Review of: "Prescribing of direct oral anticoagulants and warfarin to older people with atrial fibrillation in UK general practice: a cohort study"

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In the warfarin era, oral anticoagulant (OAC) therapy was largely underused in older people with atrial fibrillation (AF) (1-3), despite evidence of increasing net clinical benefit of warfarin anticoagulation in the oldest patients and in those with the highest risk of ischemic stroke (4). Advanced age, short life expectancy, difficult management of therapy, fear of bleeding and perceived unfavorable benefit-risk balance were the most common reasons reported to withhold Vitamin K Antagonists (VKAs) (3).
The introduction of Direct Oral Anticoagulants (DOACs), with their greater clinical net benefit over VKAs, has boosted the clinical attention on AF. Meanwhile, there has been a progressive increase in worldwide prevalence and incidence of AF (5,6), which is particularly relevant in the growing elderly population (5,7). AF-related incident ischemic strokes in patients over 80 years of age have trebled during the last 25 years, and their incidence in the oldest-old is expected to further increase in next decades (8). Previous registry-based studies during the transition period after the introduction of DOAC consistently reported increasing prescription of DOACs and slightly reduced use of VKAs and antiplatelet therapy, yet with a little impact on the overall number of patients receiving OAC, particularly among the oldest patients (9-11). Therefore, despite international guidelines strongly recommending DOACs use in older AF patients at high risk of ischemic stroke, real-world studies demonstrate that several uncertainties remain in daily clinical practice about OAC prescription in oldest-old AF patients perceived with poor clinical net benefit from this therapy (10, 12, 13). Notwithstanding, recent reports consistently demonstrated a significantly reduced incidence of ischemic stroke along with the increasing prescription of DOAC in the overall population with AF (14,15).
On this background, the timely paper by Mitchell A et al is largely consistent with previous findings. In this study a cohort of patients aged ≥ 75 years with a diagnosis of AF was derived from the Clinical Practice Research Datalink (CPRD) between January 1, 2003, and December 27, 2017. Patients were grouped as no OAC, incident OAC (OAC newly prescribed) or prevalent OAC (entered study on OAC). The study aimed to assess 1) whether and to what extent the incidence and prevalence of OAC prescribing changed in the period prior to the introduction of DOACs (2003–2007), between the time DOACs were introduced and the time they were recommended by NICE (2008-2012), and following NICE recommendation (2013–2017), these latter strongly recommending DOACs over VKAs as first choice in AF patients without valular AF; 2) How older people switch between different OACs; 3) Which patient characteristics and co-morbidities affect

the chance of being prescribed an OAC and has this changed since the introduction of DOACs; 4) whether and how persistence with therapy differ between different OACs.
In keeping with several other cohort studies, the present study's main finding is that both incidence and prevalence of OAC prescribing increased over time, and this increase further accelerated after DOAC marketing and the National Institute for Health and Care Excellence (NICE) favourable technology appraisals for all four DOACs (between 2012 and 2015). Notably, the incidence of OAC prescribing increased from 111 per 1000 person-years to 587 per 1000 person-years between 2003 and 2017, along with a more than doubling prescribing of DOACs over warfarin. Therefore, it appears that this remarkable increase of OAC prescription is largely accounted for by very low prescription rates in the warfarin era. Although similar low prescription of VKAs was reported in older AF patients in real world clinical practice (16), use of these drugs was consistently more elevated in landmark studies including hospital discharged older patients (which reported prescription of VKAs around 45-to 60% in people over 75-80 years of age) (1,2) and in cardiology registry-based studies including slightly younger populations (17-20).

Findings about drug switching (mainly from warfarin to DOACs) and its characteristics are merely descriptive but barely informative in a retrospective study including older people with the inherent limitations of a retrospective electronic medical study. At the same way, despite the burden of statistical methods deployed, it appears hard to derive useful clinical information about different persistence with DOAC and VKAs therapies. The observation that in the first and second years of treatment, patients were more likely to stop a DOAC than warfarin, but from the third year onwards, they were more likely to persist with DOACs than warfarin, is flawed by missing information about propensity score adjusted predictors of being prescribed with DOACs vs VKAs, and may be explained by several clinical variables and occurring events, which were not captured by medical records, and it is further complicated by the heterogeneity among DOACs. Therefore. these findings about persistence and switching should be wisely considered by readers, because reliable data in these settings may derive only from prospective dedicated clinical studies.

Notwithstanding the huge increase in OAC prescription, 68,859 out of 165,596 older persons with AF were never prescribed OAC (40.4%), whereas 47,916 were 'incident OAC users' (newly prescribed an OAC during the study), and 50,821 patients were prescribed an OAC in the year preceding study entry ('prevalent OAC user' group). The incidence of OAC prescription reached 587 per 1000 person-years in 2017, largely accounted for by DOACs, wherein apixaban was preferred over rivaroxaban and dabigatran. These results are in keeping with a previous electronic health records study from ResearchOne in England (384 General Practices), including 61177 patients aged >65 years with AF (median age 79.7 years). Among the 58,204 patients qualifying for OAC, only 30,916 (53.1%) received OAC (23.7% DOAC) (21). In keeping with previous studies (11), Mitchell and coll reported that patients aged ≥85 years were up to 45% less likely to receive an OAC. Low use of OAC therapies and its clinical backgrounds in older persons, and in the

oldest-old specifically, have been demonstrated in a number of studies, as reported in previous reviews on this topic (22,23). On the background of international recommendations for DOAC prescription to AF older persons at high risk of stroke, these real-world findings raise some questions about the reasons for this persistent underuse of OAC among community-dwelling older people. Although clinical inertia or malpractice as well as economic local limitations to the use of DOACs may have a role, evidence from a huge number of studies suggest that this underuse of OAC may be intentional, since several variables (female gender, very advanced age, low body mass, chronic kidney disease, previous or high risk of bleeding, previous or high risk of falls) have been consistently associated with OAC denial even in the DOAC era. (9,10,24,25). Not unexpectedly, Mitchell and coll reported that the association between very advanced age and OAC withholding remained when comorbidities were adjusted for. However, chronological age and count of comorbidities as well as of other demographic variables fail to reflect the complexity of the individual older patient and are inadequate proxies for health in the geriatric population (26). In older people, the interplay between patho-physiological changes and multimorbidity can result in health states termed “geriatric syndromes” (e.g., cognitive impairment, functional dependence, and frailty) that are not captured at all by traditional disease classifications (26,27), but that have been demonstrated to predict survival and other adverse outcomes better than the comorbidity burden (28, 29) and to drive the physicians’ decision about OAC use in older patients (13,24,30-33). Unfortunately, these information are not retrievable from most retrospective electronic studies.

The 2020 European Society of Cardiology (ESC) guidelines for the diagnosis and management of AF hasty stated that “*frailty, comorbidities, and increased risk of falls do not outweigh the benefits of oral anticoagulant*” therapy, also suggesting an “holistic” approach to AF (34). However, the Authors of the recently published 2021 EHRA practical guide on the use of NOACs have set a milestone, acknowledging that “*there may be no benefit to OAC in states of severe frailty or where life expectancy is likely to be limited*”, thereby accepting the option of not prescribing (or de-prescribing) OAC for some “frail” older AF patients (35). With the growing numbers of older patients with AF, there is an unmet need to provide appropriate standardized tools according to different clinical settings to assist physicians in clinical decision making in order to provide the best individualized treatment. Despite in this setting recent guidelines have focused their attention on „frailty“, when feasible, at least in Internal Medicine and Geriatric wards, as well as in primary care, the Comprehensive Geriatric Assessment and the Multidimensional Prognostic Index should represent the gold standard (36) to identify patients with reduced life-expectancy and poor benefit from OAC. As second option , at least a formal evaluation of functional autonomy and cognitive function would be advisable, to prompt further assessment in those presenting at least moderate impairments (29, 37). Despite the not negligible inherent limitations of an inexperienced eye-ball assessment, the Clinical Frailty Scale (38) recommended in the EHRA practical Guide (35) represents at the moment the only handy frailty tool for everyday cardiology clinical practice. Mitchell and coll should therefore be commended for their precious contribution, highlighting once more persistent clinical uncertainties on OAC/DOAC prescription in older AF patients, prompting

experts of different clinical areas to provide some „operating instructions“ for a true holistic approach to the patient with AF rather than to AF.

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