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LETTER TO THE EDITOR

Comment on "Drug–Drug Interaction of the Sodium Glucose Co-Transporter 2 Inhibitors with Statins and Myopathy: A Disproportionality Analysis Using Adverse Events Reporting Data"

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Dear Editor,

We have read with great interest the recent paper of Alkabbani et al. [1] on the risk of myopathy related to sodium glucose co-transporter 2 (SGLT-2) inhibitors and statin use. Alkabbani et al. used 2202 myopathy cases and 686,186 non-cases from the US FDA Adverse Events Reporting System (FAERS). For their statistical analyses, they referred to the methods published by Thakrar et al. [2], who proposed two different models (an additive model and a multiplicative model) to assess the association between a disease and two drugs. Thakrar et al. especially emphasized to assess interactions between both drugs, where these interactions can be given on either an additive or multiplicative scale. Both of these models are generalized linear models with a binomial error and an identity/log link in the additive/multiplicative case. Binary indicators for the two drugs and their interaction are included as covariates. Thakrar et al. gave advice as to how these models can be fit with the GENMOD procedure in SAS (SAS Institute Inc., Cary, NC, USA). In the Appendix, we report the SAS code for the additive model based on the data given in Table 2 of the study by Alkabbani et al. [1].

Conveniently, the parameters from the additive model can be interpreted as risk differences. Thus, taking statins is associated with a larger absolute risk for myopathy of 0.818 percentage points compared with the reference group that took none of the two drugs. In contrast, taking SGLT-2 inhibitors is associated with a reduced absolute risk of myopathy of 0.045 percentage points. If there were no interaction between statins and SGLT-2 inhibitors, the two risk differences would sum up, yielding (with some minimal rounding error) a risk difference of $0.818 + (-0.045) = 0.772$ percentage points when taking both drugs compared with the reference group. However, when directly calculating this risk difference for taking both drugs, we found $60 / (60 + 13{,}293) - 735 / (735 + 481{,}097) = 0.449\ \% - 0.152\% = 0.297$ percentage points. This value is substantially smaller than the value that is expected under the assumption of no interaction (0.772 percentage points). The interaction parameter from Table 1 is, by definition, equal to the difference of the two figures: $0.297 - 0.772 = -0.475$ percentage points $= -0.00475$ with a 95% confidence interval [CI] of -0.00603 to -0.00347.

Therefore, there is a clear clinically relevant and statistically significant additive interaction between statins and SGLT-2 inhibitors. If we would assume the observed results to be causal, this interaction would be highly protective, and additionally taking SGLT-2 inhibitors to statins would reduce the detrimental effect of statins on myopathy

Table 1 Results from fitting the additive model of Thakrar et al. [2] to the data set for SGLT-2 inhibitors and statins on the risk of myopathy, as given in Table 2 of the study by Alkabbani et al. [1]

Parameter	Estimate	95% CI	*p*-Value
SGLT-2	−0.00045	−0.00075 to −0.00016	0.0027
Statin	0.00818	0.00765 to 0.00870	<0.0001
Interaction	−0.00475	−0.00603 to −0.00347	<0.0001

CI confidence interval, *SGLT-2* sodium glucose co-transporter 2

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by 0.00475 / 0.00818 = 59% [95% CI 44%–73%]. The respective public health impact would be considerable. Focusing on the German situation, we refer to Ihle et al. [3], who obtained population-based nationwide data. They reported a 1-year incidence of myopathy in German incident statin users of 1.93% (= 10,250 / 531,672). Thus, one could prevent 0.00475 / 0.00818 * 10,250 = 5960 [95% CI 4469–7450] myopathy cases each year only in Germany, if new statin users started simultaneously with SGLT-2 inhibitor therapy.

In line with the findings from the additive model, the interaction from the multiplicative model is also negative and statistically significant (data not shown). Thus, SGLT-2 inhibitors also lower the statin effect on myopathy on the multiplicative scale. This is in contrast to the assertion of Alkabbani et al., that "both estimates of the interaction were not significant from the additive and multiplicative models".

It should be noted that our computations were based on the crude data from Table 2, whereas Alkabbani et al. had additional access to potential confounders and have used them in their analyses. While there are some differences between adjusted and unadjusted analyses, we are confident that the negative interactions would also be found in adjusted analyses.

Interestingly, we recently saw a similar potentially protective drug–drug interaction for the use of dipeptidyl peptidase 4 (DPP-4) inhibitors and statins on myopathy risk [4], and we refer to this previous letter for an explanation of the multiplicative model of Thakrar et al. [2].

To conclude, the main aim of this letter is not to criticize Alkabbani et al. for the problems in their statistical analysis. Indeed, we have also seen the same problems with the Thakrar models in other publications [4]. Unfortunately, the original paper by Thakrar et al. is unnecessarily technical, whereas the actual software code for model fitting and the interpretation of parameters is rather simple. As demonstrated above, the central results of interest such as risks, risk differences, and sums of risk differences can even be calculated from the raw data using a pocket calculator (albeit without their CIs). We thus encourage future researchers who are assessing drug–drug interactions and are uneasy with the technical details of the Thakrar models to contact a biostatistician. The safety data from the large pharmacovigilance databases are just too precious to allow suboptimal statistical analyses to limit their value for pharmacoepidemiology and clinical research.

Appendix

```
data SGLT2iStatin;
     input SGLT2i Statin NCases NNonCases;
     NObservations=NCases+NNonCases;
     cards;
     0 0  735 481097
     1 0   58  54097
     0 1 1349 137699
     1 1   60  13293
;run;

proc genmod data=SGLT2iStatin;
     class SGLT2i Statin / param=ref ref=first;
     model NCases/NObservations=SGLT2i Statin SGLT2i*Statin /
                                dist=binomial link=identity;
     ods output ParameterEstimates=AdditiveModelGENMOD;
     title"Alkabbani, Myopathy with SGLT2-Inhibitors and Statins,
           Additive model, GENMOD";
run;

proc print data=AdditiveModelGENMOD;
     var Parameter Estimate LowerWaldCL UpperWaldCL ProbChiSq;
     format Estimate LowerWaldCL UpperWaldCL  7.5;
run;


proc nlmixed data=SGLT2iStatin df=10000;
     parms Intercept 0.1 b_SGLT2i 0 b_Statin 0 b_Interaction 0;
     LinearPredictor= Intercept + b_SGLT2i*SGLT2i + b_Statin*Statin +
                      b_Interaction*SGLT2i*Statin;
     model NCases ~ binomial(NObservations,LinearPredictor);
     estimate "Percentage reduction" b_Interaction/b_Statin;
     estimate "Reduction of cases in Germany"
               (b_Interaction/b_Statin)*10250;
     title"Alkabbani, Myopathy with SGLT2-Inhibitors and Statins,
           Additive model, NLMIXED";
run;
```

Declarations

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Conflicts of interest Oliver Kuss has received honoraria for biostatistical education from Berlin-Chemie. Wolfgang Rathmann has received consulting fees from AstraZeneca, Boehringer Ingelheim and Novo-Nordisk for attending educational sessions or advisory boards, and institutional research grants from NovoNordisk, outside the topic of this work. Both authors have noted the journal's policy on competing interests and confirm that they have reported all interests that could impart bias on the submitted work.

Ethics approval This work only includes aggregated data that were published in the original work of Alkabbani et al. on which this comment is based. Therefore, ethics approval was not applicable and was not applied for.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The full data set is reported in the Appendix

Code availability The full SAS analysis code is reported in the Appendix.

Authors' contributions OK conceived the initial idea for this letter, performed the statistical analysis, and wrote the first draft of the paper. WR is the guarantor for the clinical content, commented on the analysis, and reworked the initial draft. Both authors have read and approved the final version of this letter.

References

1. Alkabbani W, Pelletier R, Beazely MA, Labib Y, Quan B, Gamble JM. Drug-drug interaction of the sodium glucose co-transporter 2 inhibitors with statins and myopathy: a disproportionality analysis using adverse events reporting data. Drug Saf. 2022;45:287–95. https://doi.org/10.1007/s40264-022-01166-3.
2. Thakrar BT, Grundschober SB, Doessegger L. Detecting signals of drug-drug interactions in a spontaneous reports database. Br J Clin Pharmacol. 2007;64:489–95. https://doi.org/10.1111/j.1365-2125.2007.02900.x.
3. Ihle P, Dippel FW, Schubert I. Statin-associated myopathy. Assessment of frequency based on data of all statutory health insurance funds in Germany. Pharmacol Res Perspect. 2018;6(3):e00404. https://doi.org/10.1002/prp2.404.
4. Kuss O, Rathmann W. A missed protective drug-drug interaction of DPP-4 inhibitors and statins on myopathy risk. Acta Diabetol. 2020;57(1):113–4. https://doi.org/10.1007/s00592-019-01440-4.