Review 2: "Impact of Glucose-Lowering Drugs on Mortality and Other Adverse Outcomes in Patients with Type 2 Diabetes Admitted for COVID-19"

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RR:C19 Evidence Scale rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

Review:

This multi-center retrospective study aims to ascertain the impact of various glucose-lowering medications on outcomes including death and composite outcomes such as the need for ICU or mechanical ventilation in those with type 2 diabetes mellitus hospitalized with COVID-19 in Spain. They ultimately found that the glucose-lowering drugs had a neutral effect on mortality and adverse outcomes.

There is a growing body of evidence on the impact of diabetes in those infected with COVID-19. Many studies have so far shown that those with diabetes tend to have more severe disease and that diabetes control may play a role as well.[1] There is a paucity of evidence concerning the impact of glucose-lowering drugs and their effect on those infected with COVID-19; thus, this study is relevant and brings insight to this ever-growing topic. The research so far is predominantly theoretical such as the potential physiologic protective effects of DPP4 inhibitors.[2] Few retrospective observational studies have found mixed results such as insulin associated with poorer outcomes, metformin having a protective effect, and other drugs having neutral effects.[3] The effect of metformin in minimizing disease severity and prevention of COVID-19 is currently being formulated as a randomized-control trial.[4] Thus it is difficult to analyze whether the results of this study are congruent with other available evidence due to the very limited available studies and lack of randomized-control trials completed to date.

This study concluded that these medications in general tended to have a neutral effect in terms of outcomes and disease severity. What was not taken into account was in-hospital management of diabetes, glycated hemoglobin levels and thus glycemic

control, and utilization of steroids. All of these factors could play a role in potentially affecting outcomes independent of these medications and are potential confounders. It is therefore important to realize that these were medications that patients were on prior to admission and that no data is provided about in-hospital management. Most likely none of the oral medications were continued during hospitalization. These results of neutral effect should therefore be taken in this context and not mitigate the risk of some these medications during acute illness such as the risk of DKA in those taking SGLT-2 inhibitors. Patient adherence to medications could not have been assessed given the retrospective nature of the study. Another limitation is the fact that not all glucose-lowering drugs were analyzed. Also, the study is observational and looks at a single population in Spain and does not state race in the demographic description. Both of these factors can prohibit the generalizability of these findings. The manuscript does address and acknowledge many of these limitations, and recognizes the need for a prospective study.

What was helpful is that they utilized propensity scores, thus assisting in eliminating some confounders by matching population with similar characteristics. This is particularly helpful in strengthening their conclusions as recent studies about statin use as well as angiotensin receptor converting enzymes inhibitor use have been studied in those with COVID-19 and both commonly prescribed in diabetics.[5,6] What was unique is the comparison performed with each glucose-lowering drug to others as well as drug combinations while at the same time adjusting for potentially confounding variables. The sample size studied was a reasonable number when compared to similar studies and the multi-center nature of the study strengthens it as well.

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