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Anticoagulant treatment of cancer-associated venous thromboembolism: Interpreting real-world data with caution

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To the editor: Anticoagulant treatment of venous thromboembolism (VTE) in cancer patients requires careful attention as rates of recurrent VTE and bleeding complications during treatment are substantially higher than in non-cancer patients. Current clinical practice guidelines recommend treatment with low molecular weight heparin (LMWH) over warfarin or non-vitamin K antagonist oral anticoagulants (NOAC). However, there is a growing interest in the use of NOACs for cancer patients though their safety and efficacy remain unclear. The first two head-to-head comparisons between LMWH and NOAC in cancer patients were published in 2017, other trials are ongoing [1, 2].

While we await results of the ongoing trials to clarify the value of NOACs in cancer patients, we commend the effort by Streiff et al [3] who recently published real world data in the *American Journal of Hematology* on the safety and effectiveness of anticoagulant treatment regimens for cancer-associated VTE. Using claims data from the US Humana database, the authors assessed the comparative effectiveness and safety of LMWH, warfarin, and rivaroxaban in a cohort of newly diagnosed cancer patients treated for VTE during 2013-2015. Using three sets of pairwise inverse probability of treatment (IPT) weighted comparisons of 'rivaroxaban users vs. LMWH users', 'rivaroxaban vs. warfarin', and 'warfarin vs. LMWH', the authors concluded that treatment with rivaroxaban is associated with significantly lower rates of recurrent VTE and similar rates of major bleeding as treatment with LMWH or warfarin.

However, based on the findings reported by Streiff et al., we find it difficult to answer the clinical question of interest *"what should be the treatment of choice for cancer patients who could reasonably get any of the three treatments regimens?"* To answer this, the cohorts should have represented exchangeable patients among whom the comparative effectiveness and safety of the

three treatment regimens could have been compared; essentially reflecting a head-to-head comparison resembling a three-arm RCT, where patients are in clinical equipoise at the time of randomization.

Assumming no unmeasured confounding and no treatment-effect heterogeneity the pairwise comparisons would yield unbiased estimates of an average treatment effect. However, these assumptions are not often held when using observational data. In the presence of treatment-effect heterogeneity, use of IPT weighting is an appropriate analytic approach, since this allow for estimation of the average treatment effect in the population (i.e. warfarin users, rivaroxaban users, and LMWH users). This theoretically mimics a randomized trial with three treatment arms, assuming that the IPT weighting sufficiently accounted for observed confounding. However, the choice of pairwise weighted analyses correspond to conducting three RCTs with different sets of inclusion and exclusion criteria per pair of treatments. Instead of using an analytic strategy that accounted for the multilevel treatments, the authors chose to apply three separate pairwise comparisons, which runs the risk of comparing estimates that are based on vastly different cohorts. With that approach it is unknown (and unlikely) if e.g. the rivaroxaban population resemble the same patients in the rivaroxaban-LMWH comparison as in the rivaroxaban-warfarin comparison. As appears from Table 1 in the paper, the prevalence of rivaroxaban users with very high risk (13.5% vs. 8.7%) and high risk cancer (34.7% vs. 29.1%) differ substantially in the treatment comparisons groups. This complicates the comparison of the three treatment regimens and the interpretation is not as straightforward as it may seem when reading the paper.

We further draw the attention to the magnitude of the event rates reported in Figure 1. These are unusual high compared with previous trials and real-world data [1, 2, 4], and we therefore raise a

concern on the generalizability of the study findings. We do not concur with the author's statement that failure to account for the competing risk of death was not a limitation as the assumption was that "the rates were the same across treatment cohorts". In our opinion, the reliability of the reported hazard rates is more a question about the generalizability of the study cohort. If the mortality risk in this setting is lower than in other cancer cohorts, this would lead to exaggerated event rates and therefore also imprecisely estimated cause-specific hazard ratios.

In addition, the authors used the Kaplan-Meier estimator to contrasts events between treatment allocations. However, in the prescence of competing risks, the Kaplan-Meier estimator overestimate the cumulative risk of recurrent VTE and major bleeding [5]. This is paticularly evident in populations with high mortality rates such as cancer patients. For the Kaplan-Meier estimator to be valid, censoring at the time of death should be noninformative. In other words, the risk of events in patients who are censored because of death should not differ from that of patients still at risk. Obviously, we know that dead persons are no longer at risk of recurrent VTE or major bleeding, and this violates the assumption about noninformative censoring. As a consequence, results of the log-rank tests is also invalid [6]. Thus, the failure to account for the competing risk of death, led to overestimation of the cumulative probability of both recurrence and bleeding outcomes.

The anticipated trials on NOACs for cancer patients will likely represent a highly selected subset of cancer patients encountered in routine clinical care. In this respect, data on the uses of NOACs in clinical practice (i.e. real-world data) *is* important. Additional investigations are encouraged to fill the knowledge gap on safe prescribing of NOACs in this challenging patient segment. Notwithstanding, such investigations requires conscientiously study designs and cautious

interpretation that, however, would allow for causal inference between choice of treatment and treatment outcomes.

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