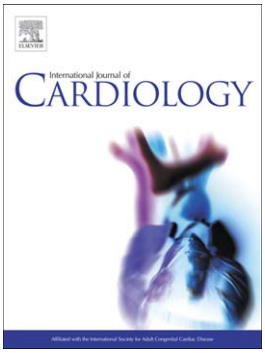
New-onset atrial fibrillation after recent coronary stenting: Warfarin or non-vitamin K-antagonist oral anticoagulants to be added to aspirin and clopidogrel? A viewpoint

Rubboli, Andrea; Agewall, Stefan; Huber, Kurt; Lip, Gregory Y.h.

DOI:
10.1016/j.ijcard.2015.06.006

Document Version
Peer reviewed version

Citation for published version (Harvard):
Rubboli, A, Agewall, S, Huber, K & Lip, GYH 2015, 'New-onset atrial fibrillation after recent coronary stenting: Warfarin or non-vitamin K-antagonist oral anticoagulants to be added to aspirin and clopidogrel? A viewpoint', *International Journal of Cardiology*, vol. 196, pp. 133-138. https://doi.org/10.1016/j.ijcard.2015.06.006



New-onset atrial fibrillation after recent coronary stenting: Warfarin or non vitamin K-antagonist oral anticoagulants to be added to aspirin and clopidogrel? A viewpoint

Andrea Rubboli, Stefan Agewall, Kurt Huber, Gregory Y.H. Lip

PII: S0167-5273(15)01307-8
DOI: doi: 10.1016/j.ijcard.2015.06.006
Reference: IJCA 20662

To appear in: *International Journal of Cardiology*

Received date: 9 May 2015
Accepted date: 12 June 2015

Please cite this article as: Rubboli Andrea, Agewall Stefan, Huber Kurt, Lip Gregory Y.H., New-onset atrial fibrillation after recent coronary stenting: Warfarin or non vitamin K-antagonist oral anticoagulants to be added to aspirin and clopidogrel? A viewpoint, *International Journal of Cardiology* (2015), doi: 10.1016/j.ijcard.2015.06.006

Review article

NEW-ONSET ATRIAL FIBRILLATION AFTER RECENT CORONARY STENTING: WARFARIN OR NON VITAMIN K-ANTAGONIST ORAL ANTICOAGULANTS TO BE ADDED TO ASPIRIN AND CLOPIDOGREL? A VIEWPOINT.

Andrea Rubboli[a], Stefan Agewall[b], Kurt Huber [c], Gregory YH Lip [d]

[a] Division of Cardiology, Laboratory of Interventional Cardiology, Ospedale Maggiore, Bologna, Italy

[b] Institute of Clinical Sciences, University of Oslo and Department of Cardiology,
Oslo University Hospital Ullevål, Oslo, Norway

[c]3rd Medical Department, Cardiology and Intensive Care Medicine, Wilhelminenhospital, Vienna, Austria.

[d] University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

Short title: New-onset AF after PCI: which anticoagulant to add?

Disclosures:

A.Rubboli reports lecture honoraria from and/or consulting for: Bayer, BoehringerIngelheim, Daiichi Sankyo, Pfizer-Bristol Myers Squibb, Astra Zeneca. S. Agewall reports lecture honoraria from: Astra Zeneca, TermoFisher Scientific. K. Huber reports lecture honoraria from: Astra Zeneca, Bayer, BoehringerIngelheim, Daiichi Sankyo, Pfizer-Bristol Myers Squibb.G. Y. H. Lip reports lecture honoraria from Bayer, Pfizer-Bristol Myers Squibb, BoehringerIngelheim, Daiichi-Sankyo, Medtronic, and consulting for Bayer, Merck, Sanofi Aventis, Pfizer-Bristol Myers Squibb, Daiichi-Sankyo, Biotronik, Medtronic, Portola.

Address for correspondence:

Andrea Rubboli, MD, FESC

Division of Cardiology, Laboratory of Interventional Cardiology

Ospedale Maggiore

Largo Nigrisoli 2, 40133 Bologna, Italy

Tel +390516478976

Fax +390516478635

Email andrearubboli@libero.it

ABSTRACT

The antithrombotic management of patients on oral anticoagulation (OAC), with either warfarin or non vitamin K-antagonist oral anticoagulants (NOACs), undergoing percutaneous coronary intervention with stent (PCI-S) has been recently addressed in a joint European consensus document. In accordance, triple therapy (TT) of OAC, aspirin and clopidogrel should generally be given as the initial therapy. More uncertainty exists over whether warfarin or a NOAC should be added in patients already on dual antiplatelet therapy of aspirin and clopidogrel (DAPT) after recent PCI-S. Upon review of available data, it appears that the risk of major bleeding of TT as compared to DAPT is similar with either warfarin or a NOAC. In particular, TT consistently appears associated to an approximately 2.5 fold increase in the risk of major bleeding. Because of the higher convenience, NOACs might be considered the preferred OAC to be added to DAPT. Given the reported different safety profile of the various NOACs on the incidence of major, and gastrointestinal, bleeding, the NOACs, and the dose, showing the greatest safety in this regard should be selected. In accordance, dabigatran 110 mg and apixaban 2.5 mg twice daily appear as the most valuable options in patients who are not and who are respectively, at increased risk of bleeding. As an alternative, apixaban 5 mg twice daily might be considered in patients at risk of bleeding not increased, whereas rivaroxaban 15 mg once daily may be considered in the presence of increased risk of bleeding (essentially when related to moderate renal impairment).

KEY WORDS: warfarin, non vitamin K-antagonist oral anticoagulants, triple therapy, stent, percutaneous coronary intervention

1. INTRODUCTION

The management of the antithrombotic therapy following percutaneous coronary intervention with stent (PCI-S) in patients with atrial fibrillation (AF) on oral anticoagulation (OAC) with warfarin has been recently addressed in a joint consensus document issued by the European Society of Cardiology (ESC) Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), and the European Association of Acute Cardiac Care (ACCA), and endorsed by the Heart Rhythm Society (HRS) and the Asia-Pacific Heart Rhythm Society (APHRS) (1). In accordance, triple therapy (TT) of warfarin, aspirin and clopidogrel should generally be given as the initial therapy, the duration of TT should be as short as possible (based on the clinical setting in which PCI-S has been performed, the type of stent implanted and the patient's risk of bleeding), and the intensity of OAC (i.e., the target International Normalized Ratio [INR]) should be reduced as long as TT is ongoing (1). Also, newer $P2Y_{12}$-receptor inhibitors, including ticagrelor and prasugrel, should be avoided as part of TT (1), and gastric protection with proton-pump inhibitors should be extensively used throughout TT (1, 2).

Both by analogy with warfarin and because in the clinical trials where they were compared with warfarin for the prevention of stroke/systemic embolism in AF, currently available non vitamin-K antagonists oral anticoagulants (NOACs) (including the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban and apixaban) (3), proved at least as effective and safe as (and more convenient than) warfarin (4-6) (Table 1), recommendations similar to those given for patients on warfarin undergoing PCI-S are also given for patients on NOACs (1, 7). In summary, TT of NOAC, aspirin and clopidogrel should be generally prescribed as the initial therapy, the duration of the given TT should be as short as possible (again based on the clinical setting in which PCI-S has been performed, the type of stent implanted and the patient's

risk of bleeding), and the intensity of OAC (i.e., the dose of NOAC) should be reduced as long as TT is ongoing (1, 7). Avoidance of the newer $P2Y_{12}$-receptor inhibitors ticagrelor and prasugrel as part of TT (1, 7), and extensive use of proton-pump inhibitors during TT are again recommended (1, 2, 7).

In practical terms, the above implies that an AF patient on OAC, with either warfarin or NOAC, who is submitted to PCI-S should be kept on the ongoing OAC. But, what if the indication for OAC (e.g., because of new-onset AF) arises in a patient who has recently undergone PCI-S and therefore is being treated with dual antiplatelet therapy of aspirin and clopidogrel (DAPT)? Should warfarin be preferred? Or should a NOAC be used instead? If so, is there a specific NOAC to be preferred? Also, is there a preferable dose of the NOAC chosen to be selected?

Because of the lack of comparative data between warfarin and NOACs and between the individual NOACs, answer the above questions is anything but obvious. To address the everyday management of such patients on DAPT also requiring OAC, the available evidence, derived from 3 different clinical contexts (Fig. 1), will be discussed and practical suggestions proposed.

2. CONSIDERATIONS ON AVAILABLE EVIDENCE

Nearly all of the available evidence on the efficacy and safety of TT in AF patients undergoing PCI-S has been obtained with warfarin as OAC. Albeit of suboptimal quality (as it mostly derives from small size, observational, non-randomized studies or administrative databases), and not univocal, such evidence supports TT of warfarin, aspirin and clopidogrel as the most effective antithrombotic regimen for the prevention of major adverse cardiac and cerebrovascular events (MACCE), including death, myocardial infarction, need for re-revascularization, stent thrombosis and stroke (8, 9). The reported increase in efficacy however, comes at the price of an increased risk of major bleeding (8, 9). Rather consistently, albeit again

not univocally, the relative risk (RR) of major bleeding has been shown to be approximately 2.5 fold that of DAPT (10-18) (Table 2).

No such data are currently available for TT of NOAC, aspirin and clopidogrel. The only piece of evidence in this regard comes from a *post-hoc* analysis of the RE-LY trial (4), where the NOAC dabigatran at two doses of 110 and 150 mg twice daily was compared to warfarin for the prevention of stroke/systemic embolism in patients with AF. In the 812 patients (i.e., 4.5% of the entire population) who at some time during the study were simultaneously on the randomized OAC treatment and DAPT, the RR of major bleeding compared to OAC alone was 2.31 (97% Confidence Intervals [CI] 1.79-2.98), regardless of whether OAC was with warfarin, dabigatran 110 mg or dabigatran 150 mg (19). When considering that the incidence of major bleeding in AF patients treated with either DAPT or warfarin appears comparable, as it has been observed in the ACTIVE-W trial (20) (RR 1.10; 95% CI 0.83-1.45; p=0.53), it might be assumed that again the RR of major bleeding with TT of the NOAC dabigatran (either 110or 150 mg twice daily) plus aspirin and clopidogrel is about 2.5 times that of DAPT alone.

In support of the above conjecture are the data coming from the APPRAISE-2 trial (17), where in the different clinical context of an acute coronary syndrome (ACS), patients (without AF) were randomized to either DAPT or TT of aspirin and clopidogrel plus the NOAC apixaban, which was given at the same dose of 5 mg twice daily tested in the ARISTOTLE trial (6) for the prevention of stroke/systemic embolism in AF patients. While acknowledging that the study was terminated prematurely because of both the absence of benefit on the primary outcome of cardiovascular death, myocardial infarction or stroke, and the concomitant significant increase in major bleeding, it is of note that again the RR of major bleeding with TT of the NOAC apixaban plus aspirin and clopidogrel was about 2.5 times that of DAPT (RR 2.48; 95% CI 1.72-3.58) (Table 3).

A higher risk of major bleeding has been reported in the similar ATLAS ACS-2 trial (21) where again ACS patients (without AF) were randomized to either DAPT or TT of aspirin and clopidogrel plus the NOAC rivaroxaban, which was given at two doses of 2.5 mg (RR 3.46; 95% CI 2.08-5.77) and 5 mg (RR 4.47; 95% CI 2.71-7.36) twice daily. Because the doses of rivaroxaban used in the ATLAS ACS-2 trial (21) correspond to one-quarter and one-half of the dose of 20 mg daily tested in the ROCKET AF trial (5) for the prevention of stroke/systemic embolism in AF patients, reliable considerations about the true safety of TT of aspirin, clopidogrel and standard AF dose of rivaroxaban compared to DAPT cannot be made. Also, because of the so-called "thrombin paradox", according to which thrombin can both promote and inhibit coagulation depending on its concentration (as depicted by a U-curve) (22), a further increase in the risk of bleeding with standard AF dose of rivaroxaban compared to the low doses tested in the ATLAS ACS-2 trial (21) may not necessarily be expected. Whether on the other hand, TT of aspirin, clopidogrel and rivaroxaban 2.5 mg twice daily is safe (and effective) in AF patients undergoing PCI-S is currently being evaluated in the randomized, multi-center PIONEER AF trial (23).

Finally supporting the consistency of about a 2.5 increase in RR of clinically significant bleeding with TT of NOAC, aspirin and clopidogrel compared to DAPT alone, are the results of a meta-analysis where more than 26.000 patients enrolled in randomized, placebo-controlled clinical trials comparing DAPT to TT of aspirin and clopidogrel plus a NOAC (either factor Xa inhibitor rivaroxaban, apixaban and darexaban or direct thrombin inhibitor dabigatran) after an ACS, were evaluated (RR 2.34; 95% CI 2.06-2.66) (18) (Table 2).

3. CHOICE AND MANAGEMENT OF THE ANTICOAGULANT

It has been advocated that warfarin should be the preferred agent when the indication for OAC arises in patients on DAPT (24, 25). This is because the experience and the evidence regarding

TT with warfarin rather than a NOAC as OAC are larger, as are the experience and the evidence regarding OAC with warfarin in general. The availability of a specific antidote, namely vitamin K, and established non-specific reversal agents, including prothrombin complex concentrates, recombinant factor VIIa, and fresh frozen plasma, are additional elements in support of warfarin as the preferential OAC. Warfarin however, requires several days before being effective, so that it may be questionable whether to start an anticipated short course of warfarin when a NOAC has been identified as the best option for long-term treatment. Also, it should not be overlooked that the prolonged induction phase of OAC with warfarin is associated with an increased risk of bleeding (26).

3.1 Bleeding and reversal agents

Recent data from clinical trials show that the use of antidotes and reversal agents in response to major bleeding during OAC with warfarin is limited, and nonetheless the outcome is generally favorable (27, 28). In the same (27, 28), as well as another (29), dataset from the real world, a similar favorable outcome of major bleeding has also been shown for all available NOACs, in spite of the current lack of a specific antidotes. While these latter are currently in development (30), the data mentioned above, as well as the short half-life of NOACs allowing for a nearly complete disappearance of the OAC effect within about 48 hours of discontinuation (provided that the renal function is normal) (31), apparently make the antidote question a less major issue.

3.2 Warfarin or NOACs

Based on all the above, the choice of OAC (i.e., with warfarin or NOAC) to be combined with aspirin and clopidogrel in a TT regimen should generally be guided by the same considerations made for the choice of OAC in general. Thus, the individual risk of stroke and

bleeding (as estimated by the CHA_2DS_2-VASc and HAS-BLED score, respectively) (32), renal function and associated diseases, as well as the anticipated quality of OAC with warfarin (i.e., the time the patient is likely to spend with the INR within the therapeutic range, as estimated by the SAMe-TT_2R_2 score) (33, 34), should be taken into account when choosing between warfarin and a NOAC (Table 3), largely regardless of the fact that OAC is going to be combined with DAPT. Indeed, such strategy is endorsed in the recent ESC Guidelines on Myocardial Revascularization (35).

The question then, is whether a specific NOAC should be preferred. Whereas all currently available NOACs have been shown to be at least as effective and safe as warfarin in patients with AF (4-6) (Table 1), two relevant issues, namely the associated risk of myocardial infarction and gastrointestinal bleeding, need to be taken into account.

3.3 Myocardial infarction and gastrointestinal bleeding

In clinical trials, dabigatran (either 110 or 150 mg twice daily) was shown to be associated with an approximate 30% increase in the incidence of myocardial infarction compared to warfarin (4, 36, 37) (Table 4). Nonetheless, such effect, which may be attributed to the recognized cardioprotective action of warfarin (38), appeared not to have a significant impact on prognosis (36). Also, subsequent real-world data disproved the finding of an increased incidence of myocardial infarction, which instead was (significantly) reduced (39, 40). At present therefore, the fear of a higher risk of myocardial infarction with dabigatran as compared to rivaroxaban and apixaban should not be a factor for the selection of a NOAC rather than another in patients on DAPT after PCI-S who also need OAC.

Whereas currently available NOACs taken together increase the risk of gastrointestinal bleeding compared to warfarin (41), differences in this regard have been reported in clinical trials for the individual NOACs and doses (4-6) (Table 4). In particular, as compared to warfarin the use

of dabigatran 110 mg and apixaban show a neutral effect on the incidence of major gastrointestinal bleeding, which on the contrary is significantly increased with dabigatran 150 mg and rivaroxaban (4-6) (Table 4). Available real-world data confirm that compared to warfarin the incidence of gastrointestinal bleeding is decreased with dabigatran 110 mg and increased with dabigatran 150 mg (39, 40). Because the gastrointestinal tract is the most frequent site of bleeding in patients on TT after PCI-S, the individual NOAC showing (in the absence however, of direct comparisons) the greatest safety with regard to this specific aspect should be considered when choosing the agent to be added to DAPT.

3.4 Considerations for practice

In accordance with what discussed above, dabigatran at the reduced dose of 110 mg twice daily appears the most valuable OAC option to be added to DAPT, provided that the patient displays no features of increased risk of bleeding, and thus is <75 years old, is not underweight (i.e., >60 kg), has normal or only mildly impaired renal function (i.e., creatinine clearance >50 ml/min), and has no history of previous bleeding. In AF patients, dabigatran 110 mg twice daily, has been shown as effective as and significantly safer than warfarin regarding the incidence of stroke/systemic embolism and major bleeding, respectively (4) (Table 1), comparably safe as warfarin regarding the incidence of gastrointestinal bleeding (4) (Table 4), and associated with an increased risk of major bleeding when combined to DAPT comparable to that of any combination of OAC plus DAPT (19) (Table 2).

As an alternative, apixaban 5 mg twice daily might be considered. Such regimen has been shown in AF patients to be significantly more effective and safer than warfarin regarding the incidence of stroke/systemic embolism and major bleeding, respectively (6) (Table 1), and comparably safe as warfarin regarding the incidence of gastrointestinal bleeding (6) (Table 4), and

to be associated, albeit in a population of ACS patients without AF (17), to an increased risk of major bleeding comparable to that observed with any combination of OAC plus DAPT (Table 2).

The options of reduced-dose apixaban 2.5 mg twice daily and rivaroxaban 15 mg once daily, which have been tested in AF clinical trials as dose adjustments based on patient characteristics (6, 42), seem less suitable. In the absence of factors increasing the risk of bleeding, and particularly renal dysfunction, the net clinical benefit (i.e., the combined incidence of MACCE and major bleeding) of the above reduced-dose regimens appears uncertain. Whereas in fact, the safety might likely be increased, the efficacy on stroke/systemic embolism prevention might be insufficient (possibly due to the rapid renal clearance of the drug, as it has been hypothesized for the results observed with edoxaban in AF patients with normal renal function enrolled in the ENGAGE AF-TIMI 48 trial) (43, 44). Of note however, the anticipated weaker effect on the prevention of stroke/systemic embolism exerted by the reduced doses of apixaban and rivaroxaban might benefit from the additive effect of DAPT, which reduces the risk of stroke/systemic embolism by approximately 30% compared to placebo (45).

In patients at increased risk of bleeding, including those aged >75 years and/or underweight (i.e., < 60 kg) and/or moderate renal impairment (i.e., creatinine clearance 30-50 ml/min) and/or history of previous bleeding, apixaban at the reduced dose of 2.5 mg twice daily appears the most suitable option. Such regimen, which was tested in a subgroup of patients at increased risk of bleeding (i.e., presence of ≥ 2 of the following: age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine ≥ 1.5 mg/dl) who were enrolled in the ARISTOTLE trial (6), showed no significant interaction as regards the overall results of a significant superior efficacy and safety of apixaban compared to warfarin on stroke/systemic embolism and major bleeding, respectively (6). As an alternative, rivaroxaban 15 mg once daily might be considered, essentially when the increased risk of bleeding is related to moderate renal impairment (i.e., creatinine clearance 30-50

ml/min). In such subgroup of AF patients enrolled in the ROCKET AF trial (5), reduced-dose rivaroxaban 15 mg once daily showed no significant interaction as regards the comparable efficacy and safety to warfarin on stroke/systemic embolism and major bleeding, respectively (42). Whether dabigatran at the reduced dose of 75 mg twice daily, which is currently approved only in the U.S.A. for patients with severe renal failure (i.e., creatinine clearance 15-30 ml/min), might be an option for patients on DAPT who are at increased risk of bleeding, is at present undetermined. Albeit approved in the absence of clinical data, and based only on pharmacokinetic modeling (46), initial real-world evidence suggests that such regimen, apparently even when used in the absence of severe renal failure, may indeed have a favorable efficacy and safety profile (40).

Finally, in patients at increased risk of bleeding who are on DAPT after PCI-S and also require OAC, standard adjusted-dose warfarin therapy targeted to a reduced INR of 2.0-2.5 may be considered.

A practical algorithm for the selection of OAC in AF patients on DAPT after PCI-S is outlined in Fig. 2.

4. CONCLUSIONS

While acknowledging that adequate evidence is lacking, and unanswered questions still remain when translating clinical trials to practice (47, 48), NOACs might nonetheless be considered as the preferred OAC to be added to DAPT in patients recently submitted to PCI-S who develop AF. Because of the differences in the individual safety profiles, the NOAC, and dose, associated with the lowest bleeding rate, especially at the gastrointestinal tract (which is the site most frequently affected in patients on TT), should be carefully selected. Further adjustment in the choice of NOAC and dose should be considered in the patient at increased risk of bleeding. Whether the dual combination of NOAC and one antiplatelet agent, namely the newer and more potent $P2Y_{12}$-

receptor inhibitors ticagrelor and prasugrel, may have a more favorable net clinical benefit compared to TT, is as yet undetermined and therefore not recommended. Ongoing clinical trials are addressing this issue (23, 49).

REFERENCES

1. Lip GY, Windecker S, Huber K, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J 2014; 35:3155-3179
2. Agewall S, Cattaneo M, Collet JP, et al.; ESC Working Group on Cardiovascular Pharmacology and Drug Therapy and ESC Working Group on Thrombosis. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. Eur Heart J 2013; 34:1708-1713
3. Schulman S. New oral anticoagulant agents - general features and outcomes in subsets of patients. Thromb Haemost 2014; 111:575-582
4. Connolly SJ, Ezekowitz MD, Yusuf S, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med2009; 361:1139-1151
5. Patel MR, Mahaffey KW, Garg J, et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883-889
6. Granger CB, Alexander JH, McMurray JJ, et al.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365:981-992

7. Rubboli A, Faxon DP, Airaksinen KE, et al. The optimal management of patients on oral anticoagulation undergoing coronary artery stenting. The 10th anniversary overview. Thromb Haemost 2014; 112;1080-1087
8. Zhao HJ, Zheng ZT, Wang ZH, et al. "Triple therapy" rather than "triple threat": a meta-analysis of the two antithrombotic regimens after stent implantation in patients receiving long-term oral anticoagulant treatment. Chest 2011; 139:260-267
9. Singh PP, Singh M, Bedi U, Molnar J, Arora R, Khosla S. Safety and efficacy of triple antithrombotic therapy after percutaneous coronary intervention in patients needing long-term anticoagulation. Ther Adv Cardiovasc Dis 2011; 5:23-31
10. Andrade JG, Deyell MW, Khoo C, Lee M, Humphries K, Cairns JA. Risk of bleeding on triple antithrombotic therapy after percutaneous coronary intervention/stenting: a systematic review and meta-analysis. Can J Cardiol 2013; 29:204-212
11. Brulotte S, Sénéchal M, Poirier P, et al. Safety of the cardiac triple therapy: the experience of the Quebec Heart Institute. Can J Cardiol 2007; 23 Suppl B:80B-83B
12. Olson KL, Delate T, Johnson SG, Wilson ED, Witt DM. Incidence of hemorrhage among anticoagulated patients receiving antiplatelet therapy after percutaneous coronary intervention. J Thromb Thrombolysis 2010; 29:316-321
13. Sambola A, Ferreira-González I, Angel J, et al. Therapeutic strategies after coronary stenting in chronically anticoagulated patients: the MUSICA study. Heart 2009; 95:1483-1488
14. Nikolsky E, Mehran R, Dangas GD, et al. Outcomes of patients treated with triple antithrombotic therapy after primary percutaneous coronary intervention for ST-elevation myocardial infarction (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI] trial). Am J Cardiol 2012; 109:831-838

15. Rubboli A, Magnavacchi P, Guastaroba P, et al. Antithrombotic management and 1-year outcome of patients on oral anticoagulation undergoing coronary stent implantation (from the Registro Regionale Angioplastiche Emilia-Romagna Registry). Am J Cardiol 2012; 109:1411-1417
16. Rubboli A, Saia F, Sciahbasi A, et al.; WARfarin and Coronary STENTing (WAR-STENT) Study Group. Outcome of patients on oral anticoagulation undergoing coronary artery stenting: data from discharge to 12 months in the Warfarin and Coronary Stenting (WAR-STENT) Registry. J Invasive Cardiol 2014; 26:563-569
17. Alexander JH, Lopes RD, James S, et al.; APPRAISE-2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011; 365:699-708
18. Oldgren J, Wallentin L, Alexander JH, et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. Eur Heart J 2013; 34:1670-1680
19. Dans AL, Connolly SJ, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation 2013; 127:634-640
20. ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartanfor prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006; 367:1903-1912
21. 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; 366:9-19
22. Bassand JP. Novel oral anticoagulants in acute coronary syndrome: re-evaluating the thrombin hypothesis. Eurointervention 2014; 9:1333-1341

23. Gibson CM, Mehran R, Bode C, et al. An open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin k antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention (PIONEER AF-PCI). Am Heart J 2015; 169:472-478
24. Palareti G, Ageno W, Ferrari A, et al. Clinical management of rivaroxaban-treated patients. Expert Opin Pharmacother 2013; 14:655-667
25. Ahrens I, Bode C, Zirlik A. Anticoagulation during and after acute coronary syndrome. Hamostaseologie 2014; 34:72-77
26. Palareti G, Cosmi B. Bleeding with anticoagulation therapy - who is at risk, and how best to identify such patients. Thromb Haemost 2009; 102:268-278
27. Majeed A, Hwang HG, Connolly SJ, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation 2013; 128:2325-2332
28. Held C, Hylek EM, Alexander JH, et al. Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. Eur Heart J 2014; Dec 12. pii: ehu463
29. Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood 2014; 124:955-962
30. Gomez-Outes A, Suarez-Gea ML, Lecumberri R, Terleira-Fernandez AI, Vargas-Castrillon E. Specific antidotes in development for reversal of novel anticoagulants: a review. Recent Pat Cardiovasc Drug Discov 2014; 9:2-10
31. Siegal DM, Crowther MA. Acute management of bleeding in patients on novel oral anticoagulants. Eur Heart J 2013; 34:489-500

32. Camm AJ, Lip GY, De Caterina R, et al.; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33:19-47

33. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of oral anticoagulation control among patients with atrial fibrillation on warfarin. The SAMe-TT_2R_2 score. Chest 2013; 144:1555-1563

34. Abumuaileq RR, Abu-Assi E, Raposeiras-Roubin S, et al. Evaluation of SAMe-TT_2R_2 risk score for predicting the quality of anticoagulation control in a real-world cohort of patients with non-valvular atrial fibrillation on vitamin-K antagonists. Europace 2015 Feb 5. pii: euu353

35. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014; 35:2541-2619

36. Hohnloser S, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized evaluation of long-term anticoagulation therapy) trial. Circulation 2012; 125:669-76

37. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events. Meta-analysis of noninferiority randomized controlled trials. Arch Intern Med 2012; 172:397-402

38. Verheugt FW. Long-term oral anticoagulation in patients with coronary disease, and future developments. Curr Opin Cardiol 2008; 23:315-319

39. Larsen TB, Rasmussen LH, Skjøth F, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation. A prospective nationwide cohort study. J Am Coll Cardiol 2013; 61:2264-2273

40. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation 2015; 131:157-164

41. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ETTL. New oral anticoagulants increase the risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology 2013; 145:105-112

42. Fox KA, Piccini JP, Wojdyla W, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 2011; 32:2387-2394

43. Giugliano RP, Ruff CT, Braunwald E, et al.; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369:2093-2104

44. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugs/AdvisoryCommittee/UCM20704.pdf

45. Alberts MJ, Eikelboom JW, Hankey GJ. Antithrombotic therapy for stroke prevention in non-valvular atrial fibrillation. Lancet Neurol 2012; 11:1066-1081

46. Beasley BN, Unger EF, Temple R. Anticoagulant options – why the FDA approved a higher but not a lower dose of dabigatran. N Engl J Med 2011; 364;1788-1790

47. Hylek EM, Ko D, Cove CL. Gaps in translation from trials to practice: non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation. Thromb Haemost 2014; 111:783-788

48. Chan NC, Paikin JS, Hirsh J, Lauw MN, Eikelboom JW, Ginsberg JS. New oral anticoagulants

for stroke prevention in atrial fibrillation: impact of study design, double counting and unexpected findings on interpretation of study results and conclusions. Thromb Haemost 2014; 111:798-780

49. US National Institutes of Health, ClinicalTrials.gov. Evaluation of dual therapy with dabigatran vs. triple therapy with warfarin in patients with AF who undergo PCI with stenting (RE-DUAL PCI). http//clinicaltrials.gov/ct2/show. Accessed August 14, 2014

LEGEND OF FIGURE

Figure 1. Clinical contexts from which evidence regarding triple therapy of OAC, aspirin and clopidogrel is derived.

OAC = oral anticoagulation; AF = atrial fibrillation, ACS = acute coronary syndrome; PCI-S = percutaneous coronary intervention with stent

Figure 2. Suggested algorithm for the selection of OAC, and dose, to be combined with DAPT in patientsrecently submitted to PCI-S who develop AF.

DAPT = dual antiplatelet therapy of aspirin and clopidogrel; AF = atrial fibrillation; PCI-S = percutaneous coronary intervention with stent; CrCl = creatinine clearance; INR = International Normalized Ratio; BID = twice daily

[a] if ongoing, $P2Y_{12}$-receptor inhibitor prasugrel or ticagrelor should be interrupted and switching to clopidogrel performed

[b]as an alternative, rivaroxaban 15 mg once daily may be considered (essentially in the presence of moderate renal impairment, i.e., creatinine clearance 30-50 ml/min)

Figure 1

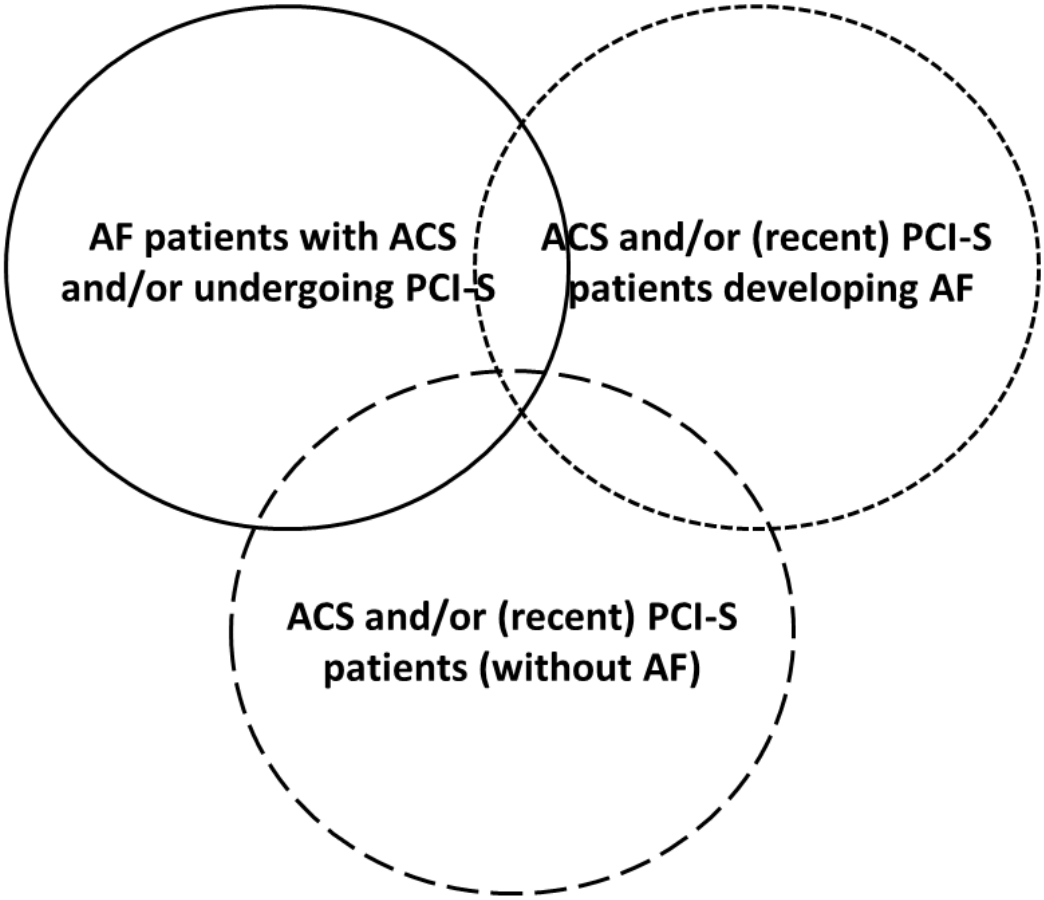


Figure 2

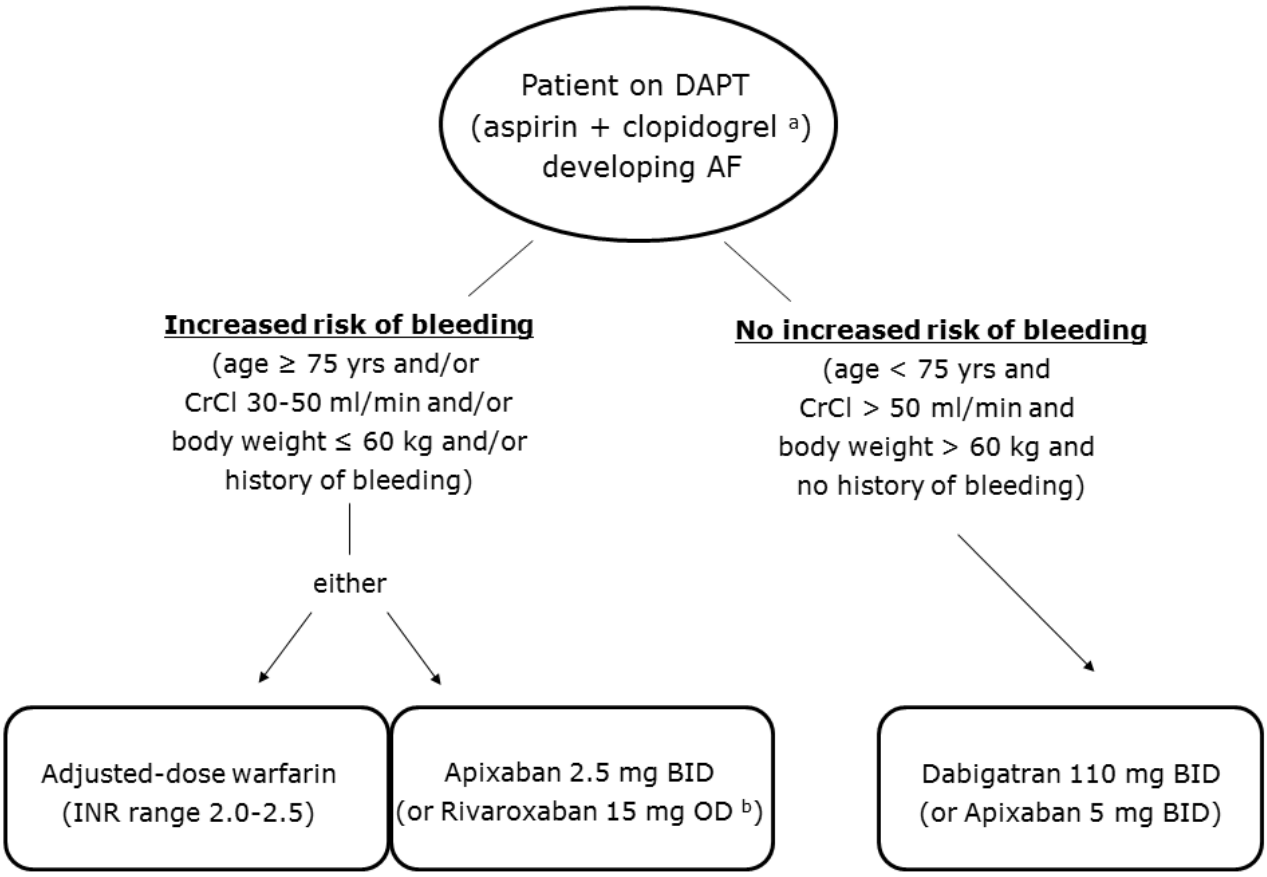


Table 1. Relative risk (95% Confidence Interval) of major clinical outcomes with NOACs vs. warfarin in AF randomized clinical trials.

Study	*NOAC*	*Stroke/Systemic embolism*	*Major Bleeding*	*ICH*
RE-LY (4)	Dabigatran 110 mg BID	0.91 (0.74-1.11)[a]	0.80 (0.69-0.93)[d]	0.31 (0.20-0.47)[e]
	Dabigatran 150 mg BID	0.66 (0.53-0.82)[a b]	0.93 (0.81-1.07)	0.40 (0.27-0.60)[e]
ROCKET AF (5)	Rivaroxaban 20 mg OD	0.88 (0.74-1.03)[a]	1.04 (0.90-1.20)	0.67 (0.47-0.93)[f]
ARISTOTLE (6)	Apixaban 5 mg BID	0.79 (0.66-0.95)[c]	0.69 (0.60-0.80)[e]	0.42 (0.30-0.58)[e]

[a]p<0.001 for non-inferiority; [b]p<0.001 for superiority;[c]p=0.01; [d]p = 0.03; [e]p<0.001; [f]p=0.02

AF = atrial fibrillation; BID = twice daily; ICH = intracranial hemorrhage; NOAC = non vitamin K-antagonist oral anticoagulant; OD = once daily

Table 2. Relative risk of major bleeding with TT of oral anticoagulant (either VKA or NOAC), aspirin and clopidogrel vs. DAPT of aspirin and clopidogrel in various studies.

Author/Study	*Type of study*	*OAC*	*N. of patients*	*Population*	*RR*[a]	*95% CI*
Zhao HJ et al. (8)	Meta-analysis	VKA	1996	OAC	2.12	1.05-4.29
Singh PP et al. (9)	Meta-analysis	VKA	1482	OAC	2.74	1.08-6.98
Andrade JG et al. (10)	Meta-analysis	VKA	2499 [b]	OAC	2.87	1.47-5.62
Average					***2.57***	
Brulotte S et al. (11)	Cohort, retrospective	VKA	183	OAC	1.44	0.13-15.53
Olson KL et al. (12)	Cohort, retrospective	VKA	175	OAC	4.84	2.38-9.85
MUSICA (13)	Registry, prospective	VKA	405	OAC	3.49	0.46-26.48
HORIZONS-AMI (14)	RCT [c]	VKA	3320	OAC	2.63	1.69-4.09
Rubboli A et al. (15)	Cohort, retrospective	VKA	632	OAC	2.50	0.49-12.58
WAR-STENT (16)	Registry, prospective	VKA	401	OAC	1.73	0.23-12.85
Average					***2.77***	
APPRAISE-2 (17)	RCT	NOAC [d]	7392	ACS	2.48	1.72-3.58
Oldgren J et al. (18)	Meta-analysis	NOAC [e]	26731	ACS	2.34 [f]	2.06-2.66
Average					***2.41***	
Overall average					***2.65***	

[a] as reported in the original study or calculated as: a/(a+b) divided by c/(c+d), where a and b are the number of patients with and without major bleeding, respectively in the TT group, and c and d the number of patients with and without major bleeding, respectively in the DAPT group

[b] on TT only

[c] post-hoc analysis

[d] apixaban

[e] apixaban, darexaban, rivaroxaban and dabigatran

[f] major and non-major clinically relevant bleeding

CI = Confidence Interval; DAPT = dual antiplatelet therapy; NOAC = non vitamin K-antagonist oral anticoagulant; RCT = randomized clinical trial; RR = relative risk; TT = triple therapy; VKA = vitamin K-antagonist

Table 3. Suggestions regarding the choice of OAC in AF patients based on currently recommended scores for risk stratification (1, 32-34).

Score	*Points*	*Interpretation*	*Suggestions*
CHA_2DS_2-VASc	0	Low risk of stroke	No antithrombotic therapy
	≥ 1	Moderate-high risk of stroke	OAC (with either warfarin or NOACs)
HAS-BLED	0-2	Low-moderate risk of bleeding	Consider either warfarin or NOACs
	≥ 3	High risk of bleeding	Preferably consider NOACs (associated with less bleeding than warfarin)
SAMe-TT_2R_2	0-1	High TTR (> 65-70%) on warfarin likely	Consider either warfarin or NOACs
	≥ 2	High TTR (> 65-70%) on warfarin unlikely	Preferably consider NOACs

CHA_2DS_2-VASc: ***C***ongestive heart failure 1 point, ***H***ypertension 1 point, ***A***ge (≥ 75 years) 2 points, ***D***iabetes 1 point, previous ***S***troke 2 points, ***V***ascular disease (previous myocardial infarction, peripheral artery disease, aortic plaque) 1 point, ***A***ge 65-74 years 1 point, ***S***ex category (female) 1 point

HAS-BLED: ***H***ypertension (systolic blood pressure > 160 mmHg) 1 point, ***A***bnormal renal (chronic dialysis or renal transplantation or serum creatinine ≥ 200 µmol/L) and liver disease (chronic hepatic disease or biochemical evidence of significant hepatic derangement) 1 point each, previous ***S***troke 1 point, ***B***leeding (history of and/or predisposition to) 1 point, ***L***abile INRs (TTR < 60%) 1 point, ***E***lderly (age > 65 years) 1 point, ***D***rugs (concomitant antiplatelets, non-steroidal anti-inflammatory drugs) or alcohol 1 point each

SAMe-TT_2R_2: ***S***ex (female) 1 point, ***A***ge (< 60 years) 1 point, ***M***edical history (≥ 2 of: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease) 1 point, ***T***reatment (interacting drugs, such as amiodarone for rhythm control) 1 point, ***T***obacco (within 2 years) 2 points, ***R***ace (nonwhite) 2 points

AF = atrial fibrillation; NOAC = non vitamin-K oral anticoagulants; OAC = oral anticoagulation; TTR = Time in Therapeutic Range

Table 4. Relative risk (95% Confidence Intervals) of myocardial infarction and gastrointestinal bleeding with NOACs vs. warfarin in AF randomized clinical trials.

Study	*NOAC*	*Myocardial Infarction*	*Gastrointestinal Bleeding*
RE-LY (4)	Dabigatran 110 mg BID	1.35 (0.98-1.87)	1.10 (0.86-1.41)
	Dabigatran 150 mg BID	1.38 (1.00-1.91) [a]	1.50 (1.19-1.89) [b]
ROCKET AF (5)	Rivaroxaban 20 mg OD	0.81 (0.63-1.06)	1.60 (1.29-1.98) [b]
ARISTOTLE (6)	Apixaban 5 mg BID	0.88 (0.66-1.17)	0.89 (0.70-1.15)

[a] p=0.048; [b] p<0.001

AF = atrial fibrillation; BID = twice daily; NOACs = non vitamin K-antagonist oral anticoagulant; OD = once daily

HIGHLIGHTS

- There is consensus on the antithrombotic therapy for AF patients undergoing PCI
- There is uncertainty on the antithrombotic therapy for PCI patients developing AF
- The risk of bleeding with triple therapy is comparable regardless of type of OAC
- NOACs might be selected as the preferred OAC to be combined in triple therapy
- The dose of selected NOAC should be individualized based on patient characteristics