








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]

Benjamin Skov Kaas-Hansen ¹⁻³, Cristina Leal Rodríguez ², Davide Placido ², Hans-Christian Thorsen-Meyer ^{2,4}, Anna Pors Nielsen ², Nicolas Dérian ⁵, Søren Brunak ², Stig Ejdrup Andersen¹

¹Clinical Pharmacology Unit, Zealand University Hospital, Roskilde, Denmark; ²NNF Center for Protein Research, University of Copenhagen, Copenhagen, Denmark; ³Section for Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; ⁴Department of Intensive Care Medicine, Copenhagen University Hospital (Rigshospitalet), Copenhagen, Denmark; ⁵Data and Development Support, Region Zealand, Denmark

Correspondence: Benjamin Skov Kaas-Hansen, Department of Intensive Care, Copenhagen University Hospital — Rigshospitalet, Blegdamsvej 9, Copenhagen, 2100, Denmark, Tel +45 60 19 68 01, Email epiben@hey.com

Dear editor

We would like to thank Houliand 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/1.73m² 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/1.73m² as one of the inclusion criteria (p. 214 in Kaas-Hansen et al²) and to operationalise the notion of inappropriate dosing (p. 214 and figure 1 in Kaas-Hansen et al²), 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/1.73m² 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 Houliand et al. First, as the Conclusion reflects (p. 221 in Kaas-Hansen²), 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,

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.

References

1. Hvad indeholder en præparatbeskrivelse? - Medicin.dk; 2022. Available from: <https://pro.medicin.dk/Artikler/Artikel/151#a000>. Accessed 31 May 2022.
2. Kaas-Hansen BS, Leal Rodríguez C, Placido D, et al. Using Machine Learning to Identify Patients at High Risk of Inappropriate Drug Dosing in Periods with Renal Dysfunction. *Clin Epidemiol.* 2022;14:213–223. doi:10.2147/CLEP.S344435
3. KDIGO Board Members. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Supplements.* 2012;2:279. doi:10.1038/kisup.2012.3

Dove Medical Press encourages responsible, free and frank academic debate. The content of the Clinical Epidemiology 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the Clinical Epidemiology editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

Clinical Epidemiology

Dovepress

Publish your work in this journal

Clinical Epidemiology is an international, peer-reviewed, open access, online journal focusing on disease and drug epidemiology, identification of risk factors and screening procedures to develop optimal preventative initiatives and programs. Specific topics include: diagnosis, prognosis, treatment, screening, prevention, risk factor modification, systematic reviews, risk & safety of medical interventions, epidemiology & biostatistical methods, and evaluation of guidelines, translational medicine, health policies & economic evaluations. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use.

Submit your manuscript here: <https://www.dovepress.com/clinical-epidemiology-journal>

<https://doi.org/10.2147/CLEP.S375668>