

Targeting blood pressure in people with diabetes mellitus

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KEY WORDS

blood pressure, cardiovascular disease, diabetes mellitus, hypertension, target

ABSTRACT

Hypertension is a strong risk factor for cardiovascular (CV)-related morbidity and mortality, and its treatment has been shown to be beneficial. Hypertension is common in people with diabetes mellitus, and the combination of these conditions markedly increases CV risk in comparison with individuals with neither condition. Although there is increasing clarity as to blood pressure (BP) targets in numerous conditions, the target in people with diabetes remains unclear, and, as a result, many clinical practice guidelines differ on the optimal BP goal. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial did not demonstrate benefit when systolic BP (SBP) was lowered to less than 120 mmHg compared with a target of less than 140 mmHg. This was in contrast to the recent SPRINT trial (Systolic Blood Pressure Intervention Trial), which demonstrated the superiority of a target SBP of less than 120 mmHg in reducing CV events. However, people with diabetes mellitus were excluded. Recent meta-analyses have suggested that lowering BP in patients with diabetes mellitus should be reserved for a baseline SBP greater than 140 mmHg, targeting an SBP of between 130 and 140 mmHg. Lower targets may reduce the risk of stroke but may also be harmful with respect to other important CV outcomes. The methodological limitations of these meta-analyses highlight the need for a large randomized controlled trial comparing lower and standard BP targets in people with diabetes mellitus.

Introduction It has long been recognized that hypertension is a strong risk factor for cardiovascular (CV)-related morbidity and mortality. Although an initial report suggested that treatment of primary hypertension was ineffective, despite baseline blood pressure (BP) as high as 280/160 mmHg,¹ a subsequent randomized controlled trial (RCT) demonstrated a reduction in morbidity with treatment.² An RCT conducted by the Hypertension Detection and Follow-up Program Collaborative Group³ then provided convincing evidence that mortality was reduced in patients with severe diastolic hypertension. Since that time, successive RCTs have demonstrated that lowering BP reduces CV events and mortality in people with hypertension. This has led to a temporal reduction in baseline BP as a starting point for newer trials conducted to evaluate even lower BP targets (FIGURE 1), culminating in the most recently published SPRINT trial.⁴

Hypertension is very common in people with diabetes mellitus. About one-third of people with type 2 diabetes have hypertension at the time of

diagnosis,⁵ and the risk increases over time.⁶ Diabetes patients also have a much higher risk of CV-related mortality than those without diabetes for any given BP.⁷ The mortality risk in an individual with both diabetes and hypertension is 2.5-fold higher than that in an individual without any of these conditions.⁸ Observational data suggest the presence of a strong relationship between systolic BP (SBP) and incidence of a variety of CV events in people with diabetes.⁹

Blood pressure targets in patients with diabetes Intensive treatment of BP in individuals with diabetes may be warranted in view of the relationship between SBP and CV risk, the high prevalence of hypertension and CV disease, and the increased mortality risk that comes with these conditions. The ACCORD study¹⁰ examined this viewpoint by randomizing participants with diabetes to either a target SBP of less than 120 mmHg or less than 140 mmHg. The study found no difference between the groups in the composite CV endpoint despite substantial BP separation, although a

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FIGURE 1 Relationship between average baseline blood pressure (BP) and the year in which the trial was started. Each pair of systolic BP and diastolic BP points represents the mean value from an individual trial. Trials shown are those included in the meta-analysis by Brunstrom and Carlberg²⁰ with a minimum of 1000 participants. The much earlier HDPF study³ is not included for the presentation purposes. Selected well-known trials are highlighted; SPRINT is also included for reference.

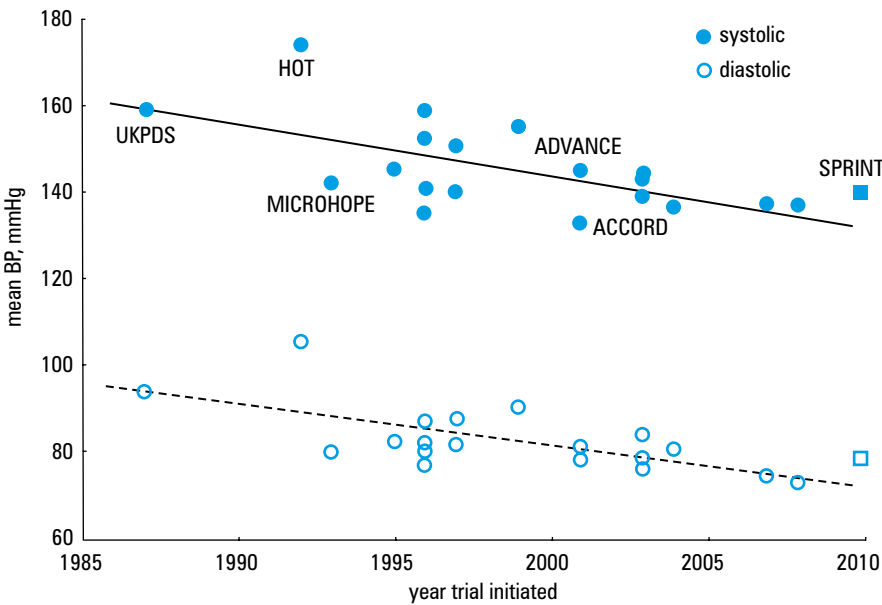


TABLE 1 Comparison of blood pressure targets in selected clinical practice guidelines

Country/Region	Organization	Year of publication	Blood pressure target, mmHg	Evidence level
Canada	Canadian Hypertension Education Program (CHEP) ¹²	2016	<130/80	grade C for SBP, grade A for DBP
United States	8th Joint National Committee (JNC8) ¹⁴	2014	<140/90	grade E, expert opinion
	American Society of Hypertension (ASH) ^{38,39}	2014	<140/90	unknown
Japan	Japanese Society of Hypertension (JSH) ¹³	2014	<130/80	grade 1B
Europe	European Society of Hypertension (ESH)/European Society of Cardiology (ESC) ¹⁶	2013	<140/85	grade 1A
United Kingdom	National Institute for Health and Care Excellence (NICE)/British Hypertension Society (BSH) ^{40,41}	2011	<140/90	unknown

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significant reduction in the rate of stroke, a pre-specified secondary endpoint, was observed in the lower-BP-target group. However, the absolute risk of stroke was low and there was a 2- to 3-fold increase in the risk of adverse events in the lower-BP group. It should be noted that the ACCORD study¹⁰ was ultimately underpowered to answer the primary study question due to a lower than anticipated event rate.¹¹

Perhaps not surprisingly, there is a lack of consensus amongst leading clinical practice guidelines as to appropriate BP targets in people with diabetes. Canadian and Japanese guidelines recommend an SBP target of less than 130 mmHg in diabetes patients (TABLE 1).^{12,13} In contrast, the United States 8th Joint National Committee (JNC8) guidelines on hypertension modified their original SBP target of less than 130 mmHg, recommended in JNC7, to less than 140 mmHg.^{14,15} This was presumably in response to the findings of the

ACCORD study,¹⁰ combined with the lack of any high-quality evidence supporting the original lower target.¹⁴ European guidelines mirror the JNC8 guidelines with respect to SBP targets, but differ on the target for diastolic BP (DBP).¹⁶

The SPRINT trial⁴ has turned the hypertension-treating community figuratively on its head. A large RCT of more than 9000 participants considered to be at high CV risk compared a target SBP of less than 140 mmHg to that of less than 120 mmHg. Similarly to ACCORD,¹⁰ a systolic rather than diastolic target was chosen, presumably because of the higher prevalence of systolic hypertension versus diastolic hypertension in individuals at increased age. This approach was supported by the findings of ALLHAT,¹⁷ where it was observed that 92% of individuals had adequate BP defined by DBP, compared with only 67% based on SBP. The trial was halted earlier than planned due to evidence of efficacy in the intensive treatment

group, with a reduction in the primary composite CV outcome and mortality (secondary outcome). There were 562 primary outcome events, above the threshold recommended when considering premature trial stoppage.^{18,19} This trial included a large number of elderly participants, individuals who historically have had a much higher treatment target. Importantly, people with diabetes were excluded from SPRINT.⁴ The authors noted that their findings were not necessarily discordant with those of ACCORD¹⁰ when considering the overlapping confidence intervals (CIs) of both studies (SPRINT: hazard ratio [HR], 0.75; 95% CI, 0.64–0.89; ACCORD: HR, 0.88; 95% CI, 0.83–1.06).^{4,10} Since the publication of SPRINT,⁴ there has been renewed interest in definitively establishing the optimal BP target in people with diabetes, recognizing the sample size limitations of ACCORD.¹⁰

A recently published systematic review and meta-analysis has evaluated the effect of BP lowering therapy in people with diabetes.²⁰ RCTs with at least 1 year of follow-up and involving at least 100 participants with diabetes were included. In total, 49 trials involving more than 73 000 participants were included; about half of the trials (and one-third of the study participants) involved studies which included people with diabetes as a subgroup, while the remainder were studies specific to individuals with diabetes. Twelve studies (~9000 participants) represented previously unpublished data. Studies that compared one agent versus another (eg, angiotensin-converting enzyme inhibitors [ACEIs] versus diuretics) or those that used combined interventions were excluded.

Using an intriguing approach, the impact of antihypertensive therapy in people with diabetes was evaluated; the included studies were stratified based both on baseline and attained SBP at 10-mmHg increments (eg, 130–139 mmHg). As the mean difference between baseline and follow-up SBP in the intervention groups was about 10 mmHg, the trials included in each baseline SBP stratum generally tended to be in the stratum that was 10 mmHg lower for attained SBP. The prespecified outcomes of interest that were available for meta-analysis included: all-cause mortality, CV mortality, myocardial infarction, stroke, heart failure, and end-stage renal disease. Unfortunately, there was insufficient data available to evaluate the impact of treatment on the measures of the quality of life.

All-cause mortality, CV mortality, and indeed most outcomes were reduced when SBP was lowered from a baseline SBP greater than 150 mmHg. These risk reductions ranged from 11% for all-cause mortality to approximately 25% for the various CV outcomes, including myocardial infarction and stroke. A similar but smaller effect of lowering SBP was observed when the baseline SBP was between 140 and 150 mmHg. In contrast, there was no evidence of benefit when the baseline SBP was below 140 mmHg for any of the outcomes of interest, with a trend towards harm

both for all-cause and CV mortality. The rate of end-stage renal disease was not reduced at any of the baseline SBP ranges.

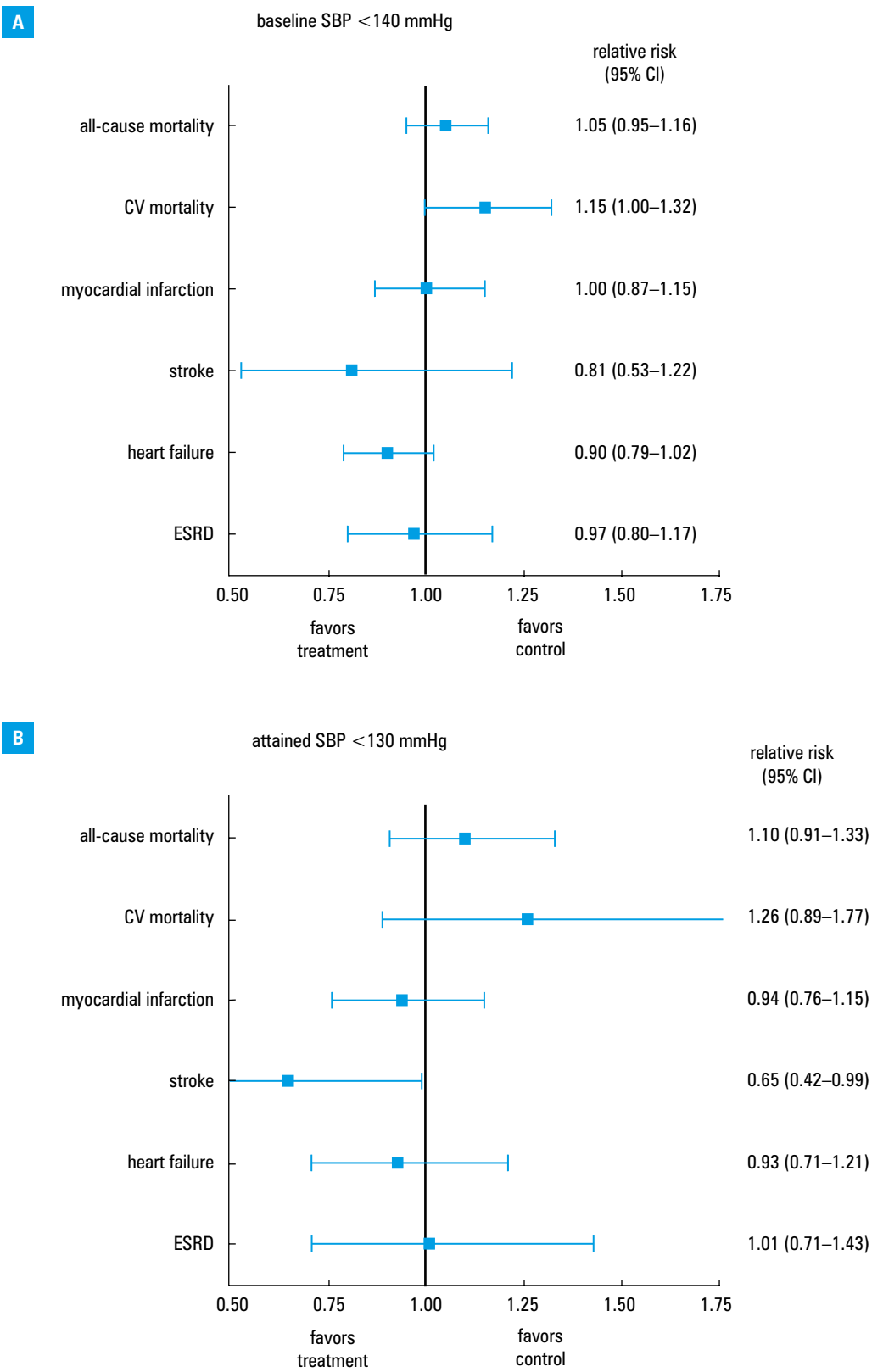
When the authors stratified the studies based on attained SBP, all-cause mortality was reduced by 14% when SBP was between 130 and 140 mmHg. Similar risk reductions ranging between about 10% and 20% were seen for the various CV outcomes, with myocardial infarction and heart failure, but not stroke or CV mortality, reaching significance. At an average achieved SBP level of less than 130 mmHg, only stroke was significantly reduced with an impressive relative risk of 0.65, albeit with wide CIs (95% CI, 0.42–0.99). A trend towards harm was seen for all-cause and CV mortality at an SBP of less than 130 mmHg, a level recommended by some clinical practice guidelines as previously mentioned. Once again, the rate of end-stage renal disease was not reduced at any of the attained SBP levels. The results for baseline SBP of less than 140 mmHg and attained SBP of less than 130 mmHg are shown in [FIGURE 2](#).

The authors also examined more directly whether there was a relationship between the impact of lowering SBP by 10 mmHg and the baseline SBP. In other words, if baseline SBP was lowered on average from 145 to 135 mmHg in one study, and from 155 to 145 mmHg in another, was there a difference in the magnitude of benefit (or harm) between the 2 studies. As one might anticipate, there was a tendency towards greater benefit at higher levels of baseline SBP. Specifically for CV mortality and myocardial infarction, this relationship was significant; the effects of SBP lowering appeared to become harmful when the baseline SBP dropped below 141 and 132 mmHg, respectively.

Earlier meta-analyses have also examined the evidence for optimal BP targets in people with diabetes. A systematic review in 2012 identified RCTs that evaluated the effect of standard versus intensive BP management in people with diabetes.²¹ Only 5 trials (including the ACCORD study)¹⁰ involving more than 7000 participants were identified. With the exception of a reduction in the rate of stroke, no benefit was observed in those participants treated with more intensive therapy. A subsequent Cochrane review in the following year identified the same 5 trials and reached similar conclusions.²² Expanding on the previous reviews, a subsequent meta-analysis also considered trials that included participants with impaired fasting glucose, as well as trials that did not specifically look at different BP targets.²³ This study found evidence of benefit of SBP lowering in many outcomes, including mortality. However using meta-regression methodology, lowering SBP to less than 130 mmHg only reduced the risk of stroke while significantly increasing the risk of adverse events.

A more comprehensive meta-analysis²⁴ demonstrated findings largely similar to those of the most recent study by Brunstrom and Carlberg.²⁰ In that review, the lowering of SBP by 10 mmHg

FIGURE 2 Comparison of results from meta-analyses for various outcomes based on baseline (A) and attained (B) systolic blood pressure of less than 140 and 130 mmHg, respectively (adapted from Brunstrom and Carlberg)²⁰



was associated with benefit with respect to most of the outcomes, including mortality, CV mortality, myocardial infarction, and stroke when the attained SBP was greater than 130 mmHg. In contrast to the more recent review, stroke risk was also reduced by BP-lowering therapy when the baseline SBP was less than 140 mmHg. This difference may be explained by the differences in the studies that were included in the respective analyses, and a trial standardization approach used in

the former study, which more heavily weighted the ACCORD trial,¹⁰ despite the relatively small number of events. The differences in statistical approaches used and the reported findings between the 2 studies highlight some of the challenges and limitations of this methodology.

Finally, a recent systematic review including study participants with and without diabetes used a similar approach to that of the above studies.²⁵ Overall, the authors found that all-cause

mortality was reduced with SBP lowering, even at a baseline SBP of less than 130 mmHg. When they compared the subset of trials that included only participants with diabetes (~31 000 participants) versus the subset of trials in which they were excluded, an attenuated benefit of SBP lowering in people with diabetes was observed in most outcomes of interest. Whether the benefit persisted when baseline BP was less than 140 mmHg was not evaluated. Therefore, these findings are not necessarily discordant with the findings of the other meta-analyses.

The strength of these recent meta-analyses lies in the large number of participants that were included in the respective analyses. The meta-analysis by Brunstrom and Carlberg²⁰ included a significant number of previously unpublished studies, reducing the potential for publication bias. However, there are a number of limitations to these meta-analyses that should be addressed. A meta-analysis of individual-level patient data, rather than aggregated study data, would be preferred in order to draw stronger inferences as to the effects of baseline and attained SBP on the effectiveness of BP-lowering treatment.

Specifically for the Brunstrom and Carlberg review,²⁰ only 11 of the 49 included studies were trials that directly compared 2 BP targets; the remaining 38 evaluated a drug vs placebo or drug-combination vs a single drug. Using the data provided in the article, the weighted average baseline SBP in the 11 trials that evaluated 2 BP targets was 151.4 mmHg, compared with 142.2 mmHg in those studies that did not compare 2 BP targets. Additionally, the weighted average SBP difference between the 2 arms in the BP-target trials was 10.4 compared with only 3.6 mmHg in the remaining studies. Therefore, one would expect that the 2 types of trials would not be equally distributed amongst the various BP strata. The validity of such an approach is unclear at least to me and makes one question whether it is a reasonable strategy to combine such trials.

As a case in point, the ALTITUDE study²⁶ compared previous renin-angiotensin blockade with or without aliskiren, a direct renin inhibitor. The intervention only lowered the average baseline SBP of 137.3 mmHg by 1.3 mmHg, yet was associated with a trend towards harm. It is widely viewed that it was the combination of the 2 specific agents, rather than the relatively minor effect on BP, that led to this finding.²⁷ The authors addressed ALTITUDE²⁶ specifically by performing a sensitivity analysis without the results of ALTITUDE²⁶ and found similar results, albeit with greater uncertainty. Nevertheless, this type of limitation just further highlights the need for a large trial in people with diabetes that compares the 2 BP-lowering strategies. Finally, the results of HOPE-3,²⁸ an RCT comparing the combination of an angiotensin receptor blocker (ARB) and thiazide diuretic with placebo in participants with intermediate CV risk, were published after this

meta-analysis was conducted.²⁸ Nevertheless, only 6% of HOPE-3 participants had “early” diabetes; therefore, it seems unlikely that the inclusion of these results would tangibly change the findings described in this recent meta-analysis.

If one is convinced by the findings of this meta-analysis that are in contrast to those of SPRINT,⁴ then one must consider potential reasons as to why there would be differences between patients with and without diabetes. The etiology of hypertension in diabetes is multifactorial and is not specifically unique to those with diabetes. Nevertheless, the relative importance of each mechanism may differ in people with and without diabetes. Mechanisms postulated have included sodium retention and vascular stiffening mediated through obesity and insulin resistance, sympathetic excitation, and endothelial dysfunction.²⁹ The authors hypothesized that in people with diabetes and premature arterial stiffening, the increased dependence of myocardial perfusion on SBP may lead to chronic ischemia if the SBP is aggressively lowered.³⁰ One would anticipate that a significant proportion of participants of the SPRINT study,⁴ who tended to be older with high CV risk, would also have clinically important vascular stiffening. Nevertheless, it is worth noting that despite achieving a similar SBP in the intensively treated groups in ACCORD¹⁰ and SPRINT,⁴ the DBP was substantially lower in ACCORD participants (TABLE 2). As lower DBP has been associated with vascular stiffening and atherosclerosis, this observation may point to important physiological differences between the participants of the 2 studies, and the potential response to more intensive BP-lowering strategies.^{31,32}

It has been hypothesized that the striking results of SPRINT⁴ may be attributable to class differences of antihypertensives used in the 2 arms, particularly ACEIs and ARBs.³³ Indeed, when one compares utilization of either an ACEI or ARB in ACCORD¹⁰ versus SPRINT,⁴ there are striking differences. In SPRINT,⁴ 76.7% of participants received an ACEI or ARB in the intensive arm vs 55% in the standard arm. This is in contrast to ACCORD¹⁰ where 90% and 80% of the groups, respectively, received an ACEI or ARB. Additionally, the diuretic chlorthalidone, which may be preferable to hydrochlorothiazide although there is conflicting evidence,^{34,35} was available for use in both trials. However, it is unclear to what extent it was used in those trials compared with other thiazide diuretics. On the other hand, there is evidence to suggest that no single antihypertensive agent confers a greater benefit over other agents in those with diabetes.³⁶

For a variety of reasons, including a higher prevalence of orthostatic hypotension,³⁷ people with diabetes may be more susceptible to the adverse events of antihypertensive therapy, which may offset the benefits of more aggressive BP lowering. It is difficult to compare serious adverse event rates between ACCORD¹⁰ and SPRINT⁴ due to interstudy differences in how these were

TABLE 2 Comparison of selected study characteristics between the ACCORD and SPRINT trials^{4,10}

Characteristics	ACCORD ¹⁰		SPRINT ⁴	
	intensive arm	standard arm	intensive arm	standard arm
n		4733		9361
age, y		62.2		67.9
female sex, %		47.7		35.6
follow-up, y		5.0		3.26
baseline blood pressure, mmHg	139.2/76.0	139.0/75.9	139.7/78.2	139.7/78.0
achieved blood pressure, mmHg	119.3/64.4	133.5/70.5	121.4/68.7	136.2/76.3
number of primary outcome events	208	237	243	319
primary outcome event rate/year, %	1.87	2.09	1.65	2.19
death rate, %/y	0.52	0.49	1.05	1.44
number of antihypertensive medications	3.4	2.1	2.8	1.8

defined. However, if one examines specifically disorders of potassium or hypotension/syncope, events that would likely be related to the intervention, the rates are reported to be substantially higher in SPRINT⁴ compared with ACCORD.¹⁰ Therefore, this would not support the above hypothesis, despite the fact that ACCORD participants required more antihypertensive medications than participants in SPRINT (TABLE 2).^{4,10}

Conclusions These meta-analyses add important information on the target BP in people with diabetes and should be carefully considered by clinical practice guideline committees going forward. The best information to date, with all of the caveats mentioned, would suggest that if SBP is above 140 mmHg, BP-lowering strategies are warranted. However, if SBP is less than 140 mmHg, there is evidence to suggest that additional BP-lowering therapy has the potential to be harmful. However, these analyses have significant limitations as the authors point out, which has been highlighted and expanded upon here. Ultimately, it seems probable that pending the outcome of a trial evaluating an intensive BP-lowering strategy as was done in the ACCORD¹⁰ and SPRINT⁴ trials, with a sample size comparable to that of SPRINT,⁴ uncertainty will persist and clinical practice guideline committees will continue to find it difficult to make graded high-quality recommendations as to optimal BP targets in patients with diabetes.

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Wartości docelowe ciśnienia tętniczego u chorych na cukrzycę

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SŁOWA KLUCZOWE

ciśnienie tętnicze, cukrzyca, nadciśnienie tętnicze, choroby sercowo-naczyniowe, wartości docelowe

STRESZCZENIE

Nadciśnienie tętnicze jest silnym czynnikiem ryzyka wystąpienia powikłań sercowo-naczyniowych i zgonów z ich powodu, którego leczenie okazało się korzystne. Nadciśnienie tętnicze często występuje u chorych na cukrzycę, a współwystępowanie obu tych chorób znacznie zwiększa ryzyko sercowo-naczyniowe, w porównaniu z osobami, u których one nie występują. Pomimo coraz bardziej precyzyjnego określenia wartości docelowych ciśnienia tętniczego (BP) w różnych grupach chorych, docelowe wartości BP u chorych na cukrzycę nie zostały jak dotąd jednoznacznie ustalone, w wyniku czego występują rozbieżności dotyczące optymalnych wartości BP w różnych wytycznych praktyki klinicznej. W badaniu ACCORD (Action to Control Cardiovascular Risk in Diabetes) nie stwierdzono korzyści z obniżania wartości ciśnienia tętniczego skurczowego (SBP) <120 mm Hg, w porównaniu z utrzymywaniem ich <140 mm Hg. Wyniki te różnią się od wyników badania SPRINT (Systolic Blood Pressure Intervention Trial), w którym wykazano przewagę utrzymywania wartości docelowych SBP <120 mm Hg wyrażoną zmniejszeniem ryzyka zdarzeń sercowo-naczyniowych. Co istotne, z badania tego wykluczono chorych na cukrzycę. W ostatnio opublikowanych metaanalizach zasugerowano, że obniżanie BP u chorych na cukrzycę należy zarezerwować wyłącznie dla tych osób, u których wyjściowe wartości SBP przekraczają 140 mm Hg, przyjmując wartości docelowe SBP na poziomie 130–140 mm Hg. Mniejsze wartości docelowe SBP mogą zmniejszać ryzyko udaru mózgu, ale jednocześnie wiązać się z większym ryzykiem innych poważnych zdarzeń sercowo-naczyniowych. Ograniczenia metodologiczne wspomnianych metaanaliz wskazują na konieczność przeprowadzenia dużego badania z randomizacją, w którym porównano by utrzymywanie wartości docelowych BP u chorych na cukrzycę na poziomie obecnie powszechnie stosowanym lub niższym.

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