LETTER

ADVANCE and glycaemia thresholds: a need to clarify the statistical approach

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To the Editor: The recent study published by the ADVANCE Collaborative Group confirming that there is a lower threshold of optimal HbA_{1c} [1] is a welcome confirmation of the original work published in *The Lancet* [2]. However, there is at least one important analytical failing that simply must be addressed for this study to be considered valid. Furthermore, the authors' analysis may violate an assumption of the survival methods that were applied in the original study.

The impact of HbA_{1c} on vascular outcome can only have one true association. However, Zoungas and colleagues report two consistently differing patterns of association dependent upon whether participants were randomised to their intensive treatment arm or to standard care (see Fig. 1 in Zoungas et al [1]). Explained simply, the association between the hazard of major macrovascular events and HbA_{1c} was higher at lower HbA_{1c} levels in the intensive treatment arm. These systematic differences must relate to residual confounding. The authors are aware of this potential problem since they point out in the Discussion section that '…despite extensive multiple variable adjustment, these analyses may be unable to completely eliminate the effects of residual confounding attributable to disease severity'.

The original report by the ADVANCE Group published in *The New England Journal of Medicine* [3] reported

clearly that the most striking differences between the treatment arms by the end of the study related to differences in treatment regimens (Table 1). In fact, there was remarkably little difference between the two arms in any of the other reported variables at the end of the study (see Table 1 in ADVANCE Collaborative Group et al [3]). Two of the most obvious differences between the two arms were the increased use of sulfonylureas and/or insulin in the intensive arm (Table 1). Both of these treatments are hypothesised to increase the risk of adverse outcome vs alternative treatments [4, 5].

Regarding the issue of violation of the assumptions of the Cox model [6], HbA_{1c} appears to have been introduced into the model as the mean of all HbA_{1c} observations between baseline and the end of the study. This is technically incorrect in that the survival model should not include fixed values following baseline. The original *Lancet* paper used sensitivity analysis to explore this matter [2]. Whilst I agree that this is unlikely to have impacted on their findings, it is important that HbA_{1c} be introduced as a time-dependent covariate to check the sensitivity of this covariate. After all, this is the central focus of their epidemiological study.

It is vital that the authors re-run their analysis and evaluate potential treatment-related effects. The fact that this has not been done already is surprising and deserves an explanation, since it is important in terms of the interpretation of both the original study and the secondary analysis. Their discussion point relating to residual confounding in terms of disease severity is bewildering given that the most obvious source of residual confounding is well-documented in their reports.

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Table 1 Glucose-lowering treatment regimens of participants enrolled in the ADVANCE study at baseline and at end of study

Treatment regimen	Baseline					End of follow-up				
	Intensive		Standard		RR	Intensive		Standard		RR
	n	%	n	%		n	%	n	%	
Gliclazide (modified-release)	422	7.6	443	8.0	1.0	4,209	87.2	80	1.7	51.7
Other sulfonylurea	3,578	64.2	3,513	63.1	1.0	89	1.8	2,606	55.0	0.0
Any sulfonylurea	4,000	71.8	3,956	71.0	1.0	4,298	89.0	2,686	56.7	1.6
Metformin	3,397	61.0	3,355	60.2	1.0	3,455	71.6	3,057	64.5	1.1
Thiazolidinedione	201	3.6	206	3.7	1.0	788	16.3	495	10.4	1.6
Acarbose	512	9.2	448	8.0	1.1	891	18.5	576	12.1	1.5
Glinide	103	1.8	84	1.5	1.2	58	1.2	127	2.7	0.4
Insulin	82	1.5	77	1.4	1.1	1,953	40.5	1,142	24.1	1.7
None	487	8.7	524	9.4	0.9	42	0.9	220	4.6	0.2
All participants	5,571		5,569			4,828		4,741		

Modified from ADVANCE Collaborative Group et al [3]

References

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