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Original article

Association between difference in blood pressure reduction and risk of cardiovascular events in a type 2 diabetes population: A meta-regression analysis

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ABSTRACT

Aim. – Recent US recommendations indicate a target blood pressure (BP) of 130/80 mmHg for patients with type 2 diabetes (T2D). Our aim was to characterize the association between risk of cardiovascular events and differences in BP decreases in randomized trials of a T2D population.
Methods. – A systematic search was made for randomized clinical trials assessing the effects of antihypertensive treatments in T2D patients on mortality, and fatal and non-fatal cardiovascular events, using a meta-regression technique to explore the influence of BP decreases on treatment effects.
Results. – A total of 88,503 patients from 44 randomized trials were included. There was no significant association between BP decreases and risk of all-cause or cardiovascular mortality, cardiovascular events or myocardial infarction. However, stroke risk was influenced by BP decreases: compared with no reduction, a 10-mmHg reduction in systolic BP was associated with a relative odds ratio (OR) decrease of 33% (OR: 0.67, 95% CI: 0.54–0.82), and a 5-mmHg diastolic BP reduction was associated with a relative OR decrease of 38% (OR: 0.62, 95% CI: 0.50–0.76). Restricting the analysis to double-blind studies did not change the results for diastolic BP.
Conclusion. – A reduction in BP lowers the risk of stroke, but does not appear to affect the risk of other cardiovascular events in a T2D population.

Introduction

High blood pressure (BP) is a major cardiovascular (CV) risk factor and, in the general population, the CV benefits of antihypertensive drugs may be partially explained by the different BP values achieved [1]. Indeed, BP decrease has been proposed as a surrogate endpoint of risk of stroke [2]. When BP is reduced, it appears to influence mainly the risk of stroke compared with other CV outcomes [3]. However, even for stroke, systolic BP (SBP) reduction explains only half of the risk reduction in the general population [4]. In the past, based on a subgroup analysis of the Hypertension Optimal Treatment (HOT) trial in diabetes patients, more stringent BP targets were recommended for patients with type 2 diabetes (T2D) compared with the general population [5,6]. However, as this BP target for the diabetes population became a subject of debate [7–9], eventually the same BP target as for the general population was proposed [10,11]. Yet, since those

Abbreviations: ACC, American College of Cardiology; ACE, Angiotensin-converting enzyme; AHA, American Heart Association; BP, Blood Pressure; CV, Cardiovascular; CVD, Cardiovascular Disease; DBP, Diastolic Blood Pressure; FDA, Food and Drug Administration; OR, Odds Ratio; RCT(s), Randomized Clinical Trial(s); REML, Restricted Maximum Likelihood; SBP, Systolic Blood Pressure; T2D, Type 2 Diabetes.

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recommendations were made, meta-analyses have shown some discrepancies among BP targets for CV prevention in T2D patients. Bangalore et al. [12] described an association between more intensive treatment targeting an SBP of 135 mmHg and a decrease in macrovascular events, while Reboldi et al. [13] confirmed that BP reduction appeared to lower the risk of stroke, but not the risk of myocardial infarction. A meta-analysis by Emdin et al. [14] suggested a decrease in risk of mortality for every 10-mmHg SBP reduction, whereas Brunström and Carlberg [15] reported an increased risk of CV death, but no benefit when baseline SBP was < 140 mmHg. In the general population, it has been suggested that lowering SBP to < 130 mmHg might be beneficial [16,17], but other meta-analyses found conflicting results [18]. Recently, the American College of Cardiology (ACC) and American Heart Association (AHA) recommended reducing BP to $< 130/80$ mmHg for patients with T2D [19].

The meta-regression approach investigates whether particular covariates (potential effect modifiers) might explain some of the differences in treatment effects observed across multiple studies [20,21], and explores whether any of the considered outcomes are influenced by BP changes [22]. In T2D populations, recent studies have focused on the influence of either baseline BP or achieved BP in intensive-treatment groups [12,15], or used a standardized approach (log of the risk of outcome multiplied by [10 mmHg/systolic BP reduction]) [14] which could bias the results [23]. In a previous study of differences in baseline and achieved BP in active-treatment vs control groups in T2D populations, outcomes were limited to myocardial infarction and stroke [13]. Our present study updates that exploration with more recent trials, and extends the analysis to overall and CV mortality as well as CV events.

Thus, the purpose of this study was to characterize the association between intensity of BP reduction and magnitude of clinical benefit on several CV events in T2D patients.

Material and methods

As no protocol has been previously published, the present study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Appendix A.1; see supplementary materials associated with this article online).

Eligibility criteria

Only studies fulfilling the inclusion criteria described below, following the PICO (population/problem, intervention/exposure, comparison, outcome) framework, were eligible for inclusion in our analysis.

Participants

Only patients aged ≥ 18 years with T2D were included. The diagnosis of T2D had to have been established using either standard criteria or, if necessary, the author's definition. Studies that included patients on dialysis, patients with solid organ transplants, pregnant women, patients with impaired glucose tolerance or impaired fasting glucose, or the metabolic syndrome only, were excluded.

Interventions

Eligible interventions were any antihypertensive drugs, such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, sartans (angiotensin receptor blockers), calcium-channel blockers, diuretics and intensive antihypertensive treatments. In trials combining the intervention of interest with another intervention, only data for the intervention of interest were included if the subgroup met our inclusion criteria. For example, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial, only data from the antihypertensive groups were considered and, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only data from the diabetes subgroup were included.

Comparisons

All comparisons against a control group (placebo, active treatment, usual care) were included.

Outcomes

Trials designed to evaluate CV events as either their primary or secondary endpoints were included, whereas trials reporting CV events for safety purposes only were not. The considered outcomes were: total deaths; CV deaths; CV events (CVEs); all myocardial infarctions (MIs; fatal, non-fatal); all strokes (fatal, non-fatal); major microvascular events; and major combined macrovascular and microvascular events.

Study design

Only parallel-group randomized clinical trials (RCTs) were included.

Outcomes of meta-analysis

Outcomes of this analysis were total deaths, CV deaths, CVEs, all MIs (fatal, non-fatal), all strokes (fatal, non-fatal), major microvascular events, and major combined macrovascular and microvascular events.

Information sources and search strategy

Published trials were identified through a computerized search of: (i) Medline (PubMed, www.pubmed.org, from inception to 1 March 2016); (ii) Embase (www.embase.com); and (iii) the Cochrane Central Register of Controlled Trials (CENTRAL). Our search terms comprised disease terms, a study design filter and drug terms. The study design filters were designed to identify placebo-controlled or head-to-head RCTs using a combination of index and free-text terms. The PubMed database was searched using a specific sensitive strategy (as described by Haynes et al. [24]), including type of "randomized clinical trial" and MeSH terms (Appendix A.2; see supplementary materials associated with this article online). Unpublished trials were searched for in: (i) abstracts and presentations from appropriate conferences (using the ISI Web of Knowledge database that indexes conference proceedings); (ii) reference lists from studies, reviews and meta-analyses obtained from the PubMed search; and (iii) the Internet, including websites dedicated to the dissemination of results from clinical trials (Medscape) and the US Food and Drug Administration (FDA), and those maintained by drug manufacturers, including product information sheets. Also included were trials published only in abstract form to limit the influence of potentially relevant trials unpublished when completed. When an abstract from proceedings and a full paper referred to the same trial, only the full article was included in our analysis. When two or more papers used the same data, only the most complete report was used.

Study selection, data collection and risk of bias assessment in individual studies

Study selection was performed by three independent reviewers (M.C., G.G., H.H.L.), among whom a consensus had to be reached in cases of disagreement. The study flow diagram (Appendix A.3; see

Table 1
Characteristics of the trials included in the meta-regression analysis.

Trial	Blinding	Sample size (*N*)	Treatment 1	Treatment 2
ABCD 2V, 2006	Assessment[a]	66 vs 63	Intensive DBP control (< 75 mmHg) with valsartan	Moderate BP control (DBP 80–90 mmHg, SBP < 140 mmHg), placebo
ABCD Hypertension, 1998	Double	235 vs 235	Nisoldipine	Enalapril
ABCD Normotensives, 1993	Open	237 vs 243	Intensive (10 mmHg below baseline) DBP control	Moderate (80–89 mmHg) DBP control
ACCOMPLISH	Double	1432 vs 1410	Benazepril + amlodipine	Benazepril + hydrochlorothiazide
ACCORD BP, 2010	Open	2363 vs 2371	Intensive	Standard
ACTION	Double	565 vs 545	Nifedipine	Placebo
ADVANCE	Double	5569 vs 5571	Low-dose fixed combination of perindopril + indapamide	Placebo
ALLHAT (amlodipine vs chlor)	Double	2664 vs 4498	Amlodipine	Chlorthalidone
ALLHAT (lisi vs chlor)	Double	2431 vs 4498	Lisinopril	Chlorthalidone
ASCOT (subgroup), 2008	Double	2565 vs 2572	Amlodipine + added perindopril	Atenolol + added thiazide
CAPP	Assessment[a]	309 vs 263	Captopril	Thiazide diuretic or beta-blocker
Chan, 1992	Double	50 vs 52	Enalapril	Nifedipine
DETAIL	Double	120 vs 130	Telmisartan	Enalapril
DIABHYCAR	Double	2443 vs 2469	Ramipril	Placebo
DREAM	Open	2623 vs 2646	Ramipril	Placebo
EUROPA (PERSUADE substudy)	Double	721 vs 781	Perindopril	Placebo
FACET	Open	191 vs 189	Amlodipine	Fosinopril
Fogari et al., 2002	Open	103 vs 104	Amlodipine	Amlodipine + fosinopril
Fogari et al., 2002	Open	102 vs 104	Fosinopril	Amlodipine + fosinopril
GEMINI	Double	498 vs 737	Carvedilol	Metoprolol
GUARD, 2008	Double	166 vs 166	Benazepril + amlodipine	Benazepril + hydrochlorothiazide
HOPE	Double	1808 vs 1759	Ramipril	Placebo
HOT	Open	499 vs 500	Target DBP ≤ 80 mmHg	Target DBP ≤ 90 mmHg
IDNT (irbesartan vs amlodipine)	Double	579 vs 567	Irbesartan	Amlodipine
IDNT amlodipine	Double	567 vs 569	Amlodipine	Placebo
IDNT irbesartan	Double	579 vs 569	Irbesartan	Placebo
INSIGHT	Double	649 vs 653	Nifedipine	Co-amilozide hydrochlorothiazide + amiloride
INVEST (subgroup), 2003	Open	3169 vs 3231	Calcium antagonist strategy (verapamil sustained-release)	Non-calcium antagonist strategy (atenolol)
IPDM	Double	195 vs 201	Irbesartan	Placebo
JMIC-B	Open	199 vs 173	Nifedipine	ACEI
LIFE	Double	586 vs 609	Losartan	Atenolol
MERIT-HF	Double	495 vs 490	Metoprolol	Placebo
NAGOYA HEART, 2011	Open	575 vs 575	BP-lowering based on valsartan	BP-lowering based on amlodipine
NORDIL	Open	351 vs 376	Diltiazem	Thiazide diuretic or beta-blocker at step 1
ORIENT	Double	288; 289	Olmesartan	Placebo
PROFESS	Double	2840 vs 2903	Telmisartan	Placebo
PROGRESS (diabetic subgroup)	Double	393 vs 368	Perindopril	Placebo
RENAAL	Double	751 vs 762	Losartan	Placebo
ROADMAP	Double	2232; 2215	Olmesartan	Placebo
SANDS	Open	252 vs 247	Aggressive SBP control ≤ 115 mmHg (DBP ≤ 75 mmHg)	Standard SBP control ≤ 130 mmHg (DBP ≤ 85 mmHg)
SCAT	Double	25 vs 25	Enalapril	Placebo
SCOPE (diabetic subgroup), 2003	Double	313 vs 284	Candesartan	Control
SHEP	Double	283 vs 300	Chlorthalidone + atenolol or reserpine	Placebo
SOLVD	Double	646 vs 664	Enalapril	Placebo
STOP-2 (ACEI vs CCB) (diabetic subgroup), 2000	Assessment[a]	235 vs 231	ACEI	Calcium antagonists
STOP-2 ACEI (diabetic subgroup), 2000	Assessment[a]	235 vs 253	ACEI	Conventional (diuretic or beta-blocker)
STOP-2 CCB (diabetic subgroup), 2000	Assessment[a]	231 vs 253	Calcium antagonists	Conventional (diuretic or beta-blocker)
Syst-Eur (diabetic subgroup), 1999	Double	252 vs 240	Calcium-channel blocker	Placebo
UKPDS 38	Open	758 vs 390	Target < 150/85 mmHg (captopril or atenolol as main treatment)	Target < 180/105 mmHg (avoiding ACEIs or beta-blockers)
UKPDS 39	Open	400 vs 358	Captopril	Atenolol

DBP/SBP: diastolic/systolic blood pressure; BP: blood pressure; ACEI: angiotensin-converting enzyme inhibitor.
[a] Open design with blinded assessment of outcomes; number of subjects in each group the same as in treatment description.

supplementary materials associated with this article online) shows that detailed inclusion criteria, treatment type and duration of follow-up were extracted (as available) from each individual study. The blinding design of the study was also evaluated.

Statistical methods

Our analysis used weighted meta-regression of the logarithm (log) of the odds ratio (OR) against differences in BP reduction, defined as the difference in BP change (expressed as mmHg) during the trial (final value minus baseline value) between active-treatment and control (active control or placebo, depending on the study) groups. If not available, the difference in final BP values was used.

Also used were the restricted maximum likelihood (REML) estimator [25], weighted log OR and an additive between-study variance component (ε^2) to take into account residual heterogeneity, such that $yi = \log(ORi) = N(\alpha + \beta xi, \sigma i + \varepsilon^2)$, where σi is the variance of the log OR within trial i, ε^2 is the between-study variance, β is the slope and represents change in the log OR of the considered endpoint per each 1-unit change in BP reduction xi, and α is the log OR at a BP reduction of zero (intercept). The weight of the trials was defined as $\omega i = 1/\sigma i$.

EASYMA [26] with R [27] software was used in our analyses. For each CV outcome, the analysis was run twice [for SBP and for diastolic BP (DBP) values]. Sensitivity analyses restricted to double-blind studies only were also conducted. No correction for multiple testing was applied.

Risk of publication bias

Funnel plots were used to assess the risk of publication bias [28].

Results

A total of 44 RCTs, involving a total of 88,503 patients, were included in our analysis. ACE inhibitors were used as either first or second line treatment in 20 arms, calcium-channel blockers in 16 arms, sartans in 12, beta-blockers in 12 and diuretics in 11. Non-specific intensive strategies were also included (four trials). The average study sample size was 1948 patients (range: 50–11,140), and the first study was published in 1992. Among our RCTs, 28 were double-blind, 13 were unblended (open), and three were open, but blinded when assessing the outcome (not taken into account in the sensitivity analysis). Three trials were unpublished. Table 1 summarizes the main characteristics of the included trials.

Meta-regression showed a significant relationship between SBP reduction and the log(OR) of stroke, but not for the other outcomes (total mortality, CV mortality, CVEs and MIs). Equations and *P* values of regression are summarized in Table 2. The effect of SBP reduction on the log(OR) of those outcomes is illustrated in Fig. 1. The significant ($P = 0.01$) relationship between risk of stroke and SBP reduction was $\log(OR) = -0.0192 + (0.0386 \times [\text{SBP reduction}])$. Compared with no BP reduction, every 10-mmHg SBP reduction was associated with a relative 33% decrease in risk of stroke [OR: 0.67, 95% confidence interval (CI): 0.54–0.82].

Meta-regression also revealed a significant relationship between DBP and the log(OR) of stroke, but not for the other outcomes (total mortality, CV mortality, CVEs, MIs). Equations and P values of regression are summarized in Table 2. The effect of DBP reduction on the log(OR) of those outcomes is illustrated in Fig. 2. The significant ($P = 0.001$) relationship between risk of stroke and DBP reduction was $\log(OR) = -0.0013 + (0.0969 \times [\text{DBP reduction}])$. Compared with no BP reduction, every 5-mmHg reduction in DBP was associated with a relative 38% decrease in risk of stroke (OR: 0.62, 95% CI: 0.50–0.76).

Regarding microvascular outcomes, their reporting in the eligible studies did not allow for meta-regression analysis to be conducted. Sensitivity analyses were restricted to double-blind studies and so included only 28 trials. The relationship between DBP reduction and the log(OR) of stroke remained significant ($P = 0.04$) with no correction for multiple testing (Appendix A.4; see supplementary materials associated with this article online). Funnel plots showed no evidence of potential publication biases (Appendix A.5; see supplementary materials associated with this article online).

Discussion

Decreases in BP do not appear to influence the risk of all-cause or CV mortality, CVEs or MIs. Our present results suggest, however, that lowering BP does affect the risk of stroke. This association was observed with both SBP and DBP reductions, but persisted on sensitivity analyses restricted to double-blind RCTs for DBP only. In fact, our findings confirm the results of Reboldi et al. [13], albeit extended to total and CV deaths, and CVEs. In a T2D patient population, Bangalore et al. [12] suggested a linear relationship between stroke risk and achieved SBP in the intensive-treatment group, while Brunström et al. [15] suggested an increased risk of CV mortality with baseline SBP < 140 mmHg. Emdin et al. [14] suggested an association between lowering SBP and decreases in mortality, CV disease, coronary heart disease and stroke. However, for their results, they standardized risk according to BP-lowering (log of risk was multiplied by [10 mmHg/SBP reduction]) [14], which may have overestimated the overall effect, as recently described [23]. For this reason, Brunström et al. [15] proposed that, before using such a standardized approach, a linear relationship within trials between different risk factors (differences in BP evolution) and treatment effects on the outcome of interest should be determined first. Our study suggested that such a relationship was observed only for risk of stroke, and not for risk of mortality or risk of CVEs.

Our study has some limitations. Open clinical trials were included, resulting in a risk of bias. Unfortunately, open trials of diabetes were common during the last few decades. Also, our analysis focused on severe clinical outcomes that were

Table 2
Summary of meta-regression of log(OR) of outcomes for systolic (SBP) and diastolic blood pressure (DBP) reductions.

Outcome	Comparisons (*N*)		Equation		P	
	SBP	DBP	SBP	DBP	SBP	DBP
Total deaths	26	25	$-0.142 + (-0.0094)^{*} X$	$-0.1408 + (-0.0205)^{*} X$	0.423	0.437
CV deaths	17	16	$-0.1118 + (-0.0094)^{*} X$	$-0.158 + (-0.0416)^{*} X$	0.645	0.327
CV events	21	21	$-0.0839 + (0.0109)^{*} X$	$-0.0736 + (0.0293)^{*} X$	0.372	0.249
MI	25	24	$-0.1101 + (-0.0023)^{*} X$	$-0.1392 + (-0.0175)^{*} X$	0.887	0.609
Stroke	27	26	$-0.0192 + (0.0386)^{*} X$	$-0.0013 + (0.0969)^{*} X$	0.01*	0.001*

In equations, "X" stands for difference in blood pressure reduction in mmHg; CV: cardiovascular; MI: myocardial infarction. *Nominal $P < 0.05$.

mostly CV-related and not the only complications found in T2D patients, but nonetheless representative of the main causes of death in such a population. In addition, it was not possible to explore the risk of haemorrhagic vs ischaemic stroke or CV risk at baseline, and microvascular complications were not explored due to a lack of data. Furthermore, the definition of outcomes may have differed across the included studies, with some studies reporting the number of non-fatal strokes and others the number of fatal strokes. Moreover, exact details concerning BP evolution across different treatment groups were not always available, leading to a smaller number of analyzed studies. Likewise, it was not possible to take into account the heterogeneity of BP

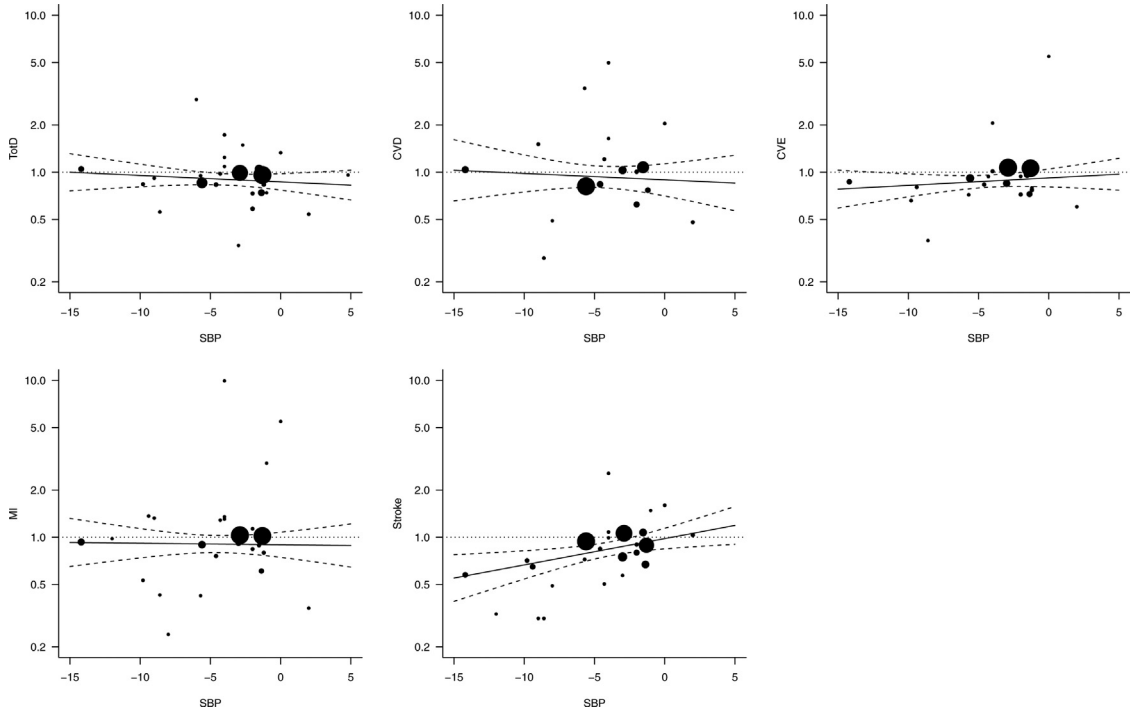

Fig. 1. Regression plots of the odds ratio (OR; log scale) for each outcome against differences in systolic blood pressure (SBP). Each black point represents a comparison (size varies according to weight); the solid line represents the meta-regression line, the dashed line its 95% confidence interval, and the dotted line the null effect on outcome (OR = 1). TotD: total deaths; CVD: cardiovascular deaths; CVE: cardiovascular events; MI: myocardial infarction.

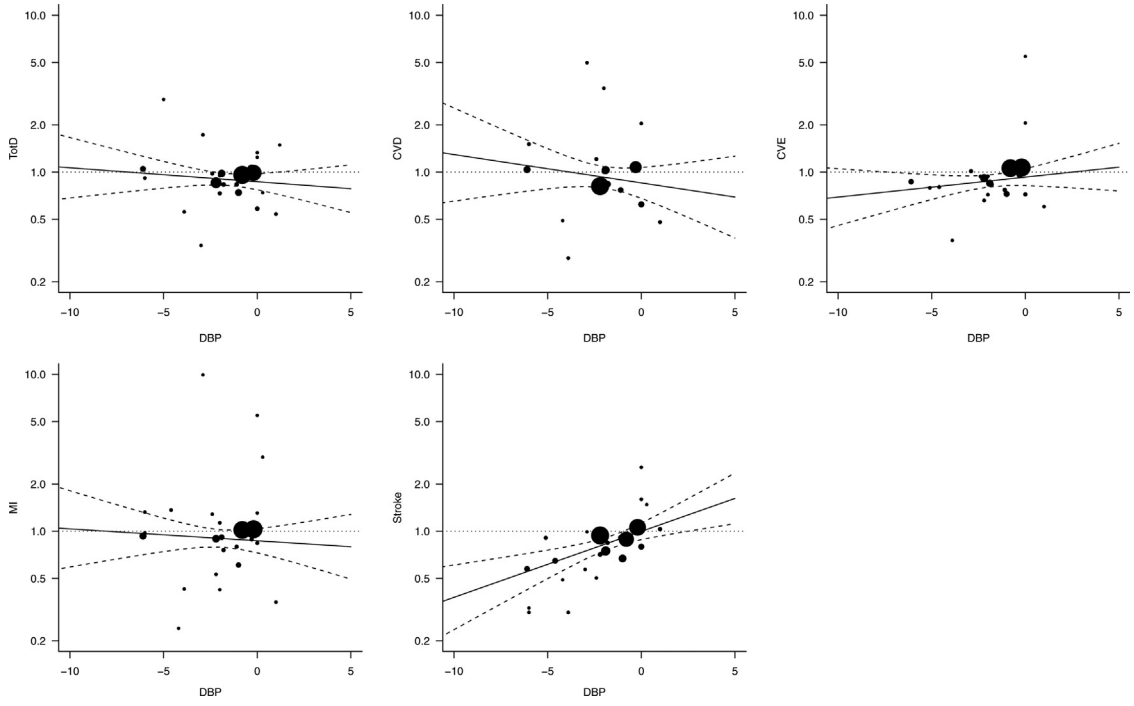

Fig. 2. Regression plot of the odds ratio (OR; log scale) for each outcome against differences in diastolic blood pressure (DBP). Each black point represents a comparison (size varies according to weight); the solid line represents the meta-regression line, the dashed line its 95% confidence interval, and the dotted line the null effect on outcome (OR = 1). TotD: total deaths; CVD: cardiovascular deaths; CVE: cardiovascular events; MI: myocardial infarction.

measurements. Our study could only analyze aggregate data and could not explore individual patients' data. Thus, the possibility that the association between the OR of stroke and BP decreases might be due to an ecological bias cannot be excluded. Also, meta-regression approaches are not protected against confusion bias, and meta-analyses at the individual data level would be helpful in future studies. On the other hand, false-negative results for the other outcomes due to a lack of power also cannot be excluded. Finally, it has been observed that BP variability itself could be a predictor of risk of stroke [29].

Recent recommendations of the ACC and AHA [19] have revealed some disagreement with the recent Position Statement of the American Diabetes Association [30] regarding BP targets in patients with T2D. Indeed, our present results and the current literature appear to suggest heterogeneity of organ sensitivity to BP decreases. This observation could lead to BP targets being adapted according to the individual patient's characteristics with a personalized medicine perspective. For example, the association between stroke and BP appears to be stronger in Asian populations, leading Park et al. [31] to propose a specific BP target of 130/80 mmHg in Asians.

Conclusion

Our present study confirms the potential association between BP-lowering and risk of stroke, but not for other CV events in a T2D population. Nevertheless, our findings contribute towards clarifying the effect of BP decreases in reducing CV risk in T2D patients, and quantitative estimates of this association could lead to more precise models of the public-health benefits of BP-lowering treatments in such a patient population.

Ethics

Ethics approval and consent to participate: not applicable.
Consent for publication: not applicable.

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Contribution

M.C. proposed the idea of the review, and made substantial contributions to the conception and design of the protocol. M.C., G.G. and H.H.L. performed the study search and selection, and contributed to the data acquisition and analyses. G.G. wrote the article. M.C., H.H.L., F.G., T.B.-A., S.E., P.M., R.B. and B.K. have been involved in revising the manuscript critically for important intellectual content.

All authors read and approved the final manuscript.

Disclosure of interest

G.G. has received support for travel to scientific meetings from Novo Nordisk and Eli Lilly.

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The authors T.B.-A., S.E., R.B., B.K. declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabet.2019.05.003.

References

[1] Staessen JA, Wang GJ, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. Lancet 2001;358:1305–15.
[2] Lassere MN, Johnson KR, Schiff M, Rees D. Is blood pressure reduction a valid surrogate endpoint for stroke prevention? An analysis incorporating a systematic review of randomised controlled trials, a by-trial weighted errors-in-variables regression, the surrogate threshold effect (STE) and the Biomarker-Surrogacy (BioSurrogate) Evaluation Schema (BSES) BMC Med Res Methodol 2012;12:27.
[3] Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke, and coronary heart disease part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990;335:827–38.
[4] 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.
[5] Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2007;115:114–26.
[6] Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105–87.
[7] Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. J Hypertens 2009;27:923–34.
[8] Mancia G. Effects of intensive blood pressure control in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Circulation 2010;122:847–9.
[9] Deedwania PC. Blood pressure control in diabetes mellitus: is lower always better, and how low should it go? Circulation 2011;123:2776–8.
[10] Mancia G, Fagard G, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;31:1281–357.
[11] Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson G, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens 2014;32:3–15.
[12] Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011;123:2799–810 [9 p following 810].
[13] Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. J Hypertens 2011;29:1253–69.
[14] Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA 2015;313:603–15.
[15] Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:i717.
[16] Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–67.
[17] Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol 2017;2:775–81.

[18] Brunstrom M, Carlberg B. Association of blood pressure lowering with mortality and cardiovascular disease across blood pressure levels: a systematic review and meta-analysis. JAMA Intern Med 2018;178:28–36.
[19] Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2018;71:e127–248.
[20] Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002;21:1559–73.
[21] van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21:589–624.
[22] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Kirby A, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
[23] Brunstrom M, Carlberg B. Standardization according to blood pressure lowering in meta-analyses of antihypertensive trials: comparison of three methodological approaches. J Hypertens 2018;36:4–15.
[24] Haynes RB, McKibbon KA, Wilczynski NL, Walter SD, Were SR, Hedges Team. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ 2005;330:1179.
[25] Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med 1999;18:2693–708.
[26] Cucherat M, Boissel JP, Leizorovicz A, Haugh MC. EasyMA: a program for the meta-analysis of clinical trials. Comput Methods Programs Biomed 1997;53:187–90.
[27] R Core Team. R: A Language and Environment for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/. 2017.
[28] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[29] Gaciong Z, Sinski M, Lewandowski J. Blood pressure control and primary prevention of stroke: summary of the recent clinical trial data and meta-analyses. Curr Hypertens Rep 2013;15:559–74.
[30] De Boer IH, Bangalore S, Benetos A, Davis AM, Michos ED, Muntner P, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–84.
[31] Park S, Kario K, Park CG, Huang QF, Cheng HM, Hoshide S, et al. Target blood pressure in patients with diabetes: Asian perspective. Yonsei Med J 2016;57:1307–11.