Review

Is HbA$_{1c}$ a valid surrogate for macrovascular and microvascular complications in type 2 diabetes?

T. Bejan-Angoulvant [a,b,c], C. Cornu [d,e,f,g], P. Archambault [h], B. Tudrej [h], P. Audier [h], Y. Brabant [h], F. Gueyffier [d,e,f,g], R. Boussageon [h,*]

[a] CHRU de Tours, Service de Pharmacologie, 37000 Tours, France
[b] UMR 7292, CNRS, Université François-Rabelais, 37000 Tours, France
[c] Université François-Rabelais, GICC, 37000 Tours, France
[d] Inserm, Clinical Investigation Centre (CIC1407), 69000 Lyon, France
[e] CHU de Lyon, Service de Pharmacologie Clinique et Essais Thérapeutiques, 69000 Lyon, France
[f] CNRS, UMR5558, 69000 Lyon, France
[g] Université Claude Bernard Lyon 1, Faculté de Médecine Laennec, 69376 Lyon Cedex 08, France
[h] Département de médecine générale, Université de Poitiers, 86000 Poitiers, France

Abstract

Recent recommendations regarding type 2 diabetes (T2D) patients' treatments have focused on personalizing glycosylated haemoglobin (HbA$_{1c}$) targets. Because the relationship between HbA$_{1c}$ and diabetes prognosis has been established from large prospective cohorts, it is valid to question the extrapolation from population-based risk reduction estimations to individual predictions. Our study aimed to investigate the relationship between HbA$_{1c}$ reductions and clinical outcomes in randomized controlled trials (RCTs), using a meta-regression approach. Included were RCTs comparing intensive vs. standard glucose-lowering regimens for cardiovascular events and microvascular complications in T2D patients. Eight studies (33,396 patients) providing data for HbA$_{1c}$ reductions were found. In our meta-regression, HbA$_{1c}$ decreases were not significantly associated with reductions in our main study outcomes: total and cardiovascular mortality. They were also not associated with any of the secondary endpoints, including myocardial infarction, stroke and severe hypoglycaemia. Sensitivity analysis showed a significant correlation only between HbA$_{1c}$-lowering and severe hypoglycaemia ($P = 0.014$). Meta-regression analysis could find no significant association between HbA$_{1c}$-lowering and a decrease in clinical outcomes, thereby questioning the use of HbA$_{1c}$ as a surrogate outcome for T2D-related complications. Thus, RCTs vs. placebo are urgently required to evaluate the risk–benefit ratios of therapeutic strategies beyond HbA$_{1c}$ control in T2D patients.
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1. Introduction

Recent recommendations from American and European diabetes societies [1] have focused on personalizing glycosylated haemoglobin (HbA$_{1c}$) targets in type 2 diabetes (T2D) patients. This new 'personalized' strategy, based on diabetes duration and comorbid conditions, was established after the last major studies—the ACCORD, ADVANCE, and VADT [2–4]—were

published. However, these recommendations do not question the 'treat-to-target' model, nor do they discuss reviews of the available scientific evidence [5–9].

How did the HbA$_{1c}$ dogma become so popular? In 2000, Stratton et al. [10] found an independent, log-linear relationship between mean HbA$_{1c}$ and diabetes-related complications, with no evidence of a threshold, in a large prospective cohort of T2D patients. The authors further estimated that, for each 1% reduction in HbA$_{1c}$, an estimated risk reduction of 21% for T2D-related mortality, 21% for all T2D-related criteria, 14% for myocardial infarction (MI) and 37% for microvascular complications could be anticipated.

However, extrapolation from population-based risk reduction estimations to individual predictions is questionable. In addition, the model should take into account the impact of pharmacological treatment, as has already been pointed out in the field of hypertension [11,12]. Furthermore, recent trials in T2D patients have not only confirmed that lowering HbA_{1c} to target did not translate into clinical benefit for any macrovascular complications [13–15] except non-fatal MI, but they also have suggested it could be harmful by increasing cardiovascular mortality and heart failure [14–16]. Finally, the expected reductions in microvascular complications were also not observed in clinical trials [17,18].

For these reasons, several authors have questioned the use of surrogate markers and stressed the need for studies based on important patient outcomes in T2D [19–21]. Our present study is therefore a further investigation of the relationship between HbA_{1c} reductions and clinical outcomes, using a meta-regression approach, in randomized controlled trials (RCTs). These RCTs were included in our previous systematic review, which aimed to assess the effect of intensive glucose-lowering treatment on cardiovascular events and microvascular complications in T2D patients.

2. Methods

The methods used to collect data from RCTs have been previously described. Briefly, all RCTs up to July 2010 assessing the effects of intensive compared with standard glucose-lowering regimens on cardiovascular events and microvascular complications in T2D patients were identified in MEDLINE, Embase and Cochrane Reviews databases.

Primary clinical outcomes for this meta-regression analysis were all cause mortality and cardiovascular death. Secondary outcomes were: all MIs; non-fatal MIs; all strokes (fatal and non-fatal); congestive heart failure; photocoagulation; retinopathy (new or worsening); visual deterioration or blindness; neuropathy (new or worsening); microalbuminuria (new or worsening); renal failure (or doubling of serum creatinine levels); peripheral vascular events (leg revascularization, peripheral arterial disease or intermittent claudication); amputation events; and severe hypoglycaemia. Outcome definitions corresponded to what was reported in the originally published papers.

This analysis only included studies that provided HbA_{1c} reductions. As meta-regression is not recommended when the number of studies is too small [22], it was arbitrarily decided to consider meta-regression only if at least five studies provided data for HbA_{1c} reduction and for non-zero events of the considered clinical outcomes.

Statistical analysis: for each trial, aggregate data were extracted for each considered outcome and for the mean difference in HbA_{1c} between intensive vs. standard glucose-lowering regimens at the end of follow-up. Using a random-effects model, the relationship between the log odds ratio [log(OR)] for the studied outcome and the difference in HbA_{1c} between trial arms were determined by univariate analyses. A sensitivity analysis, including data from three recent studies of high-risk T2D patients who reported cardiovascular outcomes, was also conducted [13–15]. All statistical analyses were carried out according to the intention-to-treat principle whenever possible. No adjustments for multiple tests were performed, as the analysis had an exploratory purpose only. A P value < 0.05 was considered significant.

3. Results

Initially, 13 trials (considered as 11 studies) were included in the systematic review and meta-analysis [8], but only eight studies (involving 33,396 patients) provided data for HbA_{1c} reductions and, thus, were included in this meta-regression [2–4,23–28]. The UKPDS 33 [22] and UKPDS 34 [23] were combined and reported as the UKPDS. Main characteristics of the included studies are shown in Table 1.

3.1. Meta-regression analysis

Data from at least five trials were available for total mortality ($n = 7$), cardiovascular mortality ($n = 8$), MI ($n = 7$), stroke ($n = 7$), heart failure ($n = 8$), microalbuminuria ($n = 6$), neuropathy ($n = 6$), peripheral vascular events ($n = 6$) and severe hypoglycaemia ($n = 5$). For MI, studies reported events as either total events or non-fatal events, or as both. As both criteria are strongly correlated, to increase the power of the meta-regression, it was decided to use total events whenever reported and non-fatal events when not. The decrease in HbA_{1c} was not significantly associated with either total or cardiovascular mortality (Table 2, Fig. 1), nor was it associated with any secondary endpoints, including severe hypoglycaemia (Table 2, Fig. 2).

3.2. Sensitivity analysis

The sensitivity analysis added three further trials and 29,098 patients to the meta-regression analysis (Table 2, Figs. 1 and 2) [13–15], and showed a softening of the association between HbA_{1c}-lowering and increases in total and cardiovascular mortality, and microalbuminuria. It also revealed a sharpening of the association between HbA_{1c} and reduction of MI. Indeed, sensitivity analysis modified the association between HbA_{1c}-lowering and changes in stroke and heart failure risk. HbA_{1c}-lowering was significantly correlated with an increase in severe hypoglycaemia ($P = 0.014$).

4. Discussion

In the field of assessment of medicinal efficacy, non-clinical and intermediate criteria can be used to demonstrate the mechanism by which drugs are supposed to be useful. These criteria have also been proposed as surrogates to speed up the process of bringing drugs to the marketplace [29]. Indeed, these criteria may be declared positive well before the corresponding clinical outcomes are confirmed, and also require considerably fewer subjects. However, these intermediate criteria should be measurable in a reliable and reproducible manner, and should also predict the impact on the clinical criterion (such as patients'

Table 1
Main characteristics of studies included in our analyses.

Study [reference]	Patients (*n*): intensive/standard	Diabetes duration[a]	Age[a]	Follow-up[a]	HbA$_{1c}$[b] (%)	Intensive/standard strategy	Glycaemic target
UKPDS [23,24]	3071/1138	< 1	53	10	0.9	Met, SU or Ins/diet	FPG < 6 mmol/L FPG < 15 mmol/L
VA 97 [25]	75/78	7.8	60	2.3	2.5	Intensive GLD/morning Ins	HbA$_{1c}$ < 7%
PROactive [26]	2605/2633	8	62	2.9	0.6	PioG + current GLD/placebo + current GLD	None
Dargie [27]	110/114	4	64	1	0.7	RosiG + current GLD/placebo + current GLD	None
ACCORD [2]	5128/5123	10	62	3.5	1.1	Intensive GLD/any GLD	HbA$_{1c}$ < 6% vs. 7–7.9%
ADVANCE [3]	5571/5569	8	66	5	0.5	Gli + GLD/standard GLD	HbA$_{1c}$ < 6.5% vs. local target
VADT [4]	892/899	11.5	60	5.6	1.5	Intensive GLD/standard GLD	HbA$_{1c}$ < 6% vs. < 9%
HOME [28]	196/194	12	61	4.3	0.2	Ins + Met/Ins + placebo	None
Total included in meta-analysis	17,648/15,748						3 studies without targets, 5 studies with targets
EXAMINE [13]	2679/2701	7.2	61	1.5	0.36	Alogliptin + current GLD/placebo + current GLD	None
SAVOR-TIMI 53 [14]	8280/8212	10.3	65	2.1	0.2	Saxagliptin + current GLD/placebo + current GLD	None
AleCardio [15]	3616/3610	8.6	61	2	0.6	Aleglitazar + current GLD/placebo + current GLD	None
Total added for sensitivity analysis	14,575/14,523						3 studies without targets

FPG: fasting plasma glucose; GLD: glucose-lowering drugs; Gli: gliclazide; Ins: insulin; Met: metformin; PioG: pioglitazone; RosiG: rosiglitazone; SU: sulphonylurea.
[a] Means or medians (years).
[b] Difference between trial arms (standard minus intensive).

Table 2
Meta-regression analysis results including sensitivity analysis for main and secondary study outcomes.

	Studies (*n*)	I^2 (%)	Tau	Coef (SE)	*P* value
Main outcomes					
Overall mortality	7	26	0.006	0.222 (0.168)	0.242
Sensitivity analysis	10	39	0.009	0.105 (0.130)	0.442
Cardiovascular mortality	8	32	0.015	0.367 (0.231)	0.164
Sensitivity analysis	11	37	0.014	0.240 (0.168)	0.186
Secondary outcomes					
Myocardial infarction	7	0	0	−0.098 (0.142)	0.518
Sensitivity analysis	10	0	0	−0.158 (0.101)	0.158
Stroke	7	0	0	0.114 (0.194)	0.584
Sensitivity analysis	10	0	0	−0.025 (0.151)	0.875
Heart failure	8	63	0.043	0.020 (0.274)	0.945
Sensitivity analysis	11	46	0.017	−0.085 (0.163)	0.616
Microalbuminuria	6	0	0.002	−0.307 (0.138)	0.091
Sensitivity analysis	7	47	0.007	−0.138 (0.133)	0.347
Neuropathy	6	0	0	−0.135 (0.085)	0.188
Peripheral vascular events	6	0	0.011	−0.189 (0.241)	0.477
Severe hypoglycaemia	5	18	0.021	0.606 (0.307)	0.143
Sensitivity analysis	7	10	0.018	0.812 (0.219)	0.014

Coef (SE): meta-regression coefficient (standard error).

Total mortality
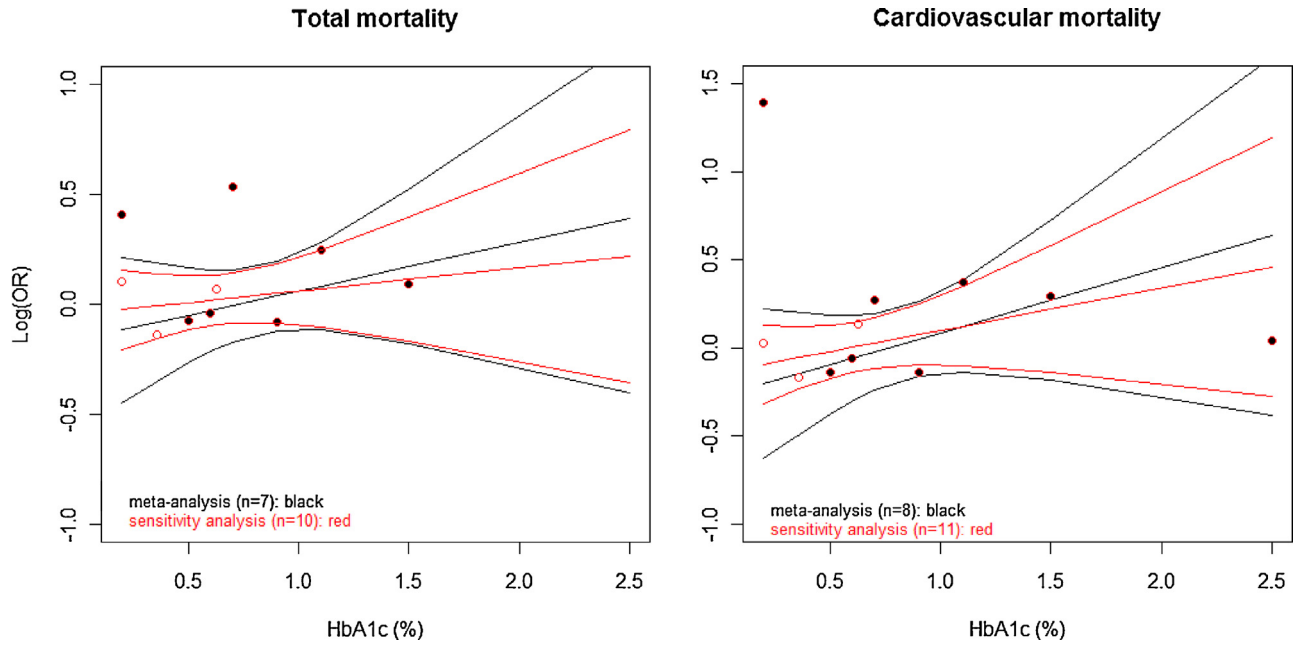
Cardiovascular mortality

Fig. 1. Graphs of meta-regression analyses of the main study outcomes: overall and cardiovascular mortality. They represent the log odds ratio [Log(OR)] of events plotted against HbA$_{1c}$ reductions observed between trial arms. Each point represents a clinical trial included in the meta-analysis (solid circles) or in the sensitivity analysis (unfilled circles). The curves represent the regression line and its 95% confidence intervals. HbA$_{1c}$ (%) = reductions of glycated haemoglobin between treatment arms; Log(OR) = log-transformed odds ratios for secondary outcomes in the trials.

Myocardial infarction (all or non-fatal)

Stroke (all)

Congestive heart failure

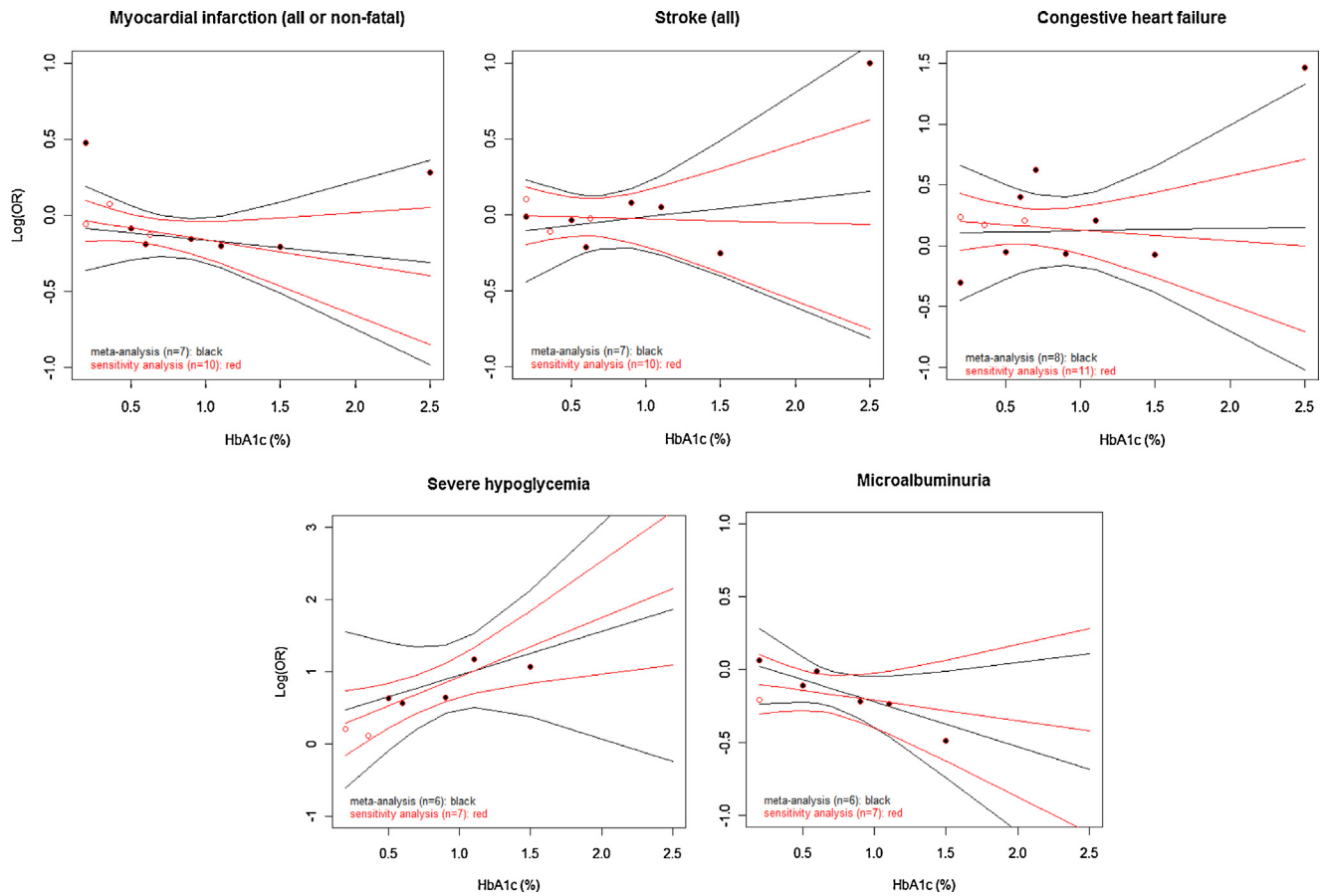## Severe hypoglycemia

Microalbuminuria

Fig. 2. Graphs of meta-regression analyses for secondary outcomes showing the log odds ratio [Log(OR)] of events plotted against HbA$_{1c}$ reductions between trial arms. Each point represents a clinical trial included in the meta-analysis (solid circles) or in the sensitivity analysis (unfilled circles). The curves represent the regression line and its 95% confidence intervals. HbA$_{1c}$ (%) = reductions of glycated haemoglobin between treatment arms; Log(OR) = log-transformed odds ratios for secondary outcomes in the trials.

symptoms, quality of life or morbidity and mortality) intended for use as the surrogate outcome [30].

Nevertheless, their use to obtain drug-marketing authorization is controversial and even highly criticized. There are many examples of clinical trials that have yielded unexpected results for clinical criteria even though the observed effect on the surrogate endpoint was favourable [31]. Many statistical techniques have been developed to validate the use of intermediate criteria as surrogates [30]. Schematically, three conditions are required [32]: correlation (statistical association), predictive effect, and capture. The first condition is usually verified through observational studies; the other two require RCTs that assess treatment effects on both surrogate endpoints and clinical criteria.

In T2D, HbA_{1c} is the biological intermediate criterion for assessment of diabetic treatment efficacy. This means that any treatment that lowers glycaemia and HbA_{1c} with no associated weight loss and no increased cardiovascular risk can be defined as 'antidiabetic' and acquire marketing authorization [33]. Such reasoning implies that any reduction in HbA_{1c} is beneficial to patients. Thus, HbA_{1c} is considered a valid criterion for surrogacy, even though several authors have seriously questioned its validity [34,35]. The condition of correlation is supported by epidemiological studies confirming the statistical association between blood-glucose levels and the occurrence of macro- [10,36] and microvascular complications [10]. However, our analysis could find no significant relationship between the decrease in HbA_{1c} observed in RCTs evaluating glucose-lowering regimens and rates of total or cardiovascular mortality, or any cardiovascular or microvascular complications in T2D patients. Also, adding nearly 30,000 patients in the sensitivity analysis did not change the results except for severe hypoglycaemia.

These findings should call into question the simple causal relationship suggested by observational studies. It must also be emphasized that the correlation between HbA_{1c} levels and diabetic complications observed in epidemiological studies is interindividual, whereas the correlation investigated by meta-regression analysis of RCTs is both inter- and intra-individual and therefore more suitable for underpinning the validity of the surrogate outcome.

Regarding macrovascular complications, our analysis showed no relationship between HbA_{1c}-lowering and changes of MI risk, while intensification of glycaemic control reduced the risk of non-fatal MI by about 15% in a manner that was reproducible by different reviews and meta-analyses [5,8,37–39]. There was also no relationship between HbA_{1c}-lowering and the available data for microvascular complications (nephropathy and neuropathy), although this association has been considered strongly established by the medical community for years in patients with either type 1 diabetes (T1D) [40] or T2D [10]. Finally, the present meta-regression analysis showed a non-significant relationship between HbA_{1c}-lowering and an expected increased risk of severe hypoglycaemia, which did reach statistical significance in the sensitivity analysis, most probably because of the increased statistical power.

Several hypotheses may explain the lack of correlation between HbA_{1c}-lowering and the diabetic complications studied [41]. It may even be argued that T2D represents a particular condition for which interventions aiming to control glycaemia, including intensive lifestyle changes, have failed to demonstrate any beneficial effect on cardiovascular outcomes [42]. However, it is worth remembering that this was also the case in the high-cardiovascular-risk primary prevention MRFIT trial [43], in which antihypertensive treatment and statins showed significant clinical benefits [44,45]. Furthermore, most of the studies were of short duration (five of the eight had mean follow-ups of < 5 years), which was possibly insufficient to demonstrate clinical benefit, considering the time scale and progressive development of diabetic complications. Yet, several interventions for cardiovascular prevention in diabetic patients have shown significant clinical benefits, including total mortality, with treatment durations of < 5 years [46–48].

An alternative hypothesis is that the observed effects in RCTs evaluating the intensification in glycaemic control are not related to HbA_{1c} decreases. Instead, such effects may be related to the prescription of concomitant treatments, such as aspirin and ACE inhibitors, in the studies that were not double-blind [49]. In the UKPDS, there were also differences in blood pressure (BP) between some groups: after the 6-year follow-up, the chlorpropamide-treated group had a mean BP considerably higher than that for the other groups (143/82 mmHg vs. 138/80 mmHg; $P < 0.001$). The UKPDS authors emphasized that the proportion of patients treated with an antihypertensive drug differed depending on the group: 43% for the chlorpropamide-treated group compared with 34%, 36% and 38% for the other groups (treated with lifestyle and dietary guidelines, glibenclamide and insulin, respectively; $P = 0.022$).

A further step to explore whether HbA_{1c} is an appropriate surrogate outcome would be to analyze data from major clinical trials at the level of the individual patient. In fact, why has this not already been carried out? We hereby call upon all authors who have access to these data to perform such analyses. After the publication of large RCTs such as the ACCORD, ADVANCE and VADT, it remains incomprehensible that marketing authorizations continue to be granted on the grounds that new drugs reduce HbA_{1c} levels and demonstrates safety rather than efficacy as regards cardiovascular risk [50]. This point is further reinforced by the recent example of aleglitazar, a drug that will not be marketed because of its adverse effects and, above all, because it has no clinical efficacy—a 0.6% reduction in HbA_{1c}—and no benefits for cardiovascular risk while increasing the risk of diabetic nephropathy [15].

Our meta-regression analysis has several limitations that need to be acknowledged. Despite an analysis based on more than 30,000 patients, the small number of included studies (< 10) and, most of all, the post-hoc observational and exploratory nature of the analysis do not allow any definitive conclusions to be drawn, as no causal inference can be established. Also, none of the studies included in this meta-analysis were originally powered to show benefits for total or cardiovascular mortality, our main outcome, but rather for a composite of multiple cardiovascular events and total or cardiovascular mortality. This could further limit our conclusions, although it is unlikely to introduce any bias to our results, as cardiovascular death was a prespecified

secondary adjudicated outcome in nine of the 11 included studies. Furthermore, studies that tested intensive vs. standard care (5/11) were combined with studies that tested a drug added to baseline therapy vs. a placebo (6/11). This approach may be challenged, as achieving glycaemic control is an observational variable that does not permit causal inferences, whereas targeted glycaemic control does. However, both approaches ultimately lead to lowering HbA$_{1c}$ and both approaches lead to the formation of two groups—'more intense' and 'less intense' glucose-lowering arms—albeit with one approach being 'targeted' while the other is not. Because our objective was to investigate the relationship between HbA$_{1c}$ reductions and clinical outcomes in clinical trials assessing intensive compared with standard regimens, grouping the two types of trials seemed appropriate. Potential factors for between-study heterogeneity could be their design (superiority vs. non-inferiority) and duration of patients' follow-up. Unfortunately, given the small number of studies available for meta-regression analysis, statistical adjustment for these factors was not possible with a multivariate approach.

5. Conclusion

Despite the results of several large clinical trials, none was able to clearly identify an HbA$_{1c}$ target because no associated overall clinical benefits were demonstrated. Our meta-regression results do not allow definitive conclusions to be drawn and, instead, seriously question the use of glycated haemoglobin as a surrogate outcome for T2D-related complications (macrovascular and even microvascular). Carrying out RCTs vs. placebo that provide high-level evidence is urgently required to improve the overall care of diabetic patients, not just controlling their glycaemia. Prescribing antidiabetic drugs to tens of millions of patients worldwide without clearly documenting the associated benefit-to-risk balance is a far greater ethical issue than submitting tens of thousands of such patients to placebo treatments.

Authors' contributions

T.B.A. and R.B. wrote the first draft of the manuscript. T.B.A. performed the meta-regression and sensitivity analysis. P.A. and B.T. helped in redaction of the manuscript. Y.B., P.A., C.C. and F.G. interpreted the results and completed the final manuscript.

Disclosure of interest

References

[1] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–9.

[2] The ACCORD study group. Effects of intensive glucose-lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59.

[3] The ADVANCE collaborative group. Intensive blood-glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–72.

[4] Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–39.

[5] Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ 2011;343:d6898, http://dx.doi.org/10.1136/bmj.d6898.

[6] Hemmingsen B, Christensen LL, Wetterslev J, Vaag A, Gluud C, Lund SS, et al. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. BMJ 2012;344:e1771, http://dx.doi.org/10.1136/bmj.e1771.

[7] Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. Arch Intern Med 2012;172:761–9 [Review. Erratum in Arch Intern Med 2012;172:1095].

[8] Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, et al. Effect of intensive glucose-lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomized controlled trials. BMJ 2011;343:d4169, http://dx.doi.org/10.1136/bmj.d4169.

[9] Boussageon R, Supper I, Bejan-Angoulvant T, Kellou N, Cucherat M, Boissel JP, et al. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomized controlled trials. PLOS Med 2012;9:e1001204.

[10] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12.

[11] Poulter NR, Wedel H, Dahlöf B, Sever PS, Beevers DG, Caulfield M, et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). Lancet 2005;366:907–13.

[12] Boissel JP, Gueyffier F, Boutitie F, Pocock S, Fagard R. Apparent effect on blood pressure is only partly responsible for the risk reduction due to antihypertensive treatments. Fundam Clin Pharmacol 2005;19:579–84.

[13] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–35.

[14] Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–26.

[15] Lincoff AM, Tardif JC, Schwartz GG, Nicholls SJ, Rydén L, Neal B, et al. Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial. JAMA 2014;311:1515–25.

[16] Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis 2014;24:689–97.

[17] ACCORD Study Group, ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010;363:233–44.

[18] Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419–30.

[19] Shaughnessy AF, Slawson DC. What happened to the valid POEMs? A survey of review articles on the treatment of type 2 diabetes. BMJ 2003;327:266–73.

[20] Montori VM, Gandhi GY, Guyatt GH. Patient-important outcomes in diabetes – time for consensus. Lancet 2007;370:1104–6.

[21] Krumholz HM, Lee TH. Redefining quality – implications of recent clinical trials. N Engl J Med 2008;358:2537–9.

[22] Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions Version 5.1.0. The Cochrane Collaboration; 2011 [Available from http://www.cochrane-handbook.org. Updated March 2011].

[23] UK prospective diabetes study (UKPDS) group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes, UKPDS 33. Lancet 1998;352:837–53.

[24] UK prospective diabetes study (UKPDS) group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–65.

[25] Abraira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP, et al. Cardiovascular events and correlates in Veterans Affairs Diabetes Feasibility trial. Arch Intern Med 1997;157:181–8.

[26] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–89.

[27] Dargie HJ, Hildebrandt PR, Riegger GA, McMurray JJ, McMorn SO, Roberts JN, et al. A randomized, placebo-controlled trial assessing the effects of rosiglitazone on echocardiographic function and cardiac status in type 2 diabetic patients with New York Heart Association Functional Class I or II Heart Failure. J Am Coll Cardiol 2007;49:1696–704.

[28] Kooy A, De Jager J, Lehert P, Bets D, Wulffelé MG, Doncker AJ, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009;169:616–25.

[29] Psaty BM, Weiss NS, Furberg CD, Koepsell TD, Siscovick DS, Rosendaal FR, et al. Surrogate end points, health outcomes, and the drug-approval process for the treatment of risk factors for cardiovascular disease. JAMA 1999;282:786–90.

[30] Gueyffier F. What is the place for intermediate outcomes one cardiovascular prevention is achieved? Therapie 2003;58:31–6.

[31] Lacchetti C, Ioannidis J, Guyatt G. Surprising results of randomized trials. In: Guyatt G, Rennie D, Meade MO, Cook DJ, editors. Users' guides to the medical literature. New York, USA: McGraw-Hill Companies, Inc; 2008. p. 113–51.

[32] Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989;8:431–40.

[33] Lehman R, Yudkin JS, Krumholz H. Licensing drugs for diabetes. BMJ 2010;341:c4805, http://dx.doi.org/10.1136/bmj.c4805.

[34] Goodarzi MO, Psaty BM. Glucose-lowering to control macrovascular disease in type 2 diabetes: treating the wrong surrogate end point? JAMA 2008;300:2051–3.

[35] Yudkins JS, Lipska KJ, Montori VM. The idolatry of the surrogate. BMJ 2011;343:d7995, http://dx.doi.org/10.1136/bmj.d7995.

[36] Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose and risk of cause-specific death. N Engl J Med 2011;364:829–41 [Erratum in N Engl J Med 2011;364:1281].

[37] Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373:1765–72.

[38] Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–98.

[39] Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet 2014;383: 2008–17.

[40] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.

[41] Scheen AJ, Charbonnel B. Effects of glucose-lowering agents on vascular outcomes in type 2 diabetes: a critical reappraisal. Diabetes Metab 2014;40:176–85.

[42] Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–54.

[43] Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial Research Group. JAMA 1982;248:1465–77.

[44] Gueyffier F, Boutitie F, Boissel JP, Pocock S, Coope J, Cutler J, et al. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators. Ann Intern Med 1997;126:761–7.

[45] Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–7.

[46] Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the, HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253–9.

[47] Patel A, ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–40.

[48] Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96.

[49] Boussageon R, Supper I, Erpeldinger S, Cucherat M, Bejan-Angoulvant T, Kassai B, et al. Are concomitant treatments confounding factors in randomized controlled trials on intensive blood-glucose control in type 2 diabetes? A systematic review. BMC Med Res Methodol 2013;13:107, http://dx.doi.org/10.1186/1471-2288-13-107.

[50] Zannad F, Stough WG, Pocock SJ, Sleight P, Cushman WC, Cleland JG, et al. Diabetes clinical trials: helped or hindered by the current shift in regulatory requirements? Eur Heart J 2012;33:1049–57.