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RESPONSE TO LETTER

Machine Learning to Identify Patients at Risk of Inappropriate Dosing for Renal Risk Medications: A Critical Comment on Kaas-Hansen et al [Response to Letter]

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Dear editor

We would like to thank Houlind et al for their carefully reading our paper and feedback but find it to miss the target on some accounts, considering the scope of our study. First, while pro.medicin.dk indeed does not cite specific sources for dosing recommendations, the summaries of product characteristics (SPCs) constitute a major source for i.a. dosing guidelines and deviations from the SPCs are supposedly occasional.[1] Second, although many drugs indeed lack straightforward dose-reduction schemes, and the article could have been more explicit (see the fourth limitation, however; p. 221), we chose these renal risk drugs because of their simple dose-adjustment rules: including drugs without directly operational guidelines, such as opioids, would be incompatible with our outcome operationalisation (in a sense making our results represent a "best-case scenario" in terms of inappropriate dosing). Third, we set out not to validate the accuracy of pro.medicin.dk but to study the predictability of inappropriate drug dosing as per these recommendations, assuming their veracity (as clinical staff does when following the very same instructions). Fourth, we respectfully point out that eGFR <30 mL/min/1.73m^2 was not an outcome in our analyses nor used to temporarily reclassify severity of chronic kidney disease, and that we used not the lowest eGFR but all eGFR values in the follow-up period (to compute the time-at-risk), which should prevent sustained underdosing. Indeed, we used eGFR ≤30 mL/min/1.73m^2 as one of the inclusion criteria (p. 214 in Kaas-Hansen et al[2]) and to operationalise the notion of inappropriate dosing (p. 214 and figure 1 in Kaas-Hansen et al[2]), in turn serving as a basis for the five actual outcomes: >0, ≥1, ≥2, ≥3 and ≥5 daily inappropriate doses. Finally, in resting on both p-creatinine and urine output,[3] the sparsity of the latter in routine clinical data such as ours would likely cause substantial misclassification of acute kidney injury (AKI), and clinical observations potentially indicative of AKI were unavailable in our data. These challenges combined with our including patients with at least one eGFR ≤30 mL/min/1.73m^2 between admission and index (meaning most eligible patients likely suffered from some degree of chronic kidney disease or AKI) would arguably defeat the purpose of using AKI as an exclusion criterion in a sensitivity analysis.

We do, however, agree with two points raised by Houlind et al. First, as the Conclusion reflects (p. 221 in Kaas-Hansen[2]), in-silico results must prove their worth in prospective evaluations in the target clinical context, before any genuine clinical utility can be claimed, and such endeavours should use hard endpoints to the extent possible. Second,

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repeating the analyses using absolute eGFRs and SPCs for outcome operationalisation could constitute an interesting alternative approach, and one that might have served our study well as a sensitivity analysis.

Disclosure

SB reports ownerships in Intomics A/S, Hoba Therapeutics ApS, Novo Nordisk A/S and Lundbeck A/S, and managing board memberships in Proscion A/S and Intomics A/S, outside this communication. All other authors report no conflicts of interest in this communication.

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