Review article

Dual antiplatelet therapy in patients with acute coronary syndrome treated by surgical revascularization

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Twelve months dual antiplatelet therapy (DAPT) based on a combination of acetylsalicylic acid and purine receptor P2Y12 inhibitor is a standard for all patients with acute coronary syndrome (unstable angina pectoris, NSTEMI and STEMI). Previous sub-analysis of CURE and ACUITY studies suggested that DAPT could bring benefit even for patients treated by surgical revascularization. Sub-analysis of PLATO trial conducted on 1261 patients, who underwent surgical revascularization within 12 months, demonstrated a reduction of cardiovascular and total mortality within a group of patients treated by ticagrelor and acetylsalicylic acid compared to patients treated by clopidogrel and acetylsalicylic acid.

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Introduction

According to current ESC guidelines for the management of acute coronary syndrome in patients presenting with or without ST-segment elevation, patients should undergo 12 months of dual antiplatelet therapy (DAPT) after the myocardial infarction irrespective of whether they are treated with percutaneous coronary intervention or conservatively, with pharmacotherapy only [1,2]. Part of the patients hospitalized due to acute coronary syndrome (ACS) are treated with a coronary artery bypass graft (CABG) in the acute stage, electively after discharge or later because of progression of atherosclerosis or development of in-stent restenosis. The number of patients treated with invasive strategy at a higher age is growing along with the improved care for patients with ACS. According to the Euroheart ACS 2001 survey of patients who underwent coronary angiography for ACS suspicion, a total of 35.2% of men and 29.8% of women aged 55–64 years, 38.8% of men and 34.1% of women aged 65–74 years, and 46.6% of men and 40.1% of women aged over 75 years had a three-vessel disease [3]. Table 1 illustrates the growing portion of invasively examined patients with ACS between 1999 and 2008 (from 43% up to 85%); increasing proportion of patients were treated with percutaneous coronary intervention (PCI) (from 21% up to 64%), while the number of patients treated with surgical revascularization remains stable and moves around 11%.

The question remains whether a patient after ACS in whom significant and unstable atherosclerotic lesions were bridged by CABG (arterial or venous) is stable and should be treated similarly as a patient after surgical revascularization for the stable form of coronary artery disease (CAD), or whether he still remains a patient after ACS with the presence of an unstable atherosclerotic plaque and should be treated with dual antiplatelet therapy for 12 months after the onset of ACS.

Antiplatelet therapy for patients post-CABG with a stable form of CAD

According to ACCF/AHA guidelines, patients with a stable form of CAD post-CABG revascularization should be treated with acetylsalicylic acid (ASA) in a dose of 100–325 mg, which should be administered perioperatively or as soon as the patient’s bleeding is stabilized – ideally 6 h after the surgery and after 48 h at the latest. Clopidogrel is the alternative in the case of ASA intolerance. This treatment lowers the risk of venous graft closure. Warfarin did not turn out to be as effective [4]. Two smaller recent studies demonstrated that DAPT based on the combination of ASA with clopidogrel could also be beneficial for such stable patients after CABG. López et al. reported in a group of 237 patients treated by CABG off-pump that during 24-month follow-up, rehospitalization for ACS decreased (10.9% vs. 3.7%, \( p = 0.035 \)), and combined end-point occurrence decreased as well (ACS, revascularization, stroke and cardiovascular deaths; 18.8% vs. 8.3%; \( p = 0.02 \)) with dual antiplatelet therapy [5]. Gao at el. have demonstrated lower risk of venous graft closure after three months of DAPT with ASA plus clopidogrel compared to ASA itself (91.6% vs. 85.7%, \( p = 0.043 \)) [6].

Dual antiplatelet treatment with clopidogrel together with ASA after CABG in CURE and ACUITY studies in ACS patients

Comparison of dual antiplatelet therapy with the combination of ASA plus clopidogrel vs. ASA itself in ACS patients presented without ST elevation was evaluated in the CURE study (clopidogrel in unstable angina pectoris to prevent recurrent ischemic events). Out of the total of 12,562 patients, 2072 underwent surgical revascularization during the course of the study. The sub-analysis results were consistent with the results of the entire study; the occurrence of combined primary end-point (cardiovascular deaths, MI or stroke) was lower in the group of patients treated with DAPT; however, without reaching statistical significance (14.5% vs. 16.2%; RR = 0.98; 95% CI 0.71–1.11). The outcome was similar in patients treated both in the early stage of ACS and during the entire course of the study. The positive effect of DAPT was seen especially during the period prior to surgical revascularization. After surgery, the median of DAPT interruption (study medication) was 10 days and DAPT was initiated again in 75.3% of the patients. The occurrence of cardiovascular events

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Table 1 – Part of patients with acute coronary syndrome in studies and registers who were examined invasively and treated by percutaneous coronary intervention (PCI) and surgical revascularization (CABG) between 1999 and 2008.

<table>
<thead>
<tr>
<th>Study</th>
<th>Coronary angiography</th>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE (1999) [13]</td>
<td>43.7%</td>
<td>21.2%</td>
<td>16.5%</td>
</tr>
<tr>
<td>EHS-ACS I (2000) [3]</td>
<td>52.0%</td>
<td>25.4%</td>
<td>5.4%</td>
</tr>
<tr>
<td>GRACE registry (2000)</td>
<td>53%</td>
<td>28%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EHS-ACS II (2004) [15]</td>
<td>62.9%</td>
<td>37.1%</td>
<td>7.4%</td>
</tr>
<tr>
<td>CZECH registry (2005)</td>
<td>85%</td>
<td>54%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLATO (STEMI and NSTE MI) (2008) [17]</td>
<td>81.4%</td>
<td>64.1%</td>
<td>10.2%</td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.
was comparable in further observations (RR 0.97; 95% CI 0.74–1.26). Patients with clopidogrel discontinuation <5 days before surgery faced an insignificant rise in the risk of serious bleeding [7].

The ACUITY study compared the effect of bivalirudin with the combination of heparin plus glycoprotein IIb/IIIa inhibitors in NSTE MI patients. Of the total number of patients, 1539 underwent surgical revascularization (11.1%). Patients pre-treated with clopidogrel registered a lower incidence of combined end-point within 30 days (deaths, MI or unplanned revascularization – 12.7% vs. 17.3%; p = 0.01), manifested especially by reduction in the number of myocardial infarctions (8.8% vs. 14.5%; p = 0.01). Patients who discontinued treatment with clopidogrel ≥5 days before surgery showed better outcome. The incidence of serious bleeding associated with surgery was comparable regardless of the clopidogrel pre-treatment [8].

According to ESC guidelines for the management of patients presenting without ST-segment elevation and according to the Canadian Cardiovascular Society, dual antiplatelet therapy may be maintained during surgery in the case of particularly hazardous localization of coronary stenosis, e.g. significant impairment of left main with significant stenosis of the right coronary artery [2,9].

Comparison of dual antiplatelet therapy with ticagrelor plus ASA compared to clopidogrel plus ASA in ACS patients treated with surgical revascularization in the PLATO study

The multicenter double-blind randomized clinical trial PLATO compared the effect of the new direct reversible antagonist of purine receptor P2Y12 ticagrelor with clopidogrel in a group of 18,624 ACS patients (unstable angina pectoris, NSTE MI and STEMI). During the course of the entire study, 1899 patients underwent surgical revascularization. According to the study protocol, discontinuation of ticagrelor/placebo was recommended 24–72 h before surgery and use of clopidogrel/placebo five days before surgery. Sub-analysis of the effect of combined DAPT was carried out in a group of 1261 patients, who were treated with study medication <7 days before the surgery (632 patients received ticagrelor; 629 patients received clopidogrel).

The baseline characteristics of both patient groups were comparable: the median age was 64 years; 21% of patients were women; the previous PCI was carried out in 10.4% of the patients and CAGB in 1.5% of them. Fifty-seven percentage of the patients underwent surgical revascularization during initial hospitalization. Approximately 80% of the surgeries were performed during the first two months and 95% of them did not require valve replacement. The number of peripheral anastomoses was 1 or 2 in 31% of the patients, 3 or 4 in 60%, and more than 5 in 8% of the patients. The interruption period for study medication prior to surgery partly differed between both groups with regard to the study protocol. Study medication was re-started post-surgery in 63% of the patients.

The incidence of combined end-point (cardiovascular deaths, MI or stroke) was lower in the ticagrelor group compared to the clopidogrel group; however, the difference was not statistically significant (10.6% vs. 13.1%) and was in keeping with the results of the entire study. This positive result was especially caused by significantly lower cardiovascular mortality (4.1% vs. 7.9%; p = 0.009) and overall mortality (4.7% vs. 9.7%; p = 0.002) [Fig. 1]. No significant difference in the incidence of myocardial infarctions, non-cardiovascular deaths or stroke was found [Table 2]. The results of the analysis, focusing on total mortality dependence on the number of days from the last intake of study drug before surgery, were very interesting [Fig. 2]. Mortality was comparable between both treated groups when the study medication (ticagrelor or clopidogrel) was discontinued in the course of 24 h or 5 and more days before surgery. When the study drug was discontinued 2, 3 or 4 days before surgery, much better prognosis was reflected in the overall mortality in patients treated with ticagrelor (3.4% vs. 15.5%; HR 0.21; 95% CI 0.10–0.42; p < 0.01) as well as in cardiovascular mortality (3.1% vs. 11.8%; HR 0.25; 95% CI 0.12–0.53; p < 0.05) [10].

Bleeding events in CABG-treated patients in the PLATO study

Nearly all the bleeding events occurred within 24 h after surgery. Bleeding was evaluated according to several definitions and criteria; however, the results were similar in both treatment groups, according to the PLATO study definitions – major CABG-related bleeding: 81.3% vs. 80.1%; life-threatening/fatal CABG-related bleeds: 42.6% vs. 43.7%; bleeding according to TIMI major criteria: 57.6% vs. 59.3%; bleeding according to TIMI minor criteria: 21.6% vs. 21.2%; according to GUSTO study severe bleeding criteria: 10.6% vs. 12.2%. There was no difference in chest tube drainage and bleeding evaluated according to the CABG-related hemoglobin drop >50 g/l in both groups. Fig. 3 indicates lower impact of perioperative bleeding on hemoglobin concentration when the interval from the last intake of the study drug was at least five days [10].

Factors affecting lower post-CABG mortality in the group of patients treated with ticagrelor compared to clopidogrel

An interesting sub-analysis was published in 2012 focusing on the causes of deaths of all patients treated with surgical revascularization (29 deaths out of 632 patients receiving ticagrelor and 58 deaths out of 629 patients in the group receiving clopidogrel). In addition to reviewing the primary cause of death, bleeding or infections that could have contributed to the death were evaluated by independent experts. As has already been stated above, a significantly lower number of cardiovascular deaths were reported in the group of patients treated with ticagrelor; however, none of the subcategories (myocardial infarction, heart failure, sudden death/arrhythmia, stroke, pulmonary embolism and bleeding) reached statistical significance. As a primary cause of death, infectious diseases appeared non-significantly more frequently in the clopidogrel group.

However, when evaluating all deaths to which bleeding contributed or of which it was the primary cause, the number
was significantly higher in the clopidogrel group compared with the ticagrelor group (4.6% vs. 1.4%; p < 0.01). Similarly, the number of deaths in the clopidogrel group was higher when evaluating infection as the primary cause of death or as contributing to death (2.9% vs. 1.0%; p < 0.05) (Fig. 4). This mechanism has not been fully clarified [11].

**Fig. 1 – Cumulative risk of total mortality (A) and cardiovascular mortality (B) after CABG in the ticagrelor group and clopidogrel group.**

*Source: Held et al. [10], published with the permission.*

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**Dual antiplatelet therapy in the Triton-TIMI 38 study based on combining prasugrel and ASA**

Information about the possible benefit of a new antiplatelet agent prasugrel compared to clopidogrel in ACS patients...
Table 2 – Incidence of selected end-points after a coronary artery bypass graft in the PLATO study population.

<table>
<thead>
<tr>
<th>End-point</th>
<th>Ticagrelor (n = 629)</th>
<th>Clopidogrel (n = 629)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end-point (CV deaths/MI/stroke)</td>
<td>66 (10.6%)</td>
<td>79 (13.1%)</td>
<td>0.84 (0.60–1.16)</td>
<td>0.286</td>
</tr>
<tr>
<td>MI</td>
<td>37 (6.0%)</td>
<td>35 (5.7%)</td>
<td>1.06 (0.66–1.68)</td>
<td>0.819</td>
</tr>
<tr>
<td>Total mortality</td>
<td>29 (4.7%)</td>
<td>58 (9.7%)</td>
<td>0.49 (0.32–0.77)</td>
<td>0.002</td>
</tr>
<tr>
<td>CV deaths</td>
<td>25 (4.1%)</td>
<td>47 (7.9%)</td>
<td>0.52 (0.32–0.85)</td>
<td>0.009</td>
</tr>
<tr>
<td>Non-cardiovascular deaths</td>
<td>4 (0.7%)</td>
<td>12 (2.0%)</td>
<td>0.35 (0.11–1.13)</td>
<td>0.075</td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (2.1%)</td>
<td>11 (2.1%)</td>
<td>1.17 (0.53–2.62)</td>
<td>0.697</td>
</tr>
</tbody>
</table>

Source: Held et al. [10], published with the permission.
CV deaths, cardiovascular deaths; MI, myocardial infarction.

Treatment with CABG was brought by a sub-analysis of the Triton-TIMI 38 study, which randomized ACS patients (STEMI, NSTEMI and unstable AP) for treatment using ASA combined with either prasugrel 10 mg or clopidogrel 75 mg. A total of 13,608 patients were randomized for invasive PCI treatment. Subsequently, 448 patients underwent surgical revascularization during the course of more than 12-month monitoring. Sub-analysis included 346 patients who received at least one dose of the study antiplatelet therapy. Most surgeries were elective with more than a 90-day interval from the ACS. Discontinuation of antiplatelet drugs was recommended seven days prior to surgery. It is interesting to note that a total of four patients in the group treated with clopidogrel experienced a myocardial infarction when medication was discontinued. A significantly higher chest tube blood loss (655 ± 580 ml vs. 503 ± 378 ml; p = 0.05) was observed with prasugrel compared with clopidogrel, without significant differences in red blood cell transfusion (2.1 U vs. 1.7 U; p = 0.442) or the total donor exposure (4.4 U vs. 3.0 U; p = 0.063). The incidence of platelet transfusion was significantly higher in the prasugrel group compared with the clopidogrel group (17.9% vs. 9.8%; p = 0.03). There was a trend toward a higher incidence of surgical re-exploration for bleeding in the prasugrel group (11 patients vs. 4 patients). DAPT was re-started after surgery in 72% of the patients (open-label or study medication). All-cause mortality was significantly reduced with prasugrel compared with clopidogrel (2.31% vs. 8.67%, OR: 0.26 (95% CI: 0.08–0.85); p = 0.025), as well as cardiovascular mortality (1.73% vs. 6.94%, OR 0.25 (95% CI: 0.08–0.98); p = 0.047) [12]. With regard

Fig. 2 – Risk of death depending on the period from the last intake of study medication prior to CABG. Source: Held et al. [10], published with the permission.
It is clear from the preceding results that DAPT may increase the risk of bleeding complications when not discontinued well in advance of surgery in line with guidelines. High-risk patients with ACS presenting without ST-segment elevation, who should undergo invasive examination within 2 h according to risk stratification and who have increased risk of acute surgery, should be treated with dual antiplatelet therapy only according to the angiography result. No data is available for patients undergoing coronary angiography within 24 h and initiation of dual antiplatelet therapy must be decided on an individual basis. This highlights the importance of risk stratification of patients with ACS without ST-segment elevation. According to ESC guidelines, acute coronary angiography should be performed within 2 h for patients with refractory angina pectoris, heart failure, malignant arrhythmia or right bundle branch block. It should be carried out within 24 h in the group of patients with a GRACE score value >140 and at least one other risk factor (positive troponin, dynamic changes of ST segment or T wave, diabetes mellitus, renal insufficiency – eGFR < 60 ml/min/1.73 m², EF < 40%, post-infarction AP, recent PCI or previous CABG), while acute angiography should be carried out within 72 h in patients with a GRACE score < 140 and one of the above-mentioned risk factors [2].

ACS patients benefit from DAPT if they are treated with surgical revascularization over the course of 12 months since the initial ischemic episode. If the patient is stable and surgical revascularization is not carried out immediately after the coronary event, he should be treated with DAPT based on the combination of ticagrelor and ASA until the surgery. Clopidogrel is the alternative in the event of intolerance or the impossibility of administering ticagrelor. Dual antiplatelet therapy should be discontinued prior to surgical revascularization: clopidogrel and ticagrelor 5 days and prasugrel 7 days before the surgery (according to ESC guidelines). In urgent cases when there is a high risk of bleeding, discontinuation of clopidogrel or ticagrelor even for 24 h before surgery may lower the risk of bleeding. Surgical revascularization with maintained DAPT is to be considered with the high-risk coronary finding. Acetylsalicylic acid should be administered perioperatively; in the case of ASA discontinuation, administration should be initiated early – 6–48 h after the surgery at the latest unless anticoagulation treatment is indicated (e.g. due to valve replacement or atrial fibrillation). DAPT should be restarted after stabilizing the patient and after management of any possible bleeding complications. DAPT based on ASA and ticagrelor (clopidogrel could be a less suitable alternative) should last 12 months since ACS (Table 3).

Finally, it must be noted that although the above review should bring the maximum currently available information about DAPT in ACS patients undergoing CABG, the individual net clinical benefit and bleeding risks associated with DAPT

Fig. 3 – Proportion of patients with a decrease in hemoglobin ≥50 g/l by days from the last intake of the study drug. Source: Held et al. [10], published with the permission.
must always be considered. Efforts to minimize the possible complications for the patient should lead to individual timing of DAPT in the period around CABG.

**Conflict of interest**

There is no conflict of interest.

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**Ethical statement**

The research was done according to ethical standards.

**REFERENCES**


