Review Article

Neth Heart J (2020) 28 (Suppl 1):S19–S24
https://doi.org/10.1007/s12471-020-01446-6

Antithrombotic management of patients with atrial fibrillation—Dutch anticoagulant initiatives anno 2020

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Abstract In recent years, as more and more experience has been gained with prescribing direct oral anticoagulants (DOACs), new research initiatives have emerged in the Netherlands to improve the safety and appropriateness of DOAC treatment for stroke prevention in patients with atrial fibrillation (AF). These initiatives address several contemporary unresolved issues, such as inappropriate dosing, non-adherence and the long-term management of DOAC treatment. Dutch initiatives have also contributed to the development and improvement of risk prediction models. Although fewer bleeding complications (notably intracranial bleeding) are in general seen with DOACs in comparison with vitamin K antagonists, to successfully identify patients with high bleeding risk and to tailor anticoagulant treatment accordingly to mitigate this increased bleeding risk, is one of the research aims of recent and future years. This review highlights contributions from the Netherlands that aim to address these unresolved issues regarding the anticoagulant management in AF in daily practice, and provides a narrative overview of contemporary stroke and bleeding risk assessment strategies.

Keywords Atrial fibrillation · Anticoagulation · Registry · Adherence · Stroke and bleeding risk · Integrated care

Introduction

Substantial improvements have recently been made in the anticoagulant management of stroke prevention in atrial fibrillation (AF) [1]. These improvements are continuously needed as AF and AF-related complications such as stroke not only affect an ever-increasing number of patients worldwide, but also impose a great burden on healthcare expenditure [2, 3].

The introduction of direct oral anticoagulants (DOACs) for stroke prevention in AF was one of the major improvements in recent years. Although DOACs are increasingly being accepted and have recently replaced vitamin K antagonists (VKAs) as the preferred anticoagulant among new patients with AF [4–6], several key concerns with respect to patient management and the organisation of anticoagulant therapy care remain. For example, (i) non-adherence and non-persistence to DOACs, (ii) safety and efficacy of DOACs in specific patient groups (such as the frail elderly), (iii) adequate monitoring for comorbidities (e.g. heart failure), and (iv) the issue of who is responsible for the long-term anticoagulant control, are

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all remaining knowledge gaps in the antithrombotic management in patients with AF.

Another major effort to improve anticoagulant management in AF patients was the development of stroke and bleeding risk prediction models, which underline differences in stroke and bleeding risks between individual patients. In the past decade, several scores have been developed and validated, all with the aim to optimise the safety and appropriate use of anticoagulation therapy in AF [7–13]. However, despite all efforts and albeit suboptimal for prediction of stroke, only the CHA_2DS_2-VASc score is currently adopted in international AF guidelines [14–16]. Risk assessment strategies that implement *both* stroke and bleeding risk scores, on which a tailored individualised anticoagulant treatment plan could be based, such as with the ABC (Age, Biomarker, Clinical history) score, have been proposed but not implemented in international AF guidelines [17].

In this review, we highlight ongoing Dutch initiatives that address unresolved issues regarding anticoagulant management in AF in daily practice and we provide a narrative overview of contemporary stroke and bleeding risk assessment strategies.

Dutch initiatives

DUTCH-AF registry—inappropriate dosing, non-adherence and non-persistence to anticoagulants

In contrast to VKAs, DOACs do not require routine anticoagulation monitoring. As a result, concerns were raised about patient adherence and persistence to DOACs [18]. In other common chronic diseases, non-adherence occurs frequently and this obviously affects the course of disease negatively [19, 20]. In line with these findings, recent practice-based and insurance claims data have provided evidence that non-adherence and non-persistence to anticoagulant therapy occur in AF patients as well, with similar adverse effects on safety and efficacy outcomes [21–27].

Another issue related to prescribing DOACs is inappropriate dosing. Several retrospective studies and prospective registries have shown that inappropriate dosing (most often underdosing) of DOACs occurs frequently in 7 to 40% of AF patients [28–30]. This may possibly be associated with an increased risk for major adverse cardiac or bleeding events [28].

The aims of the ongoing DUTCH-AF registry (ZonMw project numbers 848050006 and 848050007) are to assess the effects of inappropriate dosing, non-adherence and non-persistence on AF-related clinical outcomes, such as stroke and bleeding, and to identify predictors of inappropriate dosing, non-adherence and non-persistence. Therefore, data on the anticoagulant management and clinical course of Dutch patients with newly diagnosed AF are being collected. This nationwide registry intends to enrol 6000 patients with a follow-up of at least 2 years. Data on patient demographics, relevant medical history, pattern and anticoagulant treatment of AF, and pharmacy medication dispensing data will be collected. Also, detailed information is being collected on AF-related adverse events such as bleeding, ischaemic events and AF-related hospitalisation. As of January 2020, over 3000 patients have been included.

A unique feature of DUTCH-AF is that a prospective study on dosing, non-adherence and non-persistence to anticoagulation therapy will be conducted simultaneously. A composite questionnaire regarding anticoagulation adherence and beliefs about drugs will be sent to a subset of patients to identify predictors of non-adherence. Finally, with this prospective study, DUTCH-AF aims to validate and refine currently applied bleeding risk assessment models, and to integrate stroke and bleeding assessment models.

FRAIL-AF—optimal anticoagulant in frail elderly AF patients

Based on the landmark DOAC randomised controlled trials (RCTs), current international guidelines recommend DOACs as the first choice of anticoagulation therapy in AF [14, 15, 31–34]. However, the positive findings on the efficacy and safety of DOACs may not be generalisable to frail elderly AF patients, as they were under-represented in these RCTs. Whilst being distinctly different than the general population, these patients often encounter difficulties with anticoagulant management and have a high risk for bleeding, stroke and unplanned hospitalisations [35, 36]. Factors such as multimorbidity, polypharmacy, insufficient vitamin K intake and an altered body composition (relatively less muscle mass and more fatty tissue) could contribute to the challenges in anticoagulant management in frail elderly AF patients [37]. Moreover, cognitive and social factors such as social isolation, mood disorders and cognitive decline, which are not accounted for in most studies, could also hamper anticoagulant treatment (e.g. due to non-persistence which—as explained above—may be more likely in patients treated with a DOAC).

Currently, there are insufficient data on the association between AF, frailty, older age, anticoagulant

Dutch contribution to the field

- Investigating the impact of adherence, persistence and incorrect dosing of DOACs in AF patients.
- Determining the safety of switching anticoagulants (from VKA to DOAC) in frail, elderly AF patients.
- Evaluating whether integrated care for AF can be safely organised in primary care.
- Tailoring DOAC intensity to the individual patient based on dose reduction criteria alone.

management and clinical outcomes to guide optimal anticoagulant management in this specific population. In particular, it is unknown whether switching to a DOAC in frail elderly AF patients, treated with VKA, would result in fewer bleeding complications, as the clinical practice data that are available on the safety and effectivity of switching anticoagulant treatment are confounded by the reason to switch [38].

The Dutch FRAIL-AF RCT aimed at providing insights into the optimal anticoagulant treatment strategy in frail elderly AF patients [39]. This multicentre pragmatic open label registry-based clinical trial was designed to assess whether switching from VKA to DOAC reduces the risk of major and clinically relevant non-major bleeding in frail elderly with AF (primary endpoint). The FRAIL-AF study will include frail elderly patients (≥75 years with a Groningen Frailty Indicator ≥3) with non-valvular AF [40]. Patients randomised to the intervention group will switch from VKA to DOAC-based management. The control group continues with their VKA treatment.

ALL-IN—Integrated AF care in primary care

AF is closely intertwined with other common chronic diseases such as type 2 diabetes, chronic lung diseases, hypertension and heart failure. Integrated care, in which AF and its comorbidities are managed in a multidisciplinary setting, is suggested as a possible strategy for promoting guideline adherence and improving patient outcomes [14]. Such integrated AF care in secondary care has been shown to be effective in reducing all-cause mortality, cardiovascular hospitalisation and healthcare costs [41–44].

The ALL-IN study, a cluster randomised trial, was designed to assess safety, efficacy and cost-effectiveness of integrated AF care in primary practice [45]. AF patients were enrolled from primary care. The primary endpoint was all-cause mortality during a follow-up duration of 2 years. Practices randomised to the intervention arm provided integral AF care, consisting of regular check-ups and—in case of VKA use—INR measurements performed by the practice nurse, and easy access to consultation with cardiologists and experts in anticoagulation. Practices randomised to the control group provided care as usual.

A 45% reduction in all-cause mortality was observed in the intervention group compared with the control group (HR 0.55, 95% CI 0.37 to 0.82) [46]. Bleeding and stroke rates were similar between the intervention and control group, whereas the study did observe that the reduction in all-cause mortality was greater for non-cardiac causes of death as compared with cardiovascular death. As such, the effect on mortality was not explained by better anticoagulation monitoring. However, it was speculated that management in primary care for patients eligible for referral back to their general practitioner may allow more attention to be given to the comorbidities of AF patients, since general practice typically incorporates a holistic approach. Furthermore, integrated AF care in primary care could offer a solution for managing the increasing prevalence of AF patients (i.e. the AF epidemic) and maintaining the accessibility of VKA monitoring when anticoagulation clinics are expected to close down as more and more patients are treated with DOACs.

Contemporary stroke and bleeding risk assessment strategies

A multitude of risk prediction models have been designed to objectively assess and weigh the different stroke and bleeding risks of individual patients before initiating anticoagulant treatment. The CHA_2DS_2-VASc score, currently the only endorsed score in international guidelines, is used to identify AF patients at low risk for stroke, in whom anticoagulant treatment can be safely withheld [14, 15]. Although several modifications to the CHA_2DS_2-VASc score have resulted in an improved predictive performance [47–51], these modifications have not been adopted by international AF guidelines.

For bleeding risk assessment, the HAS-BLED score was briefly recommended in guidelines over the $HEMORR_2HAGES$ and the ATRIA score to identify AF patients with an increased bleeding risk for close monitoring [8, 13, 14, 52]. However, due to its moderate discriminatory abilities for major bleeding, especially in the elderly in which bleeding prediction matters most [8, 53] and its inability to guide anticoagulant treatment [9, 54], later or subsequent editions of the international guidelines have dropped the recommendation for a specific bleeding risk score. Instead, a list of modifiable and non-modifiable bleeding risk factors was included which clinicians could target to modify bleeding risk. Anticoagulant treatment should not be withheld based on bleeding risk assessment scores [14, 55].

In recent years, the quest for developing and improving risk prediction scores continued, all with the aim to either improve the risk prediction capabilities, to fit into the modern era of DOACs and/or to tailor anticoagulant treatment to the individual patient. Examples are (in chronological order): the ORBIT bleeding score, ABC score, GARFIELD-AF risk tool, Anticoagulation-specific Bleeding Score (ABS), and a model derived from the RE-LY trial [10, 12, 17, 56, 57]. Three interesting developments are seen in these newly developed risk models: (i) the development of an integrated risk assessment tool that allows for simultaneous calculation of stroke, bleeding and mortality risk, (ii) the addition of biomarkers and ECG markers to improve the predictive capabilities of these risk scores [51, 58], and (iii) the possibility to tailor anticoagulant treatment to the individual patient, based on the calculated stroke and bleeding risk.

Both the GARFIELD-AF risk tools [59] and the ABC scores [10, 17, 60] are continuous models which provide the opportunity to simultaneously estimate stroke, bleeding and mortality risk. Interestingly, the ABC score incorporates biomarkers to assess these risks. It was shown that high-sensitivity troponin T (hsTnT) and N-terminal B-type natriuretic peptide (NT-proBNP) were independently associated with stroke and systemic embolism, and hsTnT and growth differentiation factor-15 (GDF-15) with major bleeding. One important strength in the development of the ABC score is the analysis of treatment interaction for determining the optimal anticoagulant per risk profile, based on a net clinical outcome analysis.

The most recently published model, constructed by a Dutch working group using data from the RE-LY trial, provides guidance on anticoagulant management in AF patients as well [57]. This model estimated the absolute treatment effect of warfarin, dabigatran 150 mg and dabigatran 110 mg, based on the 5-year ischaemic stroke/systemic embolism and bleeding risk. This calculator could help make an informed decision on the optimal dabigatran dosage, based on the weight assigned to stroke and bleeding risk.

Future developments of Dutch initiatives

Integrating data from electronic medical records (EMR) into a clinical registry such as DUTCH-AF would ensure the continuity of the registry and allow for long-term follow-up at lower study costs and administrative burden. In collaboration with the Netherlands Heart Registry and EMR vendors, the dataset required for DUTCH-AF will be implemented in EMR systems in the near future. Moreover, as the Netherlands Heart Registry centralises all data from various national cardiovascular registries (e.g. cardiac device registry and percutaneous coronary intervention registry), cross-talk between registries will be possible. Data from one registry could be applicable to all the other registries a patient is enrolled in, without the need for additional follow-up separately.

Connecting these registries would enable the opportunity for future registry-based randomised controlled trials (R-RCT) or trials within cohort designs. Multiple R-RCTs have already been performed in the SWEDEHEART, Sweden's online cardiac registry [61]. Benefits seen with R-RCTs were swifter enrolments, reduction of costs and loss to follow-up compared with standard site-based follow-up. It was shown that the costs of the TASTE trial were approximately US$ 350,000, or $50 per patient, which is considerably lower than other clinical trials on average [62].

For improving risk assessment models, the implementation of risk scores in EMR systems could be valuable as well. The integration of such models in EMR systems would enable synchronisation with the bulk of data clinicians continuously collect from patients for automated real-time risk calculation. We hypothesise this could provide a novel means to improve these risk models.

Implementing risk scores in EMR systems would also facilitate viewing risk as a dynamic process, as score items such as age will and kidney function may often change over time. Recent studies have shown that changes in CHA_2DS_2-VASc and HAS-BLED scores were of more importance in predicting ischaemic stroke and bleeding, respectively, than the scores as assessed at baseline [63–65]. Finally, implementation of risk assessment tools in EMR systems can also be used as a quality of care parameter.

Conclusion

Patients and their physicians continuously encounter challenges with the appropriate use and complications of DOAC treatment in daily practice. The creation of a national AF registry provides the possibility to evaluate the appropriateness and disparities of contemporary anticoagulant care. Embedding anticoagulant control in integrated AF care, which requires a holistic approach and close collaboration between general practitioners and specialists, could partially address these daily encountered challenges effectively and promptly. The results of the studies highlighted in this review will provide important information for clinicians and patients for informed decision-making regarding the provided anticoagulant care.

Conflict of interest G. Chu is supported by a research grant of ZonMW (project numbers 848050006 and 848050007). J. Seelig is supported by a grant from the Dutch Federation of Anticoagulation Clinics (FNT). E.M. Trinks-Roerdink reports no conflicts of interests. G. J. Geersing and F. H. Rutten received unrestricted institutional grants from Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo. J. R. de Groot received research grants (through institution) from Abbot, Atricure, Bayer, Boston Scientific, Medtronic. Received speaker/consultancy fees from Atricure, Bayer, Daiichi Sankyo, Johnson&Johnson, Medtronic, Novartis, Servier. Ownership: RhythmCARE. M. V. Huisman reports unrestricted grants from and personal fees from ZONMW, Boehringer Ingelheim, Pfizer/BMS, Bayer Health Care, Aspen, Daiichi Sankyo, outside the submitted work. M. E. W. Hemels received consultancy fees from Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Roche and received a research grant from Federation of Dutch Thrombosis Services.

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