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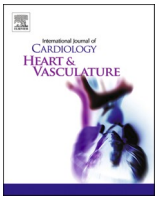

Editorial

The temporal context of oral anticoagulation outcome in atrial fibrillation

The direct oral anticoagulants (DOAC) have largely supplanted the vitamin K-dependent, coumarine-based anticoagulants (VKA) in the management of patients with atrial fibrillation (AF). The superior net safety and efficacy profile of DOAC was consistently demonstrated in the landmark trials, particularly in those patients cohorts not adequately managed with the VKA warfarin. However, observations made in controlled clinical trials, with stringent inclusion/exclusion criteria, selected endpoints and relatively short follow-ups, are difficult to translate into the real-world setting, where patient comorbidities, lifestyle and nutritional habits, and therapeutic compliance substantially influence the outcome.

The DOAC were conceived for once-daily, fixed-dose application with no requirement for monitoring. This relative ease of use was intuitively expected to improve complicance. This is a critical issue with DOACs, given that the relatively short on-off kinetics of these agents mean that forgotten doses can have immediate consequences for thrombotic risk, while inappropriate overdosing may promote serious bleeds. There have accordingly been calls to restrict DOAC use in patients with cognitive impairment, for example [1].

The two major facets of compliance are treatment adherence (taking drugs as prescribed) and persistence (continuation of drugs). Anticoagulation management in AF is a lifelong endeavour, and proper adherence and persistence are critical for efficacy and safety. A number of retrospective and prospective observation cohort studies and reviews of healthcare records performed across Europe, the UK, USA, Canada and the Asia-Pacific region show a similar temporal decline in adherence and persistence to both VKA and DOAC. While some analyses do attest improved persistence rates with DOAC compared to VKA [2–7], others report that DOAC are not better in this regard, if not worse, than VKA [8–11].

One possible reason why DOAC do not fulfill the promise of improved compliance is that compared to VKA therapy with DOAC does not encompass regular monitoring and face-time between patient and physician to ensure patient awareness of the risks that are associated with AF and the drugs used to manage it. Patients with asymptomatic AF, or those prescribed reduced dose DOAC, are not frequently reminded of the importance of strict adhesion to therapy, or may trivialise the perceived disease burden.

The concept that frequent reminder of proper drug use critically impacts on persistence was elegantly exemplified by a daily telemonitoring feedback study [12]. DOAC use was monitored by daily telephone calls with or without imemdiate additional personal feedback on proper intake. Telemonitoring alone kept adherence and compliance at over 90%, with further improvement seen with the additional direct feedback. By contrast, during an observation-only phase without daily telemonitoring, adherence rates waned rapidly and drastically. Similar improvement in DOAC adherence and persistence may conceivably be achieved with the implementation of smartphone apps to monitor proper drug use. Monitoring – either by direct face-time, telemonitoring or apps, are also likely to improve patient satisfaction, a critical determinant of compliance and outcome. As recently demonstrated, patients who showed a high time in therapeutic range (TTR) with VKA also retained high persistence after switching to DOAC, while patients with a low TTR also showed worse persistence on DOAC [13].

High on-DOAC bleeding does not seem to explain high non-persistence rates. Other candidate factors that appear to negatively influence persistence with DOAC are young age, female sex, no concomitant drug use, a constellation that respresents a rather healthier state. Improved DOAC persistence has by contrast been noted for age over 64 years, permanent AF, previous VKA requirement, stroke history (including transient ischaemic attack), and a CHA_2DS_2-VASc score ≥ 2 reflecting a rather greater disease burden and intensified patient-physician contact. A comprehensive overview of the factors that determine DOAC compliance, adherence and persistence, and by which means DOAC treatment and outcome may be optimised in patients with AF, was excellently provided recently [14].

In a report now published in this issue of the journal [15], the authors dissect one particular aspect of therapeutic persistence, namely treatment duration, and ist potential impact on outcome. While an overwhelming number of systematic reviews and meta-analyses support the predominance of the DOAC even in patients with different clinical and therapeutic characteristics, little is known regarding the temporal context. The authors essentially ask the question: is the comparative benefit of DOAC in terms of safety and efficacy an inherent quality of the drug class, or is determined by the length of time over which the drug is taken? The authors point out that in the pivotal clinical trials that led to approval of rivaroxaban and dabigatran for example, the safety/efficacy advantage over warfarin increased with longer follow-up duration, which in total, however, seldomly exceeded 12 months. The authors perceive a mismatch between observations made over several months in a tightly controlled setting, and extrapolation to the real-world situation where treatment continues over longer periods, and where comorbidities, individual behaviour and medication use is dynamic and evolving.

The present study clearly highlights that the accumulated evidence pertaining to DOAC efficacy and safety in routine practice is also limited by short follow-up durations, which may not adequately inform on long-term outcomes [15]. However, the benefit of DOAC in this regard is retained regardless of treatment duration, implying an inherent efficacy of these agents. Notably, the safety advantage of dabigatran and rivaroxaban, in terms of lower bleeding compared to VKA, becomes more

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apparent the longer treatment continues, raising the idea that these DOAC may be safer than first presumed. The converse may be true for apixaban, where the authors noted treatment duration to coincide with a reduced safety benefit compared to VKA. Such observations could be particularly applicable and relevant for patients with higher bleeding propensity, who may benefit from certain agents if treatment is to continue long-term.

While the value and quality of the plethora of published DOAC vs. VKA analyses are debatable, large-scale assessments of outcomes in diverse real-world cohorts continuously add to our understanding of how these agents can be implemented to improve and personalise management of patients with AF.

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Anke C. Fender[a,*], Dobromir Dobrev[a,b,c]

[a] *Institute of Pharmacology, Medical Faculty, University Duisburg-Essen, Germany*

[b] *Department of Medicine and Research Center, Montreal Heart Institute and Université de Montréal, Montréal, Canada*

[c] *Department of Molecular Physiology & Biophysics, Baylor College of Medicine, Houston, USA*

[*] Corresponding author at: Institute of Pharmacology, Medical Faculty, University Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany.
E-mail address: anke.fender@uk-essen.de (A.C. Fender).