

Management of antithrombotic therapy in patients with atrial fibrillation and acute coronary syndromes

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If atrial fibrillation (AF) and acute coronary syndrome (ACS) coexist, they should be treated with combined antithrombotic therapy. To reduce the risk of bleeding while maintaining the desired antithrombotic effect, choices should be made for each patient according to the balance between the bleeding and the thrombotic risk. There are many ways to select the type and dose of the oral anticoagulant (OAC) and P2Y₁₂ inhibitors. As a rule of thumb, aspirin and P2Y₁₂ inhibitors should be recommended to all patients. The duration of this combination therapy is a matter of debate; available data promote an initial period of one to four weeks of triple antithrombotic association with aspirin and P2Y₁₂ inhibitors (clopidogrel in the absence of high ischaemic risk) and preferable direct oral anticoagulants (DOACs). On discontinuing aspirin, double therapy with P2Y₁₂ inhibitors and a DOAC provides similar efficacy and superior safety for many patients on ACS medical or interventional treatment, especially if the risk of bleeding is high and that of thrombosis is low. Further studies are needed to clarify the concerns for a slight augmentation in the number of ischaemic cases (myocardial infarction and stent thrombosis) with double antithrombotic regimen in patients at high ischaemic risk.

Keywords

Atrial fibrillation; Acute coronary syndrome; Antithrombotic therapy; Percutaneous coronary intervention; Oral anticoagulants; Antiplatelets

1. Introduction

The need for antithrombotic medications in double (single antiplatelet plus OAC; also known as "double therapy" [DAT]) or triple combination (dual antiplatelet [DAPT] and OAC; also known as "triple therapy" [TAT]) is well recognized in cases where atrial fibrillation (AF) coexists with an acute coronary syndrome (ACS), with or without percutaneous coronary intervention (PCI) [1–5]. This is the case for approximately 10% to 16% of ACS patients requiring stenting along with concomitant AF. Moreover, due to the coexistence of ischaemic heart disease (IHD) in AF patients, an increasing number—up to 20–30%—of them will have urgent

coronary revascularization for an ACS or during an elective procedure [6–12]. These patients have more comorbidities, are older and have worse clinical outcomes [5]. Many AF patients need OAC to prevent and reduce the risk of cardioembolic stroke because of the low shear stress that characterises the left atrium. The thrombi thus appear frequently due to non-removal of thrombin and fibrin monomer [13–15]. Risk of stroke in AF is not only related to the left atrium stasis as described but also age (risk increases among those aged ≥65 years), diabetes, hypertension, heart failure, cerebrovascular disease (previous ischaemic stroke or transient ischaemic accident), peripheral arterial disease and aortic atheroma, as expressed in the CHA₂DS₂-VASc score [16]. The yearly stroke risk has been estimated to be between 3.7 to 5.9/100 in AF patients, excluding those treated with OAC, with CHA₂DS₂-VASc scores of 2 to 3 [17, 18]. ACS patients in the early phase after stent implantation are at the highest risk of ischaemic and thrombotic complications, secondary to inflammatory status and endothelial dysfunction activated by mechanical aggression during PCI. High shear stress characterises the thrombi and occurs during an ACS or during the PCI, which are also rich in platelets [19–22]. Furthermore, DAPT with aspirin and P2Y₁₂ inhibitors (clopidogrel, prasugrel, ticagrelor) are routinely given after a PCI with a stent implant to avoid major ischaemic adverse cardiovascular events (MACE) and stent thrombotic events [22–26]. European and North American guidelines recommend the administration of the strongest P2Y₁₂ inhibitors (ticagrelor and prasugrel) in addition to aspirin for all suitable ACS patients (with or without PCI) [27–31]. After the early phase (one to three months), DAPT's role is to offer complete protection against MACE arising from the stent or culprit lesions, coupled with a protective effect against the risk associated with atherosclerosis progression. The rate of major bleeding with DAPT during the first year is around 1–8%, which represents an acceptable haemorrhagic risk for the highest

thrombotic protection [23–26, 32–35]. The more recent and powerful P2Y12 inhibitors (ticagrelor and prasugrel) have an increased effect of platelet inhibition over clopidogrel at the price of more bleeding; until now, however, DAPT is not recommended by guidelines to prevent stroke in AF patients [1–4, 27–31, 33–35]. TAT is the theoretically ideal combination which provides greater protection against the embolic, thrombotic and MACE associated with AF and ACS with stent implantation. The bleeding risk (both major and fatal events) with TAT is up to four times greater when compared to OAC alone, and is also associated with increased mortality [36, 37]. In recent years, several trials demonstrated that the risk of bleeding could be reduced with comparable anti-ischaemic and antithrombotic efficacy using a DAT combination. However, these trials have not been calibrated for ischaemic and thrombotic events analyses [38–42]. DOAC-based therapy, instead of vitamin K antagonist (VKA), appeared to drive the reduction in bleeding events in both medically treated and interventional patients with TAT or DAT strategies. Furthermore, omitting aspirin had the same effect after being used in the initial phase as well as during hospitalisation [42]. The validation of these strategies remains controversial and data from a recent meta-analysis indicate that a DAT combination, which includes DOACs plus a P2Y12 inhibitor, reduces bleeding with no increase in thrombotic risk compared to other regimens with OAC plus DAPT [43]. Other meta-analyses, including the four recent studies with DOACs plus P2Y12 inhibitors, suggest there might be a slight but significant augmentation in the number of myocardial infarction (MI) and stent thrombotic events when omitting aspirin [44–47]. The purpose of this article is to review the many branching decision points of post-procedure and post-discharge treatment options in AF patients with a concomitant ACS. Familiarity of practitioners with the several supporting strategies for use of current antithrombotic medications is a veritable challenge in the field.

2. Commonly used antiplatelet agents in DAPT regimens and dedicated trials

Table 1 presents the principal pharmacological characteristics of commonly used oral antiplatelet agents in DAPT regimens.

Aspirin is a non-selective antiplatelet drug that suppresses the production of prostaglandins and thromboxane A₂ with an irreversible acetylation process of serine residue on the cyclooxygenase enzymes. ISIS-2 trial (International Study of Infarct Survival) was the first to report that oral aspirin reduced short-term mortality in patients with suspected MI by 23% [48]. In 1990, the newly released guidelines for patients with acute MI recommended first-time aspirin therapy for all patients, i.e., during the initial presentation which should then be continued for at least 1 month [49]. The efficacy of aspirin in reducing nonfatal acute MI and cardiovascular death among patients with new or prior ACS was also demonstrated in the well-known meta-analysis (287 stud-

ies including 212,000 patients) by the Trialists' Collaboration [50].

Clopidogrel is an oral antagonist of thienopyridine P2Y12 receptors that produces irreversible and competitive inhibition of platelets. Supplementary therapy with clopidogrel in ACS patients already treated with aspirin reduces MACE by 20% in the first 30 days and also results in similar reductions in the first year of treatment [23, 51, 52]. Thus, clopidogrel became the primary adjunctive to aspirin in DAPT regimens, following elective PCI, or in ACS patients medically or interventional treated with PCI [27, 28].

Prasugrel is another oral antagonist of thienopyridine P2Y12 receptors that produces irreversible and competitive inhibition of platelets. It is faster and more consistent compared to clopidogrel. The TRITON-TIMI 38 study showed that adding prasugrel to aspirin led to a 19% risk reduction of the primary composite end point (MACE, cardiovascular death, stroke) when compared to DAPT with aspirin and clopidogrel. This trial did not include medically managed ACS and proved a lack of clinical benefit and higher rate of major bleeding among older patients (≥ 75 years) with body weight < 60 kg [24]. In a more recent study in ACS patients, prasugrel performed better than ticagrelor, with equal bleeding but a lower incidence for cardiovascular death and ischaemic events [53]. Thus, in addition to aspirin, the current guidelines recommended prasugrel instead of clopidogrel for ACS patients with interventional treatment only [28–30].

Ticagrelor is the oral, direct acting exponent of another chemical class. It causes reversible binding of cyclopentyltriazolopyrimidine P2Y12 receptor antagonist. Because it does not require hepatic metabolism for activation, it acts more rapidly and is more potent compared to thienopyridines. Ticagrelor was superior to clopidogrel in the PLATO trial, reducing not only the composite end point of cardiovascular mortality, MI, or stroke by 16% but also the total mortality (4.5% versus 5.9%; $p < 0.001$) in ACS patients with or without PCI [25].

3. Commonly used OAC for DAT or TAT regimens and dedicated trials

The principal pharmacological characteristics for the OAC commonly used in DAT or TAT regimens and doses in AF/ACS/PCI patients are presented in Table 2.

3.1 Warfarin

Warfarin is the oldest VKA in clinical use. An early, well-known patient on this OAC was United States' president Dwight D. Eisenhower after a myocardial infarction in 1955 [54]. Warfarin acts on vitamin K's metabolism and inhibits the epoxide reductase enzyme. The ischaemic and bleeding outcomes of DAT with warfarin and clopidogrel versus warfarin plus clopidogrel plus aspirin as TAT was compared in the WOEST study—a randomized trial of more than 550 patients (70% patients with AF, 25% with ACS) undergoing PCI. The patients under TAT were treated with aspirin and clopidogrel daily for at least 1 month after bare-metal stent-

Table 1. Principals' pharmacologic characteristics and doses of oral antiplatelets agents used in DAPT regimens.

Variables	Pharmacologic class	Mechanism of action	Half-life, h	Length of action	Doses
Aspirin	NSAIDs	Irreversible inhibition of COX enzyme	Dose dependent	10 d	Loading 325 mg, then 75–325 mg QD
Clopidogrel	Thienopyridine, P2Y12 receptor antagonist	Irreversible and competitive P2Y12 receptor blockade	6 h	5–7 d	Loading 300–600 mg, then 75 mg QD
Prasugrel	Thienopyridine, P2Y12 receptor antagonist	Irreversible and competitive P2Y12 receptor blockade	7 h	7–10 d	Loading 60 mg, then 10 mg QD (wt ≥60 kg)
Ticagrelor	Triazolopyrimidine, P2Y12 receptor antagonist	Reversible and noncompetitive P2Y12 receptor blockade	8–12 h	3–5 d	Loading 180 mg, then 90 mg BID

Legend: NSAIDs, nonsteroidal anti-inflammatory drug (low-dose aspirin as in DAPT is not normally considered to be an NSAID); COX, cyclooxygenase; h, hours; d, days; QD, once daily; BID, twice daily; wt, weight; kg, kilograms.

ing (BMS), and for at least 1 year after drug-eluting stenting (DES). Patients under DAT and BMS stenting were treated with clopidogrel daily for at least one month (up to 1 year for patients with ACS) and those with DES stenting were treated for at least one year. The WOEST trial investigated the new idea of discontinuing aspirin from the TAT combination in AF patients with coronary stenting. The results showed an impressive 64% relative risk reduction (RRR) in bleeding events at one year in patients treated with DAT as opposed to TAT. Moreover, the thrombotic risk did not increase by omitting aspirin, however, the trial was small and not powered for these events—Table 4 [38, 55]. The ISAR-TRIPLE trial randomly studied if a short TAT of aspirin plus warfarin plus clopidogrel for a duration of six weeks compared with a long TAT (for six months) was different in efficacy and safety after a DES placement in 614 patients. Many patients continued DAT (warfarin and aspirin) after the study ended; less than 30% had an ACS while around 83% in each group had AF. Patients from the short TAT group had lesser combined events 9.8% (death, acute MI, definite stent thrombosis, stroke, or major bleeding) compared to the 8.8% of patients from long TAT. This difference was not statistically significant; however, bleeding frequency was statistically different in the long TAT group (27.9% vs 20.5%, HR 0.68, $p = 0.04$). The combined ischaemic end point was similar for both groups, as presented in Table 3 [56]. This study reconfirms that warfarin as OAC worked better than the combination of aspirin plus clopidogrel in AF patients and showed that, despite a lesser frequency of bleeding events, there was similar ischaemic clinical benefit in a 6-week TAT versus a 6-month TAT [55, 57].

3.2 Rivaroxaban

Rivaroxaban is an oral selective direct-acting factor Xa inhibitor that leads to the inactivation of both free and prothrombinase-bound factor Xa. It was the first DOAC exploratory investigated in the PIONEER AF-PCI trial. It was completed in patients undergoing PCI and having DAPT and then compared to TAT with VKA and DAPT. The 2124 stented subjects with non-valvular AF were randomly assigned to one of three antithrombotic combinations in a 1:1:1 ratio—low dose rivaroxaban (15 mg daily) and a P2Y12

inhibitor for 12 months, very low-dose rivaroxaban (2.5 mg twice daily) and DAPT for one, six, or twelve months, or dose-adjusted VKA and DAPT for one, six, or twelve months. The ACS represented around 50% of the subjects. The principal P2Y12 inhibitor was clopidogrel—93.1% of group 1, 93.7% of group 2, and 96.3% of group 3. Of the prescribed P2Y12 inhibitors, prasugrel-treated patients were limited to 2% and ticagrelor to 5%. The primary safety end point for bleeding events was less frequent in both groups receiving rivaroxaban, as presented in Table 3. This trial adds new data on the use of low dose rivaroxaban in ACS patients and offers the first clear signal for less bleeding with both reduced antithrombotic regimens—DAT (Rivaroxaban 15 mg/day and P2Y12 inhibitor), TAT with very low dose OAC (Rivaroxaban 2.5 mg twice daily) and DAPT [55, 58]. PIONEER AF-PCI trial was not calibrated for ischaemic and thrombotic efficacy and low doses of rivaroxaban were not demonstrated to reduce stroke in AF patients [39, 59].

3.3 Dabigatran

Dabigatran is the only oral direct thrombin inhibitor available for clinical use until now. It has no ischaemic benefit and, depending on the dose, the clinically relevant major and minor bleeding had an approximately four-fold increase in phase II of a dose-ranging randomized study in ACS patients [60]. Dabigatran was tested in AF/ACS/PCI patients in the randomized open-label REDUAL PCI trial, which assigned 2725 patients to a TAT regimen with warfarin, a P2Y12 receptor inhibitor (clopidogrel or ticagrelor) and aspirin for one to three months, or to a DAT regimen with dabigatran (110 or 150 mg twice daily) and a P2Y12 inhibitor. Antithrombotic combinations have been administered for at least six months; after one year, administration of a P2Y12 inhibitor instead of aspirin was done at the investigator's discretion. The principal P2Y12 inhibitor was clopidogrel, but ticagrelor was also chosen by the investigators in 12% to 13.5% of the patients, depending on the dabigatran regimen. The primary safety end point for bleeding events was less frequent in both groups receiving dabigatran. The combined ischaemic end point (thromboembolic events, death, or unplanned revascularization) was not that different in the DAT groups as compared with the TAT group, as

Table 2. Principal's pharmacological characteristics of OAC used in DAT or TAT regimens and doses in AF/ACS/PCI patients.

Variables	Target and bioavailability (%)	Half-life, h	Time to peak effect and interactions	Renal elimination (Unchanged drug, %)	Doses in AF/ACS/PCI patients
Warfarine	VKORC1 (100%)	40	4–5 d (multiple)	-	usually started at a dose of 5 mg per day/QD then following INR
Dabigatran	Thrombin (7%)	14–17	1–3 h (P-gp)	80%	150 mg BID/110 mg BID: no criteria for dose reductions in phase III trials
Rivaroxaban	Factor Xa (80%)	7–11	2–4 h (cyt3A4/P-gp)	33%	15 mg QD: dose reduction to 10 mg QD if CrCl 30–49 mL/min
Apixaban	Factor Xa (60%)	8–14	1–2 h (3A4/P-gp)	27%	– 5 mg BID – 2.5 mg BID if two out of three fulfilled: weight \leq 60 kg, age \geq 80 years, serum creatinine \geq 133 mmol/L (1.5 mg/dL) (or single criterion: if CrCl 15–29 mL/min)
Edoxaban	Factor Xa (62%)	5–11	1–2 h (cyt3A4/P-gp)	50%	60 mg QD: 30 mg QD if weight \leq 60 kg or CrCl 15–49 mL/min or concomitant therapy with strong P-gp inhibitor

Legend: VKORC1, vitamin K epoxide reductase complex subunit 1; cyt3A4, cytochrome P450 3A4 enzyme; P-gp, P glycoprotein; CrCl, creatinine clearance; INR, international normalized ratio; h, hours; d, days; QD, once daily; BID, twice daily; %, percentages.

shown in Table 3. However, the lower dose of dabigatran (110 mg) was associated with numerical more MI, stent thrombosis, stroke, and death events. In the United States, a lower dose of dabigatran, i.e., 110 mg, studied in the RE-LY (Dabigatran versus warfarin in patients with atrial fibrillation) is not approved in stroke prevention for AF patients [61, 62]. The REDUAL trial only included patients undergoing PCI, about 50% of whom had ACS. Due to the study design, it is not clear whether the reduction in bleeding is dependent on the use of dabigatran or avoidance of aspirin [40, 55]. Additionally, REDUAL PCI was not powered for efficacy in terms of ischaemic and antithrombotic events.

3.4 Edoxaban

Edoxaban is another selective oral, direct-acting factor Xa inhibitor that leads to the inactivation of both free and prothrombinase-bound factor. It was investigated in the Entrust-AF PCI randomised open-label trial in patients who recently underwent PCI and had edoxaban plus clopidogrel as DAT, then compared with VKA plus DAPT as TAT. A number of 1506 patients were assigned to DAT with 60 mg edoxaban and 75 mg clopidogrel daily for one year versus a TAT regimen with VKA, clopidogrel (75 mg daily for one year) and aspirin (100 mg daily, for 1–12 months). A lower dose of Edoxaban (30 mg daily) was used if the creatinine clearance was 15–50 mL/min, weight <60 kg, and specific potent P-glycoprotein inhibitors were administered. Prasugrel and ticagrelor were used in few selected patients (less than 2%); the trial thus realised a comparison of clopidogrel antiplatelet therapy, like in previous DOAC – AF PCI studies. ACS was present in 52% of the subjects, with the others exhibiting chronic coronary syndromes. The primary safety outcome (major or clinically relevant nonmajor bleeding at 12 months) occurred less in the edoxaban group at 17%, compared with 20% of the AVK group; however, it was statistically significant only with respect to non-inferiority. The secondary composite clinical end point (cardiovascular death, MI, stroke, systemic embolism, or definite stent thrombosis) was not different between groups, as presented in Table 3. Additionally, the effects on ACS or chronic coronary syndromes disease were similar. Entrust – AF PCI included only patients undergoing PCI, but due to the study design (like in RE-DUAL PCI trial), it is unclear whether the numerical reductions in bleeding events, 14 days after PCI, were determined by edoxaban or omission of aspirin. The trial was not calibrated for ischaemic and thrombotic efficacy and more details around the timing of aspirin withdrawal were needed [41].

3.5 Apixaban

Apixaban is an oral selective, direct-acting FXa inhibitor of both free and prothrombinase-bound factor Xa. It was investigated in the AUGUSTUS trial with the scope of determining the optimal antithrombotic strategy among AF patients and recent ACS, with or without PCI. The trial adopted a 2 × 2 factorial design and patients were randomized 1:1:1:1

to four treatment regimens- open-label warfarin or apixaban and double-blind aspirin or aspirin placebo on P2Y12 inhibitors, for all patients during the next six months. Due to this design, the study tested the noninferiority of apixaban versus warfarin, and, for the first time, if a single P2Y12 inhibitor would be superior to DAPT (P2Y12 inhibitor plus aspirin) with respect to safety for bleeding events. A prior OAC was present in only half of all 4614 patients; of them, 92.6% were treated with clopidogrel and the others with ticagrelor or prasugrel. ACS treated with stent was present in 37.3% of the subjects; 23.9% had an ACS that was only medically treated and 38.8% underwent PCI. The primary safety end point for major bleeding was present in significantly lower rates in patients under apixaban compared to the VKA group (10.5% vs 14.7%), while those treated with aspirin had significantly higher rates of bleeding events compared to patients that had been assigned to placebo (16.1% vs 9.0%). The rates of death or ischaemic events (14.3% apixaban vs 15.3% VKA) were not different but hospitalization was more frequent in the VKA group (57.2% vs 69.2%) as compared to the apixaban group. The difference between aspirin vs placebo (65.7% vs 60.6%) was not significant regarding death and hospitalization, or composite ischaemic events [death, stroke, MI, stent thrombosis (definite or probable), urgent revascularization], as shown in Table 3. However, even if they were not statistically significant, there were more ischaemic events [stent thrombosis (definite or probable) numerically –11 (0.5%) vs 21 (0.9%), MI 68 (2.9%) vs 84 (3.6%), urgent revascularization 37 (1.6%) vs 47 (2.0%)] in patients that were assigned placebo rather than aspirin. Analysis of these clinically significant ischaemic and thrombotic events showed that the increased risk was present early, especially in the first thirty days after randomization. Bleeding events in the placebo group were much more common than stent thrombosis events –204 (9%) vs 21 (0.9%). However, this observation justifies an initial course of TAT in all patients with AF and ACS with PCI until new data will be available [42, 63, 64].

A summary of findings from the four pivotal RCTs on DOACs in AF/ACS/PCI patients, especially encompassing the benefit of the regimens, is presented in Table 4.

4. Areas of uncertainty concerning DAT or TAT regimens post procedure and post discharge

The therapeutic goal in ACS is to prevent platelet adhesion and clot formation by interrupting platelet activation and the coagulation cascade. Two factors (factor Xa and thrombin – factor II a) are involved in the process of clot formation. The thrombin production persists beyond acute presentation, and, consequently, antithrombin therapy, in addition to platelet inhibition, has been proposed [65–67]. Warfarin plus aspirin reduce the risk of ischaemic events after ACS with or without stenting when compared to aspirin alone. However, oral VKA is prone to interaction with food and drugs, needs laboratory monitoring, and increase

Table 3. Principals results of DAT and TAT trials.

Trial	Population	Groups/comparison	Intervention	Endpoints	Results
WOEST 2013 N = 573 Open label, RCT-1 year	AF-69%, ACS-27%	Group 1 DAT	VKA (INR = 2) Clopidogrel 75 mg QD: 1 to 12 m	1. Any bleeding	1. any bleeding at 1 yr.: group 1 DAT - 19.4% vs group 2 TAT - 44.4%, HR = 0.36, $p < 0.0001$
		Group 2 TAT	VKA (INR = 2) Aspirin 80–100 mg/QD Clopidogrel 75 mg QD: 1 to 12 m	2. Death, MI, stroke, TVR, ST	2. group 1 DAT - 11.1% vs group 2 TAT - 17.6%, HR = 0.6, $p = 0.025$
ISAR TRIPLE 2015 N = 614 Open label, N = 614 RCT-1 year	AF-80%, CCS-65%	Group 1 Short TAT	VKA (INR = 2) Aspirin 70–200 mg/QD + Clopidogrel 75 mg QD: 6 w	1. composite: MI, ST, stroke, TIMI major bleeding, death	1. group 1 (short TAT-6 w) 9.8% vs group 2 (long TAT-6 m) 8.8%: no significant difference at 9 months
		Group 2 Long TAT	VKA (INR = 2) Aspirin 70–200 mg/QD Clopidogrel 75 mg QD: 6 m		
PIONEER AF 2016 N = 2124 Open label RCT-1 year	AF with PCI, 52% ACS	Group 1 DAT	Rivaroxaban 15 (10) mg QD Clopidogrel 75 mg QD: 12 m (93%)	1. TIMI major + minor + CNRM	1. group 1 DAT (R15) - 16.8%; group 2 TAT (R 2.5) - 18%, group 3 TAT (AVK) - 26.7%, $p < 0.001$
		Group 2 TAT	Rivaroxaban 2.5 mg BID, Aspirin 75–100 mg/QD Clopidogrel 75 mg QD: 1, 6 or 12 m (93%)	2. composite: MI, stroke, CV death	2. no difference
		Group 3 TAT	VKA (INR = 2–3) Aspirin 75–100 mg/QD Clopidogrel 75 mg QD: 1, 6 or 12 m (96%)		
RE-DUAL PCI 2017 N = 2725 Open label RCT-1 year	AF with PCI 50% ACS	Group 1 DAT	Dabigatran 110 mg BID Clopidogrel 75 mg QD (86%)	1. ISTH major + CRNMB	1. group 1 DAT (D110) - 15.4%; group 2 DAT (D150) - 20.2%, group 3 TAT (VKA) - 25.7%, $p < 0.001$
		Group 2 DAT	Dabigatran 150 mg BID Clopidogrel 75 mg QD (87%)	2. composite: MI, stroke, SE, death	2. no difference
		Group 3 TAT	VKA (INR = 2–3) Aspirin 75–100 mg/QD for 1 to 3 m Clopidogrel 75 mg QD (90%)		

Table 3. Continued.

Trial	Population	Groups/comparison	Intervention	Endpoints	Results
ENTRUST AF 2019 N = 1506 Open label, RCT-1 year	AF with PCI, 52% ACS	Group 1 DAT Group 2 TAT	Edoxaban 60 (30) mg QD Clopidogrel 75 mg QD: 12 m (93%) VKA (INR = 2) Aspirin 70–200 mg/QD: 1 to 12 m Clopidogrel 75 mg QD (92%)	1. CRNMB and ISTH 2. composite: MI, SE, ST, stroke, CV death	1. annualized event rate group 1 DAT (E60) - 20.7% vs group 2 TAT (VKA) - 25.6 %, HR = 0.83, $p = 0.001$, noninferiority only 2. no difference
AUGUSTUS 2019 N = 4614 Double blinded RCT - 6 months	AF and PCI or ACS 37% ACS and PCI 24% ACS medical	Group1 & 2 DAT/TAT Group3&4 DAT/TAT	Apixaban 5 mg BID open label Aspirin or placebo 81 mg double blind Clopidogrel 75 mg QD: 6 m (92%) VKA (INR = 2–3) open label + Aspirin or placebo 81 mg double blind + Clopidogrel 75 mg QD: 6 m (92%)	1. CRNMB and ISTH 2. composite: MI, ST, stroke, urgent revascularization, death	1.group apixaban -10.5% vs group VKA -14.7%, HR = 0.69, $p < 0.001$ 1. group aspirin - 9.0 % vs group placebo-16.1%, HR = 0.89, $p < 0.001$ 2.group apixaban- 23.5% vs group VKA – 27.4%, HR = 0.83, $p < 0.002$, for the combined death and hospitalization due to more numerous hospitalizations on VKA group. No such difference was found on group aspirin vs group placebo

Legend: AF, atrial fibrillation; ACS, acute coronary syndrome; BID, twice daily; CV, cardiovascular; CCS, chronic coronary syndrome; CNRM, clinically relevant non-major bleeding; DAT, double antithrombotic therapy; D110, dabigatran 110 mg; D150, dabigatran 150 mg; E60, edoxaban 60 mg; HR, hazard ratio; INR, international normalized ratio; ISTH, international society on thrombosis and hemostasis bleeding criteria; m, months; MI, myocardial infarction; N, number; PCI, percutaneous coronary intervention; QD, once daily; R15, rivaroxaban 15 mg; R 2.5, rivaroxaban 2.5 mg; RCT, randomized controlled trial; SE, systemic embolism; ST, stent thrombosis; TAT, triple antithrombotic therapy; TIMI, thrombolysis in myocardial infarction bleeding criteria; TVR, target vessel revascularization; w, weeks; VKA, vitamin K antagonist; WOEST, What is the Optimal Antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting; ISAR TRIPLE, Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation; PIONEER AF, 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; RE-DUAL PCI, Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Non-valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; Entrust AF PCI, Edoxaban-Based Antithrombotic Regimen in Patients With Atrial Fibrillation; AUGUSTUS, Antithrombotic Therapy After Acute Coronary Syndrome or PCI in Atrial Fibrillation.

Table 4. Summary of findings from pivotal RCTs on DOACs in AF/ACS/PCI patients.

Trials	Groups	Intervention	Summary
PIONEER AF 2016 N = 2124 Open label RCT-1 year Not designed to assess ischemic efficacy	Group 1	Rivaroxaban 15 (10) mg QD Clopidogrel 75 mg QD: 12 m (93%)	Patients with AF and PCI and/or ACS treated with rivaroxaban (15 mg or 2.5 mg) and clopidogrel (DAT or TAT) had statistically significant less bleeding compared with warfarin and DAPT (TAT). Ischemic events were similar for all the groups, but the results are disputable due to wide confidence interval.
	Group 2	Rivaroxaban 2.5 mg bid, or 15 (10) mg QD Aspirin 75–100 mg/QD	
	Group 3	Clopidogrel 75 mg QD: 1, 6 or 12 m (93%) VKA (INR = 2–3) Aspirin 75–100 mg/QD. Clopidogrel 75 mg QD: 1, 6 or 12 m (96%)	
RE-DUAL PCI 2017 N = 2725 Open label, RCT-1 year Not designed to assess ischemic efficacy	Group 1	Dabigatran 110 mg BID Clopidogrel 75 mg QD (86%)	Patients with AF and PCI and/or ACS treated with dabigatran (110 or 150 mg) and clopidogrel (DAT) had statistically significant less or major CNRM bleeding than TAT with warfarin. Incidence of a composite secondary efficacy endpoint (thromboembolic events, death, or unplanned revascularization) was similar in the DAT group as compared with the TAT.
	Group 2	Dabigatran 150 mg BID Clopidogrel 75 mg QD (87%)	
	Group 3	VKA (INR = 2–3) Aspirin 75–100 mg/QD: 1 to 3 m. Clopidogrel 75 mg QD (90%)	
ENTRUST AF 2019 N = 1506 Open label, RCT-1 year Not designed to assess ischemic efficacy	Group 1	Edoxaban 60 (30) mg QD. Clopidogrel 75 mg QD: 12 m (93%)	Patients with AF and PCI and/or ACS, treated with edoxaban and clopidogrel (DAT) had less bleeding compared with the AVK group, but the difference was statistically significant only for the non-inferiority. Ischemic events were not statistically different.
	Group 2	VKA (INR = 2) Aspirin 70-200 mg/QD: 1 to 12 m. Clopidogrel 75 mg QD (92%)	
AUGUSTUS 2019 N = 4614 Double blinded RCT - 6 months Aspirin for all on the day of ACS or PCI and after for a median of 6 days Aspirin vs Placebo after randomization Not designed to assess ischemic efficacy	Group 1	Apixaban 5 mg bid open label. Aspirin or placebo 81 mg double blind Clopidogrel 75 mg QD: 6 m (92%)	Patients with AF and ACS ± PCI, treated with apixaban and P2Y12 inhibitor, without aspirin use (DAT), had statistically significant less bleeding and fewer hospitalizations. Ischemic events were not statistically increase compared with a regimen of VKA and/or aspirin.
	Group 2	VKA (INR = 2–3) open label Aspirin or placebo 81 mg double blind Clopidogrel 75 mg QD: 6 m (92%)	

Legend: AF, atrial fibrillation; ACS, acute coronary syndrome; BID, twice daily; DAT, double antithrombotic therapy; DAPT, dual antiplatelet therapy; CNRM, clinically relevant non, major bleeding; INR, international normalized ratio; m, months; N, number; QD, once daily; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; TAT, triple antithrombotic therapy; VKA, vitamin K antagonist; PIONEER AF, 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; RE, DUAL PCI, Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Non, valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; Entrust AF PCI, Edoxaban, Based Antithrombotic Regimen in Patients With Atrial Fibrillation; AUGUSTUS, Antithrombotic Therapy After Acute Coronary Syndrome or PCI in Atrial Fibrillation.

the bleeding events [68, 69]. Thus, the long-term use of warfarin in such patients is not recommended [70]. The DAPT regimen became the golden standard for the prevention of coronary stent thrombosis after the first trial with double antiplatelets regimens (aspirin plus ticlopidine), followed by other trials and meta-analyses [22, 71, 72]. Recent trials investigated the role of DOACs in ACS patients, but only very low-dose rivaroxaban (2.5 mg twice, daily) combined with DAPT (aspirin plus clopidogrel) reduced ischaemic events without a significant increase in fatal bleeding [58, 60, 73]. Thus, only the addition of this very low-dose rivaroxaban to aspirin and clopidogrel is recommended by the 2015 European Society of Cardiology guidelines (ESC) on selected ACS patients with low risk of bleeding [27, 28].

We describe an illustrative scenario of a patient admitted to the intensive coronary care unit (ICCU) to better emphasize the challenges and unanswered questions concerning antithrombotic management in the setting of AF/ACS patients with or without PCI.

A 71-year-old male with a history of IHD [prior MI with stenting of right coronary artery (RCA) 2 years ago] had recurrent chest pain. The electrocardiogram (ECG) showed ST-segment depression in the V2–V6 leads and paroxysmal AF. His blood pressure was 125/75 mmHg and CKD eGFR = 58 mL/min/1.73 m². The coronary angiography showed an 80% maximum diameter stenosis in the proximal left anterior descending (LAD) coronary artery and normal coronary flux on RCA previous stent. He received a stent implant (3.0 × 15 mm) on LAD with restoration of a TIMI 3 flow. The CHA₂DS₂-VASc score was 2 and HAS-BLED score was 3. TAT with aspirin, clopidogrel, and rivaroxaban 15 mg/day was prescribed. The AF reverted to sinus rhythm spontaneously 72 hours later. Blood tests on the fifth day showed a drop in haemoglobin (Hb) from the initial value of 13.0 to 10.5 g/dL. The fecal occult blood test (FOBT) was negative, and he refused the endoscopic procedures. Aspirin was stopped and the patient was discharged with DAT-rivaroxaban 15 mg/day and clopidogrel 75 mg/day. Ten days later, the patient was again faced with intense chest pain, paroxysmal AF and an anterior ST-segment elevation MI on ECG. Coronary angiography revealed a stent thrombosis of the LAD, which was resolved with repeated mechanical thrombus aspiration and balloon dilatation. Aspirin 100 mg/day and ticagrelor (loading dose 180 mg, then 90 mg twice daily) was started with rivaroxaban 15 mg/day and pantoprazole 40 mg/day. The patient recovered uneventfully with no further drop in haemoglobin and AF persistence. Clopidogrel (instead of ticagrelor) was reintroduced after 6 weeks along with continuation of DAT with rivaroxaban for 6 months.

The case challenges the following questions.

4.1 The nature of DAT or TAT trials to combine elective and urgent PCI for ACS

The ACS prevalence in different trials ranges from 28% to 61% with a focus on reducing bleeding events [41]. All these

trials were underpowered to assess ischaemic efficacy, and the effects on ischaemic events and stent thrombosis were imprecise. There are signals that suggest a slight numerical increase of acute MI and stent thrombotic events, which came from a sub analyses of ACS subgroups or from meta-analyses, in the absence of studies dedicated only for ACS patients [40, 43–47, 63, 64]. The duration and components of combination therapy for these high-risk patients are crucial, and further dedicated studies for ACS patients are needed to know the best ischaemic and thrombotic risk, and the management options.

4.2 DOACs versus VKA

The AUGUSTUS trial was the latest published study and the only one that evaluated whether DOAC (apixaban) or VKA is preferable as part of DAT or TAT. It is the only trial specially designed (2 × 2 factorial randomized design) with the aim to investigate whether apixaban works better than warfarin in terms of safety. Apixaban uses leads to lessen bleedings (4.2% absolute reduction over VKA) and less hospitalisation. The trial was not powered for ischaemic event analyses. More benefits were present in the ACS subgroup as compared to the combinations that included aspirin, VKA or both. DOACs in antithrombotic combination was superior to VKA, producing less bleeding in each of the four trials which investigated the AF/ACS/PCI patients. The use of DOACs was considered preferable in AF/ACS patients by the 2018 ESC and European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization [39–42, 74]. Until now, DOACs, as compared to VKA, seems to be non-inferior in term of ischaemic efficacy in DAT or TAT combinations. However, all four studies with DOACs were underpowered for thrombotic events analyses. Therefore, meta-analyses including the four recent studies with DOACs plus P2Y₁₂ inhibitors suggests that, when omitting aspirin, there might be a slight numerical increase of acute MI and stent thrombotic events [43–47]. Thus, until further studies clarify these aspects, it might be assumed that the aforementioned advantages of the DOACs over VKA are maintained in either DAT or TAT regimens. Recent data from an observational study documented that DOACs almost completely replaced VKA in TAT (84.3%) or DAT (84.6%) combinations [75].

4.3 Optimal duration of DAT or TAT regimens

Until now, there were no specific trials to determine the optimal duration of antithrombotic combinations on AF/ACS patients with or without PCI. The only trial that tried to investigate if a 6-week period of TAT works better than six months of TAT in terms of safety was ISAR – TRIPLE. Bleeding frequency was highest in the long TAT group (27.9% vs 20.5%, HR 0.68, *p* = 0.04) but the combined ischaemic end point was similar between the groups [56]. Thus, the trial suggested that a short TAT period of six weeks is preferable over a longer one with six months. However, these results were applicable for a mixed popula-

tion, with only 32% having an ACS. A longer TAT administration (three, six or twelve months), considering the balance between ischaemic and/or thrombotic and bleeding risk, was promoted by 2016 ESC guidelines for the management of atrial fibrillation [76]. Due to the favourable results with DAT/DOACs regimens, the 2019 updated North American AF guidelines recommend it for patients with high-risk ACS (ST segment elevation or recurrent MI) as well to minimize duration of TAT to a period of four to six weeks [5]. Recently, the 2020 ESC-AF guidelines as well as those for non-ST-elevation ACS recommend a short course of TAT for up to one week or until discharge in several AF patients (low risk of ischaemic and/or thrombotic complications) undergoing PCI [2, 31]. These new recommendations highlight the concerns regarding early stent thrombotic events with DAT and argue an initial course of TAT in all AF/ACS patients having PCI [43–47]. An important issue is that in all these trials, aspirin was administered from two up to six days even in DAT regimens until randomization [39–42]. For ACS patients with medical management, the new recommendation is a DAT [DOACs and P2Y12 inhibitor (preferably clopidogrel)] regimen from the beginning [32]. Interestingly, the post hoc results from the AUGUSTUS trial demonstrated that the ischaemic and antithrombotic efficacy of TAT was highest in the first month after the index event and lesser after this period [77]. Moreover, the data from an SCA registry with almost 5000 patients who had MI and AF, showed that one in four patients were under TAT, which increased twice the frequency of intracranial haemorrhage but did not reduce recurrent ischaemic events [78]. Therefore, while awaiting new data, an initial period of one week of TAT seems enough for low ischaemic and thrombotic risk in AF/ACS patients with uncomplicated PCI (GRACE score less than 140 in case of ACS, and high or non-correctable bleeding risk), while a longer period of up to four or six weeks of TAT is useful for patients at an increased ischaemic (recurrent events) or thrombotic risk (stents for left main or proximal descending coronary artery and bifurcation, longer or kissing stents, recurrent MI, stent thrombosis, scores over the mentioned values) and low bleeding risk [1, 2, 5, 79]. After the removal of aspirin, DAT with a P2Y12 inhibitor (usually clopidogrel) is generally continued for 12 months in AF/ACS patients with or without PCI, but could be stopped at six months (as we did for our patient) considering the ischaemic and bleeding risk [1, 2, 5]. In our case scenario, the patient had both, a high ischaemic/thrombotic as well as bleeding risk. If he had TAT, in the first four to six weeks after the index event (as guidelines recommend in such patients), he would have likely escaped from the reported stent thrombosis. While the aspirin discontinuation was motivated by possible bleeding and the increased risk of bleeding, this approach exposed him to the increase in the ischaemic and thrombotic risk in the early period after stenting.

4.4 DOACs selection and dosage

DOACs are preferred over VKA in all eligible AF patients [2, 5]. When starting and selecting a DOAC, a preliminary evaluation of kidney and liver function is required as renal function affects selection and dosing because all medications are eliminated in different proportions via the kidneys, as presented in Table 2. Frailty and bleeding risk, by themselves (usually evaluated with the HAS - BLED score), should not be a reason to deny DOACs. Outside the bio-clinical profile as mentioned above, however, different local factors (approval or regulatory restrictions, cost of the therapy) may influence selection of DOACs. All four DOACs tested in the pivotal trials for AF/ACS/PCI patients seems to be safe in terms of bleeding risks and ischaemic protection, with some differences according to the published and approved dose reduction criteria [39–42]. Therefore, the lowest, effective dose that was tested in AF trials should be used and dose reduction below the approved dose is not recommended as it may increase the thromboembolism risk [59, 61, 80–82]. While some caveats exist for rivaroxaban and dabigatran, the doses for apixaban and edoxaban remain in antithrombotic combinations similar to those for general AF patients, as presented in Table 2. Low-dose rivaroxaban (15 mg/day; dose reduction to 10 mg QD if CrCl 30–49 mL/min), and not the accepted 20 mg/day for AF, was investigated in the PIONEER AF-PCI due to the dose-dependent higher risk of bleeding [39, 59]. Both doses (110 mg and 150 mg twice a day) of are approved for stroke prevention, but the lower dose seems to be associated with more ischaemic and thrombotic events in REDUAL PCI, and, therefore, might be less appropriate for patients with high thrombotic risk [40, 83]. In the United States, as previously mentioned, the lower dose of dabigatran 110 mg studied in the RE-LY trial is not approved in stroke prevention for AF patients [61, 62]. As recommended, we treated our patient with rivaroxaban 15 mg early after PCI and switched him from TAT to DAT due to haemoglobin loss and high bleeding risk.

4.5 Antithrombotic therapy in patients who developed a new onset of AF-complicating ACS or are at a low risk of thromboembolic events

The rate of new AF onset during index hospitalisation in ACS patients is around 10% and depends on the ischaemic burden, being more frequent at the onset of an ischaemic episode or in those patients with extensive ischaemia [3, 75, 76, 84]. However, short- and long-term prognosis of AF episodes during the ACS remains unclear, especially if they are paroxysmal [6, 85, 86]. Different retrospective studies showed a lesser OAC utilisation in these patients due to the belief that the paroxysmal AF episode has a low stroke risk because it is transient and triggered by acute ischaemia [86–89]. Thus, a practical guide in 2018 manifested special attention for new onset AF/ACS patients and recommend OAC use, considering the individual risk of stroke as assessed by the CHA₂DS₂-VASc score [90]. In a recent prospective observational study, 40% of patients who developed paroxysmal AF

during hospitalisation for ACS were discharged without an OAC prescription, but almost three quarters had DAPT with potent oral P2Y₁₂ inhibitors [75]. In this context, there is an unmet need for specific studies on new-onset AF during or following ACS to clarify the utility of anticoagulation and its optimal duration.

Another challenging approach is the effectiveness of early OAC administration in ACS patients with a low CHA₂DS₂-VASc score [= 1 (male), = 2 (female)] who have already been treated with DAPT. The current guidelines recommended an OAC in such patients, however several studies showed that DAPT alone in AF patients receiving drug eluting stent implantation was not associated with a significant risk increase for ischaemic stroke [2, 5, 77, 91]. Also, the 2019 updated North American AF guidelines, suggest that use of DAPT alone may be enough for AF/ACS patients who have a CHA₂DS₂-VASc score of 0 to 1, with constant reassessment for anticoagulation over time [5]. An observational study showed that, for an AF patient with a CHA₂DS₂-VASc score of 2 to 4 or a CHADS₂ score <2, OAC administration did not result in a reduction of composite ischaemic and thrombotic events and led to more bleeding instead [92]. DAPT had a higher protective effect against stroke than aspirin alone, but lesser when compared to OAC [25]. The more recent and potent oral P2Y₁₂ inhibitors seem to have a greater efficacy than clopidogrel (ticagrelor, but not prasugrel) in preventing ischaemic and embolic stroke as part of the DAPT therapy [93, 94]. These data suggest that, for AF patients with a low CHA₂DS₂-VASc score, OAC could be safely discontinued during DAPT. However, further studies are needed to reduce the gap of knowledge between the protective role of OAC as part of TAT, compared to DAPT [55].

4.6 Potent P2Y₁₂ inhibitors versus Clopidogrel

Clopidogrel is the P2Y₁₂ inhibitor usually recommended by guidelines in AF/ACS patients [1–5]. While ticagrelor and prasugrel had a stronger antiplatelet effect and were superior to clopidogrel, prasugrel performed better in a more recent ACS study with equal bleedings [24, 25, 53]. However, they are not recommended in TAT due to more bleeding events, especially with prasugrel; this risk is less with ticagrelor, but always superior to clopidogrel [39, 40, 95–97]. Ticagrelor and prasugrel had a low percentage—6.2% and 1.2%, respectively—use in the antithrombotic trials in the AUGUSTUS trial; 5% and 2%, respectively, in the PIONEER AF-PCI trial, and 12% to 13.5% of the patients, (depending on the regimen of dabigatran) in the REDUAL-PCI trial, despite the documented superiority over clopidogrel in ACS population. Although the aforementioned studies were not powered to assess the antithrombotic preventing efficacy, it is possible that both new potent P2Y₁₂ inhibitors have more protective effects in antithrombotic regimens when compared with clopidogrel [39–42]. Clopidogrel does not assure a sufficient platelet inhibition for around 40% of the patients, which could be a particularly important point when aspirin is omitted, as the last guidelines suggest

[1, 5, 98]. Measuring the antiplatelet response to clopidogrel may warrant the reintroduction of aspirin or a switch to another P2Y₁₂ inhibitor. A recent trial found that a clopidogrel prescription after STEMI, using genotype-guided point of care, produced less bleeding and equal ischaemic events when compared with ticagrelor or prasugrel [99]. Moreover, similar results were documented in AF patients with interventional treatment [100, 101]. Thus, genetic testing could be the answer when the thrombotic risk is not high and using clopidogrel in a DAT regimen represents the best option to reduce bleeding complications. Moreover, DOACs had similar efficacy as VKA in preventing strokes in AF patients and was also associated with less bleeding [102]. Therefore, for most patients, different DAT regimens (clopidogrel or ticagrelor with DOACs) are valuable alternatives to TAT to reduce bleeding events. However, future studies are needed until this strategy can be widely implemented and the choice of P2Y₁₂ inhibitor used is better documented [1, 5, 38]. We choose clopidogrel instead of ticagrelor for the six months treatment in combination with rivaroxaban as part of a guidelines recommended strategy to avoid bleeding complications in high bleeding risk patients (HAS-BLED score = 3, drop in Hb, possible gastrointestinal bleeding in our patient) [2, 28, 29, 98]. As mentioned above, recent trials suggest the use of genotype-guided point of care to identify clopidogrel non – responders (a potentially risk for our patient), but the current guidelines do not recommend the routine testing [28].

4.7 Aspirin versus no aspirin in DAT or TAT regimens

The effect of DAPT administration for less than three months on ischaemic and bleeding events and the use of only a potent P2Y₁₂ inhibitor was studied in recent ACS clinical trials [103–106]. In AF/ACS/PCI patients, the AUGUSTUS trial and other sub analyses showed that the use of aspirin was important, mainly during the initial treatment, and can be generally safely dropped at discharge with the continuation of DAT alone (OAC plus P2Y₁₂ inhibitor) for at least six months [42–47, 63, 64]. The signals for such an approach began with the exploratory WOEST study, followed by the DOACs trials, that showed that bleeding events were less with DAT (OAC plus P2Y₁₂ inhibitor) as compared to TAT [38–42]. However, these trials were not designed to explore the anti-ischaemic and antithrombotic efficacy even though the cardiovascular deaths and stroke were similar between DAT and TAT regimens. The data coming from the subgroups of ACS/PCI patients demonstrated that there exist more numerical ischaemic (OR 1.43, 95% CI 1.02–2.00, $p = 0.04$ for MI), thromboembolic events, or stent thrombosis in DAT groups with lower doses of DOACs (e.g., dabigatran 110 mg, twice a day in REDUAL-PCI), or placebo versus aspirin, or early after index events as in the AUGUSTUS trial (or 1.92, 95% CI 0.98–3.75, $p = 0.06$ for stent thrombotic events) [47, 107]. High thrombotic (e.g., prior stent thrombosis, stents at bifurcation, left main stent, or long/complex stented lesions) or ischaemic risk patients (recurrent or mul-

tiple MI, GRACE score risk >140) were almost absent in DOACs trials as well as TAT and should be considered for these cases. However, DAT (aspirin dropped after the early phase) might be enough for effective ischaemic protection and to reduce bleeding events for most AF/ACS/PCI patients with low or moderate ischaemic risk [1, 5].

4.8 Bleeding versus ischaemic and thrombotic risk stratification

Finally, an accurate balance of risks is crucial for both regimens, and bleeding and ischaemic/thrombotic risk should be assessed on a case-by-case basis. It determines the type and duration of the DAT or TAT regimens. In our case scenario, all patients taking OAC are at an increased risk of bleeding compared to those not taking OAC, and the risk is higher in the first weeks after initiation of anticoagulation [36, 108]. The same pattern applies for ischaemic and thrombotic risk in cases when antithrombotic therapy is discontinued after a bleeding event, i.e., in the early days and weeks after the ACS [109]. There are no specific risk scores estimating bleeding or thrombotic risk for AF/ACS patients; however, scores such as the DAPT, PRECISE – DAPT, CHA₂DS₂-VASc and HAS-BLED, generally used for the IHD or AF patients, are accepted tools for estimating those risks [17, 29, 110, 111]. To date, no direct comparison between DAT or TAT and current DAPT regimens is available in order to ascertain which is safer, but OAC therapy (DOACs recommendation as first line) is the guidelines' recommendation for prevention of cardioembolic events for all AF patients with a CHA₂DS₂-VASc score ≥ 1 for male or ≥ 2 in female [2, 5]. The embolic risk and relationship with the CHA₂DS₂-VASc score in the early phase for AF/ACS patients is likely different from those with AF alone, because many strokes could be procedure related and/or atheroembolic. Current specific guidelines for AF/ACS patients initially recommend TAT (preferably with DOACs) for all patients at high ischaemic risk and with a CHA₂DS₂-VASc score > 1 [3, 112]. The guidelines for general AF patients, on the other hand, recommend OAC using the CHA₂DS₂-VASc score (considering the risk associated with the female sex). The data available on DAT versus TAT in AF/ACS patients undergoing PCI does not present the analysis as stratified by sex. Therefore, it is important to note that the recommendation is provided in the context of overall CHA₂DS₂-VASc score [2, 3, 5, 112]. Cardioembolic risk is considered as an all-or-nothing categorical variable that is not affected if AF is paroxysmal, persistent or permanent; those patients have a guidelines indication for OAC [2, 3, 5, 89, 112]. As we already mentioned, there is an unmet need for specific studies to clarify the utility of anticoagulation and its optimal duration, especially for patients who developed new-onset or paroxysmal AF during or following ACS [90]. In case of high bleeding risk, an early switch to DAT is recommended for most patients [1, 5]. The HAS-BLED score is helpful to calculate bleeding risk in all AF patients and, if the score ≥ 3 , there is a crucial need to address the modifiable risk factors and check the patient on a regular basis [2, 5]. Therefore, the HAS-BLED score itself should not

be a reason to not prescribe OAC or to reduce the DOACs doses. Moreover, to minimize the bleeding risk, radial access is preferred over femoral access, and routine use of prophylactic proton-pump inhibitors is advisable in AF/ACS patients taking antithrombotic regimens [1–5]. However, as in our illustrated case scenario, AF/ACS patients are older and often associated with high ischaemic and bleeding risk, making both TAT and DAT regimens critically inadequate.

5. Conclusion and recommendations

Among AF patients developing ACS with or without PCI, the DAPT loading should be considered in all patients. In addition to an OAC, a DOAC (if there is no metallic valvular prosthesis or moderate to severe mitral stenosis) is usually needed to reduce cardioembolic stroke for those at increased risk based on their CHA₂DS₂-VASc score as well as in exchange for more bleeding events. Clopidogrel is the preferred P2Y₁₂ inhibitor for most patients, but for patients with high ischaemic risk or recurrent events, ticagrelor or prasugrel may be considered. A regimen of DAT with a P2Y₁₂ inhibitor and DOAC is now recommended for many patients due to its comparable anti-ischaemic efficacy and significantly lower bleeding risk than TAT. However, an initial period of one to four weeks of TAT (now recommended until discharge for patients with low ischaemic and thrombotic risk) is recommended by the last guidelines due to a higher thrombotic and ischaemic risk early after stent implant. Furthermore, for those patients with high ischaemic (recurrent events) and thrombotic risk (multi-stenting or complex lesions), and without excessive bleeding risk, a longer period of four to six weeks of TAT is useful. After aspirin removal, DAT with a P2Y₁₂ inhibitor (usually clopidogrel) is continued, generally for 12 months, in AF/ACS patients with interventional or medical treatment. It can, however, be stopped at six months after considering the ischaemic and bleeding risk. A thorough assessment of both the ischaemic and bleeding risks is extremely important, but future trials are needed to document which P2Y₁₂ inhibitor is the best as well as the optimal duration of an antithrombotic regimen.

A summary of the practical recommendations is given below:

- Ischaemic and bleeding risks need to be assessed using validated risk score predictors (e.g., CHA₂DS₂-VASc, HAS-BLED).
- TAT is to be kept as short as possible considering the ischaemic, thrombotic and bleeding risk.
- DAT (preferably DOACs and clopidogrel) may be considered early after TAT in select patients.
- Clopidogrel is the P2Y₁₂ inhibitor of choice.
- Low-dose (≤ 100 mg daily) aspirin is recommended.
- Target INR is 2.0–2.5 when warfarin is used.
- Prophylactic proton pump inhibitors should be routinely used for patients taking antithrombotic regimens, especially for those with a history or with increased risk of gastrointestinal bleeding.

Author contributions

CP, DT, AP conceived, structured, and organized this review. CP and DT performed the literature research and reviewed the studies' data. CP and AP wrote the original draft. DT organized the tables and references. CP, DT and AP updated and revised the original draft by analysing the latest published studies and reports. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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