Invited Editorial

To accompany Hohmann et al, Hohnloser et al, and Field et al

Anticoagulation for atrial fibrillation in older adults – using big data for big questions

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Atrial fibrillation (AF) is predominantly a disease of older age, with a doubling of risk for each decade lived.[1] As well as experiencing more AF, older adults are more likely to suffer the consequences of AF, most notably stroke, and they are more likely to be left dead or disabled following an AF-related stroke.[1] Despite this age-associated 'treble whammy', the majority of evidence around treatment of AF has focussed on middle-aged adults. This apparent disconnect between evidence and practice may be one reason why there is marked variation in clinical practice around treating AF in older adults.[2]

Of course age is just a number and even within the oldest old, there will be a spectrum of health from robust, community-dwelling through to frail, multi-morbid older adults. It is in this latter group that clinical trial evidence is especially lacking. AF is often associated with frailty and comorbidity.[3] Yet traditional, large cardiovascular randomised controlled trials (RCT) have generally excluded such patients. Certainly, including older adults living with frailty in AF-based RCTs poses challenges, for example there will be issues with capacity, attrition, test burden and competing risk.[4] Encouragingly, there are emerging examples of trials that focus on frailty and also examples of trials that describe frailty syndromes as study outcomes.[4]

A potential solution to the perceived lack of generalisability of RCTs is to use existing clinical data from large registries and databases. Many such studies have been published, that have examined treatment patterns and outcomes [5-7]. Secondary analysis of big data from real world settings offers a number of advantages, not least that clinical hypotheses can be tested at scale for a fraction of the cost, time and man-power required for a prospective study.[8] In this issue of *Thrombosis & Haemostasis*, there are a number of papers where real world data are used to improve our understanding of AF treatment in older adults. These papers are

exemplars of what can be achieved through analysis of routine data, but they also highlight some of the limitations of the big data approach.

Hohmann and colleagues[9] used information held in a German healthcare claims database to look at risk profiles of various anticoagulation treatment approaches in older adults. The dataset included 70,501 patients newly started on anticoagulation for AF (n=42,562 (60.4%) with non-vitamin K antagonist (VKA) oral anticoagulant [NOAC]). The population were categorised by age, frailty, comorbidity and polypharmacy. Across all these categories the risk of stroke and systemic embolism was higher than had been described in the seminal RCTS of NOACs.[1] Comparing OAC treatments (NOAC vs. phenprocoumon), there was no signal of differential treatment efficacy between NOAC and a traditional VKA. However, when comparing safety profiles, in this case defined by major bleeding, there was a clear difference between groups in favour of NOAC prescribing.

Using a similar approach of interrogating a large German healthcare claims database, Hohnloser and colleagues[10] describe rates of OAC discontinuation and switching (VKA to NOAC, NOAC to VKA, and NOAC to NOAC) for a cohort of older adults newly prescribed anticoagulation for AF. Again the cohort was impressively large, with 51,606 patients (30,138 (58.4%) prescribed NOAC). We often think of anticoagulation for AF as a life-long treatment, however, in this cohort around one-third had discontinued anticoagulation at one year. Rates of discontinuation were similar across group, NOAC (29.5%) and VKA (29.9%). Older adults were more likely to persist with OAC; a reassuring finding given that this group are at higher risk of AF-related stroke. In total 5149 (10%) patients switched from their initial anticoagulant to another agent, with those initially prescribed VKA more likely to switch than those prescribed NOAC (2298 (11%) vs. 2851 (9.5%)). Change of OAC was associated with clinical

events, both stroke and bleeding. There was also a temporal prescribing change with more conversion to NOAC over time, perhaps as physicians become more familiar with these new medications.

Finally, Field and team [11] focussed their attention on one of the outcomes of greatest concern to older adults, namely dementia. Using the UK Clinical Practice Research Database they created matched cohorts with and without AF, totalling 91,372 (15,276 (16.7%) with AF). By linking the primary care dataset to UK NHS secondary care registries, they examined incident dementia over an average of two-years of follow-up. They report an increased risk between AF and incident dementia [aHR 1.31 (95% CI 1.15-1.49], albeit with a smaller effect than demonstrated in previous studies.[12] By performing subgroup analyses looking at anticoagulation prescription and incident stroke we can speculate on potential mechanisms underlying this association. Prescription of anticoagulation seemed to ameliorate the risk of dementia, suggesting that cardioembolism is likely to be a factor in any cognitive decline. However, the risk of dementia remained significant even after removing all those with stroke or transient ischaemic attack. This suggests that it is not only stroke that is driving cognitive change, or at least not clinically apparent stroke. A disheartening observation in this contemporary cohort was that around one third of older adults with AF received no anticoagulation treatment.

So, what messages can we take from these three complementary analyses? Clearly, routinely collected data represents a powerful resource for research in older adults. The numbers included in these analyses would be almost impossible to replicate in a bespoke, prospective study. However, 'big data' are not necessarily better data and if the data have inherent limitations, the large sample size will only serve to make a biased estimate more precise. Of

particular concern, are those patients who are not captured in the databases, for example the two German studies only included AF patients newly-initiating OAC. Yet, other data tell us that often the highest risk AF groups are not prescribed evidence based therapies and so will not feature in these prescribing based registers.[2]

The studies described looked at syndromes of older age through the lens of what is recorded and available in large databases. In this regard, comorbidity and polypharmacy are relevant. However, for many older adults, the outcomes of interest may not be routinely recorded and clinical register based research may struggle to assess factors such as falls, disability and admission to care-homes. Even where data are available, the validity is not guaranteed. Taking dementia as an example, recording of dementia in clinical registers tends to be specific but insensitive and may miss many living with the disease.[13] VKA medications are problematic for big data approaches, as the interpretation requires additional information on dosing and INR, which is often lacking. In this regard, big data researchers will be glad of the increasing use of NOACS which are analytically easier to handle.

Even with the most sophisticated analyses, matching and adjustment, we must be cautious about how we interpret these observational data. Retrospective analyses can miss the nuance and clinical rationale for prescribing decisions and the preference for a particular anticoagulant strategy will not be made at random. This is likely to be a particular issue in older adults where the evidence to guide treatment decisions may be best practice recommendations rather than from RCTs.[14]

For all these reasons, big data approaches are best regarded as complementing other study methods including mechanistic pre-clinical experiments, bespoke cohorts and large scale clinical trials (see Figure). Using routinely recoded data can generate new hypotheses to be

tested or can validate results generated using other research methods. From the data presented in these three papers, we can be reasonably confident about prescribing NOACs in older adults but whether these drugs will reduce frailty syndromes such as dementia will require testing in large scale trials.[12]

Legend and footnote for figure:

Incorporating big data into all aspects of drug development

This illustrates a hypothetical scenario of repurposing an existing drug for a new indication.

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