapy after Coronary Artery Bypass Graft Surgery, Inconsistency of Clinical Practice and Clinical Significance of Proven Resistance to Antiplatelet Agents

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Abstract

Antiplatelet therapy is a very important part of medical therapy for patients after acute coronary syndrome (ACS) as well as in a stable coronary artery disease (CAD). The use of antiplatelet therapy after coronary artery bypass graft surgery (CABG) still is a controversial theme in daily clinical practice. While guidelines referring to dual antiplatelet therapy (DAPT) after ACS with proceeding percutaneous coronary intervention (PCI) are uniform, there are doubts regarding DAPT after CABG, especially in setting of chronic coronary syndrome (CCS). Recommendations are mostly based on expert opinion and not on multiple randomized controlled trials (RCT) or meta-analyses. Resistance to aspirin (acetylsalicylic acid, ASA) or other antiplatelet drugs is known after CABG, and further RCTs are needed to assess the effect on clinical outcome as well as the role of DAPT after CABG.

Keywords: antiplatelet therapy, coronary artery bypass grafting (CABG), resistance to antiplatelet drugs, acute coronary syndrome (ACS), chronic coronary syndromes (CCS)

1. Introduction

An important and integral part of an optimal medicament therapy for patients with CAD in an acute as well as in a stable, chronic phase of the disease is antiplatelet therapy. The estimated number of patients requiring DAPT, consisting of a combination of ASA 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. Based on population estimates from 2015, in Europe 1.4–2.2 million patients per year may have an indication for DAPT after coronary intervention or myocardial infarction (MI), respectively [1]. There is, however, confusion about the optimal type and duration of DAPT in patients with established CAD,

undergoing coronary revascularization or not. This derives from apparently conflicting results given in the available studies and limited evidence on various patient subsets [1]. Depending on the disease stage (ACS with PCI, CCS or coronary surgical revascularization), and comorbidity of each patient (e.g., atrial fibrillation, left ventricular thrombus, etc.), the strategy of antiplatelet/anticoagulant therapy is altered (combination of drugs, dosing, and duration of therapy). In patients with ACS treated with coronary stent implantation, DAPT is recommended for 12 months (preferring ticagrelor combined with ASA) [1]. In a patient 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, level of evidence A), and DAPT up to 12 months may be 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]. As opposite, guidelines and especially clinical practice are not uniform and specific regarding patients who will undergo CABG. Latest guidelines regarding DAPT after CABG give general recommendation for duration and choice of antiplatelet therapy with relatively strong class of recommendation I or IIa/IIb¹. Still, level of evidence in recommendations is mostly C or B² which points out that the foundation of recommendations is based on expert opinion and not on multiple RCTs or meta-analyses [1].

This chapter will give an overview of antiplatelet drugs, their mechanism of action, possible resistance to antiplatelet drugs, and clinical significance of resistance to antiplatelet drugs. Also, it will give an overview of literature regarding duration and choice of antiplatelet therapy after CABG in setting of ACS or CCS.

2. Antiplatelet therapy

2.1 Aspirin

Aspirin (acetylsalicylic acid, ASA) is classified among the nonsteroidal anti-inflammatory drugs (NSAIDs) and has analgesic, antipyretic, and antiplatelet properties. ASA achieves its effect primarily by interfering with the biosynthesis of cyclic prostanoids: thromboxane A₂ (TXA₂), prostacyclin, and other prostaglandins [2]. Low dose of ASA blocks the enzymatic effect of cyclooxygenase-1 (COX-1) on the transformation of arachidonic acid into prostaglandin G₂ and then into prostaglandin H₂ which is modified by specific synthases, producing prostaglandins and TXA₂, an important mediator of the platelet aggregation response and in vasoconstriction [2–4]. One of the earliest placebo-controlled RCTs of ASA in patients with ACS consisted of 1266 men with unstable angina, and the combined primary end point of death and nonfatal MI at 12 weeks was reduced by 50% in patients receiving ASA rather than placebo [5]. The Second International Study of Infarct Survival (ISIS-2) study involving patients administered with daily 160-mg ASA started within the first day of MI and continued for 5 weeks and showed a significant risk reduction in total vascular mortality (23%) as well as a similar risk reduction of from all-cause mortality [6, 7]. Therapy with ASA has become regular for all patients suspected of having an ACS [7, 8].

¹ Class I, strong; Class IIa, moderate; Class IIb, weak; Class III, no benefit/harm.

² A, multiple RCTs/meta-analyses; B, single RCTs/large observational studies; C, expert opinion/small studies.

2.2 Clopidogrel

Clopidogrel is a second generation of thienopyridine antiplatelet agents and a P2RY12 inhibitor (purinergic receptor P2Y, G-protein coupled 12) which achieves its effect by irreversibly binding to the platelet P2RY12 receptor and blocking ADP-mediated platelet activation and aggregation [9]. It also inhibits collagen and thrombin-induced platelet aggregation which can be overcome by increased concentration of this agonist [10]. Clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) trial demonstrated that long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than ASA in reducing the combined risk of ischemic stroke, MI, or vascular death, and the overall safety profile of clopidogrel is at least as good as that of medium-dose ASA [11]. The rate of reported gastrointestinal bleeding complication was significantly lower in the clopidogrel group than in the ASA group, and no difference in intracerebral hemorrhage, hemorrhagic death, thrombocytopenia, or neutropenia was noted between the two groups [7, 12]. Clopidogrel was then in 1997 approved by Food and Drug Administration (FDA) for use in secondary prevention of cardiovascular disease [7].

2.3 Ticagrelor

Ticagrelor is an orally administered direct-acting P2Y12-receptor antagonist [13, 14]. In vitro studies have demonstrated that ticagrelor binds reversibly and noncompetitively to the P2Y12 receptor at a site distinct from that of the endogenous agonist ADP [13]. In contrast, the thienopyridine compounds clopidogrel and prasugrel bind irreversibly to the P2Y12 receptor for the life of the platelet [15]. Ticagrelor was evaluated in patients with stable CAD in the Dose Confirmation Study Assessing Antiplatelet Effects of AZD6140 vs. Clopidogrel in Non-ST-Segment Elevation Myocardial Infarction (DISPERSE) trial [16]. In this randomized trial, patients with stable CAD who were taking ASA were administered either ticagrelor or clopidogrel, and after trial findings, the formulation of ticagrelor was changed, and the new corresponding doses of 90 mg and 180 mg twice a day were targeted in future studies [16, 17]. In the ONSET/OFFSET trial, the pharmacodynamic response of ticagrelor was assessed in patients with stable CAD, and significantly greater inhibition of platelet activation has been achieved in patients treated with ticagrelor plus ASA than with clopidogrel plus ASA [18].

2.4 Prasugrel

Prasugrel is an irreversible antagonist of the platelet ADP P2Y12 receptor and characterized by more potent antiplatelet effects, lower interindividual variability in platelet response, and faster onset of activity than clopidogrel [19]. The TRITON-TIMI 38 trial comparing prasugrel with clopidogrel in patients with moderate to high risk ACS (ST-elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina) who underwent PCI demonstrated improved clinical outcomes with prasugrel as compared to clopidogrel [20]. A systematic review and recent meta-analysis suggest that prasugrel might have a better efficacy profile than ticagrelor in patients with ACS undergoing PCI, but this advantage was only seen in pooled observational studies and is likely to be affected by selection bias [21]. The latest trial comparing ticagrelor with prasugrel randomized 4018 patients which presented with ACS with or without ST-segment elevation (in whom invasive evaluation was planned), and the incidence of death, MI, or stroke was significantly lower among those who received prasugrel than among those who

received ticagrelor, and the incidence of major bleeding was not significantly different between the two groups [22]. On the other hand, in the observational analysis of STEMI patients who underwent primary PCI, ticagrelor was associated with improved outcomes compared with clopidogrel and prasugrel [23].

3. Resistance to antiplatelet therapy and its clinical significance

The success of CABG depends mainly on the patency of the graft vessels; vein graft patency and disease have been shown to be closely related to long-term survival after CABG [24]. Vein graft disease consists of three different but related pathological processes: thrombosis, intimal hyperplasia, and atherosclerosis, where early thrombosis is a major cause of vein graft friction during the first month after CABG, while later on intimal hyperplasia is the leading cause of graft disease [25, 26]. Platelets participate in forming of blood clots, likewise they have an important role in graft thrombosis after CABG, and ASA is the primary antiplatelet drug that has been shown to improve vein graft patency within the first year after CABG [26–28]. Laboratory investigations showed that the expected inhibition of platelet function is not always achieved, which is called “aspirin nonresponse” or “aspirin resistance.”

Speaking about nonresponse and resistance to aspirin, there are two terms in use. The first one is aspirin treatment failure which is defined as the occurrence of occlusive cardiovascular disease events despite the regular intake of aspirin in recommended doses [29]. Platelets are activated by many different pathways, and there are many factors that contribute to thrombotic event in addition to platelet aggregation. Occurrence of an ischemic event or treatment failure during single antiplatelet therapy is not synonymous with antiplatelet resistance. The second term is aspirin resistance or nonresponsiveness, and it is a laboratory phenomenon; therefore persistent presence of COX-1 activity after treatment with aspirin is an indicator of aspirin resistance [29]. Antiplatelet resistance to aspirin is only meaningful when it is highly associated with clinical outcomes. In a review article of antiplatelet treatment after CABG, a summary of benefit and failure of aspirin therapy is given [26]. It is emphasized that in the early period after CABG, increased risk of bypass thrombosis (among others, due to platelet activation and endothelial cell disruption of the graft) occurs simultaneously with increased prevalence of aspirin resistance [26, 30]. The underlying mechanisms of aspirin resistance are uncertain and largely hypothetical, i.e., increased platelet turnover, enhanced platelet reactivity, systemic inflammation, and drug–drug interaction are discussed [26, 31, 32]. It is also important to differentiate transient aspirin resistance after surgery from permanent aspirin nonresponse due to genetic polymorphisms [33] or comorbidities, such as hypercholesterolemia or diabetes [26, 34].

In clinical practice, patient nonadherence is the most common cause of aspirin nonresponse or treatment failure. Genetic variability and the number of single nucleotide polymorphism (SNPs) have been reported as the cause of aspirin resistance based on laboratory testing, but there is no evidence for strong relation between genetic variability and aspirin resistance [35]. Enteric-coated aspirin and delayed absorption may result in an insufficient antithrombotic effect, especially in the acute setting (pseudoresistance) [36]. Two studies (case–control, retrospective) have suggested that the use of proton pump inhibitors increases platelet aggregation and the risk of thrombotic events, but randomized trials are needed [37, 38]. Treatment failure attributable to other causes than genetic variability or lack of adherence is common. Functional and biochemical evaluation of platelet aspirin resistance in patients undergoing CABG suggested that aspirin resistance

involves an impairment of both in vivo and in vitro inhibition of platelet functions and is probably due to a disturbed inhibition of platelet COX-1 by aspirin [39]. Aspirin resistance has been described in more than two-thirds of patients early after CABG [39, 40]. It has been shown that off-pump CABG (OPCABG) reduces platelet activation and turnover compared to on-pump CABG which may indicate that aspirin should be more effective after OPCABG [41], while other RCT showed no significant difference between off-pump and on-pump CABG in the rate of the 30-day composite outcome, but at 1 year of follow-up, patients in the off-pump group had worse composite outcomes and poorer graft patency [42]. In a group of patients with OPCABG, aspirin resistance was observed in nearly 30% on day 1 after OPCABG, but this is a transient phenomenon with only 4.5% of patients remaining so by postoperative day 10 [43]. The period of time passed after CABG is an important variable in measuring and analysis of the prevalence of aspirin resistance because results depend on it and vary from 10% up to >90% [26, 44, 45].

Regarding CABG, the number and size of trials investigating aspirin resistance with clinical endpoints are limited. A review of studies related to aspirin use after CABG suggested that clinical studies investigating the critical period early after CABG are necessary to correlate the results of reproducible assays with clinical outcomes that can possibly be improved by alterations in antiplatelet strategy [26]. The benefits and risks of ASA on thrombosis (BRAT) was the first prospective multicenter study with the objectives to determine the prevalence of aspirin responder or nonresponder status in patients undergoing CABG and to determine the clinical significance [46]. The 2-year follow-up period failed to show significant differences in thrombotic event rates (MI, unstable angina, cardiac death, or stroke) between aspirin responders and nonresponders [46]. In a setting of 225 patients undergoing elective OPCABG, aspirin resistance was defined by diagnostic findings on at least two of three separate assays (thromboelastography, whole blood aggregometry, and whole blood flow cytometry), and after multivariate logistic regression analysis, aspirin resistance on day 1 was retained as an independent predictor of vein graft thrombosis [47].

In the prospective randomized study to address the clinical impact of augmented antiplatelet therapy after elective CABG in patients with aggregometry-documented aspirin resistance, the addition of clopidogrel in patients found to be aspirin resistant after CABG did not reduce the incidence of adverse events, nor did it increase the number of recorded bleeding events [48]. A study on 60 patients who went to elective OPCABG and were divided into two groups to receive mono-antiplatelet treatment (MAPT) with ASA or DAPT with ASA and clopidogrel has shown that clopidogrel in addition to ASA reduces the incidence of OPCABG-related aspirin resistance, DAPT can be safely applied early after surgery, and there were no significant differences between two groups in postoperative bleeding [49]. A recent prospective, observational, bicentric cohort study indicated a high incidence of perioperative ASA nonresponse in patients following CABG, and no effect on the incidence of cardiovascular events was recorded in the 1-year follow-up [50]. Similar was concluded in a small low-risk cohort patients in which reduced ASA responsiveness as assessed with impedance aggregometry was not associated with increased incidence of major adverse cardiac and thromboembolic events and mortality after CABG surgery [51]. In a randomized trial on 68 patients, it was tested whether more frequent dosing improves ASA response following CABG surgery, and it was noted that twice-daily compared with once-daily dosing reduces ASA hyporesponsiveness after CABG surgery, but the efficacy of twice-daily ASA needs to be tested in a trial powered for clinical outcomes [52]. In comparison, meta-analyses of studies consisting of patients with cardiovascular disease (not only CABG patients) suggested that patients who were resistant to aspirin were at a greater risk

of clinically important cardiovascular morbidity long term than patients who were sensitive to aspirin [53–55].

Concerning clopidogrel, patients with “high on-treatment platelet reactivity” (HPR) are divided into groups—nonresponsive, hyporesponsive, or resistant [56]. The term resistance or nonresponsiveness to an antiplatelet drug is used to describe a pharmacodynamics phenomenon where there is no clinically meaningful change in platelet function after treatment as compared with the baseline. In studies where light transmittance aggregometry was used, a change in maximal aggregation ≤ 10 percent from baseline, using ADP as the agonist, is defined as “resistance” [56]. In a systematic review of literature on clinical importance of ASA and clopidogrel resistance, almost all included studies have suggested a positive association between the risk of cardiovascular events and laboratory antiplatelet nonresponsiveness, and it was concluded that specific treatment recommendations are not established for patients who exhibit HPR during aspirin/clopidogrel therapy or who have poor platelet inhibition by clopidogrel [57]. A meta-analysis provided evidence that P2Y₁₂ G52T/C34T polymorphism is related to a poor response of clopidogrel in patients; also a lack of association between T744C polymorphism and clopidogrel resistance was found [58]. Clopidogrel response in patients undergoing CABG remains unknown due to the fact that ASA is the drug of first choice after CABG, and clopidogrel administration (in addition to ASA) is recommended mainly in patients with ACS. However, previous reports indicate that the clopidogrel resistance rate in coronary stent patients varies between 5 and 56% [59]. Prospective, observational study on clopidogrel platelet reactivity in 859 patients who underwent OPCABG demonstrates that high residual platelet reactivity after clopidogrel administration is strongly associated with 1-year major adverse cardiovascular events (MACE)-free survival, and incidence of late MACEs was significantly higher in the HPR group than in the low platelet reactivity group, as such routine measurement of platelet reactivity and thorough monitoring of patients with HPR after OPCAB are suggested [60].

The latest review of literature on resistance to P2Y₁₂ receptor antagonism in CAD showed that the prevalence of HPR is greater in patients treated with clopidogrel (approximately 30%) than in patients on the more novel antiplatelet agents prasugrel (3–15%) and ticagrelor (0–3%) [61]. Although meta-analyses show an effect of adjusting standard clopidogrel treatment based on platelet function testing, personalized therapy is not recommended because no large-scale RCT have shown any clinical benefit [61]. Nevertheless, it should be noticed that the performed RCTs were underpowered to show any clinical effect, and personalized therapy is recommended neither for patients on prasugrel nor those on ticagrelor due to low occurrence of HPR on these respective drugs [61]. The pharmacodynamic response of ticagrelor in clopidogrel nonresponders with stable CAD was assessed in an RCT: The response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies (RESPOND) trial [62]. Inhibition of platelet function was significantly increased in clopidogrel nonresponders treated with ticagrelor compared with clopidogrel, and platelet aggregation decreased from 59 to 35% in patients who switched from clopidogrel to ticagrelor [62]. Despite the low platelet reactivity for both agents, comparisons have shown that ticagrelor is the most potent platelet inhibitor and has the lowest prevalence of HPR [63, 64]. Prasugrel resistance or variability in response is not clearly defined and depends on the in vitro system use, prasugrel resistance has been reported to occur in very few cases, and the mechanism of prasugrel resistance is still under investigation [65]. Despite small studies that have shown a few prasugrel-resistant patients due to low inhibition of platelet aggregation, the clinical significance of this phenomenon remains uncertain [65].

3.1 Platelet function tests for monitoring antiplatelet agent therapy

Platelet function testing is traditionally done to identify congenital and acquired platelet function defects. It is considered qualitative testing requiring interpretation in the context of patient condition. There exist multiple methods, each with its advantages and disadvantages.

Six major platelet function tests are most commonly used in the assessment of the prevalence of aspirin resistance in patients with stable CAD:

- Light transmission aggregometry (LTA) after stimulation arachidonic acid (AA)
- LTA after ADP stimulation
- Whole blood aggregometry
- PFA-100®
- VerifyNow Aspirin®
- Urinary 11-dehydro-thromboxane B2 concentrations that are measured [66]

4. CABG and antiplatelet therapy

CABG is an effective treatment for left main or multivessel ischemic heart disease, but long-term results are compromised by the development of saphenous vein graft (SVG) disease. ASA has always been a golden standard to prevent graft occlusion and adverse cardiac events after CABG [67]. DAPT was assessed in previous trials, but there is no clear evidence regarding its utility after CABG for preserving graft patency and reducing adverse cardiac events, especially in patients with stable ischemic heart disease (SIDH), recently referred as CCS. In the next subsections, it will be given an overview of available literature about efficacy of DAPT in preserving graft patency in setting of SIDH and CCS.

4.1 Antiplatelet therapy after CABG in setting of ACS

DAPT using ASA with either clopidogrel or ticagrelor is a standard of care for patients after ACS whether they were treated with PCI or medication therapy only, preferring ticagrelor over clopidogrel [1, 68–71]. Latest guidelines recommend use of DAPT 1 year after CABG for patients with ACS [1, 71], although available evidence is limited to small RCTs and meta-analyses are substudies of larger RCTs. However, the choice between ASA and which P2Y12 inhibitor to use remains unclear in CABG. Synergistic antithrombotic effect of clopidogrel with ASA after ACS was evaluated in Unstable Angina to Prevent Recurrent Events (CURE) trial [72, 73]. Treatment with DAPT (ASA + clopidogrel) reduced the risk of the primary composite outcome—MI and recurrent ischemia, cerebrovascular event, and death from cardiovascular causes (MACCE), but the risk of major bleeding is increased among patients treated with clopidogrel [72]. The postoperative benefit with DAPT was analyzed in subgroup of CURE patients who underwent CABG and then were randomized to ASA and to ASA and clopidogrel. The benefits of DAPT with ASA and clopidogrel were consistent among groups undergoing CABG, PCI, or medical therapy, although the impact of DAPT among CABG patients did not reach significance for the primary composite outcome [73]. In a nationwide Danish cohort of real-life

patients revascularized with CABG after MI, the benefit and efficacy of postoperative clopidogrel treatment in reducing risk of death or recurrent MI were confirmed [74]. The Platelet Inhibition and Patient Outcomes (PLATO) trial randomized patients with ACS to DAPT with either ASA plus ticagrelor 90 mg twice daily or ASA plus clopidogrel 75 mg once daily [75]. The composite primary end point of death from vascular causes, MI, or stroke was significantly reduced in the ticagrelor group, and ticagrelor was associated with a higher rate of major bleeding (no statistical difference in overall major bleeding). In a subgroup of patients who underwent CABG, effect on the primary outcome at 1 year was again consistent but did not reach significance. Cardiovascular mortality and all-cause mortality were significantly lower with ticagrelor, and there was no significant statistical benefit of ticagrelor related to MI and stroke [75]. DAPT with clopidogrel and ticagrelor in patients with non ST-elevation acute coronary syndrome (NSTEMI-ACS) was evaluated 3 months after off-pump CABG (only arterial grafts were used) in retrospective observational study, and there was no significant difference in overall survival or composite outcome of MACCE or major bleeding [76]. Prasugrel was compared with clopidogrel in patients with acute coronary syndrome RCT (TRITON-TIMI 38) where DAPT with ASA plus clopidogrel 75 mg daily or ASA plus prasugrel 10 mg daily was used [77]. Although major bleeding complications were significantly higher with prasugrel, the primary composite outcome of MACCE was significantly lower in prasugrel group, and all-cause mortality within 30 days in a subgroup of patients undergoing CABG was significantly reduced [77]. Meta-analysis of nine RCT that confirms benefit of DAPT among the subset of patients after ACS who had undergone CABG suggests that higher-intensity (prasugrel or ticagrelor) than lower-intensity (clopidogrel) DAPT is associated with an approximate 50% lower all-cause mortality in such patients, but data are primarily based on post-randomization subset from a single RCT [78]. Latest review on DAPT and CABG with focus on ACS supports the use of DAPT with ASA and ticagrelor for patients with ACS after CABG [79].

4.2 Antiplatelet therapy after CABG in setting of CCS

Stable ischemic heart disease (SIHD) refers to patients with known or suspected ischemic heart disease, including those with new-onset chest pain and those who have undergone PCI or CABG, and this term is used in 2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease [80]. However, the disease is chronic, most often progressive and serious, even in clinically apparently silent periods. The new 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes (CCS) emphasize that the dynamic nature of the CAD process results in various clinical presentations, which can be conveniently categorized as either ACS or CCS [81]. Latest guidelines note limited evidence on the role of DAPT after CABG in SIHD [1, 71]. 2016 ACC/AHA DAPT guideline update provides a class IIb recommendation for 12 months of DAPT to improve SVG patency [71]. The 2017 ESC focused update guideline suggests insufficient evidence to generally recommend DAPT postoperatively to reduce vein graft occlusion in stable patients who underwent CABG, unless concomitant or prior indication overrides [1]. Several studies have provided conflicting results on the effects of DAPT on the SVG patency. Graft patency was assessed with invasive coronary angiography or computerized tomography (CT). In Clopidogrel After Surgery for Coronary Artery disease (CASCADE) randomized trial, the combination of aspirin plus clopidogrel did not significantly reduce the process of SVG intimal hyperplasia (assessed with coronary angiography and intravascular ultrasound, IVUS) compared with ASA monotherapy [82]. Graft patency was not significantly improved

in ROOBY trial [83] and a trial that randomized 100 patients after CABG [84]. In secondary analysis of CASCADE, the superiority of DAPT over ASA monotherapy in reducing the incidence of new occlusions within native coronary arteries after CABG was demonstrated [85]. Contradictorily, in Prevention of Coronary Artery Bypass Occlusion After Off-Pump Procedure (CRYSSA) trial, DAPT with ASA and clopidogrel was associated with significantly lower SVG occlusion rates than ASA monotherapy [86], and similar was shown in a previous RCT but with no significant differences in MACCE [87]. Observational studies in the cardiac surgery literature have suggested that clopidogrel may improve postoperative outcomes [88] and also demonstrated that the addition of clopidogrel to ASA was associated with a trend toward improved SVG patency 6 months after surgery [89], and it noted that postoperative clopidogrel was associated with less symptom recurrence and fewer adverse cardiac events [90]. Meta-analysis of DAPT with clopidogrel and ASA over monotherapy with ASA established that DAPT reduces the risk of SVG occlusion [91, 92] and was associated with a smaller incidence of early mortality but also linked with major bleeding episodes in the early postoperative period [92]. There is lack of studies that compare the effect of ticagrelor or prasugrel in addition to ASA on SVG patency. Effect of ticagrelor plus aspirin, ticagrelor alone, or aspirin alone on SVG patency 1 year after elective CABG was assessed in RCT and demonstrated that DAPT with ticagrelor and aspirin significantly improved graft patency, but there was no significant improvement with ticagrelor alone or aspirin alone, no statistically significant difference in event rates of MACCE, and no major bleeding in DAPT group [93]. And most recently, the Ticagrelor Compared with Aspirin for Prevention of Vascular Events in Patients Undergoing Coronary Artery Bypass Grafting (TiCAB) trial randomized patients in either ticagrelor twice daily or aspirin once daily group (study did not evaluate DAPT), and the primary outcome of MACE at 12 months did not differ significantly between two groups [94]. In latest meta-analyses data were also contradictory. One meta-analysis showed that DAPT appears to be associated with a reduction in graft occlusion and major adverse cardiac events in all-cause mortality, without significantly increasing major bleeding [95]. Improved graft patency with DAPT compared with aspirin was also shown in a meta-analysis of RCTs only [96]. Combined meta-analysis among patients undergoing CABG suggested association of DAPT with lower cardiovascular mortality in observational studies, but such findings were not replicated in RCTs [97].

4.3 Triple therapy (aspirin, P2Y₁₂ inhibitor, and OAC) in patients after PCI or CABG

Addition of DAPT to oral anticoagulant (OAC) therapy increases bleeding complications for two- to threefolds [98, 99]. Therefore, patients who need triple therapy (comorbidity such as atrial fibrillation, thrombus in left ventricle, deep venous thrombosis, mechanical heart valve) are at high risk of bleeding. Assessing ischemic and bleeding risks using validated risk predictors (e.g., CHA₂DS₂-VASc³, ABC⁴, HAS-BLED⁵) 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 (1 month if concerns about bleeding risks are prevailing and up

³ CHA₂DS₂-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, and sex category.

⁴ Age, biomarkers (GDF-15, cTnT-hs, hemoglobin), and clinical history (ABC).

⁵ Hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol (HAS-BLED).

to 6 months if concerns about ischemic risks are prevailing), and then dual therapy is to be considered (OAC and clopidogrel) up to 12 months [1]. Non-vitamin K oral anticoagulant (NOAC) should be considered instead of vitamin K antagonist (VKA). International normalized ratio (INR) is suggested to be in the lower part of the recommended target range, and time in therapeutic range should be maximized (i.e., >65–70%) when VKA is used [1, 71]. Using low dose (≤ 100 mg) of ASA is recommended and also routine use of proton pump inhibitors (PPIs) [1, 71]. Clopidogrel is the P2Y₁₂ inhibitor of choice in such regimen of therapy; the use of prasugrel and ticagrelor should be avoided [1]. In a study of 377 patients who underwent drug-eluting stent implantation and had an indication for oral anticoagulation, prasugrel was evaluated as alternative to clopidogrel, and results showed an increased risk of bleeding in patients needing triple therapy [100]. Recent meta-analysis demonstrated that the use of ticagrelor as part of dual or triple therapy is associated with significantly higher rates of clinically relevant hemorrhagic complications than clopidogrel [101]. Latest review article on this subject points out already known stronger antiplatelet effect of ticagrelor and prasugrel, yet they are not used because of the increased risk, whether real or perceived, which has not been confirmed with large RCT in patients with ACS and atrial fibrillation [102]. In patients eligible for CABG surgery, DAPT should be avoided on the top of OAC and is not suggested in which antiplatelet agent in addition to OAC should be used [1].

5. Conclusion

- There is no strong evidence based on RCTs or meta-analysis regarding duration and choice of antiplatelet agents after CABG, especially in setting of stable CAD.
- The 2017 ESC focused update guideline suggests insufficient evidence to generally recommend DAPT postoperatively to reduce graft occlusion in stable patients who underwent CABG, unless concomitant or prior indication overrides. In setting of ACS, combination of ASA with P2Y₁₂ inhibitor is recommended up to 12 months after CABG, but the choice between ASA and which P2Y₁₂ inhibitor to use is not clearly defined. In patients perceived at high ischemic risk with prior MI and CABG who have tolerated DAPT without bleeding complications, treatment with DAPT for longer than 12 months and up to 36 months may be considered [1].
- There is no clear evidence of aspirin resistance in CABG patients and effect on their clinical outcome. Also, there is no uniform data regarding addition of clopidogrel to ASA in reducing the incidence of CABG-related aspirin resistance.
- Available data suggests that the incidence of late MACEs was higher in the HPR group after clopidogrel administration post CABG, and also higher prevalence of HPR was shown in CAD patients treated with clopidogrel than patients treated with ticagrelor or prasugrel. Positive effect of adjusting standard clopidogrel treatment based on platelet function testing was shown; however, personalized therapy is not recommended because no large RCT demonstrated any clinical benefit.
- Ticagrelor and prasugrel have a low occurrence of HPR, and platelet function testing is not recommended; in addition there are no large RCT studies available on this subject.

- Resistance to antiplatelet drugs and its impact to the clinical outcomes (bypass patency, major adverse cardiovascular events such as MI, PCI, re-do CABG, and cardiac mortality) of patients requires further investigation with larger studies.
- It is reasonable to assume (and meta-analyses of studies consisting of patients with cardiovascular disease suggest) that patients who are resistant to ASA have a greater risk of clinically important cardiovascular morbidity long term than ASA-sensitive patients.
- Further studies are needed in order to define the role of more aggressive antiplatelet therapy post CABG on graft patency and clinical outcome.
- 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, the degree of reduction of systolic function of left ventricle before CABG, and other associated comorbidity (e.g., diabetes, chronic renal failure, etc.) have to be taken into consideration when interpreting MACCE and CABG patient outcomes.

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