Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: Similarities and dissimilarities between North America and Europe

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The optimal antithrombotic management of patients with atrial fibrillation (AF) who need permanent anticoagulation due to their increased thromboembolic risk but have an additional need for antiplatelet therapy has not been standardised in prior guidelines, because no prospective randomised studies with this topic have been performed in such patient populations. Accordingly, wide variability in practice and the lack of consensus regarding the best antithrombotic therapy for these patients is evident (1). These include a wide range of monotherapies (vitamin K antagonists [VKAs] or aspirin or clopidogrel), dual therapeutic approaches (aspirin or clopidogrel plus a VKA), or also triple therapy (all three agents).

The driving principle for choice of the respective antithrombotic strategies and duration of therapy is frequently the fear from increased bleeding hazards, which are sometimes perceived to be more important than the prevention of stroke and stent thrombosis plus distal embolisation. This topic has become even more complicated in the recent two years since the recommendations to use new anticoagulants in atrial fibrillation (AF) (e.g. dabigatran as replacement of VKAs, with rivaroxaban and apixaban soon to follow) or new antiplatelet agents in acute coronary syndromes (ACS) with or without percutaneous coronary intervention (PCI) (with prasugrel or ticagrelor as replacement of clopidogrel).

In this issue of *Thrombosis and Haemostasis*, a consensus document from North American experts has been published in order to support physicians in their decision-making processes (2). This document complements a recently published consensus document (which includes a systematic review of the literature) of the European Society of Cardiology (ESC) Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) (3). The latter as partially contributed to the recent European guidelines for management of AF (4).

**The North American view**

The focus of the North American consensus document (2) is exclusively on patients who are on oral anticoagulant therapy (OAC) for the treatment of non-valvular atrial fibrillation undergoing PCI, and does not cover other reasons for permanent anticoagulation, and also other considerations concerning the stent procedure itself (for example, the use of glycoprotein IIb/IIa blockers) are not specifically discussed. This consensus document focuses on practical treatment recommendations and discusses also potential future developments including the use of new antithrombotic agents in AF or ACS as well as new developments in coronary stenting.

Treatment recommendations following stent placement are based upon assessment of bleeding, thromboembolic risks of the individual patient, and include also the preferred site of vascular access, stent selection, and gastric protection. Indeed, the recommendations in this North American consensus document (2) are evidence-based and derived primarily from published data if available, but represent in the majority of cases expert opinion (level of evidence C classification) due to lack of prospective randomised studies and/or registries.

**Special considerations**

In patients with AF and PCI with stent implantation, there is a delicate balance between stroke prevention, stent thrombosis, recurrent cardiac ischaemia and major bleeding (especially intracranial haemorrhage). Based on current European guidelines (4), stratification for thromboembolic risk in AF is largely based on risk scoring systems, such as the CHADS2 score or even better (given the limitations of the CHADS2 score [5]), the CHA2DS2-VASc score (6, 7), while for bleeding risk assessment, the HAS-BLED score has been proposed as a simple validated tool to stratify bleeding risk (8).

Of note, the North American consensus document includes some very important considerations of high practical value: i) a paragraph about vascular access and procedural considerations points to the importance of choice of access site (preferably radial), PCI technique (pure balloon angioplasty can be considered in selected cases to avoid triple therapy) and specific stent type (bare metal stents, BMS, to be preferred unless specific anatomical situations and/or comorbidities (e.g. diabetes mellitus) force...
drug-eluting stent, DES, use). If DES are indicated, the use of second and third generation stents that afford a shorter duration of DAPT should be preferred over first generation stent products; ii) a recommendation to use proton pump inhibitors (PPIs) for the duration of antithrombotic combination therapy, whereby, the use of proton-pump inhibitors (PPIs) not interfering with bioactivation of clopidogrel (CYP2C19 activity) and clopidogrel-mediated effects (e.g. pantoprazole) should be considered in preference to those that are metabolised via CYP2C19 (9); and iii) whenever aspirin is used in combination with other antithrombotic agents a dose of 100 mg/day should not be exceeded.

Similarities and differences between North American and European recommendations

North American experts (2) recommend that in patients at low risk of stroke or embolism (CHADS2=0–1), dual antiplatelet therapy (DAPT) without warfarin is probably preferable, which is something not specifically addressed by Europeans who rather prefer DAPT only in patients with a CHADS2 score=0 (but triple therapy as soon as the CHADS2 score has increased to 1). Indeed, many patients with a CHADS2 score=1 may not be ‘low risk’ and would benefit from oral anticoagulation (OAC) (10).

Similar to the European approach, Faxon et al. (2) recommend in their consensus document to control international normalized ratio (INR) levels between 2 and 2.5 when patients are on triple therapy in order to reduce bleeding complications without an increase in major adverse cardiac events.

Although they clearly state that the risk of major bleeding in patients taking triple therapy increases at one year from 4% to 12%, and that limiting the duration of triple therapy when possible should be considered as a key step to reducing overall bleeding risk, the North American experts recommend a much longer duration of triple therapy compared to the European approach in patients with low/moderate bleeding risk but increased stent thrombosis and stroke risk: for example, in cases where BMS are used – triple therapy for at least six months (similar to Europe), then OAC + single antiplatelet therapy (aspirin or clopidogrel) for 12 months, then OAC monotherapy; in case DES are used – triple therapy for 12 months (six months in Europe). Here the wish to avoid thrombotic complications was higher whilst in Europe the concern for major bleeding complications and its sequelae was the main driving force, as demonstrated by a recent meta-analysis and position paper (11, 12).

Similar between North American and European recommendations is the recommendation that DES should be totally avoided (and BMS used) in patients with an increased bleeding risk and triple therapy should be limited to one month maximum followed by dual therapy (OAC + single antiplatelet therapy) up to 12 months.

Future developments

Importantly, the North American consensus paper includes a discussion about ongoing and future developments as the use of new oral anticoagulants in AF, of new antiplatelet agents in patients with ACS receiving stents, as well as new developments on the stent sector.

Dabigatran, an oral direct thrombin inhibitor that does not require laboratory monitoring of anticoagulation intensity, will increasingly be used to replace OAC in a significant number of AF patients, because it has been shown to better prevent stroke and systemic embolism in patients with AF compared to warfarin, with the higher dosage (150 mg BID), which has been approved in the USA (13). For combination therapy with antiplatelet agents, the lower dose (110 mg BID) seems to be more appropriate (14). However, this dose is not approved in the USA but is available in Canada and Europe. Other oral anticoagulants such as rivaroxaban and apixaban have also shown promising data and might soon become important competitors of dabigatran (15). Data on the combination of dabigatran (16) or apixaban (17) with dual antiplatelet therapy in patients with ACS suggest a substantial incidence of clinically relevant bleeding.

At the moment it is in general not advised to use the new antiplatelet agents prasugrel or ticagrelor in combination with OAC because of the lack of clinical data and the fear of increased bleeding rates. Finally, second generation (everolimus- or zotarolimus-eluting) or even biodegradable stents, which allow more rapid and complete re-endothelialisation, seem to reduce stent thrombosis to a minimum and therefore might potentially make duration of triple therapy shorter and reduce the overall hazard of severe bleeding.

Conclusion

Faxon et al. (2) have to be congratulated for an excellent review of the current knowledge including not only clear recommendations for clinical practice but also discussing potential future developments in a rapidly changing field. As outlined above, there are many similarities between the North American and European approach for the treatment of patients with AF who have undergone PCI with stent implantation based upon the estimation of the risk of stroke, stent thrombosis and major bleeding.

However, the North American experts recommend a more prolonged triple therapy regime in a subgroup of patients, as the main difference compared to European recommendations. The European perspective is partly supported by the recent EXCELLENT study, which suggests that some patients can stop clopidogrel after just six months following DES implantation (18). Nonetheless, the EXCELLENT study (using mainly everolimus DES) was not powered for hard clinical endpoints (death, myocardial infarction, or stent thrombosis) and target vessel failure rates were equivalent among non-diabetic patients treated with six- and 12-months of dual antiplatelet therapy. Also, patients with a CHADS2 score of 0–1 are not necessarily “low” whilst the CHA2DS2-VASc score is better than the CHADS2 score in identifying truly ‘low risk’ patients (7), who do not need triple therapy post-PCI/stenting (3); indeed, the net clini-
cal benefit (balancing stroke vs. intracranial haemorrhage) is only negative at a CHA2DS2-VASc score=0 (19).

Given the delicate balance between preventing thrombosis versus the risk of bleeding, the future will show, which of these different approaches (more efficacy or more safety) will lead to a better efficacy/safety outcomes. The biggest challenge for the near future, however, will be the implication of new anticoagulants and antiplatelet agents in the currently recommended antithrombotic combination strategies.

Conflict of interest
K. Huber has served as consultant and has received lecture fees from Bayer, Boehringer Ingelheim, BMS/Pfizer, AstraZeneca, and Eli Lilly/Daiichi Sankyo. J. Airaksinen has served in (national) advisory boards for Sanofi aventis, Boehringer Ingelheim, The Medicines Company, Boston Scientific and AstraZeneca. F. Marin has received research grants from Abbott Laboratories and Boston Scientific. G. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim and Sanofi Aventis. The other authors have no conflict of interest to declare.

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