Intensive and Standard Blood Pressure Targets in Patients With Type 2 Diabetes Mellitus

Systematic Review and Meta-analysis

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Background: Treatment of hypertension in patients with diabetes mellitus (DM) has been shown to improve cardiovascular outcomes; however, the value of intensive blood pressure (BP) targets remains uncertain. We sought to determine the effectiveness and safety of treating BP to intensive targets (upper limit of 130 mm Hg systolic and 80 mm Hg diastolic) compared with standard targets (upper limit of 140-160 mm Hg systolic and 85-100 mm Hg diastolic) in patients with type 2 DM.

Methods: Using electronic databases, bibliographies, and clinical trial registries, we conducted a systematic review and meta-analysis to identify randomized trials enrolling adults diagnosed as having type 2 DM and comparing pre-specified BP targets. Data on study characteristics, risk for bias, and outcomes were collected. Random-effects models were used to pool relative risks and risk differences for mortality, myocardial infarction, and stroke.

Results: The use of intensive BP targets was not associated with a significant decrease in the risk for mortality (relative risk difference, 0.76; 95% CI, 0.55-1.05) or myocardial infarction (relative risk difference, 0.93; 95% CI, 0.80-1.08) but was associated with a decrease in the risk for stroke (relative risk, 0.65; 95% CI, 0.48-0.86). The pooled analysis of risk differences associated with the use of intensive BP targets demonstrated a small absolute decrease in the risk for stroke (absolute risk difference, −0.01; 95% CI, −0.02 to −0.00) but no statistically significant difference in the risk for mortality or myocardial infarction.

Conclusion: Although the use of intensive compared with standard BP targets in patients with type 2 DM is associated with a small reduction in the risk for stroke, evidence does not show that intensive targets reduce the risk for mortality or myocardial infarction.


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See Invited Commentary at end of article

North American clinical practice guidelines recommend a target blood pressure (BP) of 130/80 mm Hg or less in patients with DM. Although early studies that compared treatment strategies in patients with DM established the benefit of a target BP of no higher than 140 to 160 mm Hg systolic and 85 to 100 mm Hg diastolic (defined herein as standard BP target), the recommendation to aim for no higher than 130/80 mm Hg (defined herein as intensive BP target) is based largely on observational data, with the diastolic target of 80 mm Hg or less supported by a subgroup analysis of patients having DM within a trial of diastolic BP targets. The Action to Control Cardiovascular Risk in Diabetes–Blood Pressure (ACCORD-BP) study is the only trial to date that has tested an intensive systolic BP target in patients with DM. The ACCORD-BP study found that intensive BP control did not significantly reduce the risk for total cardiovascular events or mortality, although it decreased the risk for stroke, a secondary end point. Moreover, treatment-related adverse events were significantly higher in the intensively treated group.
Given that 6% to 9% of adults in North America have DM16–18 (>60% of whom have hypertension16), clarifying the optimal BP target in the population with DM is critical. Because achieving a target BP of 130/80 mm Hg or less often requires the use of 3 to 4 antihypertensive medications and multiple physician visits, this strategy is reasonable only if it unequivocally improves clinical outcomes at reasonable cost.

To determine the effects of different prespecified target levels on clinical outcomes and adverse events, we performed a systematic review and meta-analysis of trials using an intent-to-treat approach and comparing clearly defined intensive and standard BP targets in patients with type 2 DM. To provide a context in which the benefits associated with reduction in BP below a standard target could be determined, we compared the effectiveness and safety of standard BP targets with historical BP management in patients with type 2 DM (eAppendix 1; http://www.archinternmed.com).

METHODS

DATA SOURCES AND SEARCHES

We searched MEDLINE (January 1, 1948, through March 10, 2011), EMBASE (January 1, 1980, through March 10, 2011), and CENTRAL (January 1, 1996, through March 10, 2011) databases according to a standardized protocol using comprehensive search terms for DM and hypertension. The MEDLINE search strategy is given in eTable 1 of eAppendix 2. The results were narrowed using a sensitive randomized controlled trials search strategy developed by the Cochrane Collaboration.19 Reference lists of identified trials and review articles were searched for additional relevant studies. We searched clinical trial registries (www.clinicaltrials.gov and www.isrctn.org) and contacted authors of published studies to locate any unpublished trials. No language restrictions were applied.

STUDY SELECTION

Two reviewers (among K.M., F.C., and B.J.M.) independently evaluated articles for inclusion. Citations and abstracts were reviewed in the first stage, and in the second stage, the full text of any article deemed potentially relevant by either reviewer was evaluated against standardized selection criteria. To be included, studies must have been parallel, randomized, or quasirandomized controlled trials (1) enrolling adults diagnosed as having type 2 DM as the primary population or subgroup, (2) comparing an intervention of antihypertensive therapy to achieve prespecified BP targets, and (3) assessing at least 1 end point of mortality, myocardial infarction, or stroke. We excluded studies that tested multifactorial interventions in which the effect of BP lowering could not be analyzed separately from other treatments.

DATA EXTRACTION AND QUALITY ASSESSMENT

We extracted data and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.20 One reviewer (K.M.) extracted data from all included studies using a standardized data extraction form, and another reviewer (L.B.) independently checked the data. Disagreements were resolved by consensus. For the Appropriate Blood Pressure Control in Diabetes hypertensive cohort (ABCD-H) study,21 data that were not reported by the study authors were obtained through the Blood Pressure Lowering Treatment Trialsist’s Collaboration.22 We recorded the following properties for each trial: outcomes data, cointerventions, therapeutic regimens (target, baseline, and achieved BP levels, as well as medication regimens and dosages), participants (age, sex, duration of DM, baseline renal function and proteinuria status, and baseline cardiovascular risk factors), and characteristics (country, design, sample size, inclusion criteria, source of funding, and duration of treatment and follow-up period). We assessed the risk for bias using a Cochrane Collaboration tool.23 We included the use of subgroup analyses as a potential source of bias. Because treatment to a target requires knowledge of the target level, we did not consider blinding of participants and personnel to treatment assignment.

DATA SYNTHESIS AND ANALYSIS

We extracted data for several outcomes. These included adverse events, all-cause mortality, medication requirements, macrovascular outcomes (cardiovascular mortality, myocardial infarction, stroke, and heart failure), and microvascular outcomes (retinopathy, nephropathy, and neuropathy). Blood pressure targets were defined as intensive or standard. The target levels chosen were pragmatic and enabled unequivocal categorization of comparator groups within the clinical trials. Consistent with clinical practice guidelines, we defined intensive BP targets as a systolic target with an upper limit of 130 mm Hg or a diastolic target with an upper limit of 80 mm Hg, and we defined standard BP targets as a systolic target with an upper limit between 140 and 160 mm Hg or a diastolic target with an upper limit between 85 and 100 mm Hg.

In a separate analysis, we analyzed studies that compared standard BP targets with historical treatment (defined as a BP target higher than standard targets or as treatment in which a placebo or usual care was provided) (eAppendix 1).

We summarized treatment effects using risk ratios and risk differences. Because of baseline heterogeneity between trial design and participant characteristics, we performed a random-effects meta-analysis for each of the outcomes. Statistical heterogeneity between studies was assessed with the I2 statistic. Risk for publication bias was assessed using funnel plot analysis and tests by Harbord et al24 and Peters et al25 for publication bias. All statistical analyses were performed using commercially available software (STATA, version 11.2, StataCorp LP).

RESULTS

STUDY SELECTION

The study selection process is summarized in Figure 1. The electronic database search yielded 3494 citations. Of these, 55 studies met criteria for full-text review, and a further 3 studies were identified from reference lists of review articles. In total, 5 studies14,15,21,26,27 met inclusion criteria, the results of which were reported in 7 individual publications.

STUDY CHARACTERISTICS

Details of the studies that met inclusion criteria are given in Table 1 and Table 2. The Hypertension Optimal Treatment (HOT) trial14 included comparisons across 3 levels of targets, resulting in a total of 6 distinct comparisons of intensive vs standard BP targets. Only 3 outcomes (all-cause mortality, myocardial infarction, and stroke) were re-
ported consistently by a sufficient number of studies and, as such, are the focus of our statistical analyses. In total, the 5 randomized controlled trials enrolled 7312 patients with DM. In the HOT trial, patients with DM were a subset of the overall trial participants, and the corresponding data were reported in subgroup analyses. The presence of hypertension was defined based on diastolic BP alone in 4 studies.21,26,27 Baseline BP, duration of DM, and overall cardiovascular risk varied across studies (Tables 1 and 2).

VALIDITY ASSESSMENT

The risk for bias varied across trials (eTable 2 of eAppendix 2). Trials deemed to be at highest risk for bias were the HOT trial14 (because patients with DM represented a subgroup of participants) and the ABCD trials (because data on loss to follow-up analysis were not reported in the ABCD-H study21 and in the ABCD normotensive cohort [ABCD-N] study27 and because the ABCD Part 2 With Valsartan cohort study26 was stopped early). The results of tests by Harbord et al24 and Peters et al25 for publication bias were not statistically significant for any of the 3 main outcomes analyzed. However, few studies were included in the analysis.

CARDIOVASCULAR OUTCOMES

Relative Risk Differences

Figure 2 shows the relative effects of aiming for intensive BP targets on all-cause mortality, myocardial infarction, and stroke. Moderate statistical heterogeneity ($I^2 = 47.8\%$) was found for the outcome of mortality. In the pooled analysis for mortality and myocardial infarction, intensive BP targets did not confer a significant benefit over standard BP targets. The effect of BP targets on the risk for stroke was significant, with a relative risk for stroke of 0.65 (95% CI, 0.48-0.86) associated with intensive vs standard targets. In all cases, the prediction interval crossed the null value. The prediction interval is used in random-effects meta-analysis to indicate the wider range of effects that may exist across heterogeneous studies, while the point estimate and its CI (depicted by the width of the diamond) are estimates of the mean effect across populations and trial properties.28

Absolute Risk Differences

The effect of different BP targets was evaluated using absolute risk differences for all-cause mortality, myocardial infarction, and stroke (Figure 3). Again, a significant effect was found only in the case of stroke, with a pooled absolute risk difference of −0.01 (95% CI, −0.02 to 0.00).

OTHER OUTCOMES

Macrovascular Outcomes

Macrovascular outcomes are summarized in eTable 3 of eAppendix 2. The difference in total combined cardiovascular events was significant in the HOT trial14 80/90-mm Hg comparison but not in the 80/85-mm Hg comparison or in the ACCORD-BP study.15 None of the ABCD trials reported this outcome. Because macrovascular outcomes were defined differently across studies, it was impossible to perform pooled analyses. Cardiovascular mortality was reported in 3 investigations of intensive vs standard targets and was significantly lower in the 2 HOT trial comparisons but not in the ACCORD-BP study.15 The difference in heart failure associated with BP targets was reported in the ACCORD-BP study or the ABCD-N study, the only trials reporting this outcome.

Microvascular Outcomes

Macrovascular outcomes (eTable 3 of eAppendix 2) were reported only in trials that focused solely on patients with DM (ie, the ABCD trials and the ACCORD-BP study).15 No trials reported a difference in the risk for end-stage renal disease or 24-hour creatinine clearance associated with BP targets. The ABCD-N study,27 but not the ABCD-H study,21 reported a slower rate of progression to microalbuminuria and a slower rate of progression from microalbuminuria to macroalbuminuria. In the ACCORD-BP study, fewer participants had macroalbuminuria at trial end in the intensive target group (6.6% vs 8.7%, P = .009). Progression of diabetic retinopathy was reported to be slower in the ABCD-N study, but no difference between groups was observed in the ACCORD-BP study, ABCD-H study, or ABCD Part 2 With Valsartan cohort study.26
Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Trial Name (Year)</th>
<th>Setting</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Target Blood Pressure, mm Hg</th>
<th>Outcomes Reported for Patients With DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estacio et al.21, 2000</td>
<td>ABCD-H (1991)</td>
<td>United States</td>
<td>RCT, 2  ×  2 factorial</td>
<td>Individuals having type 2 DM with HTN</td>
<td>Stepped antihypertensive therapy to a target vs a higher target</td>
<td>Diastolic ≤75 vs &lt;90</td>
<td>All-cause mortality, CV events</td>
</tr>
<tr>
<td>Schrier et al.27, 2002</td>
<td>ABCD-N (1991)</td>
<td>United States</td>
<td>RCT, 2  ×  2 factorial</td>
<td>Individuals having type 2 DM without HTN</td>
<td>Stepped antihypertensive therapy to a target vs a higher target</td>
<td>Diastolic ≤75 vs &lt;90</td>
<td>All-cause mortality, CV events, nephropathy, retinopathy, neuropathy</td>
</tr>
<tr>
<td>Hansson et al.14, 1998</td>
<td>HOT (1992)</td>
<td>International</td>
<td>RCT, 2  ×  2 factorial</td>
<td>Adults with diastolic HTN</td>
<td>Stepped antihypertensive therapy to 3 distinct diastolic targets</td>
<td>Diastolic ≤80 vs ≤85 vs ≤90</td>
<td>All-cause mortality, CV mortality, CV events, myocardial infarction, stroke, neuropathy</td>
</tr>
<tr>
<td>Estacio et al.26, 2006</td>
<td>ABCD-2V (1998)</td>
<td>United States</td>
<td>RCT</td>
<td>Individuals having type 2 DM without HTN</td>
<td>Stepped antihypertensive therapy to a target vs a higher target</td>
<td>Diastolic &lt;75 vs &lt;140/90</td>
<td>All-cause mortality, CV events</td>
</tr>
<tr>
<td>Cushman et al.15, 2010</td>
<td>ACCORD-BP (2003)</td>
<td>North America</td>
<td>RCT, 2  ×  2 factorial</td>
<td>Individuals with type 2 DM at increased risk for CV disease</td>
<td>Stepped antihypertensive therapy to a target vs a higher target</td>
<td>Systolic &lt;120 vs &lt;140</td>
<td>All-cause mortality, CV events, coronary events, stroke, heart failure</td>
</tr>
</tbody>
</table>

Table 2. Details About Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Trial Name (Year)</th>
<th>No. of Patients With DM (Mean Duration of DM, y)</th>
<th>Mean Age, y (Mean Follow-up Duration, y)</th>
<th>Baseline BP (mm Hg)</th>
<th>Achieved BP, mm Hg</th>
<th>History of Cardiovascular Disease, %</th>
<th>Intensive Medications, No.</th>
<th>Intensive Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estacio et al.21, 2000</td>
<td>ABCD-H (1991)</td>
<td>470 (8.6)</td>
<td>57.8 (5)</td>
<td>155/98</td>
<td>138/86</td>
<td>NR</td>
<td>NR</td>
<td>Industry</td>
</tr>
<tr>
<td>Schrier et al.27, 2002</td>
<td>ABCD-N (1991)</td>
<td>480 (9.0)</td>
<td>59.0 (5.3)</td>
<td>136/84</td>
<td>137/81</td>
<td>128/75</td>
<td>NR</td>
<td>Industry</td>
</tr>
<tr>
<td>Hansson et al.14, 1998</td>
<td>HOT (1992)</td>
<td>1501 (NR)</td>
<td>53 (3.8)</td>
<td>170/105</td>
<td>144/85, 141/83</td>
<td>140/81</td>
<td>52.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Estacio et al.26, 2006</td>
<td>ABCD-2V (1998)</td>
<td>129 (7.3)</td>
<td>56 (1.9)</td>
<td>126/84</td>
<td>124/80</td>
<td>118/75</td>
<td>NR</td>
<td>1.1</td>
</tr>
<tr>
<td>Cushman et al.15, 2010</td>
<td>ACCORD-BP (2003)</td>
<td>4733 (median 10)</td>
<td>62.2 (5)</td>
<td>139/76</td>
<td>134/70</td>
<td>119/64</td>
<td>33.7</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Abbreviations: ABCD-H, Appropriate Blood Pressure Control (ABCD) in Diabetes hypertensive cohort; ABCD-N, ABCD normotensive cohort; ABCD-2V, ABCD Part 2 With Valsartan cohort study; ACCORD-BP, Action to Control Cardiovascular Risk in Diabetes–Blood Pressure; CV, cardiovascular; DM, diabetes mellitus; HOT, Hypertension Optimal Treatment; HTN, hypertension; RCT, randomized controlled trial.

ADVERSE EVENTS RELATED TO TREATMENT

The ACCORD-BP trial15 was the only study of intensive BP targets to report details of adverse events for patients with DM. The intensively treated group had significantly higher rates (3.3% vs 1.7%, P < .001) of any serious adverse event (defined as being life threatening, causing permanent disability, or requiring hospitalization), mainly due to differences in rates of hypotension (0.7% vs 0.04%), bradycardia or arrhythmia (0.5% vs 0.13%), and hyperkalemia (0.4% vs 0.04%). Among the intensively treated group, the trial also found higher incidences of hypokalemia (potassium level <3.2 mmol/L) (2.1% vs 1.1%, P = .01), serum creatinine level elevations (12.1% vs 7.7%, P < .001), and estimated glomerular filtration rates less than 30 mL/min/1.73 m² (4.2% vs 2.2%, P < .001).

Our systematic review identified few heterogeneous studies that tested the effect of intensive BP targets in patients with type 2 DM. We observed no significant reduction in the risk for mortality or myocardial infarction associated with an intensive compared with a standard target. We found that intensive BP control was associated with a de-
creased risk for stroke. This is in contrast to pooled analyses comparing standard BP targets and historical treatment, which noted clinically significant decreases in the risk for all 3 outcomes, with relative risks (95% CIs) of 0.82 (0.69-0.98) for mortality, 0.68 (0.51-0.93) for myocardial infarction, and 0.60 (0.42-0.84) for stroke (eAppendix 1). Analysis of risk differences comparing intensive and standard BP targets demonstrated a small absolute benefit for stroke, although this was 4-fold smaller than that of standard BP targets compared with historical treatment, with relative risks (95% CIs) of −0.03 (−0.05 to 0.00) for mortality, −0.04 (−0.06 to −0.02) for myocardial infarction, and −0.04 (−0.06 to −0.02) for stroke. Moreover, the prediction interval for all outcomes (including stroke)28 crossed the null value, suggesting that for some groups of patients, intensive BP targets may not confer any benefit and may in fact be harmful.

Acknowledging that significant heterogeneity existed across studies and that the data were sparse, our findings suggest that the incremental benefit in lowering BP to an intensive target is uncertain and may be limited to a small absolute decrease in the risk for stroke. In our supplemental analysis of standard targets vs historical treatment (eAppendix 1), meta-regression results suggested that across all investigations, the effect of BP lowering was associated with baseline systolic BP. Therefore, it is possible that the benefit of antihypertensive therapy may relate more to baseline systolic BP than to the chosen target.

Two other meta-analyses have examined the association between BP lowering and cardiovascular events...
in patients with type 2 DM. Bangalore et al.29 examined the effect of achieved systolic BP on cardiovascular risk; an achieved systolic BP of 135 mm Hg or less was associated with lower risk for cardiovascular events than an achieved systolic BP of 140 mm Hg or less. Their review did not classify treatment groups based on assigned target BPs and included trials that were designed to test a specific drug. Reboldi et al.30 included a subgroup analysis of BP target trials and found that the risk for stroke but not myocardial infarction was reduced in patients allocated to “more tight” control compared with “less tight” control. Their analysis did not distinguish between different target levels and grouped trials in which the tighter target was in the standard target range with trials in which the tighter target was in the intensive target range.

Our review builds on these studies by examining the association between clearly defined BP targets and cardiovascular events. Distinguishing between BP targets and achieved BPs is of critical importance. Individuals who can achieve lower BPs in the context of a treatment trial are often systematically different from those who fail to achieve lower BPs and are likely to be at lower risk for cardiovascular events independent of their BP. By focusing on specifically defined targets, we are able to describe the incremental gains in risk reduction that can be expected from progressively lower BP targets. Furthermore, our review distinguishes between studies of intensive targets and studies of standard targets; the results suggest that, although lower BP targets may reduce the risk for stroke, increasingly stringent BP targets likely result in diminishing returns.

Our systematic review was limited by the few trials that tested BP targets in patients with DM. Because the data were sparse, it was necessary to include data from subgroup analyses and to combine trials of systolic targets with trials of dia-

**Figure 3.** Absolute risk differences, showing blood pressure targets and risk difference for all-cause mortality (A), myocardial infarction (B), and stroke (C). The width of the diamond represents the 95% CI. The prediction intervals span the following ranges: −0.06 to 0.03 for A, −0.02 to 0.01 for B, and −0.02 to 0.00 for C. Abbreviations are explained in the legend to Figure 2.
stolic targets. For example, the HOT trial\textsuperscript{13} was a study of diastolic targets in the general population with a DM subgroup analysis, whereas the ACCORD-BP trial\textsuperscript{15} was a study of systolic BP targets in patients with type 2 DM only. For this reason, we cannot draw conclusions about any specific target but can comment only on the comparative effectiveness of a strategy of intensive vs standard targets. We were also unable to perform statistical analyses on other outcomes of interest such as microvascular events and combined cardiovascular events because of variations in reporting and definitions across trials.

The number of participants varied across trials, with the ACCORD-BP study\textsuperscript{13} being the largest trial by far. Although the use of a random-effects meta-analysis should mitigate the potential for the ACCORD-BP study findings to unduly influence the results, the discrepancy in trial sizes (combined with the few trials) was a limitation. Of potential relevance, the ACCORD-BP study also randomized participants to more intensive vs less intensive glycemic control. In a prespecified subgroup analysis presented in an appendix of the ACCORD-BP study, a potential interaction ($P=.08$) was noted between the intensity of glycemic control and the effect of intensive BP lowering on total cardiovascular events.\textsuperscript{13} Of those randomized to intensive BP lowering, patients in the standard glycemic control arm had a 23% reduction in a composite cardiovascular end point, whereas patients in the intensive glycemic control arm had no benefit.

Finally, we did not include the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial\textsuperscript{14} in our study because it was not a trial of predefined BP targets. Although the study noted that a fixed combination of an angiotension-converting enzyme inhibitor and a diuretic had a beneficial effect on outcomes among patients with DM whose baseline BP was 145/81 mm Hg, it is unknown whether this effect was due to the drugs prescribed in the trial or the intensity of the BP lowering.

North American clinical practice guidelines recommend a BP target of 130/80 mm Hg or less for individuals with type 2 DM.\textsuperscript{14} Treatment of hypertension in DM is important and beneficial. However, the clinical benefit of aiming for intensive targets is less certain. Based on the estimates obtained through meta-analysis, the number needed to treat during 2 to 5 years to an intensive BP target compared with a standard BP target vs a standard BP target compared with historical treatment is 3-fold higher to prevent 1 death (100 vs 33 patients), 4-fold higher to prevent 1 myocardial infarction (100 vs 25 patients), and 4-fold higher to prevent 1 stroke (100 vs 25 patients). Moreover, findings from the ACCORD-BP study\textsuperscript{15} reveal that 1 additional serious adverse event would be expected for every 60 patients treated to an intensive systolic target.

In summary, lowering BP to standard BP targets in patients with DM is associated with significant reductions in all-cause mortality, myocardial infarction, and stroke. Although the use of intensive compared with standard BP targets in this patient population translates to a small decrease in the risk for stroke, evidence does not show that intensive targets reduce the risk for mortality or myocardial infarction. These findings should be considered in future iterations of clinical practice guidelines.

Accepted for Publication: May 7, 2012.
Published Online: August 6, 2012. doi:10.1001/archinternmed.2012.3147

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Financial Disclosure: None reported.

Funding/Support: This study was supported by an interdisciplinary research team grant from Alberta Innovates–Health Solutions. Dr McBrien was supported by a clinical fellowship award from Alberta Innovates–Health Solutions and by a postdoctoral fellowship from the Interdisciplinary Chronic Disease Collaboration. Drs Rabi, Hemmelgarn, Tonelli, and Manns were supported by career salary support awards from Alberta Innovates–Health Solutions (formerly Alberta Heritage Foundation for Medical Research). Dr Campbell was supported by the Canadian Institutes of Health Research Canada Chair in Hypertension Prevention and Control. Drs Campbell, Tonelli, Klarenbach, and Hemmelgarn were supported by an alternative funding plan.
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