IMR Press

Review

Atrial fibrillation and coronary artery disease: a review on the optimal use of oral anticoagulants

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DOI:10.31083/j.rcm2203074

Submitted: 26 May 2021 Revised: 1 July 2021 Accepted: 2 July 2021 Published: 24 September 2021

Atrial fibrillation (AF) represents the most prevalent supraventricular arrhythmia in adults population and up to 15% of AF patients undergo percutaneous coronary intervention (PCI) for coronary artery disease (CAD) during their life. While oral anticoagulants (OACs) exert a protective effect in the setting of stroke prevention and systemic embolization in AF patients, patients undergoing PCI are recommended to receive dual antiplatelet therapy (DAPT) to reduce the risk of cardiovascular death, recurrent myocardial infarction and stent thrombosis. When these two scenarios coexist, as all antithrombotic regimens are burdened by an increase in bleeding risk, antithrombotic regimen and therapy duration must be cautiously tailored on individual patients' characteristics after attentive assessment of ischemic and bleeding risks. Non-vitamin K oral anticoagulants (NOACs), directly inhibiting either thrombin or factor Xa of the coagulation cascade, have progressively replaced warfarin as first choice OACs in several scenarios; recently, randomized controlled trials have compared antithrombotic regimens including NOAC molecules vs vitamin K antagonists in AF patients undergoing PCI to explore the efficacy and safety of NOACs in this setting. These studies have provided a deeper understanding of antithrombotic therapy after PCI in AF patients and have been promptly implemented by the most recent guidelines on AF and CAD management. The aim of the present review was to summarize the current available literature on the perils and benefits of individual OAC molecules in AF patients with acute and/or chronic coronary syndromes in order to provide guidance on the optimal use of OACs in these complex scenarios.

Keywords

Atrial fibrillation; Oral anticoagulation; Coronary artery disease; VKA; NOAC

1. Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia in adult patients worldwide and its prevalence is expected to rise due to increased longevity of the general population [1–5]. The incidence of AF in patients experiencing an acute coronary syndrome (ACS) stands at 2–23% and AF itself may be associated with a higher risk of myocardial infarction (MI) [6, 7]. Moreover, it is estimated that up to 15% of AF patients undergo percutaneous coronary intervention (PCI) for coronary artery disease (CAD) during their life [8].

Plaque rupture and thrombus formation induced by platelet aggregation and coagulation cascade activation are the main drivers of ACS and persistent activation of coagulation may last for several months, leading to increased risk of unfavourable outcome [9]. For this reason, oral anticoagulants (OACs) may exert a protective effect in the setting of CAD. OACs are more protective against stroke compared to antiplatelet agents in AF patients [10], whereas patients experiencing ACS or undergoing PCI are recommended to receive dual antiplatelet therapy (DAPT) to reduce the risk of ischemic events, namely cardiovascular death, recurrent MI and stent thrombosis [11–13]. Even though triple antithrombotic therapy (TAT) including OAC, acetylsalicylic acid and clopidogrel is recommended for AF patients experiencing ACS or undergoing PCI, the benefit of antithrombotic therapy regarding cardiovascular ischemic events must be carefully balanced against an increased risk of treatment-related major and minor bleedings [14, 15]. Literary data and European Society of Cardiology (ESC) guidelines suggest that AF patients at increased ischemic risk with a recent ACS or undergoing PCI may benefit from a short course of at least one week of TAT followed by a 6 to 12 months period of dual antithrombotic therapy (DAT) with OAC and an antiplatelet agent (preferably clopidogrel) according to the acute or chronic coronary setting [1, 16–18]. OAC monotherapy is to be continued afterwards unless there were recurrent ischemic events in this timeframe. Likewise, OAC monotherapy is also recommended after one year in patients with AF and chronic CAD with no PCI in the previous year [19].

Multiple trials and meta-analyses have flourished in recent years investigating and comparing different OAC molecules in the context of AF and CAD. We aimed to review the current available literature addressing the issue of OACs in AF patients with CAD and to provide comprehensive data on risks and benefits of individual OAC molecules in this complex scenario.

2. Vitamin K antagonists: friends or foes?

The efficacy and safety of OACs in the setting of CAD has long been investigated. Most studies in the late 20th century compared OAC therapy with or without aspirin against as-

pirin therapy alone in CAD patients without AF, to assess whether OACs could provide benefit over aspirin on its own in this setting. Earlier trials in the 1980s did not show different rates of reinfarction and mortality between patients given aspirin and those given vitamin K antagonists (VKA) [20, 21]; nevertheless, these studies were relatively small, the aspirin doses were high, and the intensity of anticoagulation was not adequately controlled, thus lessening the reliability of these trials' results. Likewise, no benefit regarding cardiovascular events was observed when combination therapy with warfarin and aspirin was compared with aspirin alone in the later CHAMP study [22], CARS trial [23] and OASIS-2 [24], whereas bleeding rates were significantly increased in the combination therapy in the CHAMP study; all these studies, however, required low international normalized ratio (INR) targets and the positive effect of warfarin on hard ischemic endpoints might have been shadowed by the low intensity of the anticoagulation treatment. Conversely, later trials imposing a target INR higher than 2.0 consistently proved a significant benefit of aspirin plus OAC compared to aspirin alone regarding hard ischemic endpoints, as was the case for the Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) trial in 1994 [25], the ASPECT-2 trial in 1999 [26] and the WARIS II trial in 2002 [27].

The WOEST study was an open-label, randomized controlled trial (RCT) conducted between 2008 and 2011 to assess whether patients on OACs undergoing PCI would benefit from receiving clopidogrel alone compared to clopidogrel plus aspirin [28]. 573 patients were enrolled; at 1-year follow-up bleeding events occurred in 19.4% of patients receiving DAT compared to 44.4% of those receiving TAT (hazard ratio [HR] 0.36, 95% confidence interval [CI] 0.26 to 0.50, $p = 0.011$). Moreover, the composite of death, MI, stroke, target-vessel revascularisation and stent thrombosis occurred significantly less frequently in the DAT group compared to the TAT group (11.1% vs 17.6%, respectively; HR 0.60, 95% CI 0.38 to 0.94, $p = 0.025$), even after baseline characteristics adjustments (adjusted HR [adj-HR] 0.56, 95% CI 0.35 to 0.91) [28]. The WOEST trial showed that clopidogrel administered to patients on OAC requiring PCI is associated with significantly less frequent bleeding events at 1 year than is the combined use of clopidogrel and acetylsalicylic acid. Specifically, gastrointestinal bleeding episodes occurred substantially less frequently in the DAT than in the TAT group, likely due to the local erosive effect of acetylsalicylic acid [29]; it should be pointed out, however, that proton pump inhibitors use was not mandatory in this trial, despite being recommended, and increased administration of these drugs might have lessened the number of gastrointestinal bleeding events. Notably, the WOEST trial also reported that the rate of thromboembolic events was not different between patients who received and did not receive acetylsalicylic acid [28]. The authors suggested that inhibition of thrombin with OACs and P2Y12 receptor inhibition with clopidogrel would reduce the impact of cyclo-oxygenase-1 inhibition by acetylsalicylic acid, as also stated by prior studies [26, 27].

Following the results of the WOEST trial, two registries comparing the safety and efficacy of TAT with warfarin, acetylsalicylic acid and clopidogrel vs different DAT regimens were published [15, 30]. The study by Lamberts *et al.* [15] included 12,165 patients with AF, hospitalized for MI or undergoing PCI and reported that, relative to TAT, no significant difference regarding the risk of coronary events was found for OAC plus clopidogrel, OAC plus acetylsalicylic acid or acetylsalicylic acid plus clopidogrel at 1-year follow-up, whereas the association of clopidogrel and acetylsalicylic acid was associated with a higher risk of ischemic stroke; moreover, OAC plus acetylsalicylic acid and acetylsalicylic acid plus clopidogrel significantly increased the risk of death, while the association of acetylsalicylic acid and either OAC or clopidogrel significantly lowered bleeding risk compared to TAT. The AFCAS registry enrolled 914 AF patients undergoing coronary stent implantation and showed that no significant differences in the rate of MACE and bleeding events among 3 different antithrombotic regimens (TAT with warfarin, acetylsalicylic acid and clopidogrel, DAT with warfarin plus clopidogrel and DAPT), even after propensity score adjustment, at 1-year follow-up [30]. Detailed data regarding the aforementioned studies on VKA molecules in the setting of CAD are reported in Table 1 (Ref. [15, 20–28, 30]).

3. Non-vitamin K oral anticoagulants: a precious ally

Since 2009 non-VKA oral anticoagulants (NOAC), also known as direct oral anticoagulants, have emerged as an alternative to coumarin molecules and progressively took the place of warfarin as first choice regimen in several settings [31–35]. While dabigatran inhibits factor II of the coagulation cascade (thrombin), rivaroxaban, apixaban and edoxaban inhibit activated factor X; these molecules are characterized by rapid action onset and termination, absence of interference with dietary vitamin K intake, and fewer drug interactions than warfarin. In particular, four randomized trials, namely the RE-LY [31], ROCKET AF [32], ARISTOTLE [33], and ENGAGE AF-TIMI 48 [34] trials, first tested the safety and efficacy of these drugs in the setting of cerebrovascular and systemic thrombo-embolic event prevention in non-valvular AF. A landmark metanalysis by Ruff *et al.* [35] demonstrated how the "new oral anticoagulants", as they were initially referred to, significantly reduced stroke, intracranial hemorrhage and mortality, with no difference in major bleedings but increased gastrointestinal bleedings compared to warfarin. Moreover, these results were consistent across different populations, regardless of age, sex, presence of diabetes, creatinine clearance, previous stroke or transient ischemic attack occurrence and $CHADS_2$-score.

Unfortunately, when CAD presents in patients with AF, observational literary data as well as the 2018 ESC consensus paper on the management of antithrombotic therapy in AF patients presenting with ACS or requiring PCI report that

CAD patients less likely receive optimal antithrombotic treatment if they have a history of AF, thus posing them at higher risk of death than patients without AF [14].

Four RCTs compared DAT with P2Y12 inhibitor plus each of the four NOAC molecules versus TAT consisting of aspirin, a P2Y12 inhibitor (P2Y12i) and VKA in the setting of AF patients undergoing PCI with the primary aim to analyze NOAC safety [31–34].

The first RCT on this issue was published in 2016; it was the PIONEER-AF PCI, an open-label, randomized, multicenter study which randomly allocated 2124 patients to DAT with low-dose rivaroxaban (15 mg/die) plus a P2Y12 inhibitor for 12 months (Group 1), TAT with "very-low-dose" rivaroxaban (2.5 mg x2/die) plus DAPT for 1, 6, or 12 months (Group 2), or TAT with VKA plus DAPT for 1, 6, or 12 months (Group 3) in patients with nonvalvular AF undergoing PCI with stent deployment [36]. The study population consisted of about 30% of patients with ST-elevation MI (STEMI) and non-ST elevation MI (NSTEMI) and 20% with unstable angina; 93% of patients were on clopidogrel. Both rivaroxaban-based regimens were associated with lower rates of significant bleeding compared to TAT (16.8%, 18.0% and 26.7%, respectively in Group 1, 2 and 3; $p < 0.001$). Moreover, the three groups did not differ significantly in efficacy, showing similar rates of cardiovascular death, MI, or stroke, even though the study was underpowered for efficacy. In addition, history of stroke was an exclusion criterion from the analysis, thus potentially leading to selection bias.

In 2017 the results from the open-label, multicenter, RE-DUAL PCI trial were published [37, 38]. Cannon *et al.* [37, 38] randomized 2725 patients with AF undergoing percutaneous coronary artery intervention to receive DAT with dabigatran (150 mg or 110 mg x2/die) and a P2Y12 inhibitor or TAT with warfarin, a P2Y12 inhibitor and aspirin for 1 or 3 months, based on the type of stent delivered. The primary endpoint was again a safety outcome, defined as major or clinically-relevant non-major bleeding according to the definition by the International Society on Thrombosis and Hemostasis (ISTH). The primary endpoint occurred in 15.4% of patients in the 110-mg DAT arm compared to 26.9% in the TAT arm (HR 0.52, 95% CI 0.42–0.63; $p < 0.001$ for both non-inferiority and superiority), and 20.2% in the 150-mg DAT arm, compared with 25.7% in the TAT arm (HR 0.72, 95% CI 0.58–0.88; $p < 0.001$ for non-inferiority). The intention-to-treat analysis provided consistent results with those of the on-treatment analysis and across major subgroups. The RE-DUAL PCI trial also tested for the non-inferiority of DAT with dabigatran compared to TAT with warfarin with respect to the composite efficacy endpoint of thromboembolic events (MI, stroke or systemic embolism), death, or unplanned revascularization. The incidence of this efficacy endpoint was 13.7% in the two DAT groups combined as compared with 13.4% in the TAT group (HR 1.04, 95% CI 0.84–1.29; $p = 0.005$ for non-inferiority). Notably, if analyzed separately, the 110 mg dabigatran regimen showed a non-significant excess in the number of ischemic events as compared with TAT. Overall, almost half of the trial population presented with an ACS and the vast majority (88%) of patients received clopidogrel as P2Y12i; no patient received prasugrel in RE-DUAL PCI.

More recently, the AUGUSTUS trial, published in 2019, was a prospective, multicenter, randomized clinical trial with a two-by-two factorial design, enrolling 4614 patients and concomitantly testing two hypotheses, namely (1) that apixaban 5 mg bid would have been at least noninferior to a VKA (open-label) and (2) that isolated P2Y12i would have been superior to DAPT with a P2Y12i and acetylsalicylic acid regarding clinically relevant bleedings in patients with AF and a recent ACS or PCI and planned concomitant antiplatelet therapy [39, 40]. At 6-month follow-up, the primary outcome occurred significantly less frequently in patients on apixaban compared to those receiving VKA (10.5% vs 14.7% respectively, HR 0.69, 95% CI 0.58 to 0.81, $p < 0.001$). In the double-blind comparison of acetylsalicylic acid with placebo, acetylsalicylic acid led to a higher risk of bleeding compared to placebo (16.1% vs 9.0%; HR 1.89, 95% CI 1.59 to 2.24; $p < 0.001$). From an efficacy point of view, at 6 months the apixaban group presented a 6.7% rate of the composite outcome of death or ischemic events as compared to a 7.1% rate in the VKA group and 6.5% of patients assigned to receive aspirin presented an event of as compared with a 7.3% of those assigned to placebo, with no statistically significant difference in either comparison. Despite not reaching statistical significance, ischemic events were numerically higher in the placebo group and, not surprisingly, the incidence of stent thrombosis was nearly twice as high in the placebo group as compared to the aspirin group. Moreover, the mean time-to-randomization in the AUGUSTUS trial was 7 days from the index ACS or PCI and patients were receiving aspirin in the interim, thus limiting assumptions on this period at high risk for coronary ischemic events. Interestingly, the AUGUSTUS trial was the first study to include medically managed ACS; this might be of great interest as nowadays this population is often represented by older and more fragile patients with very high bleeding risk.

Lastly, the ENTRUST-AF PCI trial was a randomized, multicenter, non-inferiority, open-label study published in 2019, randomly allocating 1506 patients with AF and a recent PCI to a DAT regimen with edoxaban 60 mg od (reduced to 30 mg od if creatinine clearance 15–50 mL/min or body weight $\leq$60 kg or concomitant use of P-glycoprotein inhibitors) plus a P2Y12i or TAT with a VKA in combination with a P2Y12i (for 12 months) and aspirin (for a minimum of 1 month and up to 12 months) [41, 42]. At 12 months, major or clinically relevant non-major bleeding events occurred in 17% of patients in the DAT group compared to 20% in the VKA group (HR 0.83, 95% CI 0.65 to 1.05, $p = 0.001$ for non-inferiority), while the annualized event rate of the main efficacy outcome (cardiovascular death, stroke, systemic embolic events, MI and stent thrombosis) was similar between the

Table 1. Characteristics of landmark studies on vitamin K antagonists in coronary artery disease.

Study	Year	Design	Population	FU*	AF (%)	Results
German-Austrian aspirin trial [20]	1980	Multicentre randomized clinical trial	946 pts who had survived a MI for 30–42 days randomized to ASA (1.5 g daily), placebo or phenprocoumon therapy	2 years	NA	Lower total mortality in ASA group than in placebo (RR 42.3%, $p < 0.1$) and phenprocoumon groups (RR 46.3%, $p = 0.07$).
EPSIM [21]	1982	Multicentre randomized clinical trial	1303 pts randomized to ASA (1.5 g daily) or OAC (acenocoumarol, fluindione, ethylbiscoumacetate, phenindione, tioclomarol) an average of 11.4 days after the onset of MI	29 months	NA	Similar total mortality and re-MI rates between OAC and ASA groups (10% vs 11%, Z value –0.46, and 3% vs 5%, Z value –1.70, respectively). Less GI disorders and more frequent severe bleedings in OAC than ASA groups (54% vs 81%, Z value –2.53, and 89% vs 19%, Z value 6.73).
ATACS [25]	1994	Multicentre randomized open-label clinical trial	214 nonprior ASA users admitted to hospital for NSTE-ACS randomized to ASA alone (162.5 mg daily) or ASA plus anticoagulation (heparin then warfarin with target INR 2.0–3.0)	12 weeks	NA	Combination antithrombotic therapy significantly reduced the rate of ischemic events compared with ASA alone at 14 days (10.5% vs 27%, $p = 0.004$) but not at 12 weeks (13% vs 25%, $p = 0.06$). Major bleedings were slightly more common with combination therapy than ASA alone (2.9% vs 0%).
CARS [23]	1997	Multicentre randomized double-blind trial	8803 pts who had had a MI within the preceding 3–21 days randomized to 160 mg ASA, 3 mg warfarin with 80 mg ASA, or 1 mg warfarin with 80 mg ASA	14 months	NA	1-year life-table estimates for re-MI, non-fatal ischemic stroke or cardiovascular death were 8.6% (95% CI 7.6 to 9.6) for 160 mg ASA, 8.4% (95% CI 7.4–9.4) for 3 mg warfarin with 80 mg aspirin, and 8.8% (95% CI 7.6–10) for 1 mg warfarin with 80 mg ASA (non-significant difference in individual comparisons). 1-year life-table estimates for spontaneous major haemorrhage were 0.74% (95% CI 0.43–1.1) in the 160 mg ASA group and 1.4% (95% CI 0.94–1.8) in the 3 mg warfarin with 80 mg ASA group (log-rank $p = 0.014$ on follow-up).
OASIS-2 [24]	2001	Multicentre randomized open trial	3712 pts with NSTE-ACS randomized to OACs (warfarin in all countries, except Hungary where dicumarol was used) (target INR 2.5) or placebo	5 months	NA	147 (7.6%) pts suffered from cardiovascular death, MI or stroke in the OACs group compared with 155 (8.3%) in the placebo group (RR 0.90, 95% CI 0.72–1.14, $p = 0.40$). More major bleeding events with OACs (RR 2.0, $p = 0.004$).
CHAMP [22]	2002	Multicentre randomized open-label study	5059 pts within 14 days of MI randomized to warfarin (target INR 1.5–2.5) plus ASA (81 mg daily) vs ASA monotherapy (162 mg daily)	2.7 years	NA	All-cause mortality was similar in the ASA group and the combination therapy group (17.3% vs 17.6%, $p = 0.76$). More major bleeding episodes with combination therapy (rate ratio 1.78, 95% CI 1.27–2.72).
ASPECT-2 [26]	2002	Multicentre randomized open-label trial	999 pts with ACS within the preceding 8 weeks randomized to low-dose ASA (80 mg daily), high-intensity OACs (target INR 3.0–4.0), or combined low-dose ASA and moderate OACs (target INR 2.0–2.5)	12 months	0%	Death, MI or stroke occurred in 31 (9%) pts on ASA, in 17 (5%) on OACs (HR 0.55, 95% CI 0.30–1.00, p 0.0479) and in 16 (5%) on combination therapy (HR 0.50, 95% CI 0.27–0.92, $p = 0.03$). Major bleeding was recorded in 3 (1%) pts on ASA, 3 (1%) on OACs (HR 1.03, 95% CI 0.21–5.08, $p = 1.0$), and 7 (2%) on combination therapy (HR 2.35, 95% CI 0.61–9.10, $p = 0.2$).
WARIS II [27]	2002	Multicentre randomized open-label trial	3630 pts admitted for MI randomized to warfarin (target INR 2.8–4.2), 160 mg of ASA daily or combined 80 mg of ASA daily plus warfarin (target INR 2.0–2.5)	1445 days	NA	Death, nonfatal re-MI, or thromboembolic cerebral stroke occurred in 241 (20%) pts on ASA, 203 (16.7%) on warfarin (rate ratio as compared with ASA 0.81, 95% CI 0.69–0.95, $p = 0.03$), and 181 (15%) receiving warfarin and ASA (rate ratio as compared with ASA 0.71, 95% CI 0.60–0.83, $p = 0.001$). Non-significant difference between the two groups receiving warfarin. Episodes of major, nonfatal bleeding occurred in 0.62% of pts per treatment-year in both groups receiving warfarin and in 0.17% of pts on ASA ($p < 0.001$).

Table 1. Continued.

Study	Year	Design	Population	FU*	AF (%)	Results
WOEST [28]	2013	Multicentre open-label randomized controlled trial	573 pts receiving OACs and undergoing PCI randomized to clopidogrel alone (double therapy) or clopidogrel plus ASA (triple therapy)	1 year	326 (69.3%)	Bleeding episodes occurred in 54 (19.4%) pts receiving double therapy and in 126 (44.4%) receiving triple therapy (HR 0.36, 95% CI 0.26–0.50, $p < 0.0001$). No significant difference regarding death, MI, stroke, target-vessel revascularisation, and stent thrombosis between DAT and TAT groups.
Danish registry [15]	2013	Danish registry	12165 AF patients hospitalized with MI and/or undergoing PCI	1 year	12165 (100%)	Relative to TAT with OAC plus aspirin plus clopidogrel, no increased risk of recurrent coronary events for OAC plus clopidogrel, OAC plus aspirin, or aspirin plus clopidogrel; aspirin plus clopidogrel increased the risk of ischemic stroke (HR 1.50, 95% CI 1.03–2.20). OAC plus aspirin and aspirin plus clopidogrel significantly increased the risk of all-cause death (HR 1.52, 95% CI 1.17–1.99 and HR 1.60, 95% CI 1.25–2.05, respectively. When compared to TAT, bleeding risk was significantly lower for OAC plus aspirin and aspirin plus clopidogrel.
AFCAS [30]	2014	Multicentre registry	914 AF patients undergoing PCI with stent implantation	1 year	914 (100%)	No significant differences in the rate of MACE and bleeding events among 3 different antithrombotic regimens (TAT with warfarin, aspirin and clopidogrel, DAT with warfarin plus clopidogrel and DAPT).

*mean or median according to each individual study.

ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, acetylsalicylic acid; CI, confidence interval; DAT, double antithrombotic therapy; TAT, triple antithrombotic therapy; FU, follow-up; GI, gastrointestinal; HR, hazard ratio; INR, international normalized ratio; MI, myocardial infarction; NA, not available; NSTE, non ST-segment elevation; OAC, oral anticoagulant; pts, patients; RR, relative risk.

two study arms (7% vs 6%, respectively; HR 1.06, 95% CI 0.71 to 1.69). The main characteristics of these trials are detailed in Table 2 (Ref. [1, 37, 38, 40, 42]).

Noteworthily, patients at high risk for ischemic events (e.g., previous stroke, complex PCI) were under-represented in these trials; moreover, clopidogrel was largely the most common P2Y12i used (>90%) both for DAT and TAT approaches and efficacy and safety of ticagrelor or prasugrel remain uncertain in these populations. Furthermore, none of these trials was specifically focused on urgent PCI and ACS patients' prevalence ranged from 28% to 61%; this may further cloud judgment on how to manage extreme-risk patients. Finally, TAT was administered until randomization, and time to randomization varied from 72 h in the PIONEER-AF PCI up to 14 days in the AUGUSTUS trial, making assumptions on DAT effect in the hyper-acute phase after PCI unreliable.

4. Bleeding risk in atrial fibrillation patients on antithrombotic therapy

The antithrombotic therapy indicated for AF patients after ACS or PCI comes at the cost of an increased bleeding risk. Hansen *et al.* [43] performed a cohort study using nationwide registries in Denmark to identify survivors of first-time hospitalization for AF between 1997 and 2006. After analysing data on 118,606 patients, the Authors reported the highest incidence rate of bleeding events for dual antithrombotic therapy with clopidogrel and warfarin (13.9% per patient-year) and TAT with warfarin, acetylsalicylic acid and clopidogrel (15.7% per patient-year), with a HR for the combined endpoint of non-fatal and fatal bleedings compared to warfarin monotherapy of 3.08 (95% CI 2.32 to 3.91) and 3.70 (95% CI 2.89 to 4.76) respectively. Toyoda *et al.* [44] later conducted the prospective, multicentre, observational BAT study in Japan to investigate the incidence and severity of bleedings in 4009 patients with stroke and cardiovascular diseases taking oral antithrombotic drugs. At a median 19-months follow-up, in 2008 the authors reported an annual incidence of Major bleedings of 1.21% in patients receiving a single antiplatelet agent, 2.00% in those on DAPT, 2.06% patients on warfarin alone and 3.56% in those taking warfarin plus an antiplatelet agent ($p < 0.001$). Moreover, after adjusting for baseline characteristics, the BAT study showed that adding an antiplatelet agent to warfarin independently increased the risk of life-threatening or major bleeding events (relative risk: 1.76; 95% CI 1.05 to 2.95). Likewise, in 2009 Sørensen *et al.* [45] reported an increasing risk of hospital admissions for bleeding with the number of antithrombotic agents prescribed, with a four-fold increase of hospital readmission rate for patients taking TAT compared to aspirin alone during a mean follow-up of 476.5 days.

Uchida *et al.* [46] retrospectively explored the safety and effectiveness of DAPT and warfarin in 575 consecutive patients receiving drug-eluting stents; within a median 459-days follow-up, they found a 2.7% incidence of major bleeding events in patients receiving DAPT compared to 18.0% in the TAT group ($p < 0.001$), thus highlighting that warfarin use is associated with an increased risk of major bleedings. Moreover, multivariate analysis also showed that renal impairment was an independent predictor of major bleeding in the TAT group [46]; this is not unexpected, as chronic kidney disease (CKD) is associated with prolonged bleeding time and platelet dysfunction which together lead to increased bleeding risk and ischemic events [47, 48].

According to the Academic Research Consortium for High Bleeding Risk, the long-term use of OAC by itself constitutes a major criterion defining a high bleeding risk after PCI [12, 49]; nevertheless, several bleeding risk factors must also be considered when deciding upon the optimal antithrombotic regimen for AF patients undergoing PCI, hereby including severe CKD, haemoglobin <11 g/dL, prior spontaneous bleeding requiring hospitalization and/or transfusion, platelet count <100.000/mcL, chronic bleeding susceptibility, liver cirrhosis with portal hypertension, active malignancy within the past year, previous spontaneous intracranial haemorrhage at any time (or within the past year if traumatic), the presence of a brain arteriovenous malformation, at least moderate ischaemic stroke within the past 6 months, recent major surgery or major trauma within one month prior to PCI and non-deferrable major surgery on DAPT [49]. The HAS-BLED score could also be calculated, as it may help correct modifiable bleeding risk factors and recognize patients at high bleeding risk (HAS-BLED score $\geq$3) who require more frequent clinical evaluation and follow-up; moreover, the HAS-BLED score may guide the clinical decision on the optimal NOAC dosage as well as the preferred TAT and DAT duration following PCI in each individual patient, as recommended by the latest ESC guidelines for AF [1, 50]. Nevertheless, an unmatched case-control study by Paciaroni *et al.* [51] described how both the HAS-BLED and CHA_2DS_2-VASc scores performed poorly in predicting intracranial haemorrhages in patients receiving NOACs for AF, while several other factors such as age, the presence of an active malignancy, high risk of fall, hyperlipidemia, low clearance of creatinine, were associated with an increased risk of intracranial haemorrhages. On the other hand, in a similar population atrial enlargement, hyperlipemia and high CHA_2DS_2-VASc score were associated with higher occurrence of cerebrovascular events [52].

5. Acute and chronic coronary syndromes

5.1 Triple vs dual antiplatelet therapy

Four RCTs explored the issue of the combined use of NOACs (namely, dabigatran 110 mg or 150 mg bid [RE-DUAL PCI], rivaroxaban 15 mg od [PIONEER AF-PCI], apixaban 5 mg bid [AUGUSTUS], or edoxaban 60 mg od [ENTRUST-AF PCI]) or VKAs with antiplatelets agents in AF patients suffering from ACS or undergoing PCI, as previously discussed [36, 37, 39, 41]. Overall, data from these studies indicate that DAT with a NOAC plus a P2Y12i yields

Table 2. Characteristics of landmark trials on NOACs in coronary artery disease.

	PIONEER-AF PCI [37]	RE-DUAL PCI [38]	AUGUSTUS [40]	ENTRUST-AF PCI [42]
Year of publication	2016	2017	2019	2019
Total population	2124	2725	4614	1506
Arms	- Riv 15 mg od + P2Y12i - Riv iv 2.5 mg bid + DAPT - VKA + DAPT	- Dab 110 mg bid + P2Y12i - Dab 150 mg bid + P2Y12i - VKA + DAPT	- Api 5 mg bid + DAPT - Api 5 mg bid + P2Y12i - VKA + DAPT - VKA + P2Y12i	- Edo 60 mg od + P2Y12i - VKA + DAPT
Time to randomization	72 hours	120 hours	336 hours	60 hours
Follow-up	12 months	14 months	6 months	12 months
Key inclusion criteria	³18 years old, AF, recent PCI with stent deployment	³18 years old, AF, PCI with stent implantation within 120 hours	³18 years old, AF, planned long-term use of OAC, recent ACS or PCI, planned use of a P2Y12i for at least 6 months	³18 years old, AF requiring OAC, successful PCI for CCS or ACS
Key exclusion criteria	History of stroke or transient ischemic attack, clinically significant GI bleeding within 12 months, creatinine clearance <30 mL/min, anemia of unknown origin, conditions known to increase the risk of bleeding	Bioprosthetic or mechanical heart valves, severe CKD (creatinine clearance <30 mL/min), other major coexisting conditions	Already on OAC for other indications, CKD, prior intracranial hemorrhage, recent or planned CABG, coagulopathy, ongoing bleeding, contraindication to VKA, apixaban, P2Y12i or ASA	Mechanical heart valves, moderate-to-severe mitral stenosis, end-stage CKD, other major comorbidities
Baseline characteristics (%)				
Primary PCI	38.5	50.5	37.3	52.0
Medically managed ACS	0	0	23.9	0
Clopidogrel	94.4	87.9	92.6	92.0
Prasugrel	1.3	0	1.2	0.5
Ticagrelor	4.3	12.1	6.2	7.0
TAT duration (months)	1, 6 or 12	1 (BMS) or 3 (DES)	6	1–12
Enpoints				
Safety endpoint (primary)	Composite of TIMI major bleeding or minor bleeding	Major or clinically relevant non-major ISTH bleeding	Major or clinically relevant non-major ISTH bleeding	Major or clinically relevant non-major ISTH bleeding

Events (%)	Riv 15 mg	Riv 2.5 mg	TAT	Dab 110 mg	Dab 150 mg	TAT	Api 5 mg	vs VKA	ASA	vs placebo	Edo 60 mg	TAT
Trial defined safety endpoint	16.8	18.0	26.7	15.4	20.2	26.9	10.5	14.7	16.1	9.0	17.0	20.1
Intracranial hemorrhage	NA	NA	NA	0.3	0.1	1.0	0.2	0.6	0.4	0.4	0.5	1.2
Efficacy endpoint	MACE: CV death, MI, or stroke; and ST			MACE: all-cause death, stroke, MI, SE or unplanned revascularization			MACE: all-cause death, stroke, MI, ST definite/probable or urgent revascularization				MACE: CV death, stroke, MI, ST definite, SE	
Events (%)	Riv 15 mg	Riv 2.5 mg	TAT	Dab 110 mg	Dab 150 mg	TAT	Api 5 mg	vs VKA	ASA	vs placebo	Edo 60 mg	TAT
Trial defined MACE	6.5	5.6	6.0	15.2	11.8	13.4	6.7	7.1	6.5	7.3	7.0	6.0
All-cause death	NA	NA	NA	5.6	3.9	4.9	3.3	3.2	3.1	3.4	6.1	4.9
CV death	2.4	2.2	1.9	NA	NA	NA	2.5	2.3	2.3	2.5	2.3	2.1
MI	3.0	2.7	3.5	4.5	3.4	3.0	3.1	3.5	2.9	3.6	3.9	3.0
ST	0.8	0.9	0.7	1.5	0.9	1.3	0.6	0.8	0.5	0.9	1.1	0.8
Stroke	1.3	1.5	1.2	1.7	1.2	1.3	0.6	1.1	0.9	0.8	1.3	1.6

Adapted from ESC Guidelines on Atrial Fibrillation, 2021 [1].

Api, apixaban; BMS, bare metal stent; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CCS, chronic coronary syndrome; CV, cardiovascular; Dab, dabigatran; DAPT, dual antiplatelet agent therapy; DES, drug-eluting stent; Edo, edoxaban; ISTH, International Society on Thrombosis and Hemostasis; MACE, major adverse cardiovascular events; NOAC, non-vitamin K oral anticoagulant; P2Y12i, P2Y12 inhibitor; PCI, percutaneous coronary intervention; Riv, rivaroxaban; SE, systemic embolism; ST, stent thrombosis; TIMI, Thrombolysis In Myocardial Infarction; VKA, vitamin K antagonist; other abbreviations as in Table 1.

lower bleeding risk compared to TAT with VKA, acetylsalicylic acid and a P2Y12i (mostly clopidogrel). Noteworthily, the AUGUSTUS trial suggested that the bleeding risk reduction of the combination of NOAC and a P2Y12i was derived from both receiving a NOAC instead of VKA and from omitting aspirin, with this benefit being observed also in medically managed CAD patients with AF [39]. The safety issues related with DAT and TAT have been explored in a vast Danish registry of 272,315 patients with AF older than 50 years [53, 54]. This registry showed that, in comparison with VKA monotherapy, major bleeding rates were significantly increased with DAPT (adjusted HR 1.13, 95% CI 1.06 to 1.19), DAT with VKA plus an antiplatelet drug (adj-HR 1.82, 95% CI 1.76 to 1.89), DAT with a NOAC plus an antiplatelet drug (adj-HR 1.28, 95% CI 1.13 to 1.44), VKA-based TAT (adj-HR 3.73, 95% CI 3.23 to 4.31) and NOAC-based TAT (adj-HR 2.28, 95% CI 1.67 to 3.12), thus pinpointing that treatment with TAT should be as short as possible due to extremely high bleeding issues.

A network meta-analysis was performed by Lopes *et al.* [55] in 2020 to evaluate the efficacy and safety of 4 antithrombotic regimens for AF patients undergoing PCI; 5 RCTs were included in the analysis (WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, ENTRUST-AF PCI) for a total of 11,532 patients [28, 36, 37, 39, 41]. Compared with VKA plus DAPT, Thrombolysis In Myocardial Infarction (TIMI) major bleedings were significantly reduced with NOAC plus P2Y12 inhibitor (OR 0.52, 95% CI 0.35 to 0.79), with no significant difference regarding MACE (OR 1.03, 95% CI 0.77 to 1.38). Although this network meta-analysis suggests that DAT with VKA plus DAPT should generally be avoided following PCI, because acetylsalicylic acid discontinuation may carry lower bleeding risk with no difference in antithrombotic efficacy, this issue is still debated; as a matter of fact, two meta-analyses including major NOAC RCTs hint that acetylsalicylic acid discontinuation may lead to a statistically significant higher risk of coronary events (MI and stent thrombosis), but not cerebrovascular events [16, 17]. Conversely, several meta-analyses consistently demonstrated significantly reduced major bleeding rates occurrences in DAT vs TAT regimens and in NOAC- vs VKA-based strategies, in the presence of a NOAC-specific impact on intra-cranial hemorrhages reduction [16, 17, 56–60]. As MACE and mortality rates were similar in the treatment arms of NOAC landmark trials, it appears that the benefit from major bleeding and intracranial bleeding reduction is counterbalanced by higher coronary ischemic events with DAT vs TAT; moreover, the rates of MI and stent thrombosis were numerically higher with DAT vs TAT in trials and reached statistical significance in the context of meta-analyses, entailing for a possible ischemic trade-off of early aspirin withdrawal in DAT approaches. In summary, the choice of antithrombotic regimen in patients with AF and a recent PCI must be tailored on patient's characteristics and individual predominant ischemic or bleeding risks, which must be carefully assessed in each patient.

Based on these data, the latest ESC guidelines for AF recommend using a NOAC rather than a VKA when concomitant antiplatelet therapy is needed (Class I, Level of Evidence [LoE] A) [1, 37, 39].

Specifically, in patients at high risk of bleeding (HAS-BLED score $\geq$3), rivaroxaban 15 mg od should be preferred over rivaroxaban 20 mg od as long as single or DAPT is administered, to reduce the bleeding risk (Class IIa, LoE B) [36]. Likewise, in patients at high bleeding risk, the latest AF guidelines suggest that dabigatran 110 mg bid should be preferred over dabigatran 150 mg bid for the duration of concomitant single or DAPT (Class IIa, LoE B) [37]. Likewise, even though current AF guidelines give no specific recommendation regarding apixaban and edoxaban doses in patients at high bleeding risk (HAS-BLED score $\geq$3), it may be suggested that lower or reduced doses (2.5 mg bid for apixaban and 30 mg od for edoxaban) should be preferred during TAT or DAT. Lastly, in AF patients requiring a VKA combined with antiplatelet therapy, the VKA dosing should be adjusted to achieve a target INR of 2.0–2.5 and time to therapeutic range >70% (Class IIa, LoE B) [1]. Importantly, proton pump inhibitors should be advised in all patients receiving DAT with antiplatelets and anticoagulants [1].

5.2 Optimal antithrombotic therapy duration

The decision on the best antithrombotic treatment strategy following PCI, be it either for ACS or chronic coronary syndrome (CCS), can only be performed after carefully balancing bleeding vs ischemic risks. Albeit scores might provide some help to tailor antithrombotic duration in patients undergoing PCI (i.e., the DAPT score and the PRECISE-DAPT score [61, 62]), no risk score has been validated in patients on long-term OAC to date.

The Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR TRIPLE) randomized open-label trial investigated whether reducing the duration of clopidogrel therapy from 6 months to 6 weeks after drug-eluting stent deployment was associated with superior net clinical outcome (composite of death, MI, stent thrombosis, stroke and major bleeding) in patients receiving concomitant acetylsalicylic acid and VKA [63]. ISAR TRIPLE demonstrated that 6-weeks TAT was not superior to 6-months TAT regarding net clinical outcomes and that no significant difference existed between the two groups for either the composite of ischemic complications or major bleedings.

Both the 2020 ESC guidelines on AF and those on non-ST elevation ACS (NSTE-ACS) now recommend a short course of TAT for up to 1 week after PCI in all patients with AF (Class I, LoE B) [1, 12]. However, it is paramount to remember that the bleeding risk reduction reported by the four NOAC trials with the NOAC-based dual antithrombotic therapy did not translate into a reduction in all-cause mortality as compared to VKA-based TAT, as previously discussed. Therefore, a prolonged TAT with DAPT and a NOAC up to 30 days should be considered when the risk of stent thrombo-

sis outweighs the bleeding risk, with the total duration ($\leq$1 month) decided according to assessment of these risks (Class IIa, LoE C) [1]; the latter scenario encompasses patients undergoing complex PCI (three vessels treated, more than two stents implanted, more than two lesions treated, bifurcation with two stents implanted, total stent length >60 mm, or chronic total occlusion) or with a history of stent thrombosis [64, 65]. Prolonged TAT beyond 30 days rarely seems warranted, also considering the safety issues related with such therapy [53, 66].

Regardless of the initial antithrombotic regimen, dual antithrombotic therapy with OAC and an antiplatelet agent (preferably clopidogrel) is recommended for the first 12 months after uncomplicated PCI for ACS (Class I, LoE B) [12, 39, 67], or 6 months after uncomplicated PCI in patients with CCS (Class I, LoE B) [18], irrespective of the type of stent delivered, if the risk of stent thrombosis is low or if bleeding risk is more concerning than stent thrombosis risk. Factors increasing risk in CCS patients include stenting of left main or last remaining vessel, suboptimal stent deployment, extensive stent length (>60 mm), diabetes mellitus, CKD, bifurcation with two stents implanted, treatment of chronic total occlusion and previous stent thrombosis despite adequate antithrombotic therapy [1]. After the first 6 to 12 months of DAT following PCI, OAC monotherapy is to be continued, if no recurrent ischaemic events occurred in the interim. When NSTE-ACS patients are medically managed, one antiplatelet agent is added on top of OAC therapy for up to 1 year [12].

The recommended OAC therapy after one year following PCI was first investigated in the OAC-ALONE trial [68]; this open-label randomized compared OAC alone to DAT with OAC and a single antiplatelet agent among AF patients with CCS beyond 1 year after stenting in a 1 : 1 randomization fashion. OAC was warfarin in 75.2% and NOACs in 24.8% of patients. As this trial was prematurely terminated, it was underpowered and inconclusive and could not establish the noninferiority of OAC alone to combined OAC and APT (HR 1.16; 95% CI 0.79 to 1.72, $p = 0.20$ for noninferiority, $p = 0.45$ for superiority). Conversely, more definite conclusions could be driven by the Japanese AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial [19], which randomly assigned 2236 AF patients receiving PCI or coronary-artery bypass grafting more than 1 year earlier or with angiographically confirmed non-revascularized CAD to receive monotherapy with rivaroxaban or DAT with rivaroxaban plus a single antiplatelet agent. Rivaroxaban monotherapy was noninferior to combination therapy for the primary efficacy endpoint (stroke, systemic embolism, MI, unstable angina requiring revascularization or death from any cause) (HR 0.72, 95% CI 0.55 to 0.95, $p < 0.001$ for noninferiority) and superior for the safety endpoint of major bleeding (HR 0.59, 95% CI 0.39 to 0.89, $p = 0.01$ for superiority) in AF patients with CCS; moreover, the AFIRE trial was stopped prematurely because of increased mortality in the combination-therapy group. Even though it is unknown if these results can translate to other NOAC molecules, or other doses, or other settings, it appears that most AF patients with stable CAD should be switched from DAT to NOAC monotherapy after one year, as recommended by current AF and NOAC guidelines [1, 64].

It must be emphasized that the choice of OACs as well as the duration of TAT and DAT need to be patient-tailored based on atherothrombotic, cardioembolic and bleeding risks, as no single parameter or score can provide a definite solution for the matter at hand [69]. Assessment of stroke and cardiac ischaemic event risk by means of the CHA_2DS_2-VASc and Global Registry of Acute Coronary Events (GRACE) scores is highly recommended [1, 69], whereas bleeding risk estimation by means of the HAS-BLED score should lead to correct modifiable bleeding risk factors and institute more frequent clinical review and follow-up [64].

5.3 Which P2Y12 inhibitor?

Prasugrel and ticagrelor have been associated with a greater risk of major bleeding compared with clopidogrel as part of DAT in ACS patients with AF [70–74] and their use is discouraged in this setting [1]. However, even though only a minority of patients taking potent P2Y12i were included in the landmark NOAC RCTs, a sub-analysis of the RE-DUAL PCI showed that both dabigatran 110 mg and dabigatran 150 mg plus ticagrelor reduced bleeding risks compared with warfarin-based TAT with ticagrelor (hazard ratio 0.46, 95% CI 0.28 to 0.76 for dabigatran 110 mg; hazard ratio 0.59, 95% CI 0.34 to 1.04 for dabigatran 150 mg), even though numerically higher bleeding rates occurred in ticagrelor- vs clopidogrel-treated patients in both NOAC and VKA treatment arms [75]. It thus appears that in AF patients with CAD warranting more intensive platelet inhibition, such as after an ACS with high risk for new coronary ischemic events, or in non-responders to clopidogrel and thereby are exposed to a high risk of thromboembolic events, DAT with dabigatran plus ticagrelor might stand as an attractive alternative after PCI. Nevertheless, one should always bear in mind the risk/benefit assessment of such treatment strategy, as high-bleeding risk individuals may derive no net clinical benefit from combined therapy with potent P2Y12i. For instance, a prespecified sub-analysis of the POPular AGE trial was conducted on elderly NSTE-ACS patients on OAC who were randomized to clopidogrel or ticagrelor [76–78]; the analysis showed that clopidogrel reduced major and minor bleeding rates compared to ticagrelor (although not significantly), whilst yielding a significantly better net clinical benefit compared to ticagrelor; moreover, up to 75% of the patients randomized to ticagrelor had to discontinue this potent P2Y12i or were switched to clopidogrel.

Based on these data, clopidogrel generally stands as the P2Y12i of choice as part of dual/triple antithrombotic therapy with either NOAC or VKA in AF patients following PCI [1]; ticagrelor might be a valuable alternative in the small

cohort of patients at extremely high risk of coronary events or non-responders to clopidogrel after careful assessment of bleeding risk.

6. Special populations

Patients with AF undergoing PCI already represent a "special population", despite being quite a common condition. Therefore, very few dedicated studies exist on subgroups commonly presenting as challenging scenarios and recommendations result from observational data or are inferred form subgroup analyses of major trials. The following paragraphs aim to only give a glimpse of the present state of the art and gaps in evidence.

6.1 Chronic kidney disease

AF and CKD exacerbate each other [79] and the coexistence of CKD increases the risk of both thromboembolic and bleeding events, thus limiting anticoagulation options; in fact, the four NOAC molecules are, to a different extent, cleared by the kidneys (dabigatran 80%, edoxaban 50%, apixaban 35%, rivaroxaban 27%) [1]. Despite no randomized data exist on the use of either warfarin or NOACs in AF patients with severe CKD, as the four landmark trials on NOACs in the setting of AF, excluded patients with a creatinine clearance [CrCl] <30 mL/min, low-dose factor Xa inhibitors are approved in Europe for stage IV CKD patients (CrCl 15–29 mL/min) and some observational data support their use as VKA alternatives [80–82]. As for end-stage CKD patients (CrCl <15 mL/min or dialysis), data on NOACs remain conflicting. Two randomized trial comparing apixaban and VKA in end-stage CKD (RENAL-AF and AXADIA) will hopefully shed some light on this crucial setting. Nevertheless, patients with CrCl <30 mL/min were usually excluded from landmark trials on NOACs use in patients with AF undergoing PCI.

6.2 Chronic liver disease

Liver disease importantly increase both ischemic and bleeding risk for several reasons and patients with hepatic disfunction were generally excluded from randomized trials on NOACs. Probably patients on NOACs are at lower risk of bleeding as compared to patients on VKAs, but randomized data are missing and NOACs are contraindicated in patients with Child-Pugh C class [83].

6.3 Extremely high bleeding risk

Patients at very high bleeding risk pose a unique dilemma for the adequate choice of OAC therapy. In fact, no oral anticoagulant is completely safe, regardless of its dose and regimen. A valuable alternative to OACs in the setting of extreme bleeding risk might be left atrial appendage closure. Numerous studies have compared the efficacy and safety of left atrial appendage closure vs either warfarin or NOACs, overall demonstrating the non-inferiority of this procedure vs OAC therapy [84–88]. A propensity-matched analysis by Godino *et al.* [89] demonstrated that left atrial appendage closure and NOACs yield similar rates of all-cause death, thromboembolic events and major bleedings at two-years follow-up in patients with non-valvular AF at high bleeding risk (HAS-BLED ≥3). Notwithstanding, the relatively short follow-up of this study might have limited the observed benefit of left atrial appendage closure compared to a life-long administration of NOACs in high-bleeding risk individuals. A recent meta-analysis by Al-Abcha *et al.* [90] comparing left atrial appendage closure vs OACs in non-valvular AF showed a lower rate of the composite of all-cause mortality, haemorrhagic stroke and non-procedural major bleedings with left atrial appendage closure compared to OAC, with similar risk of all strokes, ischemic strokes, all major bleedings and systemic embolism between the two groups at up to 2 years of follow-up.

As left atrial appendage closure may be indicated in individuals at high haemorrhagic risk, AF patients with CAD requiring antiplatelet therapy might derive a major benefit from this procedure obviating the need for long-term OAC therapy.

6.4 AF catheter ablation

The correct dose and regimen of OACs in the peri-procedural time of catheter ablation has been a matter of debate. The COMPARE trial demonstrated that uninterrupted warfarin therapy reduced peri-procedural strokes and minor bleeding events compared to bridging with low-molecular-weight heparin in patients undergoing AF catheter ablation [91]. Nevertheless, warfarin requires adequate dosage to obtain a peri-procedural target INR in the lower normal range and thus reduce the risk of bleeding complications. The advent of NOACs, providing overall better safety and efficacy than warfarin in AF patients, raised the question of how uninterrupted NOAC treatment would perform compared to uninterrupted VKAs and, thereafter, whether an uninterrupted NOACs strategy would provide better outcomes compared to interrupted NOACs. The former point was addressed by Romero *et al.* [92], showing that uninterrupted NOACs reduced the rate of major bleeding events after AF catheter ablation compared to uninterrupted VKAs, with no differences regarding minor bleedings and thromboembolic events; the latter issue was recently investigated by Asad *et al.* [93], who demonstrated in a meta-analysis of 13 randomized and observational studies that no difference exists between the uninterrupted and interrupted NOAC strategies regarding bleeding and thromboembolic endpoints, albeit observational data suggest that uninterrupted NOACs protect against silent cerebral ischemic events. For this reason, operators have gradually moved to an uninterrupted VKA or NOAC strategy for patients undergoing AF catheter ablation [1]. As this procedure is gradually demonstrating favourable outcomes in different clinical scenarios, such as heart failure with reduced ejection fraction [94], the correct peri-procedural management of OAC therapy becomes paramount. This is especially true considering that heart failure itself may complicate acute and/or chronic CAD, thus potentially indicating catheter ablation for patients on DAT or TAT. Future studies

addressing these specific cohorts of patients are needed.

6.5 Other special populations

Several other special populations, such as patients presenting with hematologic disorders, older and frail patients, patients with extreme body weights and patients with malignancies, represent critical challenging scenarios and were commonly neglected by randomized studies; therefore, the application of AF guidelines in these contexts is controversial, especially when a PCI is needed, and therapy must often be tailored on the single patient. Studies focusing on these everyday clinical challenges are warranted to guide physicians' decisions.

7. Conclusions

The presence of concomitant AF and CAD warrants scrupulous antithrombotic therapy selection. The efficacy of NOAC molecules in preventing thromboembolic complications with relatively low bleeding risk have rapidly placed them as the mainstay of antithrombotic treatment for non-valvular AF, but their clinical use in patients with both AF and CAD is not yet thoroughly established. Based on the favourable literary data on NOAC-based combined antithrombotic therapy regarding thromboembolic and haemorrhagic risks, we believe that the Cardiologist prescribing TAT should weigh its treatment choice considering the individual AF burden (paroxysmal vs persistent vs permanent) whilst aiming at maintaining normal sinus rhythm for the longest time possible; transcatheter ablation of AF might be a valuable strategy with this regard. Conversely, left atrial appendage closure could be advised to those individuals at extreme haemorrhagic risk in whom the use of OAC therapy may be discouraged after risk/benefit trade-off evaluation. Furthermore, thorough knowledge of each patient's coronary anatomy (single-vessel vs multivessel disease, presence of prognostic lesions, complex disease requiring the implantation of multiple stents) and type of stents implanted is important to optimize long-term antithrombotic therapy. In conclusion, as detailed in our review, attentive assessment of bleeding and ischemic risks is paramount in this scenario and the optimal antithrombotic treatment must be tailored on the clinical characteristics of each individual patient.

Author contributions

ET conceived the study. PPB and FA performed the research and wrote the first draft of the manuscript. All authors critically revised the manuscript and read and approved its final version.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2021; 42: 373–498.

[2] Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, *et al.* Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation. 2019; 139: e56–e528.

[3] Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, *et al.* Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. European Heart Journal. 2013; 34: 2746–2751.

[4] Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. Circulation Research. 2017; 120: 1501–1517.

[5] Ballatore A, Matta M, Saglietto A, Desalvo P, Bocchino PP, Gaita F, *et al.* Subclinical and Asymptomatic Atrial Fibrillation: Current Evidence and Unsolved Questions in Clinical Practice. Medicina. 2019; 55: 497.

[6] González-Pacheco H, Márquez MF, Arias-Mendoza A, Álvarez-Sangabriel A, Eid-Lidt G, González-Hermosillo A, *et al.* Clinical features and in-hospital mortality associated with different types of atrial fibrillation in patients with acute coronary syndrome with and without ST elevation. Journal of Cardiology. 2015; 66: 148–154.

[7] Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, *et al.* Atrial Fibrillation and the Risk of Myocardial Infarction. JAMA Internal Medicine. 2014; 174: 107.

[8] Kralev S, Schneider K, Lang S, Süselbeck T, Borggrefe M. Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography. PLoS ONE. 2011; 6: e24964.

[9] Merlini PA, Bauer KA, Oltrona L, Ardissino D, Cattaneo M, Belli C, *et al.* Persistent activation of coagulation mechanisms in unstable angina and myocardial infarction. Circulation. 1994; 90: 61–68.

[10] Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, *et al.* Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006; 367: 1903–1912.

[11] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2018; 39: 119–177.

[12] Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, *et al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2021; 42: 1289–1367.

[13] Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, *et al.* 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal. 2020; 41: 407–477.

[14] Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, *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. 2019; 21: 192–193.

[15] Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen A, Mikkelsen A, *et al.* Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. Journal of the American College of Cardiology. 2013; 62: 981–989.

[16] Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, *et al.* Safety and efficacy outcomes of double vs triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. European Heart Journal. 2019; 40: 3757–3767.

[17] Potpara TS, Mujovic N, Proietti M, Dagres N, Hindricks G, Collet J, *et al.* Revisiting the effects of omitting aspirin in combined antithrombotic therapies for atrial fibrillation and acute coronary syndromes or percutaneous coronary interventions: meta-analysis of pooled data from the PIONEER AF-PCI, re-DUAL PCI, and AUGUSTUS trials. EP Europace. 2020; 22: 33–46.

[18] Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. 2019; 40: 87–165.

[19] Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, *et al.* Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. New England Journal of Medicine. 2019; 381: 1103–1113.

[20] Breddin K, Loew D, Lechner K, Oberla K, Walter E. German Austrian aspirin trial. Circulation. 1980; 64: 63–72.

[21] EPSIM Research Group. A controlled comparison of aspirin and oral anticoagulants in prevention of death after myocardial infarction. New England Journal of Medicine. 1982; 307: 701–708.

[22] Fiore L, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P, *et al.* Department of Veteran Affairs Cooperative Studies Program clinical trial comparing warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation. 2002; 105: 557–563.

[23] Coumadin Aspirin Reinfarction Study (CARS) investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Lancet. 1997; 350: 389–396.

[24] OASIS Investigators. Effect of long-term, moderate intensity oral anticoagulation in addition to aspirin in unstable angina. Journal of the American College of Cardiology. 2001; 37: 475–484.

[25] Cohen M, Adams PC, Parry G, Xiong J, Chamberlain D, Wieczorek I, *et al.* Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Circulation. 1994; 89: 81–88.

[26] van Es RF, Jonker JJC, Verheugt FWA, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet. 2002; 360: 109–113.

[27] Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. New England Journal of Medicine. 2002; 347: 969–974.

[28] Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman J, *et al.* Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013; 381: 1107–1115.

[29] Aalykke C, Lauritsen K. Epidemiology of NSAID-related gastroduodenal mucosal injury. Best Practice & Research. Clinical Gastroenterology. 2001; 15: 705–722.

[30] Rubboli A, Schlitt A, Kiviniemi T, Biancari F, Karjalainen PP, Valencia J, *et al.* One-Year Outcome of Patients with Atrial Fibrillation Undergoing Coronary Artery Stenting: an Analysis of the AFCAS Registry. Clinical Cardiology. 2014; 37: 357–364.

[31] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2009; 361: 1139–1151.

[32] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine. 2011; 365: 883–891.

[33] Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2011; 365: 981–992.

[34] Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, *et al.* Edoxaban versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine. 2013; 369: 2093–2104.

[35] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014; 383: 955–962.

[36] Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, *et al.* Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. New England Journal of Medicine. 2016; 375: 2423–2434.

[37] Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, *et al.* Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. New England Journal of Medicine. 2017; 377: 1513–1524.

[38] Cannon CP, Gropper S, Bhatt DL, Ellis SG, Kimura T, Lip GYH, *et al.* Design and Rationale of the re-DUAL PCI Trial: a Prospective, Randomized, Phase 3b Study Comparing the Safety and Efficacy of Dual Antithrombotic Therapy with Dabigatran Etexilate Versus Warfarin Triple Therapy in Patients with Nonvalvular Atrial Fibrillation who have Undergone Percutaneous Coronary Intervention with Stenting. Clinical Cardiology. 2016; 39: 555–564.

[39] Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, *et al.* Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. New England Journal of Medicine. 2019; 380: 1509–1524.

[40] Lopes RD, Vora AN, Liaw D, Granger CB, Darius H, Goodman SG, *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. American Heart Journal. 2018; 200: 17–23.

[41] Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, *et al.* Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet. 2019; 394: 1335–1343.

[42] Vranckx P, Lewalter T, Valgimigli M, Tijssen JG, Reimitz P, Eckardt L, *et al.* Evaluation of the safety and efficacy of an edoxaban-based antithrombotic regimen in patients with atrial fibrillation following successful percutaneous coronary intervention (PCI) with stent placement: Rationale and design of the ENTRUST-AF PCI trial. American Heart Journal. 2018; 196: 105–112.

[43] Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunsø J, Gadsbøll N, *et al.* Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Archives of Internal Medicine. 2010; 170: 1433–1441.

[44] Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y, Sakamoto T, *et al.* Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. Stroke. 2008; 39: 1740–1745.
[45] Sørensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jørgensen C, *et al.* Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. Lancet. 2009; 374: 1967–1974.
[46] Uchida Y, Mori F, Ogawa H, Takagi A, Hagiwara N. Impact of anticoagulant therapy with dual antiplatelet therapy on prognosis after treatment with drug-eluting coronary stents. Journal of Cardiology. 2010; 55: 362–369.
[47] Washam JB, Adams GL. Risks and benefits of antiplatelet therapy in uremic patients. Advances in Chronic Kidney Disease. 2008; 15: 370–377.
[48] De Filippo O, D'Ascenzo F, Raposeiras-Roubin S, Abu-Assi E, Peyracchia M, Bocchino PP, *et al.* P2Y12 inhibitors in acute coronary syndrome patients with renal dysfunction: an analysis from the RENAMI and BleeMACS projects. European Heart Journal—Cardiovascular Pharmacotherapy. 2020; 6: 31–42.
[49] Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, *et al.* Defining high bleeding risk in patients undergoing percutaneous coronary intervention: a consensus document from the Academic Research Consortium for High Bleeding Risk. European Heart Journal. 2019; 40: 2632–2653.
[50] Chao T, Lip GYH, Lin Y, Chang S, Lo L, Hu Y, *et al.* Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: a Comparison of Baseline, Follow-up and Delta has-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. Thrombosis and Haemostasis. 2018; 118: 768–777.
[51] Paciaroni M, Agnelli G, Giustozzi M, Caso V, Toso E, Angelini F, *et al.* Risk Factors for Intracerebral Hemorrhage in Patients With Atrial Fibrillation on Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention. Stroke. 2021; 52: 1450–1454.
[52] Paciaroni M, Agnelli G, Caso V, Silvestrelli G, Seiffge DJ, Engelter S, *et al.* Causes and Risk Factors of Cerebral Ischemic Events in Patients With Atrial Fibrillation Treated With Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention. Stroke. 2019; 50: 2168–2174.
[53] van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major Bleeding Rates in Atrial Fibrillation Patients on Single, Dual, or Triple Antithrombotic Therapy. Circulation. 2019; 139: 775–786.
[54] Lamberts M, Gislason GH, Lip GYH, Lassen JF, Olesen JB, Mikkelsen AP, *et al.* Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. Circulation. 2014; 129: 1577–1585.
[55] Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, *et al.* Optimal Antithrombotic Regimens for Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention. JAMA Cardiology. 2020; 5: 582.
[56] Khan SU, Osman M, Khan MU, Khan MS, Zhao D, Mamas MA, *et al.* Dual Versus Triple Therapy for Atrial Fibrillation after Percutaneous Coronary Intervention. Annals of Internal Medicine. 2020; 172: 474.
[57] Gargiulo G, Cannon CP, Gibson CM, Goette A, Lopes RD, Oldgren J, *et al.* Safety and efficacy of double versus triple antithrombotic therapy in patients with atrial fibrillation with or without acute coronary syndrome undergoing percutaneous coronary intervention: a collaborative meta-analysis of NOAC based randomized clinical trials. European Heart Journal—Cardiovascular Pharmacotherapy. 2020. (in press)
[58] Golwala HB, Cannon CP, Steg PG, Doros G, Qamar A, Ellis SG, *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. European Heart Journal. 2018; 39: 1726–1735a.
[59] Fortuni F, Ferlini M, Leonardi S, Angelini F, Crimi G, Somaschini A, *et al.* Dual versus triple therapy in patients on oral anticoagulants and undergoing coronary stent implantation: a systematic review and meta-analysis. International Journal of Cardiology. 2018; 273: 80–87.
[60] Saglietto A, D'Ascenzo F, Errigo D, Leonardi S, Dewilde WJ, Conrotto F, *et al.* Antithrombotic strategies in patients needing oral anticoagulation undergoing percutaneous coronary intervention: a network meta-analysis. Catheterization and Cardiovascular Interventions. 2021; 97: 581–588.
[61] Yeh RW, Secemsky EA, Kereiakes DJ, Normand ST, Gershlick AH, Cohen DJ, *et al.* Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy beyond 1 Year after Percutaneous Coronary Intervention. The Journal of the American Medical Association. 2016; 315: 1735–1749.
[62] Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, *et al.* Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017; 389: 1025–1034.
[63] Fiedler KA, Maeng M, Mehilli J, Schulz-Schüpke S, Byrne RA, Sibbing D, *et al.* Duration of Triple Therapy in Patients Requiring Oral Anticoagulation after Drug-Eluting Stent Implantation: the ISAR-TRIPLE Trial. Journal of the American College of Cardiology. 2015; 65: 1619–1629.
[64] Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, *et al.* 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021; euab065.
[65] Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, *et al.* Efficacy and Safety of Dual Antiplatelet Therapy after Complex PCI. Journal of the American College of Cardiology. 2016; 68: 1851–1864.
[66] Alexander JH, Wojdyla D, Vora AN, Thomas L, Granger CB, Goodman SG, *et al.* Risk/Benefit Tradeoff of Antithrombotic Therapy in Patients with Atrial Fibrillation Early and Late after an Acute Coronary Syndrome or Percutaneous Coronary Intervention. Circulation. 2020; 141: 1618–1627.
[67] Windecker S, Lopes RD, Massaro T, Jones-Burton C, Granger CB, Aronson R, *et al.* Antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome treated medically or with percutaneous coronary intervention or undergoing elective percutaneous coronary intervention: insights from the AUGUSTUS trial. Circulation. 2019; 140: 1921–1932.
[68] Matsumura-Nakano Y, Shizuta S, Komasa A, Morimoto T, Masuda H, Shiomi H, *et al.* Open-Label Randomized Trial Comparing Oral Anticoagulation with and without Single Antiplatelet Therapy in Patients with Atrial Fibrillation and Stable Coronary Artery Disease beyond 1 Year after Coronary Stent Implantation. Circulation. 2019; 139: 604–616.
[69] Valgimigli M, Bueno H, Byrne RA, Collet J, Costa F, Jeppsson A, *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2018; 39: 213–260.
[70] Andreou I, Briasoulis A, Pappas C, Ikonomidis I, Alexopoulos D. Ticagrelor Versus Clopidogrel as Part of Dual or Triple Antithrombotic Therapy: a Systematic Review and Meta-Analysis. Cardiovascular Drugs and Therapy. 2018; 32: 287–294.
[71] Fu A, Singh K, Abunassar J, Malhotra N, Le May M, Labinaz M, *et al.* Ticagrelor in Triple Antithrombotic Therapy: Predictors of Ischemic and Bleeding Complications. Clinical Cardiology. 2016; 39: 19–23.

[72] Jackson LR, Ju C, Zettler M, Messenger JC, Cohen DJ, Stone GW, *et al.* Outcomes of Patients with Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention Receiving an Oral Anticoagulant and Dual Antiplatelet Therapy: a Comparison of Clopidogrel Versus Prasugrel from the TRANSLATE-ACS Study. JACC. Cardiovascular Interventions. 2015; 8: 1880–1889.
[73] Sarafoff N, Martischnig A, Wealer J, Mayer K, Mehilli J, Sibbing D, *et al.* Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. Journal of the American College of Cardiology. 2013; 61: 2060–2066.
[74] Verlinden NJ, Coons JC, Iasella CJ, Kane-Gill SL. Triple Antithrombotic Therapy with Aspirin, P2Y12 Inhibitor, and Warfarin after Percutaneous Coronary Intervention: an Evaluation of Prasugrel or Ticagrelor Versus Clopidogrel. Journal of Cardiovascular Pharmacology and Therapeutics. 2017; 22: 546–551.
[75] Oldgren J, Steg PG, Hohnloser SH, Lip GYH, Kimura T, Nordaby M, *et al.* Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the re-DUAL PCI trial. European Heart Journal. 2019; 40: 1553–1562.
[76] Gimbel ME, Tavenier AH, Bor W, Hermanides RS, de Vrey E, Heestermans T, *et al.* Ticagrelor Versus Clopidogrel in Older Patients with NSTE-ACS Using Oral Anticoagulation: A Sub-Analysis of the POPular Age Trial. Journal of Clinical Medicine. 2020; 9: 3249.
[77] Qaderdan K, Ishak M, Heestermans AACM, de Vrey E, Jukema JW, Voskuil M, *et al.* Ticagrelor or prasugrel versus clopidogrel in elderly patients with an acute coronary syndrome: Optimization of antiplatelet treatment in patients 70 years and older–rationale and design of the POPular AGE study. American Heart Journal. 2015; 170: 981–985.e1.
[78] Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, *et al.* Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. Lancet. 2020; 395: 1374–1381.
[79] Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. American Heart Journal. 2009; 158: 629–636.
[80] Weir MR, Ashton V, Moore KT, Shrivastava S, Peterson ED, Ammann EM. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and stage IV-V chronic kidney disease. American Heart Journal. 2020; 223: 3–11.
[81] Hanni C, Petrovitch E, Ali M, Gibson W, Giuliano C, Holzhausen J, *et al.* Outcomes associated with apixaban vs warfarin in patients with renal dysfunction. Blood Advances. 2020; 4: 2366–2371.
[82] Fazio G, Dentamaro I, Gambacurta R, Alcamo P, Colonna P. Safety of Edoxaban 30 mg in Elderly Patients with Severe Renal Impairment. Clinical Drug Investigation. 2018; 38: 1023–1030.
[83] Pastori D, Lip GYH, Farcomeni A, Del Sole F, Sciacqua A, Perticone F, *et al.* Incidence of bleeding in patients with atrial fibrillation and advanced liver fibrosis on treatment with vitamin K or non-vitamin K antagonist oral anticoagulants. International Journal of Cardiology. 2018; 264: 58–63.
[84] Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, *et al.* Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet. 2009; 374: 534–542.
[85] Holmes DR, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, *et al.* Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation Versus Long-Term Warfarin Therapy. Journal of the American College of Cardiology. 2014; 64: 1–12.
[86] Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, *et al.* Left Atrial Appendage Closure Versus Direct Oral Anticoagulants in High-Risk Patients with Atrial Fibrillation. Journal of the American College of Cardiology. 2020; 75: 3122–3135.
[87] Streit SR, Buffle E, Fankhauser M, Nietlispach F, Galea R, Windecker S, *et al.* Left atrial appendage closure versus medical therapy for atrial fibrillation: the APPLY study. EuroIntervention. 2020; 16: e767–e774.
[88] Nielsen-Kudsk JE, Korsholm K, Damgaard D, Valentin JB, Diener H, Camm AJ, *et al.* Clinical Outcomes Associated with Left Atrial Appendage Occlusion Versus Direct Oral Anticoagulation in Atrial Fibrillation. JACC: Cardiovascular Interventions. 2021; 14: 69–78.
[89] Godino C, Melillo F, Bellini B, Mazzucca M, Pivato CA, Rubino F, *et al.* Percutaneous left atrial appendage closure versus non-vitamin K oral anticoagulants in patients with non-valvular atrial fibrillation and high bleeding risk. EuroIntervention. 2020; 15: 1548–1554.
[90] Al-abcha A, Saleh Y, Elsayed M, Elshafie A, Herzallah K, Baloch ZQ, *et al.* Left atrial appendage closure versus oral anticoagulation in non-valvular atrial fibrillation; a systemic review and meta-analysis. Cardiovascular Revascularization Medicine. 2021; S1553-8389(21)00207-4.
[91] Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, *et al.* Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. Circulation. 2014; 129: 2638–2644.
[92] Romero J, Cerrud-Rodriguez RC, Alviz I, Diaz JC, Rodriguez D, Arshad S, *et al.* Significant Benefit of Uninterrupted DOACs Versus VKA during Catheter Ablation of Atrial Fibrillation. JACC: Clinical Electrophysiology. 2019; 5: 1396–1405.
[93] Asad ZUA, Akhtar KH, Jafry AH, Khan MH, Khan MS, Munir MB, *et al.* Uninterrupted versus interrupted direct oral anticoagulation for catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Journal of Cardiovascular Electrophysiology. 2021; 32: 1995–2004.
[94] Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, *et al.* Catheter Ablation for Atrial Fibrillation with Heart Failure. New England Journal of Medicine. 2018; 378: 417–427.