

Management of acute coronary syndrome in patients with non-valvular atrial fibrillation: results of the European Heart Rhythm Association Survey

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Management of patients with non-valvular atrial fibrillation (AF) presenting with an acute coronary syndrome (ACS) may be particularly challenging. Given the lack of sound evidence-based recommendations for the management of such patients, the aim of this European Heart Rhythm Association survey was to provide an insight into current practice in Europe regarding management of these patients. Overall, 41 centres submitted a valid response. The majority of respondents were university hospitals (85%). The survey has shown that the principal aspects of the European Society of Cardiology guidelines on the management of AF, and those on ACS, have been adopted. The survey highlights two important areas of uncertainty regarding the optimal composition and duration of antithrombotic therapy with multiple drugs and the optimal regimen(s) of novel oral anticoagulants in patients with AF and ACS.

Keywords

Atrial fibrillation • Acute coronary syndrome • Anticoagulation • Novel oral anticoagulants • Dual antiplatelet therapy • Triple therapy • Guidelines • EP Wire • EHRA survey

Introduction

Management of patients with non-valvular atrial fibrillation (AF) and an acute coronary syndrome (ACS), either STEMI (ST-elevation myocardial infarction) or a NSTEMI-ACS (non-ST-segment elevation ACS, including unstable angina and myocardial infarction), may be particularly challenging. Most AF patients would be taking oral anti-coagulant therapy for stroke prevention,¹ and various antithrombotic drugs have to be added to facilitate the restoration of coronary flow and to reduce the risk of recurrent ischaemic events, such as stent thrombosis.^{2,3} Such complex treatments inevitably increase risk of bleeding and must be carefully balanced.^{1–5} A multiplicity of choices, including new oral anticoagulants (NOACs) and antiplatelet drugs, may add to the complexity of clinical decision-making.

Existing guidelines for the management of patients with AF and ACS acknowledge considerable gaps in the high quality evidence regarding optimal long-term antithrombotic treatment strategies in

such patients and provide recommendations based mostly on expert consensus and small non-randomized trials (level of evidence C).^{2,3,6,7}

Given the lack of sound evidence-based recommendations, the aim of this survey conducted by the European Heart Rhythm Association (EHRA) was to provide an insight into current practice in Europe regarding treatment of patients with non-valvular AF presenting with an ACS.

Methods and results

Participating centres

This survey is based on a questionnaire sent via the internet to the EHRA electrophysiology research network centres. Overall, 47 centres responded, and 41 responses entered further analysis (there were 2 duplicates and 4 blank submissions); 4 respondents (9.8%) did not answer several questions, whereby we reported

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percentages for 37 respondents. Of 41 centres, 35 (85.4%) were university hospitals, with cardiac surgery available in 34 (82.9%); 25 centres (61.0%) perform >1000 percutaneous coronary interventions (PCIs) per year, while in 2 centres (4.9%) such procedures were not available; 10 centres (24.4%) previously managed >50 AF-ACS patients on NOACs and the same number of centres had no experience with such patients.

Acute management of ST-elevation myocardial infarction within an optimal timeframe for primary percutaneous coronary intervention in atrial fibrillation patients on oral anticoagulant therapy

Acute management strategies for STEMI are shown in *Figure 1A*. Overall, 38 centres (92.7%) would proceed with primary PCI on uninterrupted warfarin, 16 (39.0%) would do PCI without NOAC interruption, and 22 centres (53.7%) would temporarily discontinue NOAC therapy prior to PCI.

Periprocedural strategies for AF patients presenting with a STEMI are shown in *Figure 1B*. Overall, dual antiplatelet therapy (DAPT) was added to warfarin in 36 centres (87.5%), or to a NOAC in 33 centres (80.5%) ($\chi^2 = 24.3$, $P < 0.001$). The combination of prasugrel or ticagrelor plus aspirin was more commonly given on top of warfarin (nine centres, 21.9%) than in addition to NOACs (six centres, 14.6%). Thirty of 37 centres (81.1%) preferred a radial approach (16 centres only if the operator was adequately experienced). Bare-metal stents (BMSs) were preferred in 20 centres (54.1%), drug-eluting stents (DES) in 9 centres (24.3%), biodegradable stents in 2 (5.4%), and 6 centres (16.2%) had no specific preference.

Management strategies for a non-ST-segment elevation-acute coronary syndrome in atrial fibrillation patients on oral anticoagulant therapy

In the setting of a NSTEMI-ACS, 14 of the 37 centres (37.9%) routinely stopped any oral anticoagulant, 3 (8.1%) stopped only warfarin, 8 (21.6%) stopped only NOACs, and 12 centres (32.4%) did not routinely stop any oral anticoagulant therapy.

Preferred first-line pharmacotherapy options on the top of oral anticoagulant therapy are shown in *Figure 2A*. Overall, 31 of the 41 centres (75.6%) added DAPT on the top of an oral anticoagulant which included aspirin and clopidogrel in 25 centres (80.6%), while 6 centres (19.4%) used aspirin and prasugrel or ticagrelor. Regarding invasive therapy (*Figure 2B*), 31 of the 37 centres (87.8%) would consider acute and long-term risks of bleeding and choose particular treatment strategies.

Oral anticoagulation plus dual antiplatelet therapy (triple therapy) after primary percutaneous coronary intervention

Triple therapy was used in all AF patients after primary PCI in 15 of the 37 centres (40.6%), or only in patients at moderate-to-high thromboembolic risk in 22 centres (59.4%) [10 (27.0%) used triple therapy only if the risk of bleeding was acceptable and 6 centres (16.2%) only in such patients with DES]. Overall, 34 of the 37 centres

(91.9%) preferably combined aspirin and clopidogrel with warfarin, and 24 such centres (70.6%) would keep anticoagulation intensity within the lower half of therapeutic range [international normalized ratio (INR) 2.0–2.5]. Aspirin and clopidogrel were less frequently combined with NOACs: for such purpose, only 5 (13.5%) and 12 centres (32.3%) used dabigatran 150 mg or 110 mg twice daily (bid), respectively, 3 centres (8.1%) used rivaroxaban 20 mg once daily (od), 9 (24.3%) used rivaroxaban 15 mg od, 2 (5.4%) used apixaban 5 mg bid, and 9 (24.3%) used apixaban 2.5 mg bid. Indeed, 29 centres (78.4%) would not add any antiplatelet drug to dabigatran 150 mg, 23 (62.2%) to dabigatran 110 mg, 30 centres (81.1%) to rivaroxaban 20 mg, 25 (67.6%) to rivaroxaban 15 mg, 33 centres (89.2%) to apixaban 5 mg, and 26 (70.3%) to apixaban 2.5 mg.

Only five centres (13.5%) would combine prasugrel or ticagrelor plus aspirin with full-range therapeutic warfarin, while eight (21.6%) would use such therapy only if INR was 2.0–2.5. Three centres (8.1%) would combine such DAPT with dabigatran 150 mg bid, two (5.4%) with dabigatran 110 mg bid, four centres (10.8%) with rivaroxaban 20 mg od, two (5.4%) with rivaroxaban 15 mg od, two centres (5.4%) with apixaban 5 mg bid, and two (5.4%) with apixaban 2.5 mg bid.

After primary PCI, 31 of the 37 centres (83.8%) would continue triple therapy for at least 1 month for BMS and for at least 3–6 months for DES, while 6 (16.2%) always continue triple therapy for 9–12 months. After NSTEMI-ACS, 10 (27.0%) of the 37 centres would always continue with triple therapy for 12 months, 25 centres (67.6%) used triple therapy for 1 month for BMS and for 3–6 months for DES, and 2 centres (5.4%) continued with triple treatment indefinitely.

Dual therapy after an acute coronary syndrome in atrial fibrillation patients

Upon completing the course of triple therapy after primary PCI, 23 centres (62.2%) would continue dual therapy (i.e. an oral anticoagulant plus an antiplatelet drug) indefinitely, 8 (21.6%) used such treatment for up to 12 months after PCI, and 6 centres (16.2%) proceeded only with an oral anticoagulant. Dual therapy preferably included warfarin plus aspirin in 21 centres (56.8%) or a NOAC plus aspirin in 14 centres (37.8%), $P = 0.048$. Clopidogrel was combined with warfarin in 22 centres (59.5%), and with a NOAC in 11 (29.7%), $P = 0.014$. Prasugrel was combined with warfarin in six (16.2%) and with a NOAC in three centres (8.1%), $P = 0.421$, while five centres (12.2%) combined ticagrelor with warfarin, and four centres (10.8%) with a NOAC.

Oral anticoagulant therapy after an acute coronary syndrome in atrial fibrillation patients

Of the 37 centres, 24 (64.9%) would continue the same oral anticoagulant the patient had been taking before ACS, 11 centres (29.7%) would switch from NOACs to warfarin, and 2 centres (5.4%) would switch from warfarin to a NOAC. If a NOAC had been temporarily discontinued prior to primary PCI, 6 centres (16.2%) re-initiated the drug immediately after parenteral anticoagulation is stopped, 11 (29.8%) within 24 h, and 16 centres (43.2%)

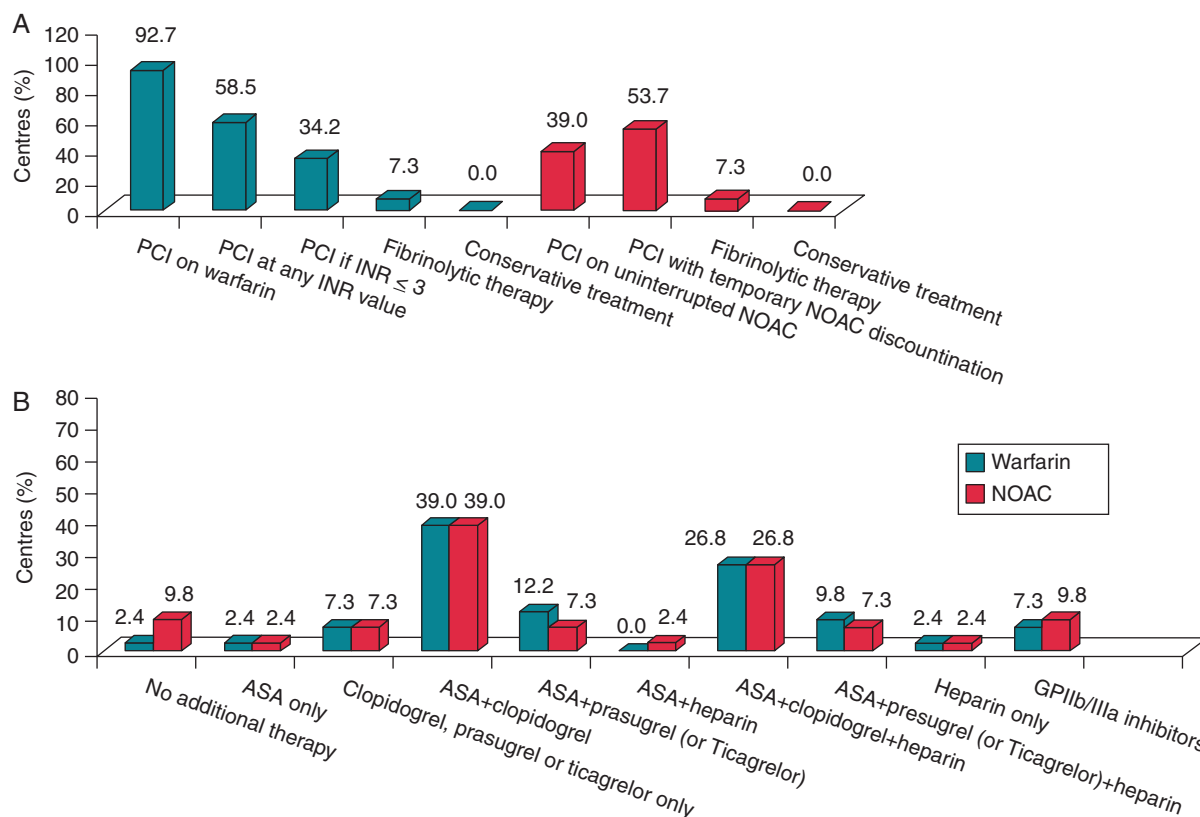


Figure 1 (A) Management strategies in AF patients presenting with a STEMI within an optimal timeframe for PCI. AF, atrial fibrillation; STEMI, acute myocardial infarction with ST-segment elevation; PCI, primary percutaneous coronary intervention; INR, international normalized ratio; NOAC, novel oral anticoagulant drug; ASA, aspirin. (B) Periprocedural management of AF patients presenting with a STEMI within an optimal timeframe for PCI. AF, atrial fibrillation; STEMI, acute myocardial infarction with ST-segment elevation; PCI, primary percutaneous coronary intervention; INR, international normalized ratio; NOAC, novel oral anticoagulant drug.

>24 h after PCI, while 4 centres (10.8%) switched from a NOAC to warfarin.

Risk assessment in atrial fibrillation patients presenting with an acute coronary syndrome

Bleeding risk was estimated using the HAS-BLED score in 32 of the 41 centres (78.0%), while 5 (12.2%) used thrombolysis in myocardial infarction (TIMI) score. For stroke risk assessment, 34 centres (82.9%) used the CHA₂DS₂-VASc score, while 8 centres (19.5%) used the CHADS₂ score. The risk of recurrent coronary ischaemic events was commonly estimated using GRACE, TIMI, or even CHA₂DS₂-VASc score in 13 (31.7%), 10 (24.4%), and 6 (14.6%) centres, respectively (Figure 3, online).

Discussion

This EP Wire survey provides some insights into the management of AF patients with ACS in Europe. However, the survey mostly reflects the clinical practice in university hospitals, and the low response rate is a limitation.

Acute management of ST-elevation myocardial infarction within an optimal timeframe for primary percutaneous coronary intervention

Almost all respondents opt for primary PCI, in line with current guidelines.² Most centres would perform primary PCI on therapeutic warfarin, and evidence suggest that such strategy is safe, without the need for bridging and additional periprocedural heparin.^{2,6} In contrast, there was heterogeneity in practice regarding the periprocedural use of NOACs. Optimal NOAC therapy for primary PCI is less evidence-based, and a recent EHRA practical guide on NOACs advocates a temporary periprocedural NOAC discontinuation and the use of additional parenteral anticoagulation (of note, parenteral anticoagulation was used in <25% of centres).⁸

Prior to primary PCI, almost all centres use DAPT on top of warfarin, while there is significant reluctance to use DAPT with NOACs. Not surprisingly, aspirin plus prasugrel (or ticagrelor) was less frequently used, particularly with NOACs. Although current STEMI guidelines generally favour periprocedural DAPT with prasugrel or ticagrelor, due to their faster onset of action, greater potency and proven superiority over clopidogrel,² these agents have not been

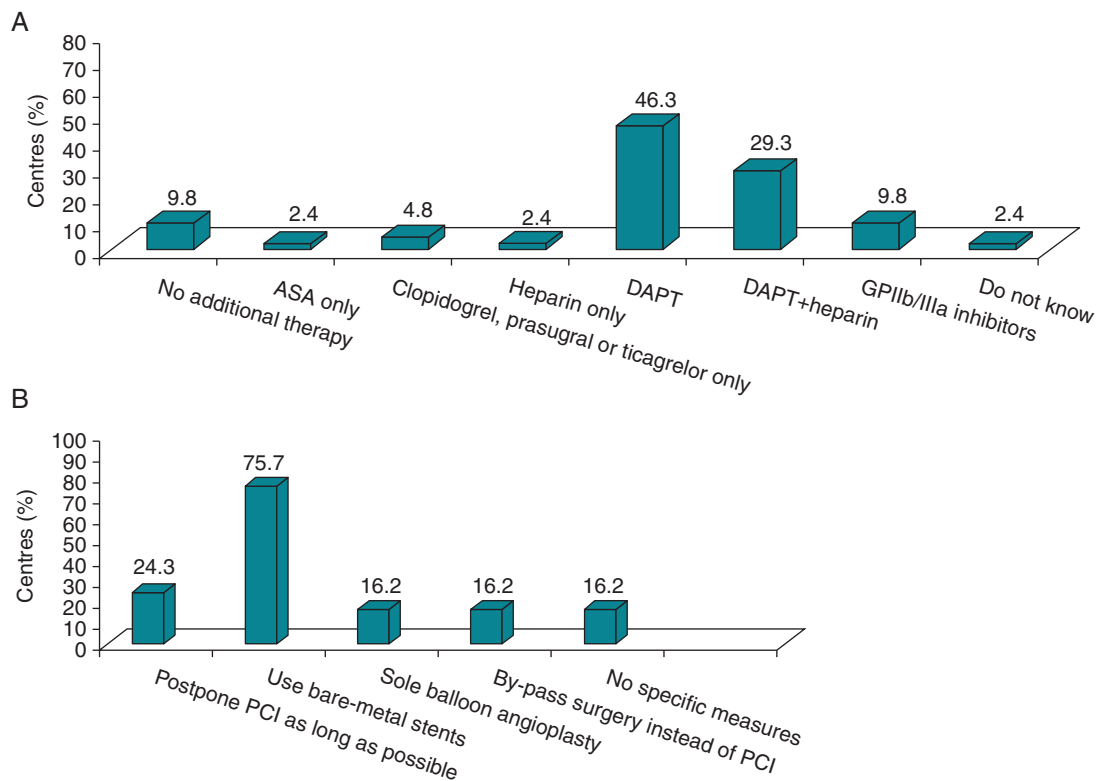


Figure 2 (A) Preferred first-line pharmacological therapies on top of oral anticoagulant therapy in AF patients presenting with a NSTEMI-ACS. AF, atrial fibrillation; NSTEMI-ACS, non-ST-segment elevation acute coronary syndrome; PCI, primary percutaneous coronary intervention; ASA, aspirin; DAPT, dual antiplatelet therapy. (B) Management strategies for AF patients on oral anticoagulant therapy presenting with a NSTEMI-ACS. AF, atrial fibrillation; NSTEMI-ACS, non-ST-segment elevation acute coronary syndrome; PCI, primary percutaneous coronary intervention.

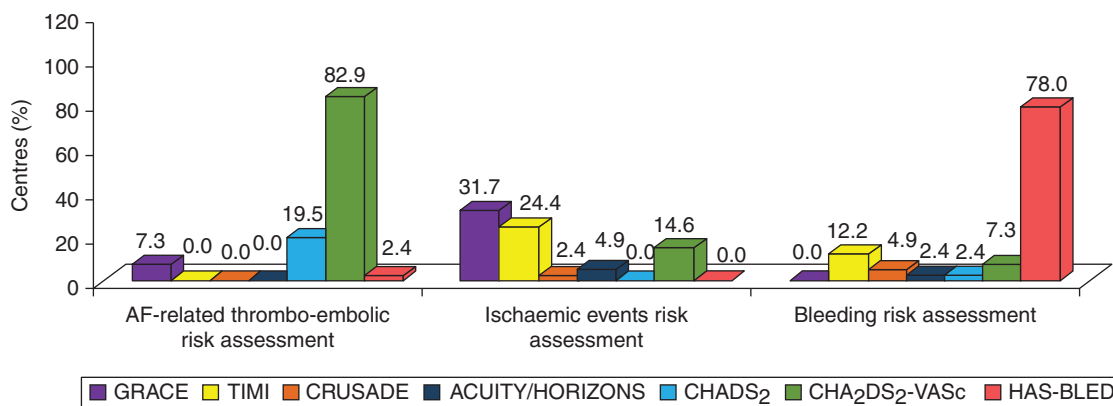


Figure 3 Preferred scores for risk assessment in AF patients presenting with an ACS.

properly evaluated with any oral anticoagulant therapy. Until more data are available, it may be prudent to avoid combining them with NOACs, particularly in the acute setting.⁸

Most centres used a radial approach and BMS, as recommended.^{2,3,6} If performed by an experienced operator, the radial

approach reduces the incidence of acute bleeding and a shorter course of triple therapy is required with BMS than with DES.^{2,3,6} A minority of respondents preferred fibrinolytic therapy over primary PCI. However, oral anticoagulant therapy is a relative contraindication to fibrinolysis; fibrinolysis could be used in patients on

NOACs only if the drug effect already waned (i.e. if appropriate coagulation tests do not exceed the upper limit of normal values).^{2,8}

Management strategies for a non-ST-segment elevation-acute coronary syndrome

The NSTEMI-ACS patients are highly heterogeneous group, and the recommended treatment strategies strongly depend on an individual patient risk profile.³ Continuation of warfarin is recommended in AF patients at moderate-to-high thrombo-embolic risk,⁶ while NOACs should be temporarily discontinued.⁸ However, more than one-third of centres routinely stopped any oral anticoagulant at presentation, and 22% centres stopped only a NOAC.

Whether NSTEMI-ACS patients undergo invasive treatment or not, DAPT is recommended immediately upon presentation.^{3,6} In general, ticagrelor is recommended in all-comers, with a few exceptions.³ In this survey, most respondents used DAPT in combination with oral anticoagulant therapy, preferably aspirin plus clopidogrel. While 16% of respondents had no specific invasive management strategy for AF patients, others used measures to reduce the risk of acute bleeding and/or the need for long-term triple therapy, as recommended.⁸

Oral anticoagulation plus dual antiplatelet therapy (triple therapy) after primary percutaneous coronary intervention

The benefits of triple therapy in AF patients at risk of both stroke and stent thrombosis may be counterbalanced by a substantial increase in the risk of serious bleeding during the treatment period.⁴ Until more data are available, current recommendations advocate triple therapy with warfarin (INR 2.0–2.5) and aspirin plus clopidogrel in AF patients at moderate-to-high thrombo-embolic risk, for the shortest possible treatment period (depending on the individual bleeding risk and the stent type).⁶ However, nearly half the centres used triple therapy in all AF patients after primary PCI. The efficacy and safety of DAPT only vs. triple therapy for PCI in AF patients at low-to-moderate stroke risk is under investigation (MUSICA-2; NCT01141153). Not surprisingly, almost all respondents preferably use the combination of warfarin (INR 2.0–2.5) with aspirin plus clopidogrel. Not so few centres would combine warfarin with aspirin plus prasugrel or ticagrelor, which is surprising given the lack of robust evidence on the safety of such combinations. Most of respondents would not use any DAPT with NOACs, and the rest would combine DAPT with the lower/reduced NOAC dose tested in the AF trials.

Emerging evidence suggests that aspirin might not be mandatory in patients treated with warfarin and clopidogrel.⁹ Although NOACs offer many advantages over warfarin, they have not been sufficiently studied in AF patients with an ACS. Rivaroxaban 2.5 mg bid has been recently approved by the European authorities for use in patients with recent ACS treated with aspirin and clopidogrel, but the efficacy of this regimen has not been tested in AF. The ongoing PIONEER AF-PCI trial (NCT01830543) will investigate the use of rivaroxaban and warfarin with various combinations of antiplatelet drugs (including prasugrel and ticagrelor) in patients with non-valvular AF undergoing PCI. The RE-DUAL PCI trial (not registered yet) will investigate

the use of dabigatran plus a single antiplatelet drug vs. conventional triple therapy in AF patients who underwent PCI.

The optimal duration of triple therapy after PCI in patients with an indication for oral anticoagulant therapy is under investigation (ISAR-TRIPLE; NCT00776633). In this survey, most respondents use triple therapy during 1 month for BMSs and during 3–6 months for DESs, as per current guidelines.^{2,3,6}

Dual therapy with an oral anticoagulant and an antiplatelet drug

Following a course of triple therapy after PCI, >60% of the respondents continued dual therapy indefinitely, in contrast to currently recommended life-long single oral anticoagulant after a course of triple and dual therapy in AF patients at moderate-to-high thrombo-embolic risk.⁶ Within dual therapy, the respondents preferred warfarin plus clopidogrel or aspirin over any other combination. However, clinical practice may change in the future, with growing clinical experience with NOACs and the availability of evidence from ongoing randomized trials.

Oral anticoagulant therapy after acute coronary syndrome in atrial fibrillation patients

Post ACS, 30% of centres often switched from NOACs to warfarin, possibly due to anticipation of prolonged dual therapy, impaired renal function, or the use of prasugrel or ticagrelor.⁸ Concerns have been raised over dabigatran, but careful analysis showed that the benefits of dabigatran far outweigh a non-significant increase in myocardial infarction compared with warfarin.¹⁰ Available data are insufficient to recommend switching to a particular NOAC because of ACS.⁸ Once the patient is stabilized (i.e. no need for additional invasive treatment), NOAC therapy can be restarted after safe discontinuation of parenteral anticoagulation.⁸

Risk assessment in atrial fibrillation patients presenting with an acute coronary syndrome

Increasing availability of various therapies will soon facilitate highly individualized treatment of AF patients with an ACS, which necessitates careful individual risk assessment. Most centres commonly used the CHA₂DS₂-VASc score for stroke risk assessment and the HAS-BLED score for bleeding risk assessment (the score has been validated in the PCI population).¹¹ Surprisingly, TIMI and CHA₂DS₂-VASc were often used to assess the risk of coronary events, although the guidelines recommended the GRACE score.³

Conclusions

This EP Wire survey shows that the principal aspects of the ESC guidelines on the management of AF, and those on ACS, are considered in the responding centres. However, the survey highlights two important areas of uncertainty in the management of AF patients with an ACS—first, the issue of optimal composition and duration of multiple antithrombotic treatment and second, the optimal regimen(s) of NOACs in treatment strategies for such patients.

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References

1. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–413.
2. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**:2569–619.
3. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2011;**32**:2999–3054.
4. Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen SL et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation* 2012;**126**:1185–93.
5. Bernard A, Fauchier L, Pellegrin C, Clementy N, Saint Etienne C, Banerjee A et al. Anticoagulation in patients with atrial fibrillation undergoing coronary stent implantation. *Thromb Haemost* 2013;**110**:560–8.
6. Lip GY, Huber K, Andreotti F, Arnesen H, Airaksinen KJ, Cuisset T et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting. *Thromb Haemost* 2010;**103**:13–28.
7. Marín F, Huber K, Lip GY. Antithrombotic therapy in atrial fibrillation and stent implantation: treatment or threats by the use of triple or dual antithrombotic therapy. *Thromb Haemost* 2013;**110**:623–5.
8. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;**15**:625–51.
9. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP 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**:1107–15.
10. Hohnloser SH, Oldgren J, Yang S, Wallentin L, Ezekowitz M, Reilly P 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.
11. Smith JG, Wieloch M, Koul S, Braun OO, Lumsden J, Rydell E et al. Triple antithrombotic therapy following an acute coronary syndrome: prevalence, outcomes and prognostic utility of the HAS-BLED score. *EuroIntervention* 2012;**8**:672–8.