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Original Article

Evaluation of safety of switching between oral P2Y12 inhibitors: a descriptive study

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Abstract: Purpose: Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is recommended for patients with acute coronary syndrome and after percutaneous coronary intervention with stenting in stable coronary artery disease to help prevent further thromboembolic events. However, there is limited guidance on appropriate strategies for switching between oral P2Y12 inhibitors. The aim of this study was to evaluate safety of switching modalities at our institution and compare them to the recently published expert consensus recommendations. Methods: This was a retrospective, descriptive analysis of patients admitted to Brigham and Women's Hospital from January 2015 to December 2018. Patients were included if they were at least 18 years of age and had documented administrations of two or more oral P2Y12 inhibitors during the same admission. The major safety endpoint was incidence of major adverse cardiac events (MACE) (cardiovascular death, myocardial infarction, stroke, and non-coronary artery bypass grafting (CABG)-related bleeding) at seven days or until hospital discharge. Minor endpoints included the incidence of in-stent thrombosis, number of patients who received appropriate loading doses (LD) before and after the recently published recommendations, and documented reason for switching between agents. Results: There were 253 patients included in the final analysis. Of these, 83 patients were on clopidogrel as the first agent prior to switching, 9 patients were on prasugrel, and 161 were on ticagrelor. There was no incidence of the primary safety endpoint observed in any group. However, the number of patients who received a LD when switching between oral P2Y12 inhibitors increased from 80.0% to 87.0% after publication of the expert consensus paper. The most common reasons for switching from one agent to another were cost/insurance coverage (19.0%), need for triple therapy (16.0%), and bleeding risk (11.0%). Conclusion: Different switching modalities were not associated with an increase in MACE at our institution; however, larger randomized controlled trials are warranted.

Keywords: P2y12 inhibitor, clopidogrel, prasugrel, ticagrelor, antiplatelet, antiplatelet therapy, escalation, de-escalation

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is recommended following an acute coronary syndrome (ACS) to help prevent further thromboembolic events [1, 2]. In the United States, there are three commercially available oral P2Y12 inhibitors: clopidogrel, prasugrel, and ticagrelor. Clopidogrel is the most commonly used agent, likely as a result of its cost effectiveness compared to the other two agents. However, clinical trials have shown that both prasugrel and ticagrelor are associated with lower rates of CV death, MI, or stroke when compared to clopidogrel in the management of ACS [3, 4].

The rationale for switching patients from one agent to another is multifactorial. Safety concerns exist surrounding the appropriate strategy for switching between oral P2Y12 inhibitors. Due to the pharmacological and pharmacokinetic differences between oral P2Y12 inhibitors, including half-life, site of action, mechanism, and onset and offset of action, there may be concern that switching between agents could lead to a period of inadequate platelet inhibition and further thromboembolic events. In contrast, there may be concern that a period of more robust platelet inhibition could occur while switching between agents, raising the risk of potential bleeding [5].

Guidance on the best modality for switching between these agents had been lacking, particularly regarding timing and the need for reloading. In December 2017, the American Heart Association (AHA) published an interna-

tional expert consensus on strategies for switching between P2Y12 receptor antagonists. The expert consensus provides an overview of the pharmacology of P2Y12 inhibitors, strategies for and definitions of switching between agents, and available literature to support these recommendations. The authors suggest giving a loading dose (LD) when switching between any of the oral P2Y12 inhibitors during the acute (< 24 hours after an ACS event or percutaneous coronary intervention (PCI)) and early phases (1-30 days after an ACS event or PCI), and only giving a LD when switching from ticagrelor to either prasugrel or clopidogrel in the late (> 30 days-1 year) and very late phases (> 1 year). They define switching from clopidogrel to a more potent agent, either ticagrelor or prasugrel, as escalation. De-escalation is defined as switching from either ticagrelor or prasugrel to clopidogrel. Switching between prasugrel and ticagrelor was defined as a change [5].

The aim of this analysis was to evaluate the safety of strategies for switching between oral P2Y12 inhibitors at our institution and compare our findings to the most recently published expert consensus recommendations.

Methods

Design

This was a single-center, retrospective, descriptive analysis evaluating the safety of strategies for switching between the currently available oral P2Y12 inhibitors in patients with ACS, peripheral arterial disease (PAD), or who underwent PCI who were admitted to Brigham and Women's Hospital within the study time frame of January 2015 through December 2018. The study protocol was reviewed by the Partners Institutional Review Board and due to the retrospective nature of the analysis, a waiver of informed consent was approved.

Population

Patients who were eligible for inclusion were at least 18 years of age and had documented administration of at least two different oral P2Y12 inhibitors during the index admission. Patients who were on an intravenous P2Y12 inhibitor (i.e. cangrelor) and were switched to an oral P2Y12 inhibitor were excluded. Furthermore, any patient who had an oral P2Y12 inhibitor held for any reason and were switched to another P2Y12 inhibitor were also excluded from the analysis.

Patients were identified through an electronic medical record database search with documented administration of more than one oral P2Y12 inhibitor (e.g., clopidogrel, ticagrelor, or prasugrel).

Outcomes

The major safety endpoint of this analysis was the incidence of major adverse cardiac events (MACE) (cardiovascular death, myocardial infarction, stroke, and non-CABG-related bleeding) at seven days after switching between oral P2Y12 inhibitors or until hospital discharge. Minor endpoints included the incidence of stent thrombosis, percent of patients who received an appropriate LD, documented reasons for omitting a LD, and documented reasons for switching to an alternative oral P2Y12 inhibitor during the same admission. Appropriate LD was defined as clopidogrel 300 mg or 600 mg, ticagrelor 180 mg, or prasugrel 60 mg [6-8].

Statistical analysis

All data were analyzed using descriptive analysis. Continuous data were expressed in mean and standard deviation or median and interquartile range (IQR), as appropriate, and were analyzed by using ANOVA test. Categorical data were expressed in number and percentage, and were analyzed by using chi-squared test or Fisher's exact test as appropriate. A p-value < 0.05 was considered statistically significant. Statistical tests were done utilizing VassarStats.

Results

Patients

From January 2015 through December 2018, a total of 276 patients were screened for eligibility. Of these, 253 patients were included in the final analysis. There were 83 patients who initially received clopidogrel, of which nine were switched to prasugrel and 74 were switched to ticagrelor. There were nine patients who initially received prasugrel, six were switched to clopi-

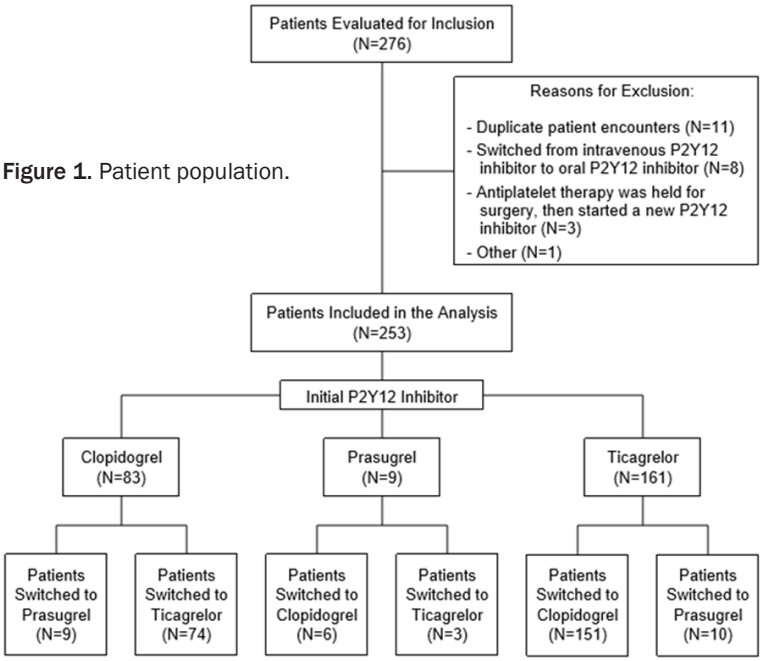

Figure 1. Patient population.

dogrel and three were switched to ticagrelor. Of the 161 patients initially on ticagrelor, 151 were switched to clopidogrel and ten were switched to prasugrel (**Figure 1**). All patients were categorized into one of three study groups based upon the initial P2Y12 inhibitor administered.

In the overall population, patients had a mean age of 66 ± 12 years old and 170 (67.2%) of the patients were men. The incidence of diabetes, hypertension, PAD, stroke, heart failure with reduced ejection fraction, and venous thromboembolism was similar between all study groups. More patients in the ticagrelor group had a diagnosis of atrial fibrillation than in the clopidogrel or prasugrel groups. A majority of patients (240) were on DAPT with aspirin (95.0%) and 82 (23.4%) patients were on concomitant anticoagulation therapy (warfarin: 38 (15.0%), apixaban: 35 (14.0%), rivaroxaban: 7 (2.7%), dabigatran: 2 (0.8%)). Other baseline characteristics were generally well-balanced between the three study groups (**Table 1**).

Among all included patients, 175 (69.0%) had new ACS and underwent PCI during the admission, 54 (21.0%) had stable coronary artery disease (CAD) and underwent PCI, 20 (8.0%) had new medically-managed ACS, and 4 (1.6%) had PAD.

Study outcomes

Major safety outcome: There was no incidence of the primary outcome of MACE observed when switching to an alternative oral P2Y12 inhibitor at seven days or until hospital discharge in all groups.

Minor safety outcomes: Similarly, no incidence of stent thrombosis was noted in any patient after switching to an alternative P2Y12 inhibitor. When we compared those patients whose encounter occurred prior to the publication of the 2017 expert consensus paper to those whose encounter occurred afterwards, the number of patients who received an appropriate LD when switching increased from 80.0% to 87.0% (**Figure 2**). The most commonly documented reasons for switching agents were cost/insurance coverage (19.0%), de-escalation to a less potent agent due to the need for concomitant anticoagulation (16.0%), and concerns for an increased risk of bleeding (11.0%), as shown in **Figure 3**. Reasons for omitting a LD when switching between agents were only documented in 27.0% of patients who did not receive a LD (**Table 2**). In all documented cases, the LD was omitted due to a concern for an increased risk of bleeding.

Discussion

In the present study, we found no incidence of MACE regardless of the switching modality (escalation, de-escalation, or change). When we analyzed whether a LD was given upon switching to an alternative P2Y12 inhibitor, we found that providers were more likely to prescribe a LD following the publication of the AHA expert consensus document when compared to prior. To date, most of the available literature is composed of subgroup analyses of large clinical trials, registries, or pharmacodynamic studies. A series of four pharmacodynamic studies have evaluated various modalities for changing, de-escalating, and escalating between the available oral P2Y12 inhibitors

Table 1. Baseline characteristics

Variable	Entire Population (n = 253)	Initial P2Y12 Inhibitor Clopidogrel (n = 83)	Initial P2Y12 Inhibitor Prasugrel (n = 9)	Initial P2Y12 Inhibitor Ticagrelor (n = 161)	*p* Value
Age, years	66 ± 12	67 ± 13	60 ± 12	66 ± 13	0.37
Gender					
Male	170 (67.2)	62 (75)	7 (78)	101 (63)	0.9
Female	73 (28.8)	21 (25)	2 (22)	50 (31)	0.9
Weight, kg	83 ± 22	82 ± 21	87 ± 24	82 ± 22	0.32
Past Medical History					
Diabetes Mellitus	126 (49.8)	43 (52)	3 (33)	81 (50)	0.57
Atrial Fibrillation	61 (24)	10 (12)	1 (11)	50 (31)	0.002
Hypertension	209 (82.6)	72 (87)	6 (67)	131 (81)	0.25
Peripheral Arterial Disease	42 (16.6)	13 (16)	-	29 (18)	0.35
Prior Stroke	31 (12.2)	9 (11)	-	22 (14)	0.08
Heart Failure	49 (19.3)	11 (13)	4 (44)	34 (21)	0.05
Prior VTE	22 (8.6)	4 (5)	2 (22)	16 (10)	0.13
Concurrent Aspirin Use	240 (95)	83 (100)	9 (100)	148 (92)	0.01
Concurrent Anticoagulation Use					
Warfarin	38 (15)	5 (6)	2 (22)	31 (19)	0.01
Apixaban	35 (14)	6 (7)	1 (11)	28 (17)	0.09
Rivaroxaban	7 (2.7)	-	-	7 (43)	0.12
Dabigatran	2 (0.8)	-	-	2 (1)	0.56
Indication for P2Y12 Inhibitor					
New ACS with PCI	175 (69)	57 (69)	8 (89)	110 (68)	0.42
Stable CAD post-PCI	54 (21)	19 (23)	1 (11)	34 (21)	0.71
New ACS "medically managed"	20 (8)	5 (6)	-	15 (9.2)	0.51
PAD stenting	4 (1.6)	2 (2)	-	2 (1.2)	0.72

Values presented as mean ± SD or n (%); VTE = venous thromboembolism; *Heart failure is defined as heart failure with reduced ejection fraction.

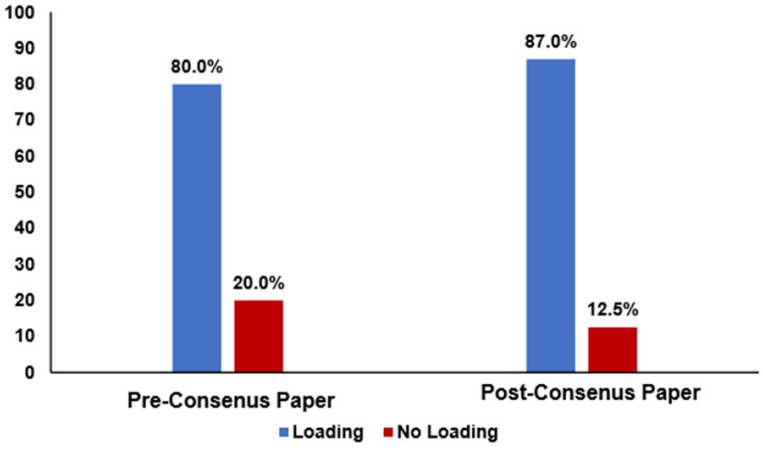

Figure 2. Percent of patients who received a loading dose.

[9-12]. The SWAP (Switching Antiplatelet) study evaluated the pharmacodynamic effects of escalating patients from maintenance clopidogrel to prasugrel with or without a preceding LD. The authors found that regardless of whether a LD was given, prasugrel resulted in a significant decrease in platelet reactivity within one week when compared to clopidogrel. Importantly, when a LD of prasugrel was given, the reduction in platelet reactivity was seen within two hours of administration. In patients who switched to prasugrel without a LD, platelet reactivity was similar to clopidogrel at 24 hours [9]. In the SWAP-2 study, platelet reactivity in patients with stable CAD was significantly higher at 24 and 48 hours after switching from ticagrelor to prasugrel when compared to patients continuing ticagrelor. Importantly, this effect was diminished in those patients receiving a LD of prasugrel upon switching [10]. In the SWAP-3 study, switching

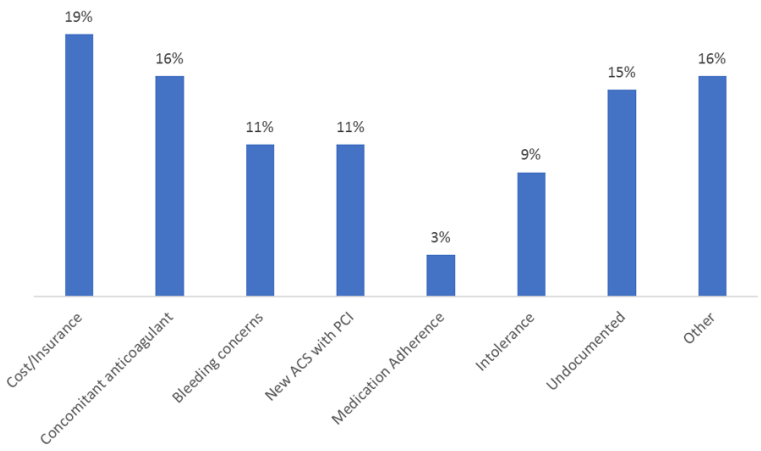

Figure 3. Documented reasons for switching between oral P2Y12 inhibitors.

Table 2. Documented reasons for omitting loading dose when switching between oral P2Y12 inhibitors

Reasons for LD Omission	Clopidogrel (n = 32)	Prasugrel (n = 2)	Ticagrelor (n = 14)
Bleeding Concerns	10 (31.3)	0	3 (21.4)
Undocumented	22 (68.7)	2 (100)	11 (78.6)

from prasugrel to ticagrelor in patients who underwent PCI in the setting of ACS resulted in transiently lower platelet reactivity, regardless of the use of a LD [11]. The SWAP-4 study showed significantly lower platelet reactivity during the first 48 hours after de-escalation from ticagrelor to clopidogrel when a 600 mg LD of clopidogrel was given, irrespective of the timing of LD administration (12 vs. 24 hours) [12]. In two open-label, randomized trials, patients received DAPT with aspirin and either ticagrelor or prasugrel and were randomized to continue or to de-escalate the P2Y12 inhibitor to clopidogrel maintenance dosing. Bleeding complications were found to be similar or reduced, which was not associated with an increase in ischemic events [13, 14].

In 2017 the European Society of Cardiology (ESC) released a focused update on DAPT and provided an algorithm based on pharmacodynamic studies for switching between oral P2Y12 inhibitors [15]. Later that year, the AHA International Expert Consensus on Switching Platelet P2Y12 Receptor-Inhibiting Therapies was published and provided similar algorithms. At the time of the present study, only the 2016 American College of Cardiology/American Heart Association Guideline Focused Update on Duration of Dual Antiplatelet Therapy in patients with CAD was available. This guideline did not provide any specific recommendations regarding switching between oral P2Y12 inhibitors due to lack of randomized clinical trials on the safety and efficacy of switching strategies [16]. Both the ESC and AHA algorithms place importance on the timing of switching between agents with respect to the index event that led to the initiation of a P2Y12 inhibitor.

There are a few important limitations to our analysis. This was a single-center, retrospective review that was limited to in-hospital outcomes and may have resulted in the inability to capture relevant outcomes post-discharge. Additionally, the lack of incidence of the primary outcome could be a result of the small sample size and should be interpreted cautiously. Second, a portion of patients who were initiated on ticagrelor during their admission were switched to a different agent after receiving only a single dose due to lack of insurance coverage or significant cost. It is unclear whether the number of doses of the initial P2Y12 inhibitor received prior to transitioning to a second agent would have any effect on outcomes. Similarly, since our inclusion criteria did not differentiate between patients who were on P2Y12 inhibitors prior to admission and those who were newly started during their admission, it is unclear if the duration of P2Y12 inhibitor therapy would have any effect on our results. Lastly, data collection was limited to one year following the publication of the AHA expert consensus document and prescribing practices may have evolved over the last several years.

Conclusion

In conclusion, there was no incidence of MACE observed when switching between oral P2Y12 inhibitors at seven days or until hospital discharge in all groups. Following the publication

of the AHA expert consensus document, there was a numerical increase in the percent of patients receiving a LD when switching from one P2Y12 to another. Larger, randomized controlled trials are warranted to evaluate the safety and efficacy of switching between oral P2Y12 inhibitors in such patient populations.

Disclosure of conflict of interest

None.

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References

[1] Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW and Zieman SJ; ACC/AHA Task Force Members; Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary. Circulation 2014; 130: 2354-2394.

[2] O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG and Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. Circulation 2013; 127: 362-425.

[3] Wiviott S, Braunwald E, McCabe C, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F, Ardissino D, De Servi S, Murphy S, Riesmeyer J, Weerakkody G, Gibson C and Antman E. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001-2015.

[4] Wallentin L, Becker R, Budaj A, Cannon C, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey K, Scirica B, Skene A, Steg P, Storey R and Harrington R. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J of Med 2009; 361: 1045-1057.

[5] Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, Sibbing D, So DYF, Trenk D, Alexopoulos D, Gurbel PA, Hochholzer W, De Luca L, Bonello L, Aradi D, Cuisset T, Tantry US, Wang TY, Valgimigli M, Waksman R, Mehran R, Montalescot G, Franchi F and Price MJ. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. Circulation 2017; 136: 1955-1975.

[6] Plavix (clopidogrel) [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2016.

[7] Effient (prasugrel) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2009.

[8] Brilinta (ticagrelor) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020.

[9] Angiolillo DJ, Saucedo JF, Deraad R, Frelinger AL, Gurbel PA, Costigan TM, Jakubowski JA, Ojeh CK and Effron MB; SWAP Investigators. Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes: results of the SWAP (SWitching Anti Platelet) study. J Am Coll Cardiol 2010; 56: 1017-1023.

[10] Angiolillo D, Curzen N, Gurbel P, Vaitkus P, Lipkin F, Li W, Jakubowski J, Zettler M, Effron M and Trenk D. Pharmacodynamic evaluation of switching from ticagrelor to prasugrel in patients with stable coronary artery disease: results of the SWAP-2 Study (Switching Anti Platelet-2). J Am Coll Cardiol 2014; 63: 1500-1509.

[11] Franchi F, Faz G, Rollini F, Park Y, Cho J, Thano E, Hu J, Kureti M, Aggarwal N, Durairaj A, Been L, Zenni M, Guzman L, Suryadevara S, Antoun P, Bass T and Angiolillo D. Pharmacodynamic effects of switching from prasugrel to ticagrelor: results of the prospective, randomized SWAP-3 study. JACC Cardiovasc Interv 2016; 9: 1089-98.

[12] Franchi F, Rollini F, Rivas Rios J, Rivas A, Agarwal M, Kureti M, Nagaraju D, Wali M, Shaikh Z, Briceno M, Nawaz A, Moon J, Been L, Suryadevara S, Soffer D, Zenni M, Bass T and Angiolillo D. Pharmacodynamic effects of switching from ticagrelor to clopidogrel in patients with coronary artery disease: results of the SWAP-4 study. Circulation 2018; 137: 2450-2462.

[13] Cuisset T, Deharo P, Quilici J, Johnson T, Deffarges S, Bassez C, Bonnet G, Fourcade L, Mouret J, Lambert M, Verdier V, Morange P, Alessi M and Bonnet J. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J 2017; 38: 3070-3078.

[14] Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Gori T, Hadamitzky M, Merkely B, Kiss R, Komócsi A, Dézsi C, Thalmeier A, Löw A,

Holdt L, Teupser D, Ince H, Felix S, Parma R, Malek L, Horstkotte J, Baylacher M, Schwinger R, Rieber J, Mudra H, Hausleiter J, Huber K, Neumann F, Koltowski L, Huczek Z, Mehilli J, Massberg S, Sibbing D and Aradi D. A randomised trial on platelet function-guided de-escalation of antiplatelet treatment in ACS patients undergoing PC: rationale and design of the testing responsiveness to platelet inhibition on chronic antiplatelet treatment for acute coronary syndromes (TROPICAL-ACS) trial. Thromb Haemost 2017; 117: 188-195.

[15] Valgimigli M, Bueno H, Byrne R, Collet J, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann F, Petricevic M, Roffi M, Steg P, Windecker S and Zamorano J. Special article 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Rev Esp Cardiol (Engl Ed) 2018; 71: 42.

[16] Levine G, Bates E, Bittl J, Brindis R, Fihn S, Fleisher L, Granger C, Lange R, Mack M, Mauri L, Mehran R, Mukherjee D, Newby L, O'Gara P, Sabatine M, Smith P and Smith S. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Thorac Cardiovasc Surg 2016; 152: 1243-1275.