Blood pressure targets for hypertension in patients with type 2 diabetes

Wilbert S. Aronow[1], Tatyana A. Shamliyan[2]

[1]Department of Medicine, Westchester Medical Center, New York Medical College, Valhalla, NY, USA; [2]Quality Assurance, Evidence-Based Medicine Center, Elsevier, Philadelphia, PA, USA

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Correspondence to: Wilbert S. Aronow, MD, FACC, FAHA. Westchester Medical Center, New York Medical College, Macy Pavilion, Room 141, Valhalla, NY 10595, USA. Email: WSARONOW@aol.com; Tatyana A. Shamliyan, MD, MS. Quality Assurance, Evidence-Based Medicine Center, Elsevier 1600 JFK Blvd, Philadelphia, PA 19103, USA. Email: t.shamliyan@elsevier.com.

Background: Clinical guidelines vary in determining optimal blood pressure targets in adults with diabetes mellitus.

Methods: We systematically searched PubMed, EMBASE, Cochrane Library, and clinicaltrials.gov in March 2018; conducted random effects frequentist meta-analyses of direct aggregate data; and appraised the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Results: From eligible 14 meta-analyses and 95 publications of randomized controlled trials (RCT), only 6 RCTs directly compared lower versus higher blood pressure targets; remaining RCTs aimed at comparative effectiveness of hypotensive drugs. In adults with diabetes mellitus and elevated systolic blood pressure (SBP), direct evidence (2 RCTs) suggests that intensive target SBP <120–140 mmHg decreases the risk of diabetes-related mortality [relative risk (RR) =0.68; 95% confidence interval (CI), 0.50–0.92], fatal (RR =0.41; 95% CI, 0.20–0.84) or nonfatal stroke (RR =0.60; 95% CI, 0.43–0.83), prevalence of left ventricular hypertrophy and electrocardiogram (ECG) abnormalities, macroalbuminuria, and non-spine bone fractures, with no differences in all-cause or cardiovascular mortality or falls. In adults with diabetes mellitus and elevated diastolic blood pressure (DBP) ≥90 mmHg, direct evidence (2 RCTs) suggests that intensive DBP target ≤80 versus 80–90 mmHg decreases the risk of major cardiovascular events. Published meta-analyses of aggregate data suggested a significant association between lower baseline and attained blood pressure and increased cardiovascular mortality.

Conclusions: We concluded that in adults with diabetes mellitus and arterial hypertension, in order to reduce the risk of stroke, clinicians should target blood pressure at 120–130/80 mmHg, with close monitoring for all drug-related harms.

Keywords: Quality of evidence; cardiovascular morbidity; diabetes mellitus; arterial hypertension; blood pressure targets

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Introduction

One of the main goals in managing type 2 diabetes in adults is prevention of cardiovascular morbidity or mortality by controlling blood glucose, normalizing blood pressure, and reducing other cardiovascular risk factors (1,2). Despite extensive review of literature, clinical practice guidelines vary in determining the optimal blood pressure targets in patients with diabetes (3-5).

To support clinical decisions at point of care with all available evidence, we conducted a rapid review of the published and unpublished data from recently completed randomized controlled trials (RCT), meta-analyses of RCTs, and primary observational studies that compared different blood pressure targets in adults with diabetes.

Methods

We used a standard recommended methodology in conducting systematic literature reviews and meta-analyses from the Cochrane Collaboration and the Agency for Healthcare Research and Quality (6,7). We developed a priori protocol (available by request) for a systematic literature review to answer the clinical question about the comparative effectiveness of blood pressure targets on mortality and cardiovascular morbidity in adults with diabetes mellitus.

Eligible studies directly compared lower versus higher blood pressure targets or examined the association between baseline or attained blood pressure with patient outcomes in people treated with hypotensive medications. Eligible outcomes included all-cause and underlying cause-specific mortality, cardiovascular morbidity, stroke, heart failure, renal failure, and all drug harms.

We conducted a comprehensive search in PubMed, EMBASE, the Cochrane Library, and www.clinicaltrials.gov up to March 2018 to find systematic reviews, published and unpublished RCTs, and nationally represented controlled observational studies that reported adjusted effect estimates (6,7). The data were extracted from the Clinical Trials Transformation Initiative (https://www.ctti-clinicaltrials.org/aact-database), checked for quality, and stored in the High-Performance Computing Cluster platform (https://hpccsystems.com).

We tested the null hypotheses of no differences in patient outcomes after more versus less extensive blood pressure lowering (6). We abstracted the information about study population, interventions, comparators, and outcomes (6). We abstracted minimum datasets (e.g., number of the subjects in treatment groups and events) to estimate absolute risk difference, relative risk, and number needed to treat for categorical variables (6). Statistical significance was evaluated at a 95% confidence level (including the use of P values).

We conducted a rapid review following the framework of the AHRQ (8). We used the AHRQ recommended methodological approach in the integration of existing systematic reviews into our comprehensive synthesis of evidence (9). Our goal was the integration of previously published high quality reviews and consistent ranking of the quality of evidence using GRADE methodology.

We performed meta-analyses when definitions of active and control interventions and patient outcomes deem similar (10). We examined consistency in results across studies with chi-square tests and I^2 statistics and concluded statistically significant heterogeneity if I^2 was >50% (6). Statistically significant heterogeneity did not preclude statistical pooling (10). However, we planned exploring heterogeneity with a priori defined patient baseline hypertensive status (10).

We defined harms as the totality of all possible adverse consequences of an intervention.

We calculated absolute risk difference, number needed to treat, and the number of attributable events based on data from the published randomized trials, using STATA software (StataCorp LP, College Station, TX, USA) (11). Correction coefficients for zero events were used as a default option, and intention to treat was used for evidence synthesis (10). Superiority of interventions under comparison was hypothesized (12). We used consensus method guidelines for systematic review and meta-analyses that do not recommend conducting post hoc analyses of statistical power (13-15). Instead, we downgraded our confidence in true treatment effects based on calculated optimal information size as the number of patients required for an adequately powered individual trial (16). Since power is more closely related to number of events than to sample size, we concluded imprecision in treatment effects if less than 250 patients experienced the event (16).

We assessed reporting bias as a proportion of published among all registered studies, unreported outcomes compared with published protocols, or unreported minimum data sets for reproducibility of the results (17). We did not conduct formal statistical tests for publication bias due to the questionable validity of such tests (18).

We evaluated the quality of the primary studies using

the Cochrane risk of bias tool on a 3-point scale: high bias, low bias, and unclear (6). We upgraded the risk of bias in the body of evidence from low to high if at least 1 RCT had high risk of bias (19,20). We defined indirectness in outcomes from intermediate outcomes (21).

Treatment effect estimates were defined as precise when pooled estimates had reasonably narrow 95% confidence intervals (CI) and the number of events were greater than 250 (22). Justification of the sample size was not included in grading of the evidence.

In assessing the quality of evidence in all studies, the authors looked for the strength of association and evidence of any reporting bias (23). The strength of the association was evaluated, defining a priori a large effect when the relative risk was greater than 2 and a very large effect when the relative risk was greater than 5 (23). A small treatment effect was construed when the relative risk was significant but less than 2 (23).

The authors assigned the quality of evidence ratings as high, moderate, low, or very low, according to risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the evidence of reporting bias, using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Supplementary file) (23). A high quality of evidence was assigned to well-designed RCTs with consistent findings. The quality of evidence was downgraded to moderate if at least 1 of 4 quality of evidence criteria were not met; for example, moderate quality of evidence was assigned if there was a high risk of bias in the body of evidence or if the results were not consistent or precise (23). The quality of evidence was downgraded to low if 2 or more criteria were not met.

A low quality of evidence was assigned to nonrandomized studies and upgraded for the rating if there was a strong association. Evidence was defined as insufficient when no studies provided valid information about treatment effects. This approach was applied regardless of whether the results were statistically significant.

Results

Our comprehensive search in PubMed, EMBASE, the Cochrane Library, and clinicaltrials.gov up to March 2018 retrieved 306 references and identified 16 publications of systematic reviews and meta-analyses and 96 publications of RCTs that enrolled adults primarily with type 2 diabetes mellitus (Supplementary file, *Figure S1*). We excluded 124 irrelevant references at the screening of the titles and abstracts and 33 publications after full text review because the studies did not address blood pressure targets in patients with diabetes (Supplementary file, *Figure S1*). Only 6 primary RCTs randomly assigned patients to lower versus higher blood pressure targets and compared systolic blood pressure (SBP) targets in patients with baseline arterial hypertension (24,25) or diastolic blood pressure (DBP) targets in patients with normal (26,27) or elevated baseline blood pressure (28,29). All other RCTs compared hypotensive drugs with placebo or with each other. Meta-analyses of such trials explored the association of baseline or achieved blood pressure with patient outcomes (3-5,30-39).

In adults with diabetes and normal arterial blood pressure, low-quality evidence suggests that there are no differences in all-cause and cardiovascular mortality or morbidity between intensive (10 mmHg below baseline DBP) and moderate blood pressure control (DBP goal 80–89 mmHg; *Table 1*). Intensive blood pressure control prevents cerebrovascular events and progression or retinopathy in some patients (*Table 1*).

In adults with diabetes and elevated arterial blood pressure (DBP ≥90 mmHg), low-quality evidence suggests that there are no differences in all-cause and cardiovascular mortality or stroke between intensive (DBP ≤85–75 mmHg) and moderate blood pressure control (DBP goal 80–90 mmHg; *Table 2*). A single RCT suggests that a reduction of DBP ≤80 mmHg results in a lower risk of major cardiovascular events but higher risk of progressing neuropathy (*Table 2*).

In adults with diabetes and elevated arterial blood pressure (SBP 130–190 mmHg), moderate-quality evidence suggests that there are no differences in all-cause or cardiovascular mortality between intensive and standard blood pressure control (*Table 3* and *Figure 1*). However, intensive blood pressure control decreases the risk of diabetes-related mortality, fatal or nonfatal stroke (*Figure 2*), prevalence of left ventricular hypertrophy and electrocardiogram (ECG) abnormalities, macroalbuminuria, and non-spine bone fractures (*Table 3*). A single RCT (ACCORD) suggests that the risk of a composite outcome (nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes) is lower after intensive blood pressure and good glycemic control but higher in adults with poorly controlled diabetes (hemoglobin A_{1c} >8.0; *Table 3*). The benefits from intensive blood pressure control sustain at 9 years of follow-up in older adults with 15% or greater 10-year coronary heart risk in the standard glucose control

Table 1 The benefits and harms of intensive versus moderate diastolic blood pressure control in normotensive adults with diabetes mellitus

Outcome	Risk with intervention/ comparator per 1,000	Attributable avoided events per 1,000 treated (95% CI)	Relative measure of association; number needed to treat (95% CI)	No. of participants (studies)
All-cause mortality**	63/65	NS	RR: 0.96 (0.53–1.75); HR: 0.96 (0.53–1.75)	609 (2 RCTs) (26,27)
Cardiovascular mortality*	55/37	NS	RR: 1.48 (0.65–3.40)	480 (1 RCT) (27,40)
Non-cardiovascular mortality*	21/45	NS	RR: 0.47 (0.16–1.32)	480 (1 RCT) (27,40)
Cardiovascular event**	73/56	NS	RR: 1.31 (0.71–2.42)	609 (2 RCTs) (26,27)
Congestive heart failure*	51/45	NS	RR: 1.12 (0.50–2.49)	480 (1 RCT) (27,40)
Myocardial infarction*	80/62	NS	RR: 1.30 (0.68–2.49)	480 (1 RCT) (27,36)
Cerebrovascular accident*	17/53	37 [4–69]	RR: 0.32 (0.10–0.95); NNTp: 27 [14–255]#	480 (1 RCT) (27,36)
Retinopathy progression**	269/369	NR	RR: 0.74 (0.60–0.93)#	609 (2 RCTs) (26,27)
Neuropathy progression**	349/337	NS	RR: 1.04 (0.83–1.29)	609 (2 RCTs) (26,27)

Population: adults with diabetes and normal arterial blood pressure; Settings: outpatient; Intervention: intensive blood pressure control (10 mmHg below baseline DBP); Comparator: moderate blood pressure control (DBP goal 80–89 mmHg). #, favors lower blood pressure target; *, very low quality evidence; **, low quality evidence. CI, confidence interval; DBP, diastolic blood pressure; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; NNTp, number needed to treat to prevent an outcome in one patient; RCT, randomized controlled trial; RR, relative risk; NS, no statistically significant difference; NR, not reported.

arm of ACCORD trial (*Table 3*). The same study reported an increased risk of adverse effects from hypotensive medications, including hypotension or hyperkalemia, after intensive blood pressure control (*Table 3*).

Primary studies did not address circadian fluctuations in blood pressure or the risk of orthostatic hypotension after intensive versus standard blood pressure targets. For the record, the ACCORD study found no differences in patient falls or trauma after intensive blood pressure control (*Table 3*).

Published meta-analyses of aggregate data from RCTs aimed at efficacy or comparative effectiveness of specific hypotensive drugs in adults with comorbid diabetes and arterial hypertension (baseline blood pressure >150 mmHg) agree that attained SBP 130–139 and DBP 75–80 mmHg is associated with lower risk of all-cause mortality and stroke (*Table S1*) (5,31,33,37). Systematic reviews and guidelines vary in determining the balance between benefits and harms of lowering blood pressure below 130 mmHg (4,5). We looked at the pooled relative risk of all reported outcomes in published reviews (*Table S1*) and found 2 meta-analyses that reported a statistically significant increase in the risk of cardiovascular mortality in association with lower baseline blood pressure (*Table S2*) (31,37). Antihypertensive treatments are associated with a higher risk of cardiovascular mortality per each 10 mmHg lower baseline SBP and DBP (*Table S2*).

Discussion

Our review found moderate direct quality evidence that in adults with diabetes and elevated SBP, intensive blood pressure control (target SBP <120–140 mmHg) decreases the risk of diabetes-related mortality, fatal or nonfatal stroke, prevalence of left ventricular hypertrophy and ECG abnormalities, macroalbuminuria, and non-spine bone fractures, with no differences in all-cause or cardiovascular mortality or falls.

We downgraded the quality of evidence due to risk

Table 2 The benefits and harms of intensive versus moderate diastolic blood pressure control in adults with diabetes mellitus and arterial hypertension

Outcome	Risk with intervention/ comparator per 1,000	Attributable avoided events per 1,000 treated (95% CI)	Relative measure of association; number needed to treat (95% CI)	No. of participants (studies)
All-cause mortality**	45/71	NS	RR: 0.63 (0.38–1.05)	1,971 (2 RCTs) (28,29,40)
Cardiovascular mortality**	27/44	NS	RR: 0.63 (0.39–1.03)	1,971 (2 RCTs) (28,29,40)
Congestive heart failure*	38/39	NS	RR: 0.98 (0.40–2.43)	470 (1 RCT) (28,40)
Major cardiovascular events, DBP ≤80*	44/90	Avoided 46 [15–77]	RR: 0.49 (0.30–0.80); NNTp: 22 [13–67]#	1,000 (1 RCT) (29)
Major cardiovascular events, DBP ≤85*	68/90	NS	RR: 0.76 (0.49–1.16)	1,002 (1 RCT) (29)
Any cardiovascular event*	63/60	NS	RR: 1.05 (0.52–2.13)	470 (1 RCT) (28,41)
Myocardial infarction*	25/38	NS	RR: 0.78 (0.38–1.61)	1,971 (2 RCTs) (28,40)
Stroke**	27/35	NS	RR: 0.81 (0.49–1.33)	1,971 (2 RCTs) (28,29,40)
Neuropathy progression*	400/310	Excessive 92 [6–178]	RR: 1.30 (1.01–1.66); NNT: 11 [6–174]†	470 (1 RCT) (28)
Retinopathy progression*	300/340	NS	RR: 0.88 (0.68–1.15)	470 (1 RCT) (28)

Population: adults with diabetes and elevated arterial blood pressure (DBP ≥90 mmHg); Settings: outpatient; Intervention: intensive blood pressure control (DBP ≤75–85 mmHg); Comparator: moderate blood pressure control (DBP goal 80–90 mmHg). #, favors lower blood pressure target; †, favors higher blood pressure target; *, very low quality evidence; **, low quality evidence. CI, confidence interval; DBP, diastolic blood pressure; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat; NNTp, number needed to treat to prevent an outcome in one patient; RCT, randomized controlled trial; RR, relative risk.

of bias, small number of events in the studies, and heterogeneity in treatment effects across the studies. We did not conduct meta-regression of few RCTs that directly compared patient outcomes after intensive versus standard blood pressure targets (6). Instead, we reviewed published meta-analyses of RCTs aimed at comparative effectiveness of blood lowering drugs in adults with diabetes that concluded no benefits from lowering blood pressure below 130 mmHg. Such publications employed meta-regression of aggregated data that can generate hypotheses of potential harms from extensive lowering blood pressure control specifically in adults with normal baseline blood pressure (45). Published meta-analyses that included the data from the Systolic Blood Pressure Intervention Trial (SPRINT) suggest similar reduction in the risk of major cardiovascular events from intensive blood pressure lowering in adults with and without diabetes (20,38,46). Individual rather than aggregate patient data meta-analyses would provide better evidence about the association between specific drugs, baseline and achieved blood pressure, and patient outcomes independent of drug effects (47).

We found no studies that addressed the risk of hospitalization or long-term quality of life in relation to blood pressure targets in adults with diabetes. Although orthostatic hypotension is associated with poor patient outcomes, the evidence regarding the risk of this complication after intensive or standard blood pressure control is insufficient (3,48,49). Primary studies and meta-analyses did not discuss the importance of pulse pressure in reducing morbidity and mortality in adults with diabetes (50).

Guidelines recommend healthy diet, weight normalization, and physical activity for all adults with diabetes (*Table S3*) (51-58).

Table 3 The benefits and harms of intensive versus standard systolic blood pressure control in adults with diabetes mellitus and arterial hypertension

Outcome	Risk with intervention/ comparator per 1,000	Attributable avoided events per 1,000 treated (95% CI)	Relative measure of association; number needed to treat (95% CI)	No. of participants (studies)
All-cause mortality***	91/82	NS	RR: 0.94 (0.75–1.18)	5,881 (2 RCTs) (25,36)
All-cause mortality, 9 years of follow-up*	224/234	NS	RR: 0.96 (0.78–1.17)	1,284 (1 RCT) (42)
Cardiovascular death, nonfatal MI, nonfatal stroke, 9 years of follow-up*	199/259	Avoided 60 [14–106]	RR: 0.77 (0.63–0.94); NNTp: 17 [9–70]#	1,284 (1 RCT) (42)
Coronary death, nonfatal MI, unstable angina, 9 years of follow-up*	201/267	Avoided 66 [20–113]	RR: 0.75 (0.62–0.92); NNTp: 15 [9–49]#	1,284 (1 RCT) (42)
Cardiovascular death, 9 years of follow-up*	58/76	NS	RR: 0.77 (0.51–1.16)	1,284 (1 RCT) (42)
Fatal myocardial infarction**	21/17	NS	RR: 0.80 (0.50–1.28)	5,882 (2 RCTs) (24,25)
Fatal stroke**	4/7	NR	RR: 0.41 (0.20–0.84)#	5,882 (2 RCTs) (24,25)
Any stroke**	24/35	Avoided 16 [7–24]	RR: 0.58 (0.43–0.78); NNTp: 63 [42–143]#	5,881 (2 RCTs) (25,36)
Nonfatal stroke**	20/29	Avoided 12 [4–20]	RR: 0.60 (0.43–0.83); NNTp: 83 [50–250]#	5,882 (2 RCTs) (24,25)
Nonfatal myocardial infarction**	57/63	NS	RR: 0.87 (0.71–1.07)	5,882 (2 RCTs) (24,25)
Non-fatal MI, 9 years of follow-up*	100/147	Avoided 47 [12–83]	RR: 0.68 (0.50–0.91); NNTp: 21 [12–87]#	1,284 (1 RCT) (42)
Myocardial infarction, any***	115/123	NS	RR: 0.90 (0.78–1.04)	5,881 (2 RCTs) (25,36)
Cancer death**	23/19	NS	RR: 1.17 (0.74–1.84)	5,882 (2 RCTs) (24,25)
Fatal or nonfatal heart failure*	33/41	NS	RR: 0.67 (0.34–1.36)	5,882 (2 RCTs) (24,25)
MACE**; subgroup: HbA_{1c} ≤8.0	444/489	Avoided 45 [17–73]	RR: 0.91 (0.85–0.97); NNTp: 22 [14–61]#	4,734 (1 RCT) (24)
MACE**; subgroup: HbA_{1c} >8.0	554/507	Excessive 47 [19–76]	RR: 1.09 (1.04–1.15); NNT: 21 (53–13)†	4,734 (1 RCT) (24)
Mortality due to congestive heart failure*	5/4	NS	RR: 1.10 (0.47–2.59)	4,734 (1 RCT) (24)
Mortality due to fatal arrhythmia*	1/1	NS	RR: 1.00 (0.14–7.12)	4,734 (1 RCT) (24)
Mortality related to diabetes*	108/159	Avoided 51 [8–93]	RR: 0.68 (0.50–0.92); NNTp: 20 [11–120]#	1,148 (1 RCT) (25)
Adverse Events from blood-pressure medications*	33/13	Excessive 20 [11–28]	RR: 2.58 (1.70–3.91); NNT: 50 [35–87]†	4,733 (1 RCT) (24)
Abnormal Q waves in ECG*	175/231	Avoided 55 [5–105]	RR: 0.76 (0.60–0.96); NNTp: 18 [10–182]#	1,148 (1 RCT) (25)

Table 3 (*continued*)

Table 3 (*continued*)

Outcome	Risk with intervention/ comparator per 1,000	Attributable avoided events per 1,000 treated (95% CI)	Relative measure of association; number needed to treat (95% CI)	No. of participants (studies)
Abnormal Q, ST, or T waves in ECG*	38/77	Avoided 39 [9–68]	RR: 0.50 (0.30–0.82); NNTp: 26 [15–112][#]	1,148 (1 RCT) (25)
Angina*	59/56	NS	RR: 1.05 (0.64–1.73)	1,148 (1 RCT) (25)
Left ventricular hypertrophy*	17/30	Avoided 13 [4–22]	RR: 0.58 (0.39–0.86); NNTp: 79 [46–273][#]	4,331 (1 RCT) (43)
Any diabetes-related end point**	342/436	Avoided 94 [35–154]	RR: 0.78 (0.67–0.91); NNTp: 11 [6–29][#]	1,148 (1 RCT) (25)
Macroalbuminuria**	56/78	NR	RR: 0.77 (0.63–0.94)[#]	5,527 (2 RCTs) (24,25)
Microalbuminuria***	253/296	NS	RR: 0.92 (0.85–1.01)	5,527 (2 RCTs) (24,25)
Renal failure*	4/3	NS	RR: 1.38 (0.18–10.81)	5,881 (2 RCTs) (24,25)
Peripheral vascular disease*	11/21	NS	RR: 0.51 (0.19–1.36)	1,148 (1 RCT) (25)
Cataract extraction*	47/36	NS	RR: 1.32 (0.72–2.42)	1,148 (1 RCT) (25)
Vision preventing driving *	42/62	NS	RR: 0.69 (0.41–1.15)	1,148 (1 RCT) (25)
Vitreous hemorrhage*	4/13	NS	RR: 0.31 (0.07–1.29)	1,148 (1 RCT) (25)
Falls*	200/206	NS	RR: 0.97 (0.84–1.11)	3,099 (1 RCT) (44)
Fatal accident*	1/3	NS	RR: 0.51 (0.03–8.20)	1,148 (1 RCT) (25)
Fatal accident/trauma*	2/1	NS	RR: 2.51 (0.49–12.92)	4,734 (1 RCT) (24)
All non-spine bone fractures*	76/98	Avoided 23 [3–43]	RR: 0.77 (0.61–0.97); NNTp: 44 [23–337][#]	3,099 (1 RCT) (44)
Ankle fractures*	16/24	NS	RR: 0.67 (0.41–1.11)	3,099 (1 RCT) (44)
Distal forearm fractures*	8/8	NS	RR: 0.94 (0.43–2.06)	3,099 (1 RCT) (44)
Foot fractures*	6/13	NS	RR: 0.46 (0.21–1.01)	3,099 (1 RCT) (44)
Hip fractures*	3/8	NS	RR: 0.43 (0.15–1.20)	3,099 (1 RCT) (44)
Proximal humerus fractures*	10/12	NS	RR: 0.81 (0.41–1.58)	3,099 (1 RCT) (44)
Hives or swelling*	88/88	NS	RR: 1.00 (0.67–1.51)	969 (1 RCT) (24)
Hyperkalemia*	4/0	Excessive 3 [1–6]	RR: 9.03 (1.15–71.25); NNT: 295 [166–1,299][†]	4,733 (1 RCT) (24)
Hypotension*	7/0	Excessive 7 [3–10]	RR: 17.06 (2.27–128.12); NNT: 148 [97–306][†]	4,733 (1 RCT) (24)

Population: adults with diabetes and elevated arterial blood pressure (SBP: 130–190 mmHg); Settings: outpatient; Intervention: intensive blood pressure control [target SBP <120 versus <140 mmHg in ACCORD study and 144/82 versus 154/87 mmHg in UKPDS 38 (66) study]; Comparator: standard blood pressure control. *, very low quality evidence; **, low quality evidence; ***, moderate quality evidence; [#], favors lower blood pressure target; [†], favors higher blood pressure target; CI, confidence interval; ECG, electrocardiogram; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat; NNTp, number needed to treat to prevent an outcome in one patient; RCT, randomized controlled trial; RR, relative risk; SBP, systolic blood pressure; MACE, major cardiovascular events including nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

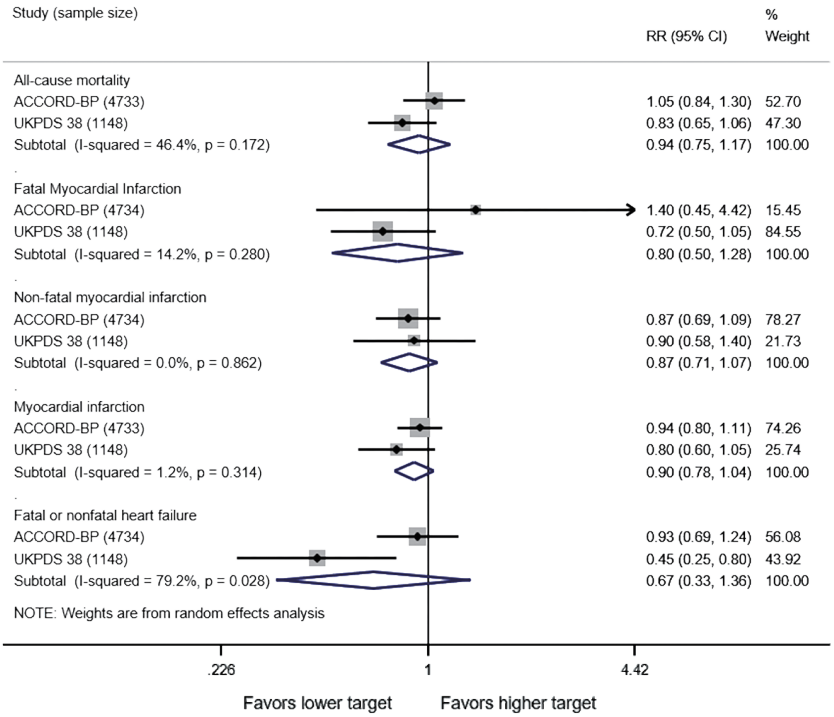

Figure 1 Cardiovascular outcomes after intensive versus standard systolic blood pressure control in adults with diabetes mellitus and arterial hypertension. Target systolic blood pressure <120 versus <140 mmHg in ACCORD study and 144/82 versus 154/87 mmHg in UKPDS 38 study. RR, relative risk.

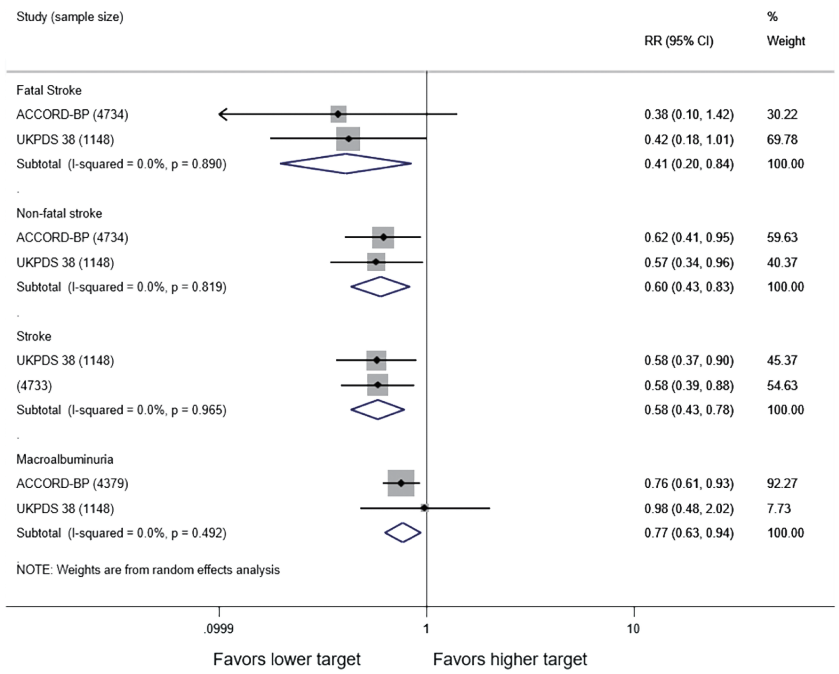

Figure 2 Stroke after intensive versus standard systolic blood pressure control in adults with diabetes mellitus and arterial hypertension. Target systolic blood pressure <120 versus <140 mmHg in ACCORD study and 144/82 versus 154/87 mmHg in UKPDS 38 study.

In addition to healthy lifestyle, recent guidelines recommend antihypertensive drug treatments in patients with diabetes and baseline blood pressure ≥130/80 mmHg (54-56,59-61). The American Heart Association recommends a treatment goal of <130/80 mmHg, while the American Diabetes Association recommends a treatment goal of <140/90 mmHg with lower targets in individuals at high risk of cardiovascular disease (54-56,59-61). Other guidelines also recommend baseline cardiovascular disease risk assessment and evaluation of kidney, eye, or cerebrovascular damage in determining individual treatment goals (51,62-65). The American Geriatrics Society guidelines acknowledge the potential harm from arterial hypotension in older adults with diabetes mellitus (66). Guidelines generally agree that high quality care for patients with diabetes include normalization of HbA1C without hypoglycemia (67-69). This definition of high quality care for patients with diabetes should include normalization of blood pressure including pulse pressure without hypotension.

Regardless of the intended blood pressure goal, the ability to maintain a lower blood pressure threshold in a real-world setting outside of a controlled trial is an important disease management consideration (70). It is often reported that more than half of treated patients are not able to maintain blood pressure control, even at a threshold of <140/85 mmHg (71). Findings from the DIALOGUE study (72), a multicenter prospective registry among patients with hypertension and type II diabetes, demonstrated that patients with a "strict" SBP target (≤130 mmHg) had more contacts with general practitioners than any other patient group. In addition, among patients with a lower blood pressure target, only half actually maintained this threshold over 6 months. More specifically, 53% of patients in the "strict" target group (≤130 mmHg) were able to maintain this blood pressure goal over time, and 55% of patients in the "medium" target group (130 to ≤135 mmHg) were able to do so.

The majority of the studies relied on office measurements of blood pressure rather than ambulatory blood pressure monitoring. However, ambulatory blood pressure monitoring improves baseline and post-treatment risk assessment (73-86). Evidence-based guidelines recommend ambulatory blood pressure monitoring for diagnosis and individualization of treatment goals in adults with arterial hypertension (51,56,87-89).

Our review has several limitations. We analyzed direct evidence from RCTs that randomly assigned patients to more versus less intensive blood pressure goals and did not abstract the data from RCTs aimed at efficacy or comparative effectiveness of hypotensive drugs. We could not reproduce the results from meta-regression, because the authors did not provide sufficient data (30,33,35-38,90). We did not contact authors of meta-analyses requesting reproducible data. We do not know how many unregistered and unpublished studies analyzed the association between baseline and attained blood pressure and patient outcomes.

Despite this limitation, we present conflicting evidence from all published and unpublished studies appraised with consistent GRADE methodology. In contrast with previous meta-analyses of direct evidence, we grouped studies by baseline hypertension status and by targeted diastolic and SBP targets (38,40).

Our review has implications for clinical practice. Clinicians should assess baseline cardiovascular risk, recommend behavioural and pharmacological treatments aiming at blood pressure normalization without hypotension or orthostatic hypotension (91). They should engage patients in life style optimization, blood pressure self-monitoring, and monitoring of drug adverse effects (92).

Our review has policy implications. High quality care in patients with diabetes and arterial hypertension should be defined as achievement of normal blood pressure without episodes of hypotension and with minimal risk of orthostatic hypotension or other serious harms from recommended drugs.

Our review has research implications. Future research should determine the optimal blood pressure targets in subpopulations with diabetes and various demographic, socioeconomic, and behavioral factors, as well as comorbidities. Composite outcomes should be avoided. Trials should use blood pressure monitoring and examine pulse pressure, the risk of orthostatic hypotension and other drug-related harms in determining optimal choice of drugs and blood pressure targets in individual patients.

Conclusions

Based on our review, we conclude that in adults with diabetes and arterial hypertension, in order to reduce the risk of stroke, left ventricular hypertrophy and ECG abnormalities, macroalbuminuria, and non-spine bone fractures, clinicians should encourage healthy lifestyle choices and antihypertensive medications targeting blood pressure of 120–130/80 mmHg, with close monitoring of

daily blood pressure fluctuations, episodes of orthostatic hypotension, and other drug-related harms.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

PICO question this report is addressing:

What are the benefits and harms of "lower" blood pressure targets compared to "standard" blood pressure targets in high-risk diabetic patients?

Population	Adults with type 2 diabetes
	Baseline blood pressure
	Patient demographics, socioeconomic status, smoking, physical activity, diet (sodium intake), prior treatment and response to medications for hypertension, comorbidities (e.g., cardiac arrhythmias, obesity, diabetes, asthma, chronic obstructive pulmonary disease), concomitant and concurrent medications
Intervention	Lower blood pressure targets as defined in the studies
Comparator	Higher blood pressure targets as defined in the studies
Primary outcome(s)	All-cause mortality
	Cardiovascular disease (CVD) events (stroke, myocardial infarction) and mortality
	All adverse events
Setting	Outpatient

Study eligibility

Inclusion criteria

Participants	Adults with type 2 diabetes
Language restrictions	English
Publication dates (from and to) for searching	2010–2018 (published high-quality reviews should address early publications of randomized trials)
Inclusion of guidelines	ECRI institute (formerly the "Emergency Care Research Institute") appraised, published since 2010
	Meeting Institute of Medicine criteria for trustworthy guidelines
Inclusion of clinical performance measures	Yes
Inclusion for systematic reviews (review quality, reviews with quantitative analyses)	Yes
Inclusion of randomized trials	Yes, published since 2010
Inclusion of observational studies for harms (study characteristics, design, applicability, sample size, statistical methods to reduce bias)	Nationally representative prospective cohort studies of adverse effects with multivariate adjustment of adverse effects

Exclusion criteria

Interventions	We exclude trials of interventions at adults without diabetes
Outcomes	Intermediate outcomes such as hemodynamic characteristics
Study design	Uncontrolled case series or uncontrolled clinical trials Meeting abstracts presenting the results of randomized controlled trials (RCT) that have been published in peer-reviewed journals or have results in clinicaltrials.gov

Search strategy

The medical librarian develops specific search strategies based on the PICOs formulated by our clinical and epidemiology staff. We search for all relevant articles published in English from 2010 up to March 2018 in PubMed, EMBASE, and the Cochrane Library. To identify grey unpublished data, we conduct a search of the trial registry clinicaltrials.gov.

We conduct the following searches:

PubMed searches for:

(I) RCTs;

(II) Observational studies of harms (multivariate adjusted estimates from nationally representative cohorts or administrative databases) (6,7);

(III) Clinical practice guidelines.

EMBASE searches for full publications of:

(I) RCTs;

(II) Observational studies (multivariate adjusted estimates from nationally representative cohorts or administrative databases).

The bibliographies of identified articles are scanned, and study investigators are contacted for additional publications.

Study selection

The study epidemiologist and an author-subject matter expert contribute equally to resolving differences and decide the determination of eligibility collaboratively.

The study epidemiologist and an author-subject matter expert determine eligibility for full text review, first screen title, and abstracts. All citations found during the searches are stored in a reference database.

Data extraction and strategy for data synthesis

Data extraction

The data was extracted from the Clinical Trials Transformation Initiative (https://www.ctti-clinicaltrials.org/aact-database), checked for quality, and stored in the HPCC platform (High-Performance Computing Cluster, https://hpccsystems.com/).

We manually abstracted the data from published articles into the abstraction form. We checked the data for ambiguity (i.e., data reported in percentiles conflicting with unit data and vice versa; values outside a normal range) and mismatch with the published data. Identified errors have been discussed and corrected.

We abstract the information about study population, interventions, comparators, and outcomes. We abstract minimum datasets (e.g., number of the subjects in treatment groups and events) to estimate absolute risk difference, relative risk, and number needed to treat for categorical variables.

Means and standard deviations of continuous variables, e.g., total scores from the quality of life scales are abstracted. Statistical significance is evaluated at a 95% confidence level (including the use of P values). All authors have access to the data.

We conduct an overview of the reviews following the framework of the Cochrane Collaboration. We perform meta-analyses or update published meta-analyses. Pooling criteria include the exact same definitions of the active and control intervention, patient outcomes, and similar follow-up time (10).

We define harms as the totality of all possible adverse consequences of an intervention. Investigators sometimes defined harmful effects as unrelated to examined treatments. Harms are analyzed regardless of how investigators related them to treatments.

We calculate absolute risk difference, number needed to treat, and the number of attributable events based on data from the published randomized trials, using STATA software. Correction coefficients for zero events are used as a default option in both software programs, and intention to treat is used for evidence synthesis. Superiority of interventions under comparison is hypothesized.

We assess reporting bias as a proportion of published among all registered studies, unreported outcomes compared with published protocols, or unreported minimum data sets for reproducibility of the results. We did not conduct formal statistical tests for publication bias due to the questionable validity of such tests (18).

To examine the role of patient characteristics, a search is undertaken for subgroup analyses by patient demographics, baseline and achieved blood pressure, prior treatment response, and comorbidities in systematic reviews and randomized trials, including significant interaction effects.

Methodological assessment of the included studies

For systematic reviews (QIRs), we use the Assessment of Multiple Systematic Reviews (AMSTAR) scale to determine the methodological strength of the systematic reviews (99).

For randomized studies, we apply the Cochrane risk of bias tool. Risk of bias is assessed on a 3-point scale: high bias, low bias, and unclear (100,101). A low risk of bias is assumed when RCTs met all the risk-of-bias criteria, a medium risk of bias if at least 1 of the risk-of-bias criteria is not met, and a high risk of bias if 2 or more risk-of-bias criteria are not met. An unknown risk of bias is assigned for the studies with poorly reported risk-of-bias criteria. We assign high risk of bias to all observational studies.

For clinical practice guidelines, we use the Appraisal of Guidelines for Research and Evaluation (AGREE) II (2009) tool, which covers 23 items in 6 domains and 2 overall global ratings (102,103).

Quality assessment of the included studies and the body of evidence by outcome according to the GRADE framework

The authors assign the quality of evidence ratings as high, moderate, low, or very low, according to risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the evidence of reporting bias, using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (23). We upgrade the risk of bias from low to high if at least 1 RCT had high risk of bias. We define indirectness in outcomes from intermediate outcomes. We review published network meta-analyses but do not conduct indirect comparisons.

Treatment effect estimates are defined as precise when pooled estimates have reasonably narrow 95% confidence intervals and the number of events are greater than 250. Justification of the sample size is not included in grading of the evidence. We do not conduct post hoc statistical power analyses.

In assessing the quality of evidence in all studies, the authors look for a dose response association, the strength of association, and evidence of any reporting bias. The strength of the association is evaluated, defining a priori a large effect when the relative risk is greater than 2 and a very large effect when the relative risk is greater than 5. A small treatment effect is construed when the relative risk was significant but less than 2. For standardized continuous measures of secondary and intermediate outcomes, the magnitude of the effect is defined according to Cohen *et al.* as small, moderate, and large, corresponding to mean differences in standard deviation units of 0 to 0.5, 0.5 to 0.8, and greater than 0.8, respectively.

A high quality of evidence is assigned to well-designed RCTs with consistent findings. The quality of evidence is downgraded to moderate if at least 1 of 4 quality of evidence criteria is not met; for example, moderate quality of evidence is assigned if there was a high risk of bias in the body of evidence or if the results are not consistent or precise. The quality of evidence is downgraded to low if 2 or more criteria are not met.

A low quality of evidence is assigned to nonrandomized studies and upgraded for the rating if there was a strong or dose-response association. Evidence is defined as insufficient when no studies provided valid information about treatment effects. This approach is applied regardless of whether the results were statistically significant.

The authors assign strength of the recommendations based on overall quality of evidence, balances between benefits and harms, healthcare consumers' and clinicians' values and preferences, and cost-effectiveness studies using the GRADE methodology.

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect. Any estimate of effect is very uncertain
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion

PubMed search of record:

((((((((((((((diabet*[Title/Abstract]) OR "Diabetes Mellitus/drug therapy"[Majr])) AND (((((hypertensi*[Title/Abstract]) OR (("Blood Pressure/drug effects"[Mesh] OR "Blood Pressure/pharmacology"[Mesh] OR "Blood Pressure/therapy"[Mesh]))) OR ((((("systolic blood pressure"[Title/Abstract]) OR "systolic pressure"[Title/Abstract]) OR "diastolic blood pressure"[Title/Abstract]) OR "diastolic pressure"[Title/Abstract])) OR normotensive[Title/Abstract]) OR "Hypertension/drug therapy"[Majr]))) AND ((((((strict*[Title/Abstract]) OR target*[Title/Abstract]) OR tight*[Title/Abstract]) OR intens*[Title/Abstract]) OR below[Title/Abstract]) OR moderat*[Title/Abstract]))))) AND ((((((("Antihypertensive Agents"[Mesh]) OR "Antihypertensive Agents"[Pharmacological Action]) OR "Angiotensin II Type 1 Receptor Blockers"[Mesh])) OR antihypertensive[Title/Abstract]) OR "angiotensin II"[Title/Abstract]))) NOT (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]))) NOT (("Animals"[Mesh]) NOT (("Animals"[Mesh]) AND "Humans"[Mesh])))) AND (((((((((random*[Title/Abstract]) OR placebo*[Title/Abstract]) OR "double blind"[Title/Abstract]) OR "triple blind"[Title/Abstract]) OR prospective[Title/Abstract]) OR multicenter[Title/Abstract])) OR "Multicenter Study"[Publication Type]) OR "Randomized Controlled Trial"[Publication Type:NoExp])))

PubMed search of record for CPGs:

((((((((((diabet*[Title/Abstract]) OR "Diabetes Mellitus/drug therapy"[Majr])) AND (((((hypertensi*[Title/Abstract]) OR (("Blood Pressure/drug effects"[Mesh] OR "Blood Pressure/pharmacology"[Mesh] OR "Blood Pressure/therapy"[Mesh]))) OR ((((("systolic blood pressure"[Title/Abstract]) OR "systolic pressure"[Title/Abstract]) OR "diastolic blood pressure"[Title/Abstract]) OR "diastolic pressure"[Title/Abstract])) OR normotensive[Title/Abstract]) OR "Hypertension/drug therapy"[Majr]))) AND ((((((strict*[Title/Abstract]) OR target*[Title/Abstract]) OR tight*[Title/Abstract]) OR intens*[Title/Abstract]) OR moderat*[Title/Abstract]))))) AND ((((((("Antihypertensive Agents"[Mesh]) OR "Antihypertensive Agents"[Pharmacological Action]) OR "Angiotensin II Type 1 Receptor Blockers"[Mesh])) OR antihypertensive[Title/Abstract]) OR "angiotensin II"[Title/Abstract]))) AND ((((((((((((((((((((("Guideline"[Publication Type]) OR "Practice Guideline"[Publication Type])) OR "Consensus Development Conference"[Publication Type]) OR "Consensus Development Conference, NIH"[Publication Type]) OR "Practice Guideline"[Publication Type]) OR "Guideline"[Publication Type]) OR ((clinical[Title]) AND guideline*[Title])) OR (((clinical*[Title]) AND guide*[Title]) AND manage*[Title])) OR ((best[Title]) AND practice*[Title])) OR ((evidence[Title]) AND synthes*[Title])) OR ((consensus[Title]) AND develop*[Title])) OR ((practice[Title]) AND guideline*[Title])) OR (("evidence based"[Title]) AND guideline*[Title])) OR ((consensus[Title]) AND statement*[Title])) OR ((committee[Title]) AND opinion*[Title])) OR ((practice[Title]) AND bulletin*[Title])) OR ((clinical[Title]) AND recommendation*[Title])) OR ((("U.S. Preventive Services Task Force"[Title/Abstract]) OR USPSTF[Title/Abstract]) OR "United States Preventive Services Task Force"[Title/Abstract])) OR ACR Appropriateness Criteria[Title])) NOT (((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]))) NOT (("Animals"[Mesh]) NOT (("Animals"[Mesh]) AND "Humans"[Mesh]))))

Embase	
No.	Query
Results	
273	#64
#53 AND #63	
2,015,375	#63
#54 OR #56 OR #57 OR #58 OR #59 OR #62	
1,509,234	#62
#61 OR 'double blind procedure'/de OR 'multicenter study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de	
1,130,198	#61

random*:ab,ti OR placebo*:ab,ti OR (double NEXT/1 blind):ab,ti OR (triple NEXT/1 blind):ab,ti

33,224

#59

'hazard ratio'/de

53,805

#58

'proportional hazards model'/de

151,708

#57

nation*:ab,ti OR registr* AND cohort OR 'cox regression':ab,ti OR 'hazard ratio':ab,ti

274,206

#56

'multivariate analysis'/exp

324,727

#54

multivar*:ab,ti

638

#53

#14 AND #52

1,471

#52

#47 NOT #51

4,776,528

#51

#48 NOT #50

15,578,685

#50

#48 AND #49

15,578,685

#49

'human'/exp

20,265,320

#48

'animal'/exp

1,488

#47

#45 NOT #46

5,188,835

#46

'letter'/de OR 'editorial'/de OR 'note'/de OR 'conference paper'/de OR 'short survey'/exp OR 'conference abstract'/it

2,124

#45

#43 AND #44

671,989

#44

#1 OR #3 OR #4

14,384

#43

#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33OR #34 OR #36 OR #37 OR #38 OR #41 OR #42

19

#42

(aggressive NEAR/3 systolic):ab,ti

4

#41

(aggressive NEAR/3 diastolic):ab,ti

464

#38

(below NEAR/3 systolic):ab,ti

352

#37

(below NEAR/3 diastolic):ab,ti

214

#36

(intensi* NEAR/3 systolic):ab,ti

81

#34

(intensi* NEAR/3 diastolic):ab,ti

12

#33

(tight* NEAR/3 diastolic):ab,ti

23

#32

(tight* NEAR/3 systolic):ab,ti

17

#31

(strict* NEAR/3 systolic):ab,ti

4

#30

(strict* NEAR/3 diastolic):ab,ti

208

#29

(target* NEAR/3 diastolic):ab,ti

403

#28

(target* NEAR/3 systolic):ab,ti

522

#27

(moderate NEAR/3 systolic):ab,ti

451

#26

(moderate NEAR/3 diastolic):ab,ti

161

#25

(standard NEAR/3 diastolic):ab,ti

324

#24

(standard NEAR/3 systolic):ab,ti

1,635

#23

(standard NEAR/3 pressure):ab,ti

1,226

#22

(moderate NEAR/3 pressure):ab,ti

394

#21

(aggressive NEAR/3 pressure):ab,ti

3,343

#20

(below NEAR/3 pressure):ab,ti

1,492

#19

(intensi* NEAR/3 pressure):ab,ti

452

#18

(tight* NEAR/3 pressure):ab,ti

420

#17

(strict* NEAR/3 pressure):ab,ti

3,756

#16

(target* NEAR/3 pressure):ab,ti

117,953

#14

#12 OR #13

53,840

#13

antihypertensive:ab,ti

78,644

#12

'antihypertensive agent'/exp/mj/dd_dt

504,814

#9

hypertensi*:ab,ti

61,009

#8

'hypertension'/exp/mj/dm_dt

83,927

#4

#3 AND 'drug therapy'/lnk

664,883

#3

diabet*:ab,ti

74,733

#1

'diabetes mellitus'/exp/mj/dm_dt

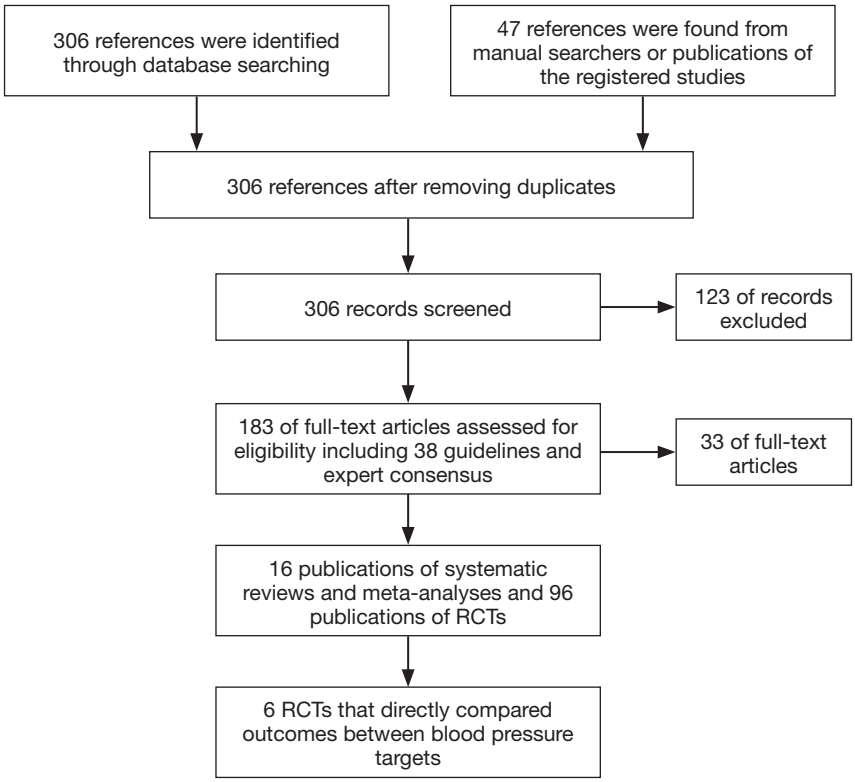

Figure S1 Study flow diagram. Publications of primary RCTs of blood pressure targets (24-29,42-44,104-107); publications of RCTs that examined efficacy or comparative effectiveness of antihypertensive drugs in 1970–1989 (108-114), 1990–1999 (41,115-135), 2000–2002 (136-152), 2003–2005 (153-174), 2006–2009 (175-190), 2010–2014 (191-207); publications of reviews (3-5,30,31,33-38,40,50,90,93,208,209); publications of guidelines published in 2010–2014 (59,60,62-66,94,95,97,210-213) and in 2015–2018 (51-56,61,87,96,98,214-217).

Table S1 Relative risk of patient outcomes depending on baseline or attained blood pressure in adults with diabetes, the results from meta-analyses of aggregate data from randomized controlled clinical trials

Outcome	Blood pressure	Relative risk	No. of participants (studies)
Meta-regression of aggregate data by baseline blood pressure			
All-cause mortality	10 mmHg lower baseline SBP	1.04 (0.98–1.10)	73,738 (49 RCTs) (31)
All-cause mortality	10 mmHg lower baseline DBP	1.08 (0.99–1.18)	73,738 (49 RCTs) (31)
Cardiovascular mortality	10 mmHg lower baseline SBP	1.15 (1.03–1.29)	73,738 (49 RCTs) (31)
Cardiovascular mortality	10 mmHg lower baseline DBP	1.28 (1.05–1.55)	73,738 (49 RCTs) (31)
End-stage renal disease	10 mmHg lower baseline SBP	1.05 (0.90–1.22)	73,738 (49 RCTs) (31)
End-stage renal disease	10 mmHg lower baseline DBP	1.13 (0.88–1.44)	73,738 (49 RCTs) (31)
Heart failure	10 mmHg lower baseline SBP	1.05 (0.93–1.20)	73,738 (49 RCTs) (31)
Heart failure	10 mmHg lower baseline DBP	1.11 (0.90–1.36)	73,738 (49 RCTs) (31)
Myocardial infarction	10 mmHg lower baseline SBP	1.12 (1.03–1.22)	73,738 (49 RCTs) (31)
Myocardial infarction	10 mmHg lower baseline DBP	1.11 (0.98–1.26)	73,738 (49 RCTs) (31)
Stroke	10 mmHg lower baseline SBP	1.07 (0.98–1.18)	73,738 (49 RCTs) (31)
Stroke	10 mmHg lower baseline DBP	1.09 (0.93–1.27)	73,738 (49 RCTs) (31)
Subgroup meta-analysis of aggregate data by baseline blood pressure			
All-cause mortality	Baseline SBP >150 mmHg	0.89 (0.80–0.99)	12,824 (16 RCTs) (31)
Cardiovascular mortality	Baseline SBP >150 mmHg	0.75 (0.57–0.99)	9,073 (11 RCTs) (31)
Myocardial infarction	Baseline SBP >150 mmHg	0.74 (0.63–0.87)	9,914 (13 RCTs) (31)
Stroke	Baseline SBP >150 mmHg	0.77 (0.65–0.91)	11,444 (15 RCTs) (31)
Heart failure	Baseline SBP >150 mmHg	0.73 (0.53–1.01)	6,510 (7 RCTs) (31)
End-stage renal disease	Baseline SBP >150 mmHg	0.82 (0.71–0.94)	4,814 (5 RCTs) (31)
All-cause mortality	Baseline SBP 140–150 mmHg	0.87 (0.78–0.98)	24,652 (10 RCTs) (31)
All-cause mortality	Baseline SBP >140mmHg	0.73 (0.64–0.84)	30,998 (13 RCT) (93)
Cardiovascular mortality	Baseline SBP 140–150 mmHg	0.87 (0.71–1.05)	24,243 (9 RCTs) (31)
Cardiovascular disease	Baseline SBP >140mmHg	0.74 (0.65–0.85)	29,044 (11RCT) (93)
Myocardial infarction	Baseline SBP 140–150 mmHg	0.84 (0.76–0.93)	23,286 (7 RCTs) (31)
Stroke	Baseline SBP 140–150 mmHg	0.92 (0.83–1.01)	30,135 (9 RCTs) (31)
Stroke	Baseline SBP >140mmHg	0.74 (0.74–0.86)	36,934 (14 RCT) (93)
Heart failure	Baseline SBP 140–150 mmHg	0.80 (0.66–0.97)	12,723 (7 RCTs) (31)
End-stage renal disease	Baseline SBP 140–150 mmHg	0.91 (0.74–1.12)	21,376 (6 RCTs) (31)
All-cause mortality	Baseline SBP <140 mmHg	1.05 (0.95–1.16)	24,350 (14 RCTs) (31)
All-cause mortality	Baseline SBP <140 mmHg	1.07 (0.92–1.26)	12,559 (7 RCTs) (93)
Cardiovascular mortality	Baseline SBP <140 mmHg	1.15 (1.00–1.32)	22,439 (10 RCTs) (31)
Cardiovascular disease	Baseline SBP <140 mmHg	0.96 (0.88–1.05)	21,574 (6 RCTs) (93)
Myocardial infarction	Baseline SBP <140 mmHg	1.00 (0.87–1.15)	18,051 (9 RCTs) (31)
Stroke	Baseline SBP <140 mmHg	0.81 (0.53–1.22)	17,911 (8 RCTs) (31)
Stroke	Baseline SBP <140 mmHg	0.69 (0.69–0.92)	17,127 (5 RCT) (93)
Heart failure	Baseline SBP <140 mmHg	0.90 (0.79–1.02)	17,392 (8 RCTs) (31)
End-stage renal disease	Baseline SBP <140 mmHg	0.97 (0.80–1.17)	19,973 (7 RCTs) (31)
Cardiovascular mortality	Baseline SBP <130 mmHg	2.95 (0.43–20.20)	4,946 (2 RCTs) (37)
All-cause mortality	Baseline DBP >90 mmHg	0.85 (0.73–1.00)	6,591 (9 RCTs) (31)
Cardiovascular mortality	Baseline DBP >90 mmHg	0.70 (0.55–0.89)	4,452 (6 RCTs) (31)
Myocardial infarction	Baseline DBP >90 mmHg	0.79 (0.62–1.00)	3,681 (6 RCTs) (31)
Stroke	Baseline DBP >90 mmHg	0.74 (0.58–0.94)	5,211 (8 RCTs) (31)
Heart failure	Baseline DBP >90 mmHg	0.50 (0.29–0.85)	1,259 (2 RCTs) (31)
End-stage renal disease	Baseline DBP >90 mmHg	0.96 (0.14–6.76)	1,259 (2 RCTs) (31)
All-cause mortality	Baseline DBP 80–90 mmHg	0.90 (0.82–0.99)	25,779 (16 RCTs) (31)
Cardiovascular mortality	Baseline DBP 80–90 mmHg	0.91 (0.78–1.07)	24,842 (13 RCTs) (31)
Myocardial infarction	Baseline DBP 80–90 mmHg	0.85 (0.76–0.95)	24,861 (13 RCTs) (31)
Stroke	Baseline DBP 80–90 mmHg	0.92 (0.83–1.03)	30,604 (14 RCTs) (31)
Heart failure	Baseline DBP 80–90 mmHg	0.81 (0.67–0.97)	13,322 (11 RCTs) (31)
End-stage renal disease	Baseline DBP 80–90 mmHg	0.83 (0.72–0.94)	20,912 (8 RCTs) (31)
All-cause mortality	Baseline DBP <80 mmHg	0.97 (0.89–1.06)	29,456 (15 RCTs) (31)
Cardiovascular mortality	Baseline DBP <80 mmHg	1.08 (0.82–1.41)	27,091 (11 RCTs) (31)
Myocardial infarction	Baseline DBP <80 mmHg	0.90 (0.79–1.02)	22,709 (10 RCTs) (31)
Stroke	Baseline DBP <80 mmHg	0.86 (0.70–1.05)	23,675 (10 RCTs) (31)
Heart failure	Baseline DBP <80 mmHg	0.89 (0.80–1.00)	22,044 (9 RCTs) (31)
End-stage renal disease	Baseline DBP <80 mmHg	0.97 (0.83–1.13)	23,992 (8 RCTs) (31)
Meta-regression of aggregate data by attained blood pressure			
All-cause mortality	Each 10 mmHg lower attained SBP	0.94 (0.89–0.99)	53,344 (20 RCTs) (33)
All-cause mortality	Each 10 mmHg lower attained SBP	1.02 (0.93–1.12)	73,738 (49 RCTs) (31)
All-cause mortality	Each 10 mmHg lower attained DBP	1.07 (0.93–1.23)	73,738 (49 RCTs) (31)
Cardiovascular mortality	Each 10 mmHg lower attained SBP	1.20 (0.99–1.44)	73,738 (49 RCTs) (31)
Cardiovascular mortality	Each 10 mmHg lower attained DBP	1.35 (0.98–1.86)	73,738 (49 RCTs) (31)
Coronary heart disease	Each 10 mmHg lower attained SBP	0.88 (0.80–0.97)	52,129 (19 RCTs) (33)
Major cardiovascular events	Each 10 mmHg lower attained SBP	0.88 (0.82–0.94)	59,773 (23 RCTs) (33)
Myocardial infarction	Each 10 mmHg lower attained SBP	1.09 (0.98–1.21)	73,738 (49 RCTs) (31)
Myocardial infarction	Each 10 mmHg lower attained DBP	1.13 (0.96–1.33)	73,738 (49 RCTs) (31)
Heart failure	Each 10 mmHg lower attained SBP	0.90 (0.83–0.98)	41,960 (13 RCTs) (33)
Heart failure	Each 10 mmHg lower attained SBP	1.05 (0.90–1.22)	73,738 (49 RCTs) (31)
Heart failure	Each 10 mmHg lower attained DBP	1.11 (0.90–1.36)	73,738 (49 RCTs) (31)
End-stage renal disease	Each 10 mmHg lower attained SBP	1.02 (0.85–1.24)	73,738 (49 RCTs) (31)
End-stage renal disease	Each 10 mmHg lower attained DBP	1.11 (0.88–1.41)	73,738 (49 RCTs) (31)
Renal failure	Each 10 mmHg lower attained SBP	0.92 (0.84–1.01)	28,190 (9 RCTs) (33)
Stroke	Each 10 mmHg lower attained SBP	0.74 (0.65–0.84)	58,064 (21 RCTs) (33)
Stroke	Each 10 mmHg lower attained SBP	0.97 (0.82–1.13)	73,738 (49 RCTs) (31)
Stroke	Each 10 mmHg lower attained DBP	0.95 (0.75–1.21)	73,738 (49 RCTs) (31)
Subgroup meta-analysis of aggregate data by attained blood pressure			
All-cause mortality	–	0.92 (0.87–0.96)	66,130 (45 RCTs) (31)
All-cause mortality	Attained SBP >140	0.96 (0.86–1.06)	21,876 (13 RCTs) (31)
All-cause mortality**	Attained SBP ≥140	0.98 (0.89–1.07)	11,559 (9 RCTs) (37)
All-cause mortality**	Attained SBP 130–139	0.85 (0.78–0.92)	23,714 (11 RCTs) (37)
All-cause mortality*	Attained SBP 130–139	0.81 (0.49–1.35)	1,654 (4 RCTs) (37)
All-cause mortality	Attained SBP 130–140	0.86 (0.79–0.93)	28,900 (18 RCTs) (31)
All-cause mortality**	Attained SBP <130	1.00 (0.82–1.21)	6,117 (2 RCTs) (37)
All-cause mortality*	Attained SBP <130	1.44 (0.81–2.57)	4,946 (2 RCTs) (37)
All-cause mortality	Attained SBP <130	1.10 (0.91–1.33)	11,050 (9 RCTs) (31)
All-cause mortality	Attained DBP >80 mmHg	0.95 (0.86–1.06)	13,092 (13 RCTs) (31)
All-cause mortality	Attained DBP 75–80 mmHg	0.86 (0.75–0.98)	14,059 (13 RCTs) (31)
All-cause mortality	Attained DBP <75	0.97 (0.89–1.04)	34,675 (14 RCTs) (31)
Cardiovascular mortality	–	0.92 (0.82–1.03)	59,956 (33 RCTs) (31)
Cardiovascular mortality	Attained SBP >140	0.87 (0.71–1.07)	20,703 (11 RCTs) (31)
Cardiovascular mortality**	Attained SBP ≥140	0.92 (0.75–1.13)	10,386 (10 RCTs) (37)
Cardiovascular mortality**	Attained SBP 130–139	0.79 (0.67–0.93)	22,942 (7 RCTs) (37)
Cardiovascular mortality*	Attained SBP 130–139	0.61 (0.15–2.47)	2459 (4 RCTs) (37)
Cardiovascular mortality	Attained SBP 130–140	0.86 (0.72–1.04)	25,095 (12 RCTs) (31)
Cardiovascular mortality**	Attained SBP <130	1.12 (0.77–1.63)	6,117 (2 RCTs) (37)
Cardiovascular mortality	Attained SBP <130 mmHg	1.26 (0.89–1.77)	10,587 (7 RCTs) (31)
Cardiovascular mortality	Attained DBP >80 mmHg	0.71 (0.53–0.97)	11,229 (10 RCTs) (31)
Cardiovascular mortality	Attained DBP 75–80 mmHg	0.85 (0.69–1.05)	13,040 (10 RCTs) (31)
Cardiovascular mortality	Attained DBP <75 mmHg	1.16 (0.92–1.47)	32,116 (10 RCTs) (31)
Coronary heart disease**	Attained SBP ≥140	0.72 (0.60–0.85)	11,559 (9 RCTs) (37)
Coronary heart disease**	Attained SBP 130–139	0.86 (0.78–0.94)	22,942 (10 RCTs) (37)
Coronary heart disease*	Attained SBP 130–139	0.67 (0.29–1.55)	1,274 (3 RCTs) (37)
Coronary heart disease*	Attained SBP <130	0.67 (0.40–1.14)	4,946 (2 RCTs) (37)
Myocardial infarction	–	0.87 (0.81–0.94)	53,512 (31 RCTs) (31)
Myocardial infarction	Attained SBP >140 mmHg	0.82 (0.72–0.92)	21,286 (12 RCTs) (31)
Myocardial infarction	Attained SBP 130–140 mmHg	0.88 (0.79–0.97)	23,828 (11 RCTs) (31)
Myocardial infarction	Attained SBP <130 mmHg	0.94 (0.76–1.15)	6,137 (6 RCTs) (31)
Myocardial infarction	Attained DBP >80 mmHg	0.76 (0.63–0.93)	9,608 (8 RCTs) (31)
Myocardial infarction	Attained DBP 75–80 mmHg	0.81 (0.72–0.91)	13,650 (12 RCTs) (31)
Myocardial infarction	Attained DBP <75 mmHg	0.95 (0.84–1.07)	27,993 (9 RCTs) (31)
Heart failure	–	0.82 (0.75–0.89)	40,196 (25 RCTs) (31)
Heart failure	Attained SBP >140 mmHg	0.83 (0.68–1.00)	19,060 (9 RCTs) (31)
Heart failure**	Attained SBP ≥140	0.86 (0.70–1.05)	8,743 (5 RCTs) (37)
Heart failure	Attained SBP 130–140 mmHg	0.81 (0.70–0.94)	11,568 (8 RCTs) (31)
Heart failure**	Attained SBP 130–139	0.82 (0.69–0.97)	20,952 (8 RCTs) (37)
Heart failure	Attained SBP <130 mmHg	0.93 (0.71–1.21)	5,997 (5 RCTs) (31)
Heart failure**	Attained SBP <130	0.89 (0.65–1.23)	6,117 (2 RCTs) (37)
Heart failure	Attained DBP >80 mmHg	0.72 (0.45–1.15)	7,656 (5 RCTs) (31)
Heart failure	Attained DBP 75–80 mmHg	0.79 (0.65–0.96)	11,135 (9 RCTs) (31)
Heart failure	Attained DBP <75 mmHg	0.90 (0.79–1.01)	17,834 (8 RCTs) (31)
Stroke	–	0.87 (0.79–0.96)	59,490 (32 RCTs) (31)
Stroke**	Attained SBP ≥140 mmHg	0.89 (0.74–1.07)	11,730 (10 RCTs) (37)
Stroke	Attained SBP >140 mmHg	0.90 (0.76–1.06)	22,045 (14 RCTs) (31)
Stroke	Attained SBP 130–140 mmHg	0.91 (0.83–1.00)	30,342 (12 RCTs) (31)
Stroke**	Attained SBP 130–139	0.85 (0.75–0.96)	28,685 (11 RCTs) (37)
Stroke*	Attained SBP 130–139	0.89 (0.45–1.78)	1,274 (3 RCTs) (37)
Stroke**	Attained SBP <130	0.66 (0.49–0.88)	5,839 (3 RCTs) (37)
Stroke*	Attained SBP <130	1.36 (0.55–3.39)	4,946 (2 RCTs) (37)
Stroke	Attained SBP <130 mmHg	0.65 (0.42–0.99)	7,103 (6 RCTs) (31)
Stroke	Attained DBP >80 mmHg	0.87 (0.73–1.04)	11,011 (10 RCTs) (31)
Stroke	Attained DBP 75–80 mmHg	0.86 (0.75–0.97)	19,380 (12 RCTs) (31)
Stroke	Attained DBP <75 mmHg	0.87 (0.70–1.08)	29,099 (10 RCTs) (31)
Stroke + CHD**	Attained SBP ≥140	0.80 (0.71–0.90)	11,568 (9 RCTs) (37)
Stroke + CHD**	Attained SBP 130–139	0.85 (0.78–0.91)	25,060 (11 RCTs) (37)
Stroke + CHD*	Attained SBP 130–139	0.73 (0.51–1.04)	2,858 (5 RCTs) (37)
Stroke + CHD*	Attained SBP <130	0.80 (0.51–1.26)	4,946 (2 RCTs) (37)
Stroke + CHD + HF**	Attained SBP ≥140	0.85 (0.74–0.97)	9,003 (7 RCTs) (37)
Stroke + CHD + HF**	Attained SBP 130–139	0.87 (0.80–0.94)	30,032 (12 RCTs) (37)
Stroke + CHD + HF*	Attained SBP <130	0.84 (0.60–1.19)	862 (2 RCTs) (37)
End-stage renal disease	–	0.88 (0.80–0.97)	47,439 (18 RCTs) (31)
End-stage renal disease	Attained SBP >140 mmHg	0.88 (0.76–1.03)	18,287 (7 RCTs) (31)
End-stage renal disease	Attained SBP 130–140 mmHg	0.84 (0.66–1.07)	17,912 (6 RCTs) (31)
End-stage renal disease	Attained SBP <130 mmHg	1.01 (0.71–1.43)	9,964 (5 RCTs) (31)
End-stage renal disease	Attained DBP >80 mmHg	0.77 (0.39–1.52)	6,171 (3 RCTs) (31)
End-stage renal disease	Attained DBP 75–80 mmHg	0.81 (0.71–0.93)	8,437 (7 RCTs) (31)
End-stage renal disease	Attained DBP <75 mmHg	0.98 (0.84–1.14)	31,555 (8 RCTs) (31)

*, low/moderate cardiovascular risk; **,high/very high cardiovascular risk. CHD, coronary heart disease; DBP, diastolic blood pressure; HF, heart failure; RCT, randomized controlled trial; RR, relative risk; SBP, systolic blood pressure.

Table S2 GRADE summary of findings. Harms of blood pressure control in adults with diabetes mellitus (low-quality evidence from published aggregate data meta-analyses of any antihypertensive treatments)

Outcome	Risk with intervention per 1,000 (95% CI)	Risk with comparator per 1,000	Relative measure of association	No. of participants (studies)
Cardiovascular mortality; baseline SBP <130 mmHg	6	2	RR: 3.96 (1.33–11.84); 2.95 (0.43–20.20)	4,946 (2 RCTs) (37)
Cardiovascular mortality; baseline SBP <140 mmHg	NR	NR	RR: 1.15 (1.00–1.32)	22,439 (10 RCTs) (31)
Cardiovascular mortality; each 10 mmHg lower baseline SBP	NR	NR	RR: 1.15 (1.03–1.29)	73,738 (49 RCTs) (31)
Cardiovascular mortality; each 10 mmHg lower baseline DBP	NR	NR	RR: 1.28 (1.05–1.55)	73,738 (49 RCTs) (31)
Myocardial infarction; each 10 mmHg lower baseline SBP	NR	NR	RR: 1.12 (1.03–1.22)	73,738 (49 RCTs) (31)

Population: adults with diabetes; Settings: outpatient; Intervention: antihypertensive treatment; Comparator: control as no active antihypertensive treatment; CI, confidence interval; DBP, diastolic blood pressure; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NR, not reported; RCT, randomized controlled trial; RR, relative risk; SBP, systolic blood pressure.

Table S3 Guideline recommendations regarding blood pressure targets in adults with diabetes

Organization	Recommendations
World Health Organization (WHO); A Global Brief on Hypertension, 2013 (4,94)	This guideline recommends that target blood pressure in patients with diabetes should be <130/80 mmHg
Eighth Joint National Committee (JNC 8). Evidence-based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the JNC 8, 2014 (53,95) (AGREE II score: 78%)	This guideline recommends initiating pharmacologic treatment to lower blood pressure at SBP 140 mmHg or DBP 90 mmHg and treat to a goal of SBP <140/90 mmHg in all adults with diabetes
AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association, 2011–2017 (56,59)	This guideline recommends that in adults with diabetes and hypertension, antihypertensive drug treatment should be initiated at a blood pressure of 130/80 mmHg or higher with a treatment goal of <130/80 mmHg
American Diabetes Association. Position Statement on the Standards of Medical Care in Diabetes, 2018 (54,55,60,61) (AGREE II score not available)	This guideline recommends that most patients with diabetes and hypertension should be treated to an SBP goal of <140/90 mmHg; lower SBP and DBP targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden
American Association of Clinical Endocrinologists and American College of Endocrinology. Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan, 2015 (96) (AGREE II score: 53%)	The blood pressure goal for persons with diabetes mellitus or prediabetes should be individualized and should generally be about 130/80 mmHg; a more intensive goal (e.g., <120/80 mmHg) should be considered for some patients, provided this target can be reached safely without adverse effects from medication; more relaxed goals may be considered for frail patients with complicated comorbidities or those who have adverse medication effects
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 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 (97)	This guideline recommends that patients with diabetes should be treated to <140/90 mmHg; this guideline acknowledges that other guidelines have recommended diagnostic values of 130/80 mmHg for patients with diabetes or chronic kidney disease. However, the clinical benefits of this lower target have not been established; some experts recommend <130/80 mmHg if albuminuria is present in patients with comorbid chronic kidney disease
The American Geriatrics Society Guidelines for Improving the Care of Older Adults With Diabetes Mellitus, 2013 (66)	This guideline states that if an older adult has diabetes and requires medical therapy for hypertension, then the target blood pressure should be less than 140/90 mmHg if it is tolerated; there is potential harm in lowering SBP to less than 120 mmHg in older adults with type 2 diabetes mellitus (1B)
American Academy of Family Physicians, 2017 (98)	The AAFP continues to endorse the 2014 Evidence-Based Guidelines for the Management of High Blood Pressure in Adults, developed by panel members appointed to the Eighth Joint National Committee, with a blood pressure target of <140/80 mmHg
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) (65)	This guideline recommends an SBP goal of <140/90 mmHg in patients with diabetes
The National Institute for Health and Care Excellence, 2011 (63); Type 2 Diabetes in Adults: Management, 2015 (51)	This guideline recommends treating adults with type 2 diabetes and arterial hypertension to achieve blood pressure <140/80 mmHg (<130/80 mmHg if there is kidney, eye, or cerebrovascular damage)
Scottish Intercollegiate Guidelines Network. Management of Diabetes: A National Clinical Guideline (62) (AGREE II score: 88%)	This guideline recommends target blood pressure <130/80 mmHg in patients with diabetes; in patients with diabetes and kidney disease, blood pressure should be reduced to the lowest achievable level to slow the rate of decline of glomerular filtration rate and reduce proteinuria
Canadian Hypertension Education Program (CHEP) Guidelines for Pharmacists, 2013 (64)	This guideline recommends that patients with kidney disease and concomitant diabetes should be treated to a target of <130/80 mmHg

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