Thrombosis Research 176 (2019) 133–139

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Short Review

Antithrombotic treatment in atrial fibrillation patients undergoing PCI: Is dual therapy the winner?

Christos Mantis[a], Dimitrios Alexopoulos[b,*]

[a] Cardiology Department, Konstantopoulio General Hospital, Athens, Greece
[b] 2nd Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece

ARTICLE INFO

Keywords:
Atrial fibrillation
Percutaneous coronary intervention
Antithrombotic therapy
Dual therapy
Triple therapy

ABSTRACT

Approximately 7% of patients undergoing percutaneous coronary intervention (PCI) with stent implantation have atrial fibrillation. The optimal antithrombotic treatment in such of patients remains one of the most challenging and difficult scenarios in Cardiology. Triple antithrombotic therapy (TAT), consisting of dual antiplatelet therapy plus an oral anticoagulant, has been used for decades in order to reduce ischemic and thromboembolic events, while significantly increasing the risk for severe bleeding. Recently, results of several clinical trials suggest that the use of dual antithrombotic therapy (DAT), consisting of single antiplatelet therapy plus an oral anticoagulant, reduces the risk of bleeding, while maintaining the same level of efficacy as compared to TAT. These data have been interpreted in a variety of ways, often giving conflicting recommendations and leaving many unanswered questions on the optimal antithrombotic treatments of patients with atrial fibrillation who undergo PCI. DAT consisting of a non–vitamin K antagonist oral anticoagulant and clopidogrel, while omitting aspirin from the immediate post discharge period, appears as an attractive, simplified strategy for most patients and supported by many experts in the field. In this review we aim to better define the role of DAT versus TAT in atrial fibrillation patients undergoing PCI and analyze remaining controversial issues and future expectations.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence of approximately 3% in adults [1]. Male patients with AF and CHA_2DS_2-VASc score ≥ 1 (**C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 [2 points], **D**iabetes Mellitus, Prior **S**troke or Transient Ischemic Attack [2 points], **V**ascular Disease, **A**ge 65–74, **S**ex **c**ategory Female) and women with AF and CHA_2DS_2-VASc score ≥ 2 have an indication of long-term treatment with oral anticoagulation (OAC) in order to prevent thromboembolic episodes such as stroke [2]. In addition, AF patients have a high prevalence of coronary artery disease (CAD) [3,4]. Patients with CAD commonly undergo percutaneous coronary intervention (PCI) with stent implantation and are candidates to receive dual antiplatelet therapy (DAPT) consisting of the combination of aspirin plus an oral $P2Y_{12}$ inhibitor, for a variable duration (1–12 months), in order to prevent stent thrombosis and other major adverse cardiovascular events (MACE) [5]. Furthermore, AF coexists in about 7% of patients undergoing PCI with stent implantation [6]. Clinical management of such patients is really challenging and problematic, as they have indication for both OAC and DAPT. This type of triple antithrombotic therapy (TAT) has been for years the treatment of choice in AF patients undergoing PCI. However, TAT increases the probability up to four times, compared to aspirin or warfarin alone, for major and non-major bleeding events, representing for most a 'necessary evil' [7].

Recently, three randomized clinical trials have been published, which directly compared dual antithrombotic therapy (DAT), consisting of an OAC and an oral $P2Y_{12}$ inhibitor, versus TAT in patients with an indication for chronic OAC who underwent PCI. Significantly lower rates of bleeding, while maintaining the same level of efficacy as for MACE and stent thrombosis, were demonstrated [8–10]. Despite the role of TAT is evidently weakening [11] and its suggested duration is

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; CrI, credible interval; DAT, double antithrombotic therapy; DAPT, dual antiplatelet therapy; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial Infarction; NOAC, novel oral anticoagulation; NSTEMI, non S-T elevation myocardial infarction; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; TAT, triple antithrombotic therapy; TIMI, thrombolysis in myocardial infarction; VKA, Vitamin K antagonist

* Corresponding author at: 2nd Department of Cardiology, Attikon University Hospital, Rimini 1, Chaidari, 12462 Athens, Greece.
E-mail address: dalex@med.uoa.gr (D. Alexopoulos).

https://doi.org/10.1016/j.thromres.2019.02.022
Received 26 November 2018; Received in revised form 20 January 2019; Accepted 20 February 2019
Available online 22 February 2019
0049-3848/

Table 1
Randomized clinical trials comparing dual versus triple antithrombotic therapy.

Study	WOEST [8]	PIONEER AF [9]	REDUAL PCI [10]
Year	2013	2016	2017
Design	RCT, open label	RCT, open label	RCT, open label
Size (n)	573	2124	2725
AF (%)	70	100	100
ACS (%)	27	52	51
DES (%)	64	68	83
Comparison	-Clopidogrel 75 mg qd for 1–12 months plus a dose-adjusted VKA -Aspirin 80–100 mg qd plus clopidogrel 75 mg qd for 1–12 months plus a dose-adjusted VKA	-Rivaroxaban 15 mg qd plus a $P2Y_{12}$ inhibitor for 12 months (group 1) -Rivaroxaban 2.5 mg bid plus DAPT for 1, 6, or 12 months (group 2) -Dose-adjusted VKA plus DAPT for 1, 6, or 12 months (group 3)	-Dual antithrombotic therapy with dabigatran (110 mg or 150 mg bid) plus clopidogrel or ticagrelor - Dose-adjusted VKA plus DAPT
Exclusion criteria	History of intracranial bleeding; cardiogenic shock; contraindication to ASA, clopidogrel, or both; peptic ulcer in previous 6 months; thrombocytopenia; major TIMI bleed in previous 12 months; and pregnancy	History of stroke or TIA; history of intracranial hemorrhage; clinically significant gastrointestinal bleeding within 1 year prior to index hospitalization; CrCl < 30 mL/min; Hgb < 10 g/dL; any condition increasing the risk of bleeding	Bioprosthetic/mechanical heart valves; gastrointestinal or other major bleeding, stroke, or major surgery within 1 month prior to screening; Anemia or thrombocytopenia; severe renal dysfunction; conditions leading to increased risk of bleeding
Primary endpoint	Any bleeding episode	Clinically significant bleeding (composite of major and minor TIMI bleeding)	Major or clinically relevant non-major bleeding
Secondary endpoints	Death, MI, stroke, target vessel revascularization and stent thrombosis	Cardiovascular death, MI, and stroke	Death, MI, stroke, systemic embolism and unplanned revascularization
Follow up	12 months	12 months	14 months
Results	-Primary endpoint (DAT vs TAT): 19.4% vs 44.4% (HR 0.36, 95% CI 0.26 to 0.50, $p < 0.0001$). -Secondary endpoint (DAT vs TAT): 11.1% vs 17.6% (HR 0.60, 95% CI 0.38 to 0.94, $p = 0.025$)	-Primary endpoint: 16.8% in group 1, 18.0% in group 2, 26.7% in group 3 (HR group 1 vs group 3, 0.59, 95% CI 0.47 to0.76; HR for group 2 vs group 3, 0.63, 95% CI 0.50to 0.80). -Secondary endpoint: 6.5% in group 1, 5.6% in group 2 and 6.0% in group 3	-Primary endpoint: 15.4% in the 110 mg DAT group and 26.9% in the TAT group (HR 0.52, 95% CI 0.42 to 0.63); 20.2% in the 150 mg DAT group and 25.7% in the TAT group (HR 0.72, 95% CI 0.58 to 0.88). -Secondary endpoint: 13.7% in combined DAT groups and 13.4% in TAT
Comments	-Not powered for efficacy −30% other indications than AF -Small number of patients	-Not powered for efficacy -Not-approved Rivaroxaban dose for stroke prevention	-Not powered for efficacy

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, acetylsalicylic acid; CI, confidence interval; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; DES, drug-eluting stent; HR, hazard ratio; MI, myocardial infarction; RCT, randomized clinical trial; TAT, triple antithrombotic therapy; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; VKA, vitamin-K antagonist.

decreasing over the last decade, as recommended in several recent practice guidelines, there are numerous unanswered questions regarding the optimal antithrombotic treatment in patients with AF who undergo PCI. Within the last year Practice Guidelines, Consensus Documents and Expert Panel Reports have interpreted in various ways randomized trials results and produced conflicting recommendations. It is still unclear which is the patient who will get most of the benefit from DAT from the immediate post-discharge period or for whom TAT and for how long is necessary. The position of the newer $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) in this combination also remains unsettled. This review aims to investigate how latest data have impacted on antithrombotic therapy strategies in patients with AF undergoing PCI, and what are the remaining controversial issues and future expectations in the field.

1.1. Data from randomized trials

The first randomized clinical trial that essentially questioned the role of aspirin in the treatment of patients with AF after PCI was published in 2013 (Table 1).

In What is the Optimal antiplatElet and anticoagulation therapy in patients with oral anticoagulation and coronary StenTing (WOEST) trial, DAT group was treated with Vitamin K antagonist (VKA) plus clopidogrel and showed significantly lower rate of bleeding events, as compared with the TAT group, that received the combination of VKA, clopidogrel and aspirin [8]. Similarly, the incidence of the composite MACE was significantly lower for patients who received DAT [8]. Major limitations of WOEST trial were the small sample size, the long duration of TAT (12 months), the fact that only one out of four patients presented with acute coronary syndrome (ACS) and 30% of patients had an indication for oral OAC other than AF. Finally, although there was a significant difference on the rates of the composite MACE, the study was not powered to detect any differences in any of the individual components of the composite efficacy end point.

The PIONEER AF-PCI trial (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention) compared two different rivaroxaban treatment strategies with the standard TAT (VKA plus DAPT for 1, 6 or 12 months) [9]. The first regimen (rivaroxaban 2.5 mg bid plus DAPT for 1, 6 or 12 months) was based on the results of the ATLAS ACS 2-TIMI 51 study (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51) [12] and the second regimen (rivaroxaban 15 mg once plus a $P2Y_{12}$ inhibitor for 12 months) was based on the results of the WOEST study. In PIONEER AF-PCI most patients (94.4%) were treated with clopidogrel, and only 4.3% and 1.3% received ticagrelor and prasugrel, respectively. In both rivaroxaban groups, lower rates of clinically significant bleeding were observed during 12 months of follow-up compared to VKA plus DAPT, while the rates of the composite MACE were similar between groups [9]. The main limitations of this trial are the use of a non-approved dose of rivaroxaban 15 mg for stroke prevention (rivaroxaban 20 mg daily is the standard dose used for stroke prevention in AF), which implies that the risk of bleeding when using recommended dosages remains unknown. Use of newer

Table 2
Latest recommendations after results of PIONEER AF-PCI and/or RE-DUAL PCI trials.

	2017 ESC DAPT guidelines [5]	2018 ESC Revascularization guidelines [19]	2018 CHEST guidelines for AF [20]	2018 EHRA consensus document [21]	2018 North American Perspective [22]	2018 CCS APT guidelines [23]
Low bleeding risk/ Concerns about ischemic risk prevailing	•TAT for 1 to 6 months (*IIa/B*) •Followed by DAT for up to 12 months (*IIa/A*) •OAC alone after 12 months (*IIa/B*)	•TAT for 1 to 6 months (*IIa/B*) •Followed by DAT for up to 12 months (*IIa/A*) •OAC alone after 12 months (*IIa/B*)	<u>Elective PCI</u> •TAT for 1 month •Followed by DAT for up to 12 months •OAC alone after 12 months (*weak recommendation, low quality evidence*) <u>ACS PCI</u> •TAT for 6 months •Followed by DAT for up to 12 months • OAC alone after 12 months (*weak recommendation, low quality evidence*)	•TAT for 1 to 6 months •Followed by DAT for up to 12 months •OAC alone after 12 months	•DAT for most patients after hospital discharge •Use aspirin peri-PCI or beyond hospital discharge only for patients at high thrombotic and low bleeding risks for limited period (1 month)	<u>Elective PCI without high risk features**:</u> • DAT for up to 12 months (*weak recommendation; moderate quality evidence*) <u>ACS PCI or elective PCI with high risk features**:</u> •TAT for up to 6 months (*strong recommendation, moderate quality evidence*) •Followed by DAT (O + C) for up to 12 months (*weak recommendation; moderate quality evidence*)
High bleeding risk/ concerns about bleeding risk prevailing	•TAT for 1 month (*IIa/B*) •Followed by DAT for up to 12 months (*IIa/A*) •OAC alone after 12 months (*IIa/B*)	•TAT for 1 month (*IIa/B*) •Followed by DAT for up to 12 months (*IIa/A*) •OAC alone after 12 months (*IIa/B*)	<u>Elective PCI</u> •TAT for 1 month •Followed by DAT for up to 6 months •OAC alone after 12 months (*weak recommendation, low quality evidence*) <u>ACS PCI</u> •TAT for 1–3 months •Followed by DAT for up to 12 months • OAC alone after 12 months (*weak recommendation, low quality evidence*)	•TAT for 1 month •Followed by DAT for up to 12 months •OAC alone after 12 months		
Comments	• DAT (OAC + C) is recommended as an alternative to initial TAT in patients with high bleeding risk (HAS-BLED ≥3, previous bleeding, anemia) that outweighs the ischaemic risk (*IIa/A*)	• DAT (OAC + C) is recommended as an alternative to initial TAT in patients with high bleeding risk that outweighs the ischaemic risk (*IIa/A*)	<u>Elective PCI in unusually high bleeding risk*</u> •DAT for 6 months •OAC alone after 12 months (*weak recommendation, low quality evidence*) <u>ACS PCI in unusually high bleeding risk*</u> •DAT for 6 to 9 months •OAC alone after 12 months (*weak recommendation, low quality evidence*) **HAS-BLED ≥ 3, recent acute bleeding*	•DAT (OAC + C) as an alternative to initial TAT in patients with very high bleeding risk (e.g. recent bleeding event) for 3–6 months	•Clopidogrel is $P2Y_{12}$ inhibitor of choice, but ticagrelor may be considered in selected patients •Prasugrel should be avoided •NOAC (rather than a VKA) should be preferred in most patients unless contraindicated	***Diabetes, renal dysfunction, prior ACS or stent thrombosis, total occlusion or bifurcation, stent length > 60 mm, multi-vessel disease, smoking*

Abbreviations: APT, antiplatelet therapy; C, clopidogrel; CCS, Canadian Cardiovascular Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; NOAC, novel oral anticoagulation; OAC, oral anticoagulation; PCI, percutaneous coronary intervention. Other abbreviations as in Table 1.

$P2Y_{12}$ inhibitors was very limited and finally, PIONEER AF-PCI study was not powered to detect differences in efficacy endpoints. Overall, PIONEER-AF PCI results were enthusiastically perceived by most cardiologists as they confirmed WOEST results showing that aspirin may be omitted and offered a clear message of reduced bleeding potential by using a simplified DAT strategy [11,13].

The RE-DUAL PCI trial (Randomized Evaluation of Dual Therapy with Dabigatran vs Triple Therapy with Warfarin in Patients with Atrial Fibrillation That Undergo a Percutaneous Coronary Intervention with Stenting) compared DAT consisting of dabigatran (110 mg or 150 mg bid) plus clopidogrel or ticagrelor with TAT consisting of warfarin, aspirin and clopidogrel or ticagrelor; overall 12% received ticagrelor [10]. The incidence of major or clinically relevant non-major bleeding events was significantly lower for dabigatran plus $P2Y_{12}$ inhibitor than for TAT. DAT groups when combined were not inferior with respect to the incidence of the composite efficacy endpoint for MACE, as compared with the TAT group [10]. Of note, stent thrombosis occurred in more patients in the dabigatran 110 mg group (1.5%) compared with dabigatran 150 mg (0.9%) and TAT (0.8%), as did acute MI (4.5% on dabigatran110mgvs 3.4% on dabigatran150mg vs 3.0% on TAT) and stroke (1.7% on dabigatran 110 mg vs 1.2% on dabigatran 150 mg vs 1.3% on TAT). Similarly to the previous studies, main limitation of the RE-DUAL PCI trial is that it was only powered to detect meaningful differences in bleeding events and not efficacy.

Overall, WOEST was the first randomized trial that verified the hypothesis of omitting aspirin is a safer choice than TAT, in patients with a need of an OAC requiring PCI. Both PIONEER-AF PCI and REDUAL-PCI trials compared a combination of a direct OAC plus a $P2Y_{12}$ inhibitor and showed significantly less bleeding episodes in patients with AF undergoing PCI, maintaining the same level of efficacy as compared with TAT. These two trials strengthened the results of WOEST concerning the safety and bleeding, setting the beginning of a new era for antithrombotic therapy in AF patients undergoing PCI, although the issue of efficacy and thromboembolic events still remains in question.

1.2. Is current evidence enough to change practice?

Following the described results, one may question whether it is time for physicians to change their daily medical practice regarding antithrombotic treatment in AF patients undergoing PCI. The use of TAT is common in clinical practice in order to minimize the risk of stent thrombosis and other ischemic events after PCI, but it is clearly associated with a risk of fatal (intracranial hemorrhage) and nonfatal bleeding. In addition, shortening the duration of TAT does not substantially reduce the bleeding risk, because most bleeding episodes occur within 30 days of PCI [8,14–16]. Thus, TAT has the potential to cause harm in many patients, even though it is administrated to prevent ischemic events. Increased bleeding episodes, related to TAT, may lead to DAPT interruption, which in turn could increase the chance of poor outcomes such as stent thrombosis [17]. On the other hand, the main knowledge obtained from these trials that remains indisputable, is that the risk of bleeding is patently lower with DAT compared with TAT. Nevertheless, none of these trials had been powered to reliably assess thromboembolic or ischemic (efficacy) outcomes with different tested strategies. Of note, there are several differences among the three trials, like the anticoagulation used (Vitamin K versus non–vitamin K antagonists), the duration of the TAT, or $P2Y_{12}$ inhibitors used (exclusively clopidogrel in WOEST).

1.3. Guidelines recommendation on DAT

European and American Guidelines, as well as Consensus documents and Expert panel reports recommendations vary based on stratification of bleeding risk [including the HAS-BLED score [18]; Hypertension, Abnormal renal and liver function (1 point each), Stroke, Bleeding history or predisposition, Labile INR, Elderly (> 65 years), Drugs and alcohol (1 point each)] and ischemic risk (ACS, stent thrombosis, other anatomical/procedural characteristics), and have been amended through years. During the last year, after PIONEER and/or RE-DUAL trials results, several documents have been published regarding antithrombotic therapy on AF patients undergoing PCI (Table 2).

The ESC 2017 DAPT [5] as well as the most recent ESC 2018 revascularization guidelines [19] come in agreement with 2018 CHEST guidelines [20] and the European Heart Rhythm Association (EHRA) consensus document [21], suggesting TAT as a default strategy in AF patients after stent implantation, except for patients on very high bleeding risk (HAS-BLED ≥ 3, recent bleeding event) and relatively low ischemic risk. In contrast, a consensus document from selected North American experts from the United States and Canada [22] recommends that a DAT regimen (OAC plus a $P2Y_{12}$ inhibitor, either clopidogrel or ticagrelor) should be considered for most patients, immediately after hospital discharge. The use of aspirin (as a part of TAT) after hospital discharge is recommended only in selected patients considered at high ischemic/thrombotic risk and low bleeding risk and for a limited period of time (1 month). Similarly, most recent CCS on Antiplatelet Therapy guidelines [23] recommends the use of DAT, except for patients with high risk features (Diabetes, renal dysfunction, ACS or stent thrombosis, total occlusion or bifurcation, multi-vessel disease). Overall, there is agreement in all published recommendations that prasugrel or ticagrelor as part of TAT should be avoided unless there is a clear need for these agents.

Regarding these latest recommendations, one can easily appreciate a different interpretation of the exact same data, ultimately giving different directions on antithrombotic therapy. Some of them reflect the fact that WOEST, PIONEER and RE-DUAL were not designed to detect significant differences in efficacy endpoints. Therefore, TAT is still recommended as the default antithrombotic strategy, for at least one month and up to six months, in several documents [5,19–21] in order to prevent cerebral and cardiovascular adverse events. An exception to this strategy is the case of low ischemic risk and very high bleeding risk that overcomes the risk of stent thrombosis. On the other hand, it is the first time that some documents [22,23] recommend DAT as the default antithrombotic strategy, after hospital discharge, in patients with AF undergoing PCI, mainly recognizing the benefit of DAT against TAT on safety (bleeding). With regard to cerebral and cardiovascular adverse events, there is an acceptance that rates of ischemic outcome were rather rare and not significantly different between DAT and TAT, even though these results were obtained through underpowered trials for efficacy endpoints. Hence, there is an urgent need for new data to come to light in order to acquire a common direction on antithrombotic therapy in AF patients after PCI.

As HAS-BLED score appears crucial for bleeding risk stratification and subsequently guidelines recommendations, it is very important to have an estimate of how common is an increased score in order to assess the magnitude of the problem. According to PIONNER AF-PCI and RE-DUAL PCI trials, 69% and 66% of patients had a high bleeding risk score (HAS-BLED score ≥ 3), respectively [9,10]. In a post hoc analysis on bleeding risk scores of two randomized trials, which included 3665 patients, a HAD-BLED score ≥ 3 was observed in 71% of the patients [24]. Data from real life and observational studies, demonstrated that one out of three patients is on high bleeding risk (HAS-BLED score ≥ 3 in 28–35% of patients) [25,26]. This would help physicians to understand what to expect in real life practice and whether DAT should be a default strategy.

1.4. Meta-analysis, post-hoc analysis and real world evidence

A recent meta-analysis of four randomized trials (WOEST, ISAR-TRIPLE, PIONEER-AF, RE-DUAL PCI) including 5317 patients, demonstrated a 47% relative reduction in the risk of composite TIMI major or

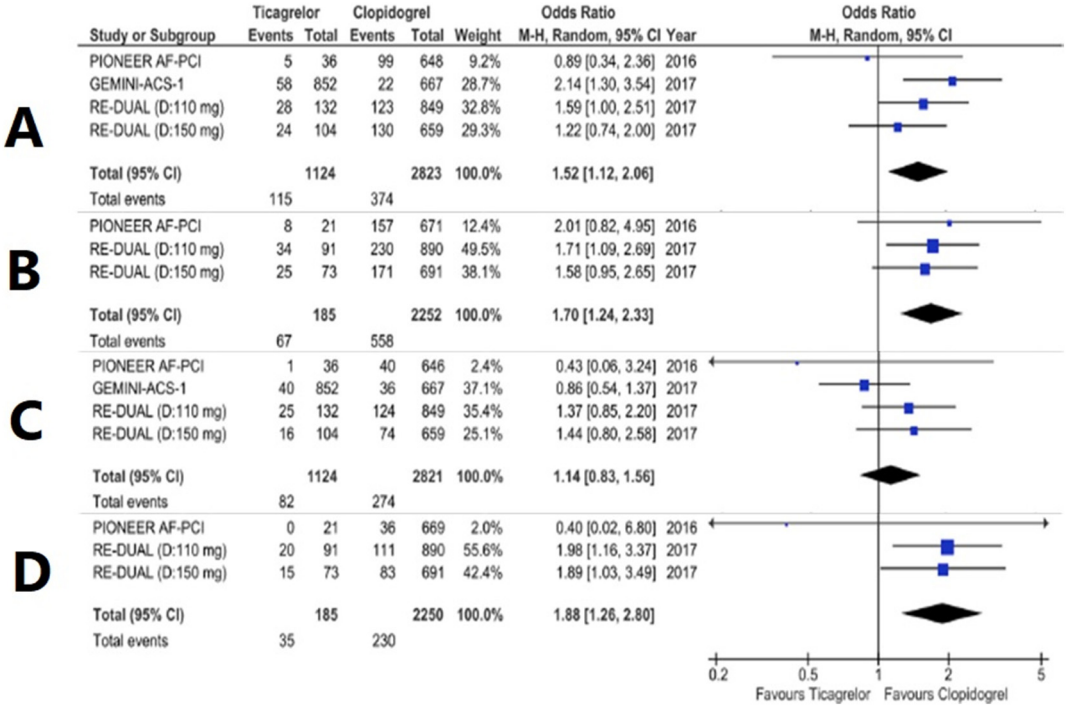

Fig. 1. Clinically significant bleeding events in (A) dual antithrombotic therapy and (B) triple antithrombotic therapy and major adverse cardiovascular events in (C) dual antithrombotic therapy and (D) triple antithrombotic therapy. (Under author's permission, *Cardiovasc Drugs Ther. 2018;32:287–294.* https://doi.org/10.1007/s10557-018-6795-9).

minor bleeding with DAT versus TAT (4.3% vs. 9.0%; HR 0.53, 95% credible interval [CrI] 0.36–0.85) [27]. Concerning efficacy, DAT appeared to be comparable to TAT in reducing the trial-defined MACE, with no difference in individual outcomes of all-cause mortality, cardiac death, MI, stent thrombosis, or stroke between arms. Of note, the risk of intracranial bleeding was 42% lower for DAT group (0.3% vs 0.8%, HR 0.58, 95% CrI 0.23–1.49). Noteworthy, a higher risk for bleeding (HAS-BLED ≥ 3) was seen in 71% and 66% of patients in TAT and DAT groups, respectively. A post hoc analysis of the PIONEER AF-PCI trial was also performed to examine a composite end point of all-cause mortality or recurrent hospitalization (after the index admission) for an adverse event [28]. Patients in the rivaroxaban 15mg plus a $P2Y_{12}$ inhibitor arm had an approximately 20% lower risk of the primary end point as compared to the patients of the TAT arm (HR = 0.79; 95% CI = 0.66–0.94, $p = 0.008$). This result was primarily led by the reduction in events leading to rehospitalization, as there was no difference in all-cause mortality between the 3 treatment groups. DAT consisting of clopidogrel plus VKA showed comparable thromboembolic event rates (MI, cardiac death, ischemic stroke) with TAT group in a large Danish registry [29] that compared different antithrombotic strategies in 12,165 patients with AF after MI and coronary intervention, suggesting that DAT reduced the risk of thromboembolic events after PCI as effectively as TAT. This finding was reinforced by other observational studies [16,26], as well as a large meta-analysis of randomized controlled trials and observational studies [30], encompassing 7182 patients, which showed that the rate of the composite endpoint (death, MI, stroke, and stent thrombosis) was comparable between DAT group (VKA plus clopidogrel) and TAT group [Odds ratio (OR) 0.89, 95% CI 0.68–1.17]. On the other hand, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) analyzed 1827 patients with AF and coronary artery disease and reported no difference in the rate of bleeding or MACE between patients with TAT and DAT (consisting of OAC and aspirin). Nevertheless, TAT was accompanied by more frequent all cause hospitalization versus DAT (HR 1.75, 95% CI 1.35–2.26) [31].

1.5. The role of newer $P2Y_{12}$ inhibitors

A well-recognized concern in patients who undergo PCI and receive clopidogrel is the possibility of poor responsiveness to this agent. The rate of high on-clopidogrel platelet reactivity shows large heterogeneity among different studies (20–50%), and it is strongly associated with poor outcome and a high risk of cardiovascular death, MI and stent thrombosis in patients after PCI [32,33]. Notably, predictors for high on-clopidogrel platelet reactivity such as elderly patients, diabetes mellitus, chronic kidney disease, commonly co-exist in patients with AF, making them more vulnerable to a suboptimal response to clopidogrel and high risk for thrombotic events. Prasugrel and ticagrelor have faster onset of action than clopidogrel, less inter-individual variation and have been shown to be more effective in reducing MACE, but they were also associated with an increased risk of bleeding [34,35]. Recent guidelines encourage the use of ticagrelor and prasugrel (over clopidogrel) in patients with ACS and PCI [5]. However, their use in the setting of TAT with aspirin and OAC is not recommended [5,19].

The only randomized controlled trial, which included the use of prasugrel, is PIONEER-AF-PCI trial. However, only 28 patients received prasugrel as part of DAT or TAT. Regarding ticagrelor's experience in the context of randomized controlled trials, in PIONEER-AF-PCI trial the subgroup of 36 patients on DAT with ticagrelor plus rivaroxaban 15 mg had lower rates of bleeding compared with the subgroup of 21 patients on TAT with VKA + aspirin + ticagrelor (16% versus 43.9%, HR 0.33, 95%CI 0.11–1.01, $p = 0.039$), with no difference in MACE [9]. Similarly, in the subgroup analysis from the RE-DUAL PCI trial, patients on ticagrelor plus dabigatran 110 mg bid ($n = 132$) and patients on ticagrelor plus dabigatran 150 mg bid ($n = 104$) showed less bleeding episodes as compared with the TAT group [TIMI Major Bleeding for dabigatran 110 mg and 150 mg vs TAT: 2.3% vs 9.9% and 1.9% vs 9.6% respectively; International Society on Thrombosis and Haemostasis (ISTH) Major or Clinically Relevant Non-Major Bleeding for dabigatran 110 mg and 150 mg vs TAT: 21.2% vs 37.4% and 23.1% vs 34.2% respectively]. All-cause death, MI and a composite endpoint of death, MI, stroke, systemic embolism or unplanned revascularization

rates, were comparable between dabigatran 110 mg and 150 mg vs TAT [36]. A recent meta-analysis by our group of three randomized controlled trials has compared the safety and efficacy between ticagrelor versus clopidogrel, as part of DAT or TAT [37] (Fig. 1). In DAT groups the use of ticagrelor increased the risk of clinically significant bleeding (OR 1.52, 95%CI 1.1–2.06, $p = 0.007$) and showed no difference in the rates of MACE or stroke. In TAT groups the use of ticagrelor increased both the risk of clinically significant bleeding (OR 1.7, 95%CI 1.24–2.33, $p = 0.001$) and the risk of MACE (OR 1.88, 95% CI 1.26–2.80, $p = 0.002$). While explaining these results, it is worth mentioning that treatment with clopidogrel versus ticagrelor was not randomized and ticagrelor most likely had been used in patients with higher ischemic risk. Moreover, relevant trials were not powered for ischemic outcomes. Finally, according to trial sequential analysis, there is not enough evidence to safely conclude that ticagrelor is associated with higher bleeding risk.

2. Perspective and conclusion

The management of antithrombotic treatment in patients with AF undergoing PCI remains challenging. The optimal treatment strategy for these patients is unclear, as current knowledge does not support a single plan or recommendation for every patient. Risk factors such as bleeding risk, type of stent used, risk of stent thrombosis or recurrent ACS (ischemic risk) should be assessed in every single occasion [19]. Following WOEST, but mostly PIONEER AF PCI and REDUAL PCI results, the choice of DAT with a novel OAC (NOAC) and clopidogrel appeared as a logical first choice in most patients [22]. Current evidence suggests that a major compromise in efficacy by omitting aspirin is unlikely to occur. More in-depth analysis however, may tamper the enthusiasm for DAT only mainly because of lack of power of relevant trials so far for the, rather rare, ischemic outcome endpoints. DAT with a $P2Y_{12}$ inhibitor plus an oral anticoagulant (with preferred use of dabigatran or rivaroxaban over warfarin – unless contraindicated e.g. metallic valve – due to reduction in bleeding complications including intracerebral hemorrhage) is an attractive option in patients with a moderate or high risk of bleeding and a low ischemic risk, reassuring less bleeding. On the other hand, TAT is considered to be more efficacious in patients at high risk of stent thrombosis or ACS, for the shortest possible duration, with a plan to transition to DAT as soon as possible. There are concerns though, as patients at high risk of stent thrombosis or ACS represented a small number on trials. In particular, approximately half of the patients presented with ACS on PIONEER and REDUAL trials, of which only a percentage of 12% and 11% respectively, presented with ST-segment elevation myocardial infarction. Unfortunately, Practice Guidelines/Consensus documents/Expert panel reports during the last year are giving conflicting recommendations, indicating different assessment of the same data. An appealing strategy for ACS patients would be the selection of ticagrelor as part of DAT, mitigating the risk of the frequent platelet unresponsiveness to clopidogrel, in case this agent has been selected.

Two more trials of NOAC in AF patients undergoing PCI are ongoing with apixaban and edoxaban, expecting to provide more data on this subject. The AUGUSTUS trial (A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart) is evaluating apixaban versus warfarin (open-label) plus $P2Y_{12}$ inhibitor along with aspirin versus no aspirin (blinded) in a 2×2 factorial design [38], thus allowing directly testing the benefit and risk of omitting aspirin with both warfarin and apixaban (NCT02415400). Of note, AUGUSTUS will be the first randomized trial comparing directly two different DAT strategies. The ENTRUST-AF-PCI trial (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) is evaluating the safety and efficacy of edoxaban (plus $P2Y_{12}$ inhibitor) versus warfarin plus $P2Y_{12}$ inhibitor plus aspirin for 1–12 months (NCT02866175) [39]. Furthermore, as the most used $P2Y_{12}$ inhibitor on randomized trials so far is clopidogrel, and future trials with the newer agents such as ticagrelor and prasugrel might be helpful. RT-AF trial [40] which evaluates the safety of rivaroxaban 2.5 mg/5 mg bid plus ticagrelor versus TAT with warfarin plus clopidogrel and aspirin (NCT02334254) and MANJUSRI trial [41], which evaluates the safety of ticagrelor plus warfarin versus TAT with warfarin plus clopidogrel and aspirin (NCT02206815), might also offer some more data on this issue. Finally, ongoing observational trials (GRAPE-AF, NCT03362788 [42]; CHAOS, NCT03558295; PERSEO, NCT03392948), are expected to provide useful information about real-world use of antithrombotic treatment and clinical outcomes.

In conclusion, assessment of bleeding and ischemic risk profile is a sine qua non. In anticipation of new data, this can be the safest way to choose the right antithrombotic strategy for every individual patient with AF undergoing PCI, as with the current evidence, it may be too early to declare DAT or TAT as a winner.

Declaration of interest

Dr. Alexopoulos has received lecturing honoraria by Astrazeneka, Bayer, BoehringerIngelheim, AMGEN; and advisory board fees by Astrazeneka, Bayer, Boehringer Ingelheim, Medtronic, Chiesi Hellas. Dr. Mantis has nothing to declare.

Funding

There was no funding.

References

[1] S. Björck, B. Palaszewski, L. Friberg, et al., Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study, Stroke. 44 (2013) 3103–3108, https://doi.org/10.1161/STROKEAHA.113.002329.
[2] P. Kirchhof, S. Benussi, D. Kotecha, et al., 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur. Heart J. 37 (2016) 2893–2962, https://doi.org/10.1093/eurheartj/ehw210.
[3] S. Kralev, K. Schneider, S. Lang, et al., Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography, PLoS One 6 (2011) e24964, , https://doi.org/10.1371/journal.pone.0024964.
[4] K. Chaikriangkrai, M. Valderrabano, S.K. Bala, et al., Prevalence and implications of subclinical coronary artery disease in patients with atrial fibrillation, Am. J. Cardiol. 116 (2015) 1219–1223, https://doi.org/10.1016/j.amjcard.2015.07.041.
[5] M. Valgimigli, H. Bueno, R.A. Byrne, et al., 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS, Eur. Heart J. 39 (2018) 213–254, https://doi.org/10.1093/eurheartj/ehx419.
[6] H.-I. Choi, J.-M. Ahn, S.H. Kang, et al., Prevalence, management, and long-term (6-year) outcomes of atrial fibrillation among patients receiving drug eluting coronary stents, JACC Cardiovasc. Interv. 10 (2017) 1075–1085, https://doi.org/10.1016/j.jcin.2017.02.028.
[7] M.L. Hansen, R. Sørensen, M.T. Clausen, et al., Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation, Arch. Intern. Med. 170 (2010) 1433–1441, https://doi.org/10.1001/archinternmed.2010.271.
[8] W.J. Dewilde, T. Oirbans, F.W. Verheugt, et al., Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomized, controlled trial, Lancet. 381 (2013) 1107–1115, https://doi.org/10.1016/S0140-6736(12)62177-1.
[9] C.M. Gibson, R. Mehran, C. Bode, et al., Prevention of bleeding in patients with atrial fibrillation undergoing PCI, N. Engl. J. Med. 375 (2016) 2423–2434, https://doi.org/10.1056/NEJMoa1611594.
[10] C.P. Cannon, D.L. Bhatt, J. Oldgren, et al., Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation, N. Engl. J. Med. 377 (2017) 1513–1524, https://doi.org/10.1056/NEJMoa1708454.
[11] D. Alexopoulos, P. Vlachakis, J. Lekakis, Triple antithrombotic therapy in atrial fibrillation patients undergoing PCI: a fading role, Cardiovasc. Drugs Ther. 31 (2017) 319–324, https://doi.org/10.1007/s10557-017-6730-5.
[12] J.L. Mega, E. Braunwald, S.D. Wiviott, et al., Rivaroxaban in patients with a recent acute coronary syndrome, N. Engl. J. Med. 366 (2012) 9–19, https://doi.org/10.1056/NEJMoa1112277.
[13] D.L. Bhatt, O PIONEERs! The beginning of the end of full-dose triple therapy with warfarin? Circulation. 135 (2017) 334–337, https://doi.org/10.1161/CIRCULATIONAHA.116.025923.

[14] K.A. Fiedler, M. Maeng, J. Mehilli, et al., Duration of triple therapy in patients requiring oral anticoagulation after drug eluting stent implantation: the ISAR-TRIPLE trial, J. Am. Coll. Cardiol. 65 (2015) 1619–1629, https://doi.org/10.1016/j.jacc.2015.02.050.
[15] W.J. Dewilde, P.W. Janssen, F.W. Verheugt, et al., Triple therapy for atrial fibrillation and percutaneous coronary intervention: a contemporary review, J. Am. Coll. Cardiol. 64 (2014) 1270–1280, https://doi.org/10.1016/j.jacc.2014.06.1193.
[16] M. Lamberts, J.B. Olesen, M.H. Ruwald, et al., Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study, Circulation. 126 (2012) 1185–1193, https://doi.org/10.1161/CIRCULATIONAHA.112.114967.
[17] S. Schulz, T. Schuster, J. Mehilli, et al., Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period, Eur. Heart J. 30 (2009) 2714–2721, https://doi.org/10.1093/eurheartj/ehp275.
[18] R. Pisters, D.A. Lane, R. Nieuwlaat, et al., A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation, CHEST. 138 (2010) 1093–1100, https://doi.org/10.1378/chest.10-0134.
[19] F.J. Neumann, M. Sousa-Uva, A. Ahlsson, et al., 2018 ESC/EACTS Guidelines on myocardial revascularization, Eur. Heart J. 00 (2018) 1–96, https://doi.org/10.1093/eurheartj/ehy394.
[20] G.Y.H. Lip, A. Banerjee, G. Boriani, et al., Antithrombotic therapy for atrial fibrillation: CHEST Guideline and Expert Panel Report, CHEST (2018), https://doi.org/10.1016/j.chest.2018.07.040.
[21] Lip GYH, Collet JP, Haude M, et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace. 2018. doi:https://doi.org/10.1093/europace/euy174.
[22] D.J. Angiolillo, S.G. Goodman, D.L. Bhatt, et al., Antithrombotic therapy in patients with atrial fibrillation treated with Oral anticoagulation undergoing percutaneous coronary intervention - a north American perspective–2018 update, Circulation. 138 (2018) 527–536, https://doi.org/10.1161/CIRCULATIONAHA.118.034722.
[23] S.R. Mehta, K.R. Bainey, W.J. Cantor, et al., 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy, Can. J. Cardiol. 34 (2018) 214–233, https://doi.org/10.1016/j.cjca.2017.12.012.
[24] M. Proietti, K. Senoo, D.A. Lane, et al., Major bleeding in patients with non-Valvular atrial fibrillation: impact of time in therapeutic range on contemporary bleeding risk scores, Sci. Rep. 6 (2016) 24376, https://doi.org/10.1038/srep24376.
[25] V. Roldán, F. Marín, S. Manzano-Fernández, et al., The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation, J. Am. Coll. Cardiol. 62 (2013) 2199–2204, https://doi.org/10.1016/j.jacc.2013.08.1623.
[26] A. Rubboli, A. Schlitt, T. Kiviniemi, et al., One-year outcome of patients with atrial fibrillation undergoing coronary artery stenting: an analysis of the AFCAS registry, Clin. Cardiol. 37 (2014) 357–364, https://doi.org/10.1002/clc.22254.
[27] Golwala HB, Cannon CP, Steg PG, et al. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. Eur. Heart J. 2018; 39:1726-1735a.doi:https://doi.org/10.1093/eurheartj/ehy162.
[28] C.M. Gibson, D.S. Pinto, G. Chi, et al., Recurrent hospitalization among patients with atrial fibrillation undergoing intracoronary stenting treated with 2 treatment strategies of rivaroxaban or a dose-adjusted oral vitamin K antagonist treatment strategy, Circulation. 135 (2017) 323–333, https://doi.org/10.1161/CIRCULATIONAHA.116.025783.
[29] M. Lamberts, G.H. Gislason, J.B. Olesen, et al., Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention, J. Am. Coll. Cardiol. 62 (2013) 981–989, https://doi.org/10.1016/j.jacc.2013.05.029.
[30] D'Ascenzo F, Taha S, Moretti C, et al. Metaanalysis of randomized controlled trials and adjusted observational results of use of clopidogrel, aspirin, and oral anticoagulants in patients undergoing percutaneous coronary intervention. Am. J. Cardiol. 2015; 115:1185–1193. doi: https://doi.org/10.1016/j.amjcard.2015.02.003.
[31] R.D. Lopes, M. Rao, D.N. Simon, et al., Triple vs dual antithrombotic therapy inPatients with atrial fibrillation and coronary artery disease, Am. J. Med. 129 (2016) 592–599, https://doi.org/10.1016/j.amjmed.2015.12.026.
[32] G.W. Stone, B. Witzenbichler, G. Weisz, et al., Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study, Lancet. 382 (2013) 614–623, https://doi.org/10.1016/S0140-6736(13)61170-8.
[33] D. Aradi, A. Komócsi, A. Vorobcsuk, et al., Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: systematic review and meta-analysis, Am. Heart J. 160 (2010) 543–551, https://doi.org/10.1016/j.ahj.2010.06.004.
[34] S.D. Wiviott, E. Braunwald, C.H. McCabe, et al., Prasugrel versus clopidogrel in patients with acute coronary syndromes, N. Engl. J. Med. 357 (2007) 2001–2015, https://doi.org/10.1056/NEJMoa0706482.
[35] L. Wallentin, R.C. Becker, A. Budaj, et al., Ticagrelor versus Clopidogrel in patients with acute coronary syndromes, N. Engl. J. Med. 361 (2009) 1045–1057, https://doi.org/10.1056/NEJMoa0904327.
[36] J. Oldgren, P.-G. Steg, S.H. Hohnloser, et al., Subgroup analysis from the RE-DUAL PCI trial: dual antithrombotic therapy with dabigatran in patients with atrial fibrillation undergoing percutaneous coronary intervention, Circulation 136 (24) (2017) E457.
[37] I. Andreou, A. Briasoulis, C. Pappas, et al., Ticagrelor versus clopidogrel as part of dual or triple antithrombotic therapy: a systematic review and meta-analysis, Cardiovasc. Drugs Ther. 32 (2018) 287–294, https://doi.org/10.1007/s10557-018-6795-9.
[38] R.D. Lopes, A.N. Vora, D. Liaw, et al., An open-label, 2 × 2 factorial, randomized controlled trial to evaluate the safety of apixaban vs. vitamin K antagonist and aspirin vs. placebo in patients with atrial fibrillation and acute coronary syndrome and/or percutaneous coronary intervention: rationale and design of the AUGUSTUS Trial, Am. Heart J. 200 (2018) 17–23, https://doi.org/10.1016/j.ahj.2018.03.001.
[39] P. Vranckx, T. Lewalter, M. Valgimigli, et al., Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention with stent placement: rationale and design of the ENTRUST-AF PCI Trial, Am. Heart J. 196 (2018) 105–112, https://doi.org/10.1016/j.ahj.2017.10.009.
[40] F. Gao, H. Shen, Z.J. Wang, et al., Rationale and design of the RT-AF study: combination of rivaroxaban and ticagrelor in patients with atrial fibrillation and coronary artery disease undergoing percutaneous coronary intervention, Contemp. Clin. Trials 43 (2015) 129–132, https://doi.org/10.1016/j.cct.2015.05.012.
[41] W. Lu, L. Chen, Y. Wang, et al., Rationale and design of MANJUSRI trial: a randomized, open-label, active-controlled multicenter study to evaluate the safety of combined therapy with ticagrelor and warfarin in AF subjects after PCI-eS, Contemp. Clin. Trials 40 (2015) 166–171, https://doi.org/10.1016/j.cct.2014.12.002.
[42] I. Xanthopoulou, V.M. Dragona, P. Davlouros, et al., Contemporary antithrombotic treatment in patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention: rationale and design of the Greek AntiPlatElet Atrial Fibrillation (GRAPE-AF) Registry, Cardiovasc. Drugs Ther. 32 (2018) 191–196, https://doi.org/10.1007/s10557-018-6789-7.