Kardiologia Polska 2018; 76, 6: 937–944; DOI: 10.5603/KP.a2018.0112 ISSN 0022–9032

REVIEW

Dual and triple antithrombotic therapies: current patterns of practice and controversies

Mark A. Crowther, John W. Eikelboom

McMaster University, Hamilton, Ontario, Canada

Abstract

Dual antiplatelet therapy (DAPT) has been the cornerstone of antithrombotic management for patients undergoing percutaneous coronary intervention (PCI). Despite low-quality evidence, triple antithrombotic therapy involving acetylsalicylic acid, clopidogrel, and warfarin or non-vitamin K antagonist oral anticoagulant (NOAC) has been recommended in patients with concomitant atrial fibrillation undergoing PCI, who require long-term oral anticoagulation, although such a strategy is associated with a substantially increased risk of bleeding compared with DAPT. NOAC combined with $P2Y_{12}$ inhibitor alone appears to be safer and as effective as triple therapy with warfarin in patients with acute coronary syndromes based on the results of recent randomised trials on dabigatran and rivaroxaban. The present review summarises the current data on various combinations of antithrombotic agents in terms of their efficacy and safety.

Key words: dual antiplatelet therapy, atrial fibrillation, anticoagulation, bleeding; triple therapy

Kardiol Pol 2018; 76, 6: 937–944

INTRODUCTION

Antithrombotic therapy, consisting of anticoagulant and antiplatelet agents, has become increasingly complex because of the advent of new medications, new indications, and competing clinical presentations. As a result, clinicians frequently encounter patients being treated with, or with apparent indications for, multiple antithrombotic medications, and they are left to make difficult decisions about the type of the agent(s), duration of use, and the conditions under which one or more agents can be temporarily interrupted or permanently discontinued.

Traditionally, dual antiplatelet therapy (DAPT) denotes the combination of acetylsalicylic acid (ASA) 75 to 100 mg qd plus an $P2Y_{12}$ inhibitor (clopidogrel 75 mg qd, ticagrelor 90 mg bid, or prasugrel 10 mg qd).

Triple antithrombotic therapy encompasses the use of an oral anticoagulant plus two antiplatelet agents, i.e. ASA 75 to 100 mg qd plus an $P2Y_{12}$ inhibitor, mostly clopidogrel 75 mg qd.

WHEN SHOULD I USE DUAL ANTITHROMBOTIC THERAPY?

There are very limited circumstances within which there is moderate- or high-quality evidence to support combining an antiplatelet drug with an anticoagulant. Studies done many years ago show that the combination of warfarin and ASA was more effective than ASA alone in patients following an acute coronary event, as shown by a reduced rate of myocardial infarction (MI) or death, but at the cost of increased bleeding [1–4]. However, such combination therapy has been largely replaced by DAPT, particularly in the era of percutaneous coronary intervention (PCI).

In patients with mechanical heart valves, there is moderate-quality evidence indicating that the combination of warfarin plus ASA in selected patients is superior to warfarin alone, but two things are notable: the first is that the body of evidence is quite small, consisting of less than 1000 patients; and the second is that these data came from trials conducted more than two decades ago [5–7]. Contemporary mechanical valve prostheses are less thrombogenic, and it is likely that the quality of warfarin anticoagulation has improved since the completion of these trials. Current guidelines provide conflicting recommendations about the use of the combination in patients with mechanical valves [8, 9]. Given the fact that the benefit of ASA added to vitamin K antagonists (VKAs) with contemporary target international normalised ratios (INRs) has been demonstrated predominantly in patients with atherosclerotic vascular disease [10] and such a combination increases

Address for correspondence:
Mark A. Crowther, MD, MSc, FRCPC, FRSC, Chair, Department of Medicine, Leo Pharma Chair in Thromboembolism Research, Rm 4V32 McMaster University Medical Centre, Hamilton, Ontario, Canada, e-mail: crowthrm@mcmaster.ca

Received: 14.05.2018 **Accepted:** 14.05.2018 **Available as AoP:** 17.05.2018

the risk of major bleeding [11], VKA plus ASA should not be prescribed to all patients with prosthetic valves, according to the 2017 European Society of Cardiology (ESC) guidelines [8]. Such therapy should be initiated for specific indications, particularly in patients following thromboembolic episode despite an adequate INR [8]. Low-dose ASA (75–100 mg/day) may be added to VKA in such circumstances. In patients with prosthetic heart valves who are treated with the combination of an antiplatelet drug and a VKA a target INR in the lower part of the recommended target range and a time in the therapeutic range (TTR) > 65% to 70% are suggested by current ESC guidelines [8].

In some clinical settings there is moderate- or high-quality evidence that the combination of an oral anticoagulant and an antiplatelet agent is either ineffective or harmful [12–15]. In 2007 the Warfarin Antiplatelet Vascular Evaluation (WAVE) trial investigators showed that in patients with peripheral artery disease (PAD), combination therapy was not more effective than antiplatelet therapy alone and was associated with excess bleeding [14]. Stroke, MI, or death from cardiovascular causes occurred at a similar rate among patients on combination therapy and those receiving antiplatelet therapy alone (relative risk [RR] 0.92, 95% confidence interval [CI] 0.73–1.16), whereas life-threatening bleeding was observed more frequently in the former group (4.0% vs. 1.2%, RR 3.41, 95% CI 1.84–6.35) [14]. On the other hand, in the randomised trial evaluating the efficacy and safety of the combination of antiplatelet and moderate-intensity anticoagulation therapy in 1209 patients with atrial fibrillation (AF) or mitral stenosis, the rate of vascular death, nonfatal stroke, or systemic embolism was lower in combined therapy with the cyclooxygenase inhibitor triflusal plus acenocoumarol than in the anticoagulant arm, whereas there were no differences between the anticoagulant and the combined therapy arms in the rate of severe bleeding [15].

In other situations, dual antithrombotic therapy may be used, but this has not been rigorously tested. Patients who have separate indications for anticoagulant and antiplatelet therapies, for example patients with AF who undergo coronary artery bypass grafting (CABG), or AF patients who develop acute coronary syndrome (ACS), with or without coronary stenting, may be considered for treatment with the combination of single or dual antiplatelet therapy and an anticoagulant.

In summary, there is moderate- or high-quality evidence for the use of dual antithrombotic therapy after ACS, although this is not widely used any more given the improvements in antiplatelet therapy, and in selected patients with mechanical heart valves. In the absence of evidence from randomised controlled trials, combination therapy is empirically used in some other settings, where improved efficacy is desired and where a significant increase in the risk of bleeding is also deemed acceptable. As a result of the perception of enhanced efficacy, there are large numbers of patients receiving the combination of oral anticoagulants and single or dual antiplatelet therapy.

WHEN AND FOR HOW LONG SHOULD TRIPLE ANTITHROMBOTIC THERAPY BE USED?

The available data suggest that triple therapy should be reserved for patients who have a firm indication for both DAPT and an anticoagulant. The most frequent indication is an ACS (usually treated with a coronary stent implantation) with the concomitant indication for oral anticoagulation. This is most common in patients with AF but also includes those with left ventricular thrombus, mechanical heart valves, or recent (within the preceding one to three months) venous thromboembolism. Triple antithrombotic therapy is associated with a very high risk of bleeding, and the current evidence from recent randomised trials convincingly indicates that it is no more effective than dual antithrombotic therapy in the majority of patients, as described below.

If a patient presents with AF and undergoes coronary stenting in 2018, there are three approaches to ASA therapy: none, low dose, or higher dose. Moreover, there are several choices of duration of ASA use, three different choices for adenosine diphosphate (ADP) receptor antagonists, and multiple choices for the duration of an ADP receptor antagonist. In terms of anticoagulant agents, there are five agents approved for AF (warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban) at different doses or intensities. There may be as many as three million "reasonable" combinations of these drugs within their approved dosage regimens.

There has been substantial research regarding antithrombotic therapy in patients with AF who have coronary stents [16, 17]. The antithrombotic management of patients with AF receiving warfarin, who undergo PCI with stent insertion, requires clinicians to weigh the thromboembolic risk against the risk of bleeding. It has been demonstrated that combination antithrombotic therapy increases the risk of major bleeding, which in patients with ACS is associated with a fivefold increased risk of death within 30 days [18]. Large studies driven by clinical endpoints have demonstrated that, in the acute setting, the combination of ASA plus ticlopidine is superior to ASA plus warfarin for prevention of stent thrombosis, which has led to recommendations for the routine use of DAPT post stenting [16, 17].

There is controversy about how long DAPT should be continued after coronary stenting. Guidelines recommend at least two to four weeks for a bare metal stent and three to six months for a drug eluting stent (DES). It is likely that newer generation DESs will require shorter durations of DAPT compared with older DESs.

Large randomised controlled trials have demonstrated that anticoagulation with warfarin is superior to no therapy, ASA, or DAPT for stroke prevention in patients with AF [19]. Meta-analyses of randomised controlled trials in patients with nonvalvular AF indicate that VKA therapy reduces the risk of stroke or systemic embolism by 64% compared with placebo and by 39% compared with ASA [20, 21].

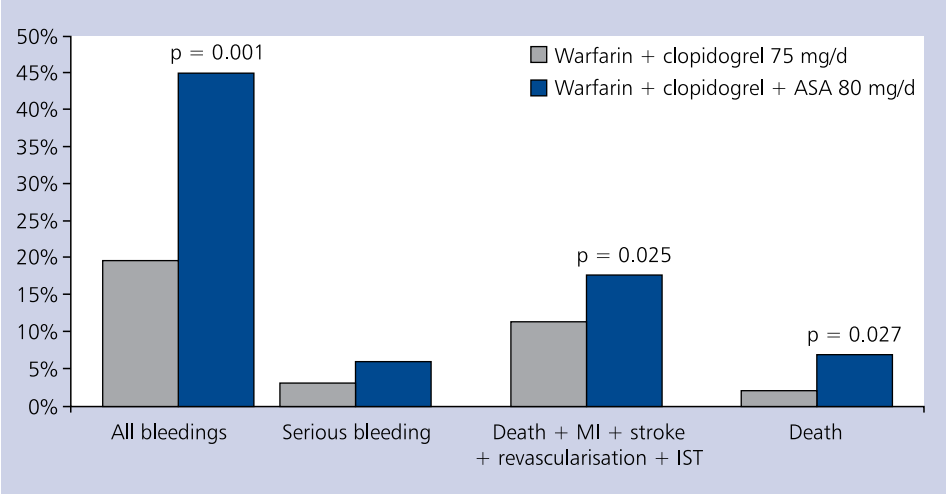

Figure 1. Rates of bleeding and vascular events in patients treated with dual antithrombotic therapy and triple therapy based on the results of the WOEST study [26]; ASA — acetylsalicylic acid; MI — myocardial infarction; IST — intracoronary stent thrombosis

The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-Aspirin (ACTIVE-A) demonstrated that in patients with AF unsuitable for VKA therapy, a combination of clopidogrel and ASA compared with ASA reduced stroke risk by 28% but increased major bleeding by 57% (2.0% vs. 1.3% per year). During a median of 3.6 years of follow-up, the rate of major vascular events was lower in patients receiving DAPT compared with those receiving ASA (6.8% vs. 7.6% per year; RR 0.89, 95% CI 0.81–0.98). The difference was primarily due to a reduction in the rate of stroke [22]. The ACTIVE-W study showed that warfarin is superior to ASA plus clopidogrel in patients at high risk of stroke (3.93% vs. 5.60%; RR 1.44, 95% CI 1.18–1.76) [23]. Therefore, oral anticoagulants are strongly preferred as the agents to prevent stroke in patients with AF, and DAPT is recommended as the intervention to reduce the risk of acute failure of a coronary stent.

A meta-analysis of ten studies published from 2004 to 2010 involving 1349 patients who received triple therapy including warfarin in most cases, showed the incidence of major bleeding at 30 days to be 2.2% (95% CI 0.7%–3.7%) [24]. Despite the fact that these small studies analysed heterogeneous patient populations, employed different co-interventions, and used various definitions of major bleeding, they provided a useful estimate of bleeding risk associated with triple therapy. On the other hand, the one-year bleeding rate is much higher than that at 30 days and reaches 12% [25], which underscores the need to minimise the exposure to triple therapy.

Several randomised trials have compared triple therapy with dual therapy in AF patients undergoing stenting. The WOEST trial was an open-label, intention-to-treat, randomised trial in which triple therapy was compared with dual therapy involving anticoagulant and clopidogrel (thus omitting ASA) [26]. Indications for warfarin in this study were AF (69%), prosthetic heart valve implantation (10%), and other conditions. Overall, 25% of patients were enrolled post ACS. At one-year follow-up, lower bleeding and mortality rates were observed in patients receiving warfarin plus clopidogrel compared with those on triple therapy (hazard ratio [HR] 0.36, 95% CI 0.26–0.50, and HR 0.39, 95% CI 0.16–0.93, respectively) with no significant differences in the rate of thrombotic events [26]. The triple therapy group had a cumulative incidence of major bleeding at 44% after one year, while in the dual therapy group this risk was much lower (Fig. 1). Major bleeding was found in similar proportions of patients in both arms when the Thrombolysis In Myocardial Infarction (TIMI) definition was used. When the Bleeding Academic Research Consortium (BARC) definition was applied, serious bleeding (BARC 3) occurred less frequently in the DAPT group than in the triple-therapy group (6.5% vs. 12.7%; HR 0.49, 95% CI 0.28–0.86) [26]. The limitations of the WOEST study included the predominance of elective PCI procedures, extension of triple therapy unnecessarily for up to one year, frequent femoral artery access, underuse of proton-pump inhibitors, and an underpowered study design that could not detect a significant difference in the risk of stent thrombosis between two antithrombotic regimens [26].

The Open-Label, Randomised, Controlled, Multicentre Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER-AF) study was published in 2016 (Fig. 2A). In this study 2124 patients with nonvalvular AF, who had undergone PCI with stenting (~12% ST-segment

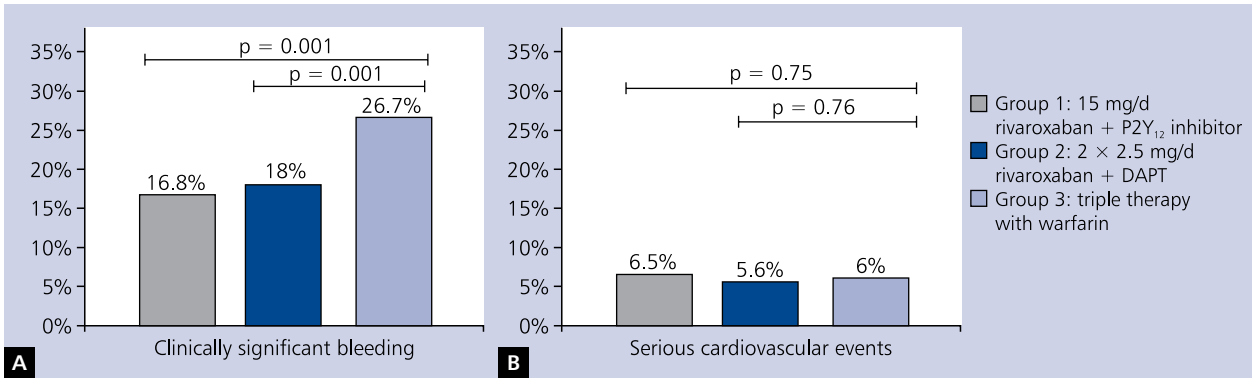

Figure 2. Efficacy and safety of rivaroxaban use in patients with nonvalvular atrial fibrillation without prior stroke, who require oral anticoagulation and have undergone percutaneous coronary intervention. Antithrombotic therapy with rivaroxaban (at a dose of 15 mg qd or 2.5 mg bid) combined with $P2Y_{12}$ inhibitor alone or with low-dose acetylsalicylic acid (ASA), respectively, reduces the risk of clinically relevant bleeding (major or minor bleeding according to Thrombolysis In Myocardial Infarction criteria or bleeding requiring medical attention) compared with the triple therapy with warfarin and target international normalisation ratio 2–3 (**A**). The efficacy of rivaroxaban-based therapy during follow-up is similar to that of triple therapy (**B**). Based on the results of the PIONEER-AF trial [27]. Dual antiplatelet therapy (DAPT) denotes dual antiplatelet treatment, i.e. ASA combined with clopidogrel or other $P2Y_{12}$ inhibitor, mainly ticagrelor

elevation MI patients) were enrolled. Patients with a history of stroke were excluded. The PIONEER AF-PCI trial allocated patients to three different antithrombotic strategies, i.e. group 1: rivaroxaban, 15 mg qd (or 10 mg qd for individuals with creatinine clearance of 30 to 49 mL/min) plus low-dose ASA; group 2: rivaroxaban, 2.5 mg bid, plus ASA (75–100 mg qd), and clopidogrel, 75 mg qd (or prasugrel, 10 mg qd, or ticagrelor, 90 mg bid); and group 3: triple therapy with dose-adjusted VKA (target INR 2–3) instead of rivaroxaban [27]. Patients receiving warfarin (TTR 65%) plus DAPT had the highest risk of TIMI major or TIMI minor bleeding requiring medical attention (Fig. 2A). With the other two strategies there was a highly significant reduction in the rate of the primary outcome of significant bleeding (HR for group 1 vs. group 3: 0.59, 95% CI 0.47–0.76, and HR for group 2 vs. group 3: 0.63; 95% CI 0.50–0.80). No difference in major bleeding or transfusion was observed across groups. There was no difference in the rate of the primary composite endpoint of cardiovascular death, MI, or stroke between the three groups (Fig. 2B) [27]. The trial was underpowered especially when individual efficacy endpoints were analysed. Previous studies showed that rivaroxaban at a dose of 5 mg bid or 2.5 mg bid combined with DAPT increases the risk of major bleeding in patients with a recent ACS compared with placebo (2.1% vs. 0.6%, $p < 0.001$) and intracranial haemorrhage (0.6% vs. 0.2%, $p = 0.009$), including the risk of fatal bleeding during a mean follow-up of 13 months when the 5-mg bid rivaroxaban group was compared with the 2.5-mg bid group among patients with ACS (0.4% vs. 0.1%, $p = 0.04$) [28, 29]. The regimen of rivaroxaban at a dose of 15 mg daily has not been approved in ACS patients or subjects with AF and creatinine clearance of 50 mL/min or more. Of note, up to 5% of patients were treated with ticagrelor in group 1–3 (5.2%, 4.8%, and 3.0%, respectively), while 1.7% in group 1, 1.6% in group 2, and 0.7% in group 3 received prasugrel. The use of ticagrelor does not appear to increase the risk of bleeding as compared to strategies involving clopidogrel [27].

The prospective, randomised, open-label Randomised Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (REDUAL-PCI) trial published in August 2017 compared the dual antithrombotic therapy regimen of dabigatran, 110 mg bid or 150 mg bid, plus clopidogrel or ticagrelor with a triple antithrombotic therapy of warfarin plus clopidogrel or ticagrelor plus low-dose ASA (Fig. 3) [30]. The incidence of major or clinically relevant non-major bleeding during a mean 14-month follow-up was significantly lower in the 110-mg dual-therapy group as compared with the triple-therapy group in which TTR was 64% (HR 0.52, 95% CI 0.42–0.63). The bleeding risk was also lower in the 150-mg dual-therapy group as compared with the triple-therapy group (HR 0.72, 95% CI 0.58–0.88; Fig. 3A, B). In this study ASA was used for one to three months based on practical recommendations [31, 32]. The incidence of MI, stroke, systemic embolism, death, or unplanned revascularisation was similar in the two dual-therapy groups combined as compared with the triple-therapy group (HR 1.04, 95% CI 0.84–1.29), with no between-group difference in the rate of serious adverse events, as shown in Figure 3C and D [30]. Twelve per cent of patients in the RE-DUAL trial received ticagrelor, with no signal of unfavourable safety profile. This trial validated

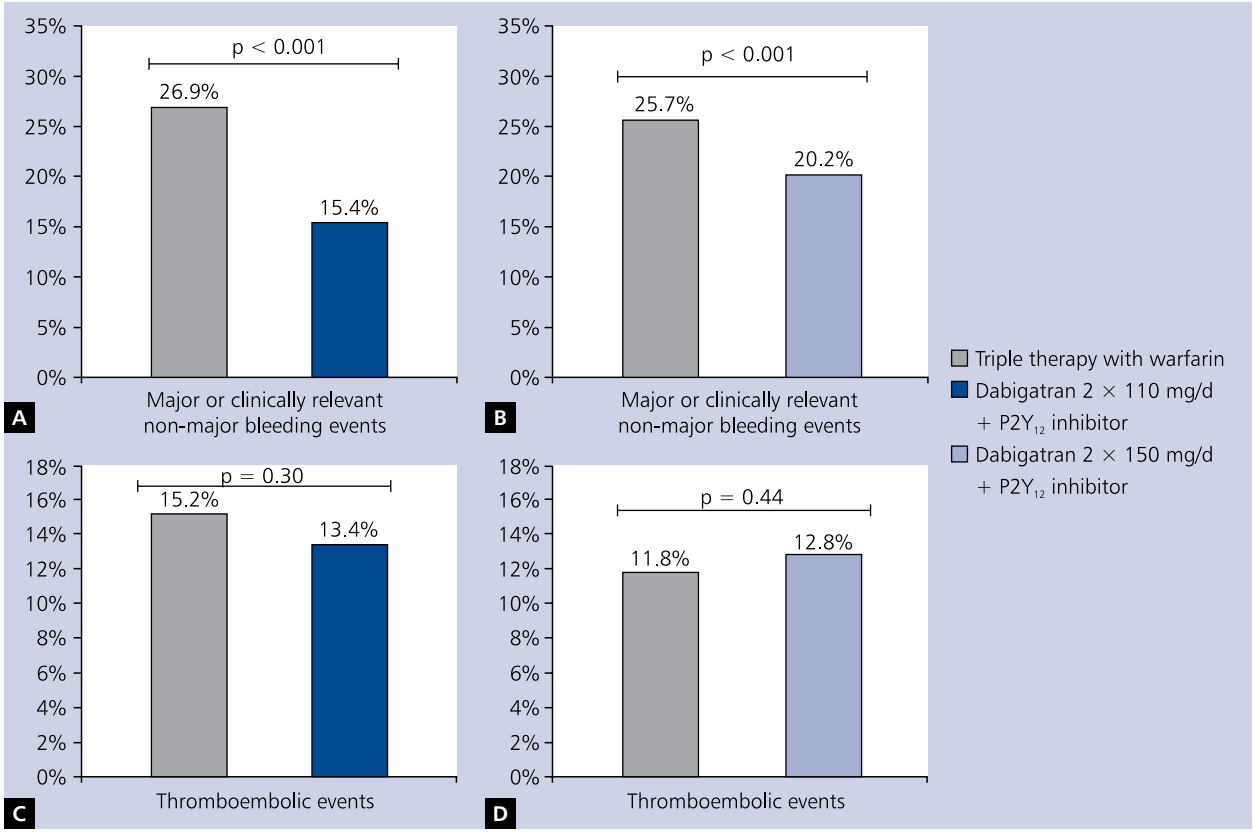

Figure 3. Efficacy and safety of dabigatran use (150 mg or 110 mg bid) in patients with nonvalvular atrial fibrillation who underwent percutaneous coronary intervention. Dual antithrombotic therapy with dabigatran, regardless of its daily dose, reduces the cumulative rate of major or non-major clinically relevant bleeding defined by the International Society on Thrombosis and Haemo-stasis, compared with the triple therapy with warfarin and target international normalisation ratio of 2–3 (**A, B**). The efficacy of dual dabigatran-based therapy in terms of serious thromboembolic events (a combined endpoint) during follow-up is similar to that for triple therapy (**C, D**). Based on the results of the RE-DUAL trial [30]

the concept that a strategy of dual antithrombotic therapy, consisting of oral anticoagulant plus $P2Y_{12}$ inhibitor at regular doses, is non-inferior to the triple therapy and could reduce the bleeding risk.

HOW LONG SHOULD WE TREAT PATIENTS UNDERGOING CORONARY STENTING?

The ISAR TRIPLE study published in 2015 was designed to examine whether shorter or longer duration of antithrombotic therapy was needed in patients undergoing coronary stenting [33]. This study compared a six-week clopidogrel and ASA treatment course after DES implantation with a six-month therapy group. Warfarin was used in this trial mainly for AF (84%). The DAPT was administered following PCI, including 32% of patients with ACS. The cumulative incidence of the primary composite thrombotic endpoint (cardiac death, MI, stent thrombosis, or stroke) was similar in both groups over the nine months of follow-up after randomisation, although an early rise in the frequency of these outcomes was seen in the patients who received short duration therapy. There was no difference in stent thrombosis. Patients allocated to the six-month treatment strategy had a higher risk of bleeding, but this difference was marginally significant [33].

The ESC published guidelines on the management of AF in 2016, including recommendations for patients with AF, who have had elective PCI with stenting [34], which were supported by the guidelines on DAPT in coronary artery disease published in 2017 [35]. It is estimated that up to 15% of AF patients will require stenting during their lifetime [34]. The ESC guidelines primarily divided patients into groups of a low and a high risk of bleeding and then recommended treatment based on their predicted risk of thrombosis (Fig. 4). In both these groups they recommend triple therapy: oral anticoagulant (dabigatran, rivaroxaban, apixaban, or warfarin) together with ASA 75 to 100 mg/day plus clopidogrel 75 mg/day. If the patient following elective PCI with stent implantation is categorised as low risk of bleeding, triple antithrombotic therapy is followed by dual therapy with an oral anticoagulant and ASA or clopidogrel, and then after 12 months for indefinite duration with an oral anticoagulant alone. For patients at high

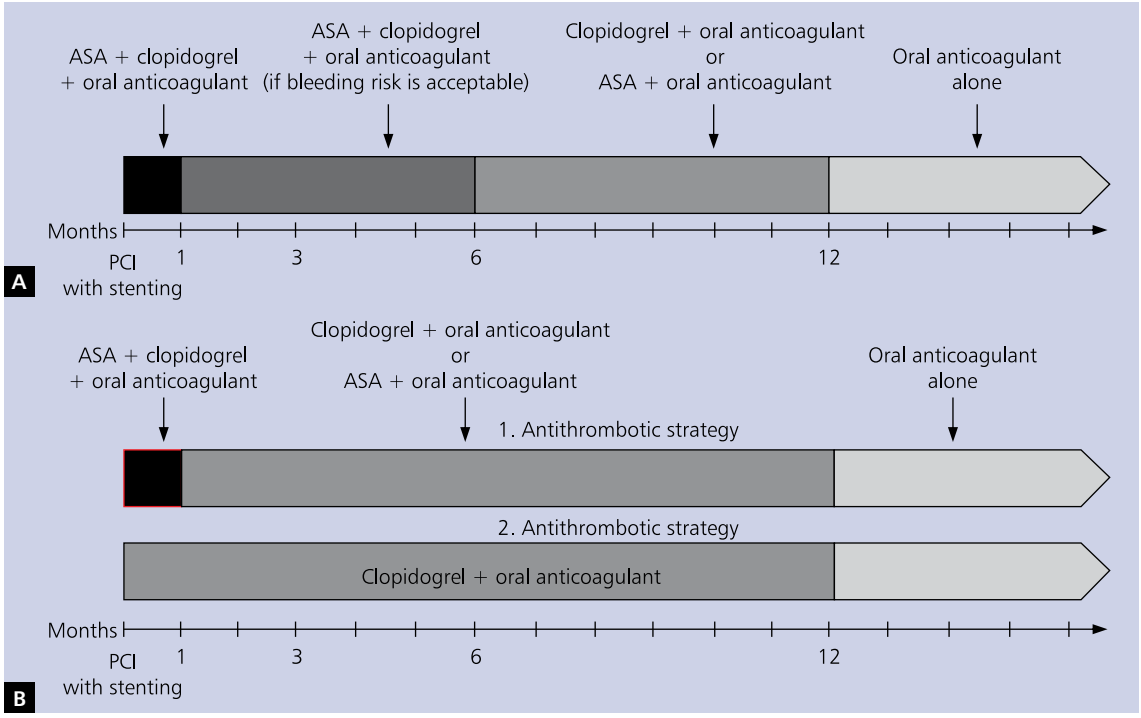

Figure 4. The use of triple and dual antithrombotic therapies in patients undergoing percutaneous coronary intervention (PCI) based on the 2017 European Society of Cardiology guidelines [35]. **A.** Patients with high ischaemic risk, including those following acute coronary syndromes treated with coronary stenting; **B.** Patients with high bleeding risk assessed using HAS-BLED or ABC scoring systems; two options are available, with or without four weeks on triple therapy. Patients receiving vitamin K antagonist should achieve international normalisation ratio values between 2 and 2.5, while those receiving non-vitamin K antagonist oral anticoagulants should use anticoagulants at the lowest approved daily dose; ASA — acetylsalicylic acid

risk the therapeutic strategy is the same but instead of the dual therapy continuing from one to 12 months, the dual therapy continues from one to six months and after six months they recommend switching to an oral anticoagulant alone [34, 35]. Dual therapy with an anticoagulant combined with ASA or clopidogrel may be considered beyond one year in patients at very high risk of coronary events, including ≥ three stents implanted, diffuse multivessel disease particularly in diabetic patients, total stent length > 6 cm, and history of stent thrombosis on antiplatelet therapy [35]. The ESC guidelines state that therapy with any oral anticoagulant plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients, including those at high risk of gastrointestinal bleeding [34].

The use of ticagrelor or prasugrel in triple therapy is not recommended [34, 35]. However, based on the results of the RE-DUAL-AF and PIONEER-AF trials, where a small subset of AF patients received ticagrelor [27, 30], this antiplatelet agent may be used if there is a clear need for its administration, particularly in patients who have experienced stent thrombosis while on dual therapy with ASA plus clopidogrel.

This is to be differentiated from patients who have ACS and AF, who are presumably higher-risk patients because they present with acute myocardial ischaemia, and who are at high risk of recurrent ischaemia. These patients are also divided into groups of low risk or high risk of bleeding. In the low-risk patients triple therapy should be continued for six months followed by six months of dual therapy (oral anticoagulant plus ASA or clopidogrel) and then indefinite duration oral anticoagulant monotherapy from one year after the ACS. Those with a high bleeding risk are allocated to one month of triple therapy followed by 11 months of dual therapy (oral anticoagulant plus ASA or clopidogrel) followed by oral anticoagulant therapy alone [32, 34, 36]. These recommendations highlight recent efforts to limit the duration of exposure to multiple antithrombotics as a mechanism to reduce the risk of avoidable bleeding.

The 2017 ESC guidelines recommend that when an NOAC is used in combination with ASA and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AF trials should be considered, namely apixaban 5 mg bid or apixaban 2.5 mg bid if ≥ two criteria are met from the following: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine level ≥ 1.5 mg/dL (133 μmol/L); dabigatran 110 mg bid, rivaroxaban 20 mg qd, or rivaroxaban 15 mg qd if creatinine clearance is 30 to 49 mL/min (the lower rivaroxaban dose is, however, suggested to reduce bleeding risk) [35].

Bleeding risk can be mitigated through other simple strategies including using the radial approach for angiography. The 2017 ESC guidelines strongly recommend that radial over femoral access should be used for coronary angiography and PCI if performed by an expert radial operator [35]. The radial approach is associated with lower rates of access site complications, including haematoma, pseudo-aneurysm, and bleeding at the access site, although time intervals from admission to balloon inflation are usually longer when the transradial access is used [37]. In a meta-analysis comprising 12 randomised controlled trials involving 5055 patients with MI treated by all regimens of anticoagulants, radial approach was associated with decreased risk of death and major bleeding [38].

Strategies that may further reduce the risk of bleeding in patients who receive triple therapy include the following:

1. Using the lowest proven effective dose of ASA to reduce the risk of gastrointestinal bleeding, i.e. based on the Antithrombotic Trialists' Collaboration analyses [39], 75 to 100 mg/day because such doses were no less effective than higher doses in secondary prevention of major cardiovascular events.
2. Adding a proton pump inhibitor as prophylaxis against gastrointestinal bleeding in patients receiving DAPT or in those requiring the combination of antiplatelet and anticoagulant therapy.
3. Avoiding nonsteroidal anti-inflammatory drugs to reduce the risk of gastrointestinal bleeding.
4. Ensuring optimal control of anticoagulation targeting an INR of 2 to 2.5 for patients receiving triple therapy, although the effectiveness and safety of this approach have not been convincingly demonstrated. Evidence-based methods to improve control of VKA therapy that might be useful also in patients receiving triple therapy include specialist anticoagulation clinics, self-monitoring with a point-of-care device, and computerised dosing algorithms [24, 40].

CONCLUSIONS

In summary, triple antithrombotic therapy, compared with dual antithrombotic therapy, is of unproven benefit in AF patients who have undergone stenting, and increases the risk of bleeding. During recent years, guidelines and expert opinions have significantly evolved in disfavour of triple therapy. They suggest that dual antithrombotic therapy with NOACs could be used in AF patients undergoing PCI with stenting, in particular those at high bleeding risk. Further experimental efforts are needed to seek new safe and effective therapeutic strategies in AF patients undergoing PCI, in whom it is extremely difficult to balance the prevention of stent thrombosis and stroke with the risk of major bleeding.

Conflict of interest: *Mark A. Crowther and John W. Eikelboom have received consulting fees and speaker honoraria from Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Janssen, and Pfizer.*

References

1. Rothberg M. Cost-effectiveness of clopidogrel plus aspirin versus aspirin alone. Ann Intern Med. 2005; 143(6): 464–465, indexed in Pubmed: 16172448.
2. Andreotti F, Testa L, Biondi-Zoccai GGL, et al. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J. 2006; 27(5): 519–526, doi: 10.1093/eurheartj/ehi485, indexed in Pubmed: 16143706.
3. Larson RJ, Fisher ES. Should aspirin be continued in patients started on warfarin? J Gen Intern Med. 2004; 19(8): 879–886, doi: 10.1111/j.1525-1497.2004.30419.x, indexed in Pubmed: 15242475.
4. Dentali F, Douketis JD, Lim W, et al. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. Arch Intern Med. 2007; 167(2): 117–124, doi: 10.1001/archinte.167.2.117, indexed in Pubmed: 17242311.
5. Laffort P, Roudaut R, Roques X, et al. Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transesophageal echocardiographic study. J Am Coll Cardiol. 2000; 35(3): 739–746, indexed in Pubmed: 10716478.
6. Massel DR, Little SH, Little SH, et al. Antiplatelet and anticoagulation for patients with prosthetic heart valves. Cochrane Database Syst Rev. 2003(4): CD003464, doi: 10.1002/14651858.CD003464, indexed in Pubmed: 14583979.
7. Iung B, Rodés-Cabau J. The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties. Eur Heart J. 2014; 35(42): 2942–2949, doi: 10.1093/eurheartj/ehu365, indexed in Pubmed: 25205532.
8. Falk V, Baumgartner H, Bax J, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur J Cardiothorac Surg. 2017; 52(4): 616–664, doi: 10.1093/ejcts/ezx324.
9. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017; 70: 252–289.
10. Iung B, Rodés-Cabau J. The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties. Eur Heart J. 2014; 35(42): 2942–2949, doi: 10.1093/eurheartj/ehu365, indexed in Pubmed: 25205532.
11. Massel D, Little S. Antiplatelet and anticoagulation for patients with prosthetic heart valves. Cochrane Database Syst Rev. 2013; 4: CD003464, doi:10.1002/14651858.cd003464.pub2.
12. Lip GY, Beevers DG. Interpretation of IST and CAST stroke trials. International Stroke Trial. Chinese Acute Stroke Trial. Lancet. 1997; 350(9075): 442–444, indexed in Pubmed: 9259676.
13. Sandercock PAG, Gibson LM, Liu M. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. Cochrane Database Syst Rev. 2009(2): CD000248, doi: 10.1002/14651858.CD000248.pub2, indexed in Pubmed: 19370555.
14. Anand S, Yusuf S, Xie C, et al. Warfarin Antiplatelet Vascular Evaluation Trial Investigators. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med. 2007; 357(3): 217–227, doi: 10.1056/NEJMoa065959, indexed in Pubmed: 17634457.
15. Perez-Gomez F, Alegria E, Berjon J, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. J Am Coll Cardiol. 2004; 44: 1557–1566.

16. Raju NC, Eikelboom JW, Hirsh J. Platelet ADP-receptor antagonists for cardiovascular disease: past, present and future. Nat Clin Pract Cardiovasc Med. 2008; 5(12): 766–780, doi: 10.1038/ncpcardio1372, indexed in Pubmed: 18957959.
17. Paikin JS, Eikelboom JW, Cairns JA, et al. New antithrombotic agents--insights from clinical trials. Nat Rev Cardiol. 2010; 7(9): 498–509, doi:10.1038/nrcardio.2010.101, indexed in Pubmed: 20585330.
18. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation. 2006; 114(8): 774–782, doi: 10.1161/CIRCULATIONAHA.106.612812, indexed in Pubmed: 16908769.
19. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. Ann Intern Med. 2007; 147(8): 590–592, indexed in Pubmed: 17938402.
20. McNamara RL, Tamariz LJ, Segal JB, et al. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. Ann Intern Med. 2003; 139(12): 1018–1033, indexed in Pubmed: 14678922.
21. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007; 146(12): 857–867, indexed in Pubmed: 17577005.
22. Healey JS, Hart RG, Pogue J, et al. Risks and benefits of oral anticoagulation compared with clopidogrel plus aspirin in patients with atrial fibrillation according to stroke risk: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W). Stroke. 2008; 39(5): 1482–1486, doi: 10.1161/STROKEAHA.107.500199, indexed in Pubmed: 18323500.
23. Connolly SJ, Pogue J, Hart RG, et al. ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009; 360(20): 2066–2078, doi: 10.1056/NEJMoa0901301, indexed in Pubmed: 19336502.
24. Paikin JS, Wright DS, Crowther MA, et al. Triple antithrombotic therapy in patients with atrial fibrillation and coronary artery stents. Circulation. 2010; 121(18): 2067–2070, doi: 10.1161/CIRCULATIONAHA.109.924944, indexed in Pubmed: 20458022.
25. Sørensen R, Hansen ML, Abildstrom SZ, 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(9706): 1967–1974, doi:10.1016/S0140-6736(09)61751-7, indexed in Pubmed: 20006130.
26. Dewilde WJM, Oirbans T, Verheugt FWA, 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(9872): 1107–1115, doi: 10.1016/S0140-6736(12)62177-1, indexed in Pubmed: 23415013.
27. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med. 2016; 375(25): 2423–2434, doi: 10.1056/NEJMoa1611594, indexed in Pubmed: 27959713.
28. Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009; 374(9683): 29–38, doi: 10.1016/S0140-6736(09)60738-8, indexed in Pubmed: 19539361.
29. Mega JL, Braunwald E, Wiviott SD, et al. ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012; 366(1): 9–19, doi: 10.1056/NEJMoa1112277, indexed in Pubmed: 22077192.
30. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med. 2017; 377(16): 1513–1524, doi: 10.1056/NEJMoa1708454, indexed in Pubmed: 28844193.
31. Faxon DP, Eikelboom JW, Berger PB, et al. Consensus document: antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: a North-American perspective. Thromb Haemost. 2011; 106: 572–584.
32. Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: a north american perspective - 2016 update. Circ Cardiovasc Interv. 2016; 9(11), doi: 10.1161/CIRCINTERVENTIONS.116.004395, indexed in Pubmed:27803042.
33. Fiedler KA, Maeng M, Mehilli J, et al. Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation: The ISAR-TRIPLE Trial. J Am Coll Cardiol. 2015; 65(16): 1619–1629, doi: 10.1016/j.jacc.2015.02.050, indexed in Pubmed: 25908066.
34. Kirchhof P, Benussi S, Kotecha D, et al. [2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS]. Kardiol Pol. 2016; 74: 1359–1469, doi: 10.5603/KP.2016.0172.
35. Valgimigli M, Bueno H, Byrne RA, et al. 2017 [ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS]. Kardiol Pol. 2017; 75: 1217–1299, doi: 10.5603/KP.2017.0224.
36. Macle L, Cairns J, Leblanc K, et al. 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2016; 32(10): 1170–1185, doi: 10.1016/j.cjca.2016.07.591, indexed in Pubmed: 27609430.
37. Valgimigli M, Gagnor A, Calabró P, et al. MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet. 2015; 385(9986): 2465–2476, doi: 10.1016/S0140-6736(15)60292-6, indexed in Pubmed: 25791214.
38. Karrowni W, Vyas A, Giacomino B, et al. Radial versus femoral access for primary percutaneous interventions in ST-segment elevation myocardial infarction patients: a meta-analysis of randomized controlled trials. JACC Cardiovasc Interv. 2013; 6(8): 814–823, doi: 10.1016/j.jcin.2013.04.010, indexed in Pubmed: 23968700.
39. Baigent C, Blackwell L, Collins R, et al. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009; 373(9678): 1849–1860, doi: 10.1016/S0140-6736(09)60503-1, indexed in Pubmed: 19482214.
40. Levi M, de Peuter OR, Kamphuisen PW. Management strategies for optimal control of anticoagulation in patients with atrial fibrillation. Semin Thromb Hemost. 2009; 35(6): 560–567, doi: 10.1055/s-0029-1240016, indexed in Pubmed: 19787560.

Cite this article as: Crowther M, Eikelboom JW. Dual and triple antithrombotic therapies: current patterns of practice and controversies. Kardiol Pol. 2018; 76(6): 937–944, doi: 10.5603/KP.a2018.0112.