

DOM-19-???? Bailey Commentary on Opinion McGuire

Commentary to:

DOM-18-1053-R1 McGuire et al

FDA Guidance on Antihyperglycemic Therapies for Type 2 Diabetes: One Decade Later

FDA guidance on cardiovascular risk of antidiabetic therapies: one decade later

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The 2008 FDA guidance for industry on cardiovascular (CV) risk of new antidiabetic therapies arose from a history of CV safety concerns brought to a head by findings with rosiglitazone and the ACCORD trial of intensive glycaemic control [1-4]. The guidance focussed mostly on pre-approval (phase 2 and 3) trials, recommending inclusion of sufficient patients at higher risk of CV events to support an analysis that could exclude an unacceptable increase in CV risk. The analysis required a risk ratio with an upper bound of a two-sided 95% confidence interval (95% CI) <1.8 and preferably <1.3 . Post-marketing trials to assess major adverse cardiac events (MACE) might then be requested to confirm an upper 95% CI <1.3 using a composite 3-point MACE (CV death, nonfatal MI and nonfatal stroke) or 4-point MACE (3-point + hospitalisation for unstable angina) in a large population of type 2 diabetes patients exhibiting a range of CV disease and/or CV risk.

Despite no increase in MACE during pre-approval phase 2/3 trials, post-marketing CV outcome trials (CVOTs) have been undertaken for all non-insulin glucose-lowering agents approved by FDA since 2008. These have confirmed a non-inferior MACE or beneficial effects on MACE compared to placebo when added to standard care. FDA is now reconsidering the 2008 guidance, and McGuire et al provide a thoughtful and constructive evaluation of lessons learned and possible modifications to this guidance in their opinion article “FDA guidance on antihyperglycemic therapies for type 2 diabetes: one decade later” [2, 5].

The main message from the deliberations of McGuire et al is that the CVOTs have provided such valuable information regarding CV outcomes and other aspects of safety and efficacy that regulators are encouraged to retain one large randomised controlled trial (RCT) for outcomes with each new glucose-lowering therapy. Given the inordinate cost of such trials (probably 200-500 million USD per trial), which might deter pharma enthusiasm to develop new glucose-lowering agents, the authors have considered potential ways to “refine” the trials to improve efficiency while increasing the amount, reliability and applicability of the data gathered.

Alternative sources of relevant information from observational ‘real world’ database interrogations are accepted as useful complementary approaches but lacking sufficient specificity to replace large well-structured RCTs. Achieving efficiency gains in RCTs might involve procedural elements such as simplification of re-consenting and adjudication protocols, and adopting the principles of ‘pragmatic’ designs could facilitate expansion of population size [6]. While active comparator trials, possibly with relaxed non-inferiority margins, are informative, they are not seen as alternatives to individual RCTs, provided that ethical aspects are fully addressed through diligent standard of care. Also, the structure-function specificities of individual agents preclude generalisations across a class.

So, the perennial problem of comparing between trials remains: higher event rates with patients who have already had a CV event enable shorter trials with fewer patients, but debate continues

over the extrapolation of safety data for secondary prevention of MACE to primary prevention in patients with varying degrees of CV risk [7-9]. One suggestion by McGuire et al is to define a minimum degree of CV risk at recruitment: other possibilities include a broader composite primary endpoint or multiple primary endpoints, which might then include hospitalisation for heart failure or all-cause hospitalisation. However, standardising the implementation of protocols and criteria for an expanded range of less specific events can be a particular challenge. Dilution of statistical power by multiple and hierarchical analyses with nominal significances requires careful evaluation: indeed, marginal differences in the upper 95% CI either side of unity have caused considerable discrepancies of interpretation between some CVOTs [9]. The possibility of supplementing outcomes with recurrent events in the same individual highlights the potential for bias, reminding that RCTs can reduce but not exclude susceptibility to bias and confounding variability.

Building on the risk-benefit insights already gained from CVOTs, McGuire et al champion the retention of at least one large randomised outcomes trial for new glucose-lowering agents, and critique a selection of options for potential cost-savings and enhanced data acquisitions that regulators might wish to consider.

References

1. US Department of Health and Human Services Food and Drug Administration. Guidance for Industry. Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008.

www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf

Accessed 5 Feb 2019

2 FDA Background Document: Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), October 24-25, 2018.

<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM623913.pdf>

Accessed 5 Feb 2019

3 Nissen SE, Wolski S. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; 356: 2457-2471.

4. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358: 2545-2559.

5. McGuire DK, Marx N, Johansen OE, Inzucchi SE, Rosenstock J, George JT. FDA Guidance on Antihyperglycemic Therapies for Type 2 Diabetes: One Decade Later. *Diabetes Obes Metab* 2019, 21, on-line. <https://doi.org/10.1111/dom.13645>

6. Ford I, Norrie J. Pragmatic Trials. *N Engl J Med* 2016; 375:454-463.
7. Cefalu WT, Kaul S, Gerstein HC, Holman RR, Zinman B, Skyler JS, Green JB, Buse JB, Inzucchi SE, Leiter LA, Raz I, Rosenstock J, Riddle MC. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care* 2018; 41: 14-31.
8. Regier EE, Venkat MV, Close KL. More than seven years of hindsight: revisiting the FDA's 2008 guidance on cardiovascular outcomes trials for type 2 diabetes medications. *Clin Diabetes* 2016; 34: 173–180
9. Bailey CJ, Marx, N. Cardiovascular protection in type 2 diabetes: Insights from recent outcome trials. *Diabetes Obes Metab* 2019, 21, 3-14.