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## Editorial

Etiological research using observational data, and net clinical benefit.

Simplicity and practicality matter

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Running head: **Simplicity and Practicality Matter**

Atrial fibrillation in an elderly patient requires oral anticoagulant (OAC) treatment, and contemporary international guidelines recommend treatment for atrial fibrillation patients at 75 years or older <sup>1,2</sup>. Substantial evidence (mostly in favour) of non-vitamin K antagonist oral anticoagulants (NOACs), in comparison with warfarin, has emerged over the past decade. In particular, the benefits from a lower risk of intracranial bleeding and the non-requirement for monitoring of anticoagulant effects have driven the uptake of NOACs as the preferred choice for stroke prevention in atrial fibrillation, although some regional differences are evident<sup>3</sup>.

A heap of observational studies comparing NOACs with warfarin have been published: some focus on particular outcomes or specific drugs <sup>4-6</sup>, some maintain focus on particular subgroups within the broad atrial fibrillation population <sup>7,8</sup>. However, these publications shared a common quest to understand the association between drug exposure and the outcome – in other words, the etiological course or the causal link between being exposed and the outcome. This is not trivial to establish using observational data, and results can only be interpreted as being causal treatment effects under very strong assumptions <sup>9</sup>. Nevertheless, causation should be what we seek, and thought leaders argue that researchers need more clearly to articulate the causal inference path when stating the research question <sup>10,11</sup>.

In this issue of the journal, Patti et al. sought to compare exposure to NOACs vs warfarin on a net composite endpoint consisting of major bleeding, stroke, transient ischemic attack, systemic embolism, acute coronary syndrome, and coronary revascularization<sup>12</sup>. A weight was applied to each individual outcome to accommodate for the difference in severity of the studied outcomes.

The principles of applying weights to incidence rates are well-known, and may provide useful clinical information in terms of net clinical benefit <sup>13</sup>. However, a more specific approach has also been suggested, where clinicians rebalance weights applied to expected outcomes such as major bleeding and ischemic stroke, reflecting safety and efficacy in well-reasoned net clinical benefit <sup>14</sup>.

Conducting a causal, observational drug-outcome study is challenging and treatment effect estimates will be biased due to confounding, selection biases and other systematic errors. Incomplete observation or adjustment for confounding factors inevitably leaves residual confounding and leads to bias in the treatment effect estimate. A clear distinction needs to be made between “confounders” and “confounding”<sup>15</sup>. Selection of covariates in an adjustment model must be based on subject matter knowledge – not on data availability or model selection based purely on statistical structure in the data. Patti et al. applied a stepwise approach of covariate inclusion into a logistic regression model to obtain associated odds ratio for the outcome under the two treatment exposures. While chance cannot be ruled out in favour of this approach, there is a risk of ruling out confounding factors that are very well established in prior research, and often common clinical knowledge.

In the current study, exclusion of sex as a potential confounding factor is an omission of this kind. It is highly likely this biased the results. Consideration of confounding factors can be helped by mapping out, with a graphical model notation, known causal pathways and the segways of confounded association that may bias the treatment-outcome inference<sup>16</sup>.

While research into net clinical benefit is of some value to guide clinical practice, the results from the study by Patti et al. require confirmation in other registries where state-of-the-art epidemiological approaches have been applied. Conducting robust research with treatment exposure and associated outcome from observational requires a rigid and perceptive approach, which is clear and practical to apply.

Net clinical benefit analyses are also bedevilled by assumptions that all components of the net clinical benefit outcome carry equal weight, but they do not. Different approaches to defining net clinical benefit have been proposed, ranging from the simple balancing of ischaemic stroke reduction against a weighted increase in serious bleeding, to more complex formulae derived from regression models.

Which approach is right? Clinical risk assessment in patients with atrial fibrillation has to balance (often marginal) improvements in prediction against the need for clarity and practicality<sup>17,18</sup>. Indeed, many risk scores have been proposed and validated in diverse atrial fibrillation cohorts, which can inform net clinical benefit calculation assumptions. Ultimately, the default for the management of atrial fibrillation patients should be to offer stroke prevention, unless the patients can be defined as ‘low

risk'<sup>1,2</sup>. Thus, guidelines have moved towards offering simple and pragmatic approaches to decision making in the AF patient management pathway, which can be distilled down to the simple ABC pathway ('A' Avoid stroke with Anticoagulation'; Better symptom management, with patient-centred, symptom directed use of rate or rhythm control; and 'C' Cardiovascular risk and comorbidity management, including lifestyle and patient values and preferences)<sup>19</sup>. Importantly, compliance with the ABC pathway has been shown to be associated with improved clinical outcomes and reduced healthcare costs<sup>20-22</sup>.

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