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LETTER TO THE EDITOR

BCPT Basic & Clinical Pharmacology & Toxicology

Cohort selection in register-based studies of direct oral anticoagulant users with atrial fibrillation: An inevitable trade-off between selection bias and misclassification

Dear Editor,

Recently, we published a descriptive drug utilization study in *Basic & Clinical Pharmacology & Toxicology* on the use of direct oral anticoagulants (DOAC) in Denmark during 2008-2016.[1] A surprising finding was the large proportion of DOAC initiators in whom we were not able to identify a likely treatment indication using "the conventional approach", *that is* through hospital-based health registers. More specifically, among 126,691 Danish DOAC initiators, a total of 35 200 (28%) could not be classified with a major treatment indication, *that is* atrial fibrillation (AF), venous thromboembolism (VTE) or VTE prophylaxis following arthroplastic knee or hip surgery. With regard to patient characteristics and treatment persistence, patients initiating DOAC treatment with "no indication" were more similar to patients with AF than patients receiving DOAC for VTE or VTE prophylaxis.[1] Importantly, data from primary care are currently not available in Danish registers. As such, non-classifiable users likely primarily reflect on-label DOAC use initiated by general practitioners rather than DOAC use outside approved indications.[2] Nevertheless, the high proportion is concerning considering the extensive use of the Danish population-based health care registers in the evaluation of safety and effectiveness of real-world DOAC use.[3] In such studies, safety and effectiveness are usually explored in the context of a specific treatment indication defined by the presence of a specific hospital-based diagnosis, such as AF. However, with this approach, many DOAC users potentially treated for the indication of interest, but without a registered diagnosis, will not be included. If non-included users with (non-registered) AF differ from included users with (registered) AF in terms of risks and characteristics, selection bias could be introduced. Another approach used in studies on DOAC use in AF is to include all but those with a specific diagnosis of another approved indication for DOAC use (*eg* VTE) in the cohort. Although DOAC use initiated in primary care seems most likely to be due to AF (since acute VTE patients are handled in the hospital setting), non-registered AF is unlikely to be the only reason for missing treatment indication proxies, as discussed in the primary paper.[1] As such, the underlying assumption that DOAC users with no registered treatment indication have AF may not be correct, and this approach may therefore introduce misclassification bias.

To qualify our concerns regarding the potential risk of bias inferred by incomplete capture of the treatment indication for DOAC use in Danish health registers, we explored this issue further within the cohort of Danish DOAC initiators. We updated the dataset to include initiators from August 2011 through December 2018 (n = 187 195). Users were classified by assumed treatment indication as previously described[1] in categories: AF (n = 76 125; 41%), non-AF (*eg* VTE) (n = 42 710; 23%) and no indication (n = 68 360; 36%). The potential for selection bias was assessed by comparing one-year risks (cumulative incidence proportions) between categories "AF" and "no indication" of all-cause mortality and of hospital admissions with a primary diagnosis of arterial thromboembolism (a composite of ischaemic stroke, transient ischaemic attack and systemic embolism) and of bleeding requiring hospitalization. To assess the potential for misclassification, we (a) searched for markers indicating DOAC use for AF (antiarrhythmic drug use; prior ischaemic stroke or supraventricular arrhythmia, cardioversion, catheter ablation and/or electrophysiological computer mapping, and specific types of index DOAC prescriptions) in the "no indication" category at the time of DOAC initiation and (b) estimated the proportion of the "no indication" category diagnosed with AF, VTE and VTE prophylaxis in the year following initiation, as we considered it likely that diagnoses registered in the year after initiation would reflect reasons for DOAC use.

DOAC users categorized with "AF" and "no indication" had similar one-year risks of arterial thromboembolism (1.7% and 1.7%, respectively) and of bleeding (2.7% and 2.8%, respectively). One-year mortality was, however, lower in the AF category (9.0%) than in the "no indication" category (10.8%), corresponding to a HR of 1.21 (95% CI: 1.17-1.25) for "no indication" vs "AF." Upon DOAC initiation, a

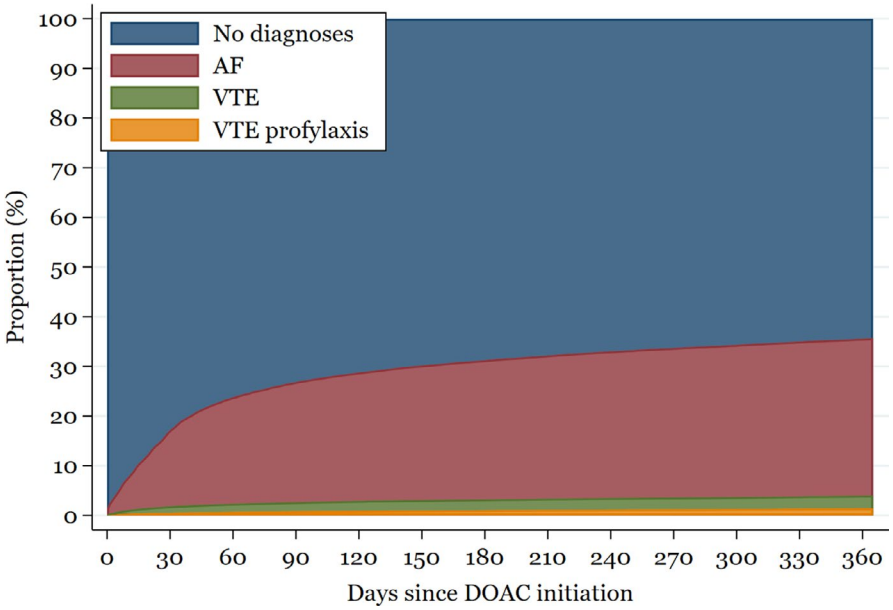

FIGURE 1 Cumulative proportion of new registrations of diagnoses compatible with an approved treatment indication in DOAC initiators with no identifiable treatment indication at the time of initiation. AF, atrial fibrillation; DOAC, direct oral anticoagulants; VTE, venous thromboembolism

proxy for AF could be identified in 40% (n = 27 674) of the "no indication" category. Most common was concomitant use of digoxin (16%; n = 10 937), prior arterial thromboembolism (15%; n = 10 546) and prior cardioversion (6%, n = 4069). In the year following DOAC initiation, 32%, 3% and 1% of DOAC users in the "no indication" category received a hospital diagnosis of AF, VTE and VTE prophylaxis, respectively (Figure 1). The majority (75%) received the diagnosis within the first 90 days following initiation. When restricting to "no indication" initiators with an AF proxy, the proportion receiving an AF diagnosis within a year increased to 47%.

These supplementary analyses of Danish DOAC users without an identifiable treatment indication at the time of initiation indicate that (a) non-inclusion of these users may introduce selection bias in studies on the effectiveness and safety of DOAC use in AF and (b) non-restrictive inclusion may lead to bias secondary to misclassification of DOAC use for AF. Based on these analyses, we suggest that a balanced trade-off between selection bias and misclassification bias in cohort studies of Danish DOAC users with AF could be obtained with a main analysis including both the "AF" and "no indication"-category supplemented by a subgroup analysis including the "AF" category only. Another approach could be to include users without an AF diagnosis but with an AF proxy. This would likely decrease the risk of selection bias associated with inclusion of AF-diagnosed users alone, as well as the risk of misclassification bias associated with inclusion of all but those with a registered non-AF indication. We believe, however, that identifying the relevant subgroup of "potential AF" patients in the "no indication" category requires further work.[4] Although the AF proxies used in the above analysis were based on guidelines and findings of prior studies in similar populations, some findings related to this group questioned the validity of our algorithm, *for example* a high yearly stroke risk (likely related to our use of "prior stroke" as an AF proxy) and a very high proportion (27%) with recent ultrasound of the leg.

We encourage a further refinement and subsequent validation of an algorithm to identify DOAC users likely treated for AF using Danish Healthcare data. Diagnosis data from Danish primary care are expected to become available within few years as part of The Danish Clinical Quality Program—National Clinical Registries (RKKP) and will be important to include in such algorithm. Until then, data on the prescriber type (primary vs. secondary care physician) of the initial prescription are likely to provide further information on the potential indication of drug use and could be relevant to include as part of an algorithm identifying DOAC users likely treated for AF.[5]

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CONFLICT OF INTEREST

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