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Can The Diabetic War Be Fought By Aggressive Blood Pressure Control?

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Current epidemiologic evidence indicates that the risk of cardiovascular disease (CVD) is increased two to four-fold among patients with diabetes mellitus (DM), and that having hypertension (HTN) with DM confers a greater risk of microvascular and macrovascular complications than either condition alone.[1] Therefore, the current American Diabetes Association (ADA) guidelines recommend a blood pressure (BP) goal of <130/80 mmHg in patients with DM.[2] Specifically, a systolic blood pressure (SBP) of <130 mmHg is recommended for most patients and a diastolic blood pressure (DBP) <80 mmHg is recommended for all patients with DM. However, this recommendation was mainly driven by expert consensus and data on microvascular complications rather than cardiovascular (CV) events. Recent clinical data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial re-ignited questions regarding the appropriateness of the SBP goal for patients with DM and whether attaining this goal leads to better CV outcomes.

United Kingdom Prospective Diabetes Study

One early landmark trial that provided strong evidence of CVD risk reduction by lowering BP in patients with DM was the United Kingdom Prospective Diabetes Study (UKPDS).[3] The UKPDS trial investigated DM-related endpoints in 1148 patients with type 2 DM randomized to either "tight" (<150/85 mmHg) or "less tight" (<180/105 mmHg) BP control. The study showed a significant reduction in deaths related to DM (11% vs. 16%; RR 0.68, 95% CI 0.49 to 0.94; p=0.019), and a significant reduction in stroke (5% vs. 8.7%, RR 0.56, 95% CI 0.35 to 0.89; p=0.013) in the tighter control group versus the less tight. There was not a statistically significant difference in all-cause mortality. The UKPDS trial concluded that tight BP control (achieved SBP of 144 mmHg compared to 154 mmHg) in patients with type 2 DM was associated with significant reductions in CV and other DM-related events. Observational cohort studies from UKPDS suggest a linear correlation between lowerSBP and myocardial infarction (MI), stroke, and microvascular disease.[4,5] These results were seen as SBP fell from >160 mmHg to <120 mmHg.[5]

Hypertension Optimal Treatment Trial

Another landmark trial that supported the link between aggressive BP lowering and decreased CVD risk was the Hypertension Optimal Treatment (HOT) trial.[6] The HOT trial investigated the effects of DBP targets of <80 mmHg, <85 mmHg and <90 mmHg on major CV events. In the cohort of subjects with DM (n= 1501), an absolute risk reduction of 4.6% in major CV events in the DBP <80 mmHg target group vs. DBP <90 mmHg target group (4.4% vs. 9.0%; RR 2.06, CI 1.24 to 3.44; p=0.005) was demonstrated. The HOT trial concluded that intensive SBP lowering in patients with DM and HTN is associated with a significant reduction in major CV events. However, one limitation is that this was a subgroup analysis and consisted of only 8% of the entire population studied.

Action to Control Cardiovascular Risk in Diabetes Trial

Although both UKPDS and HOT trials provided evidence that lowering BP is associated with reduced CVD, neither of the trials was designed to achieve a goal of SBP <130 mmHg. Actual CV benefits in these trials were observed at higher SBP than what is currently recommended (SBP <130mmHg).[3,6] The mean BP achieved in the tight BP control group of the UKPDS trial was 144/82 mmHg, whereas the mean SBP achieved in all subjects included in the HOT trial, for patients in the <80 DBP group, was 139.7 mmHg. More recent trials have challenged the established SBP goal <130 mmHg.[7,8,9,10,11] The ACCORD trial randomized 4733 hypertensive patients with type 2 DM to either "intensive" therapy with a SBP goal <120 mmHg or "standard" therapy with a SBP goal of <140 mmHg to investigate effects on CV events. There were no significant differences between the two groups with respect to the primary endpoint (1.87% vs. 2.09%; HR 0.88, 95% CI 0.73 to 1.06; p=0.20), a composite of nonfatal MI, nonfatal stroke, and death from CV causes. However, the intensive BP control group had a significantly lower risk of both any and nonfatal stroke (HR 0.59, 95% CI 0.39 to 0.89; p=0.01 and HR 0.63, 95% CI 0.41 to 0.96; p=0.03, respectively), which were secondary outcomes.[7] The average SBP achieved in the intensive control group was 119.3 mmHg compared to 133.5 mmHg in the standard control group. In addition, the ACCORD trial reported significantly higher rates of hypotension (7 fold increase), bradycardia, and hyperkalemia (10 fold increase) in the intensive therapy group.[7]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Trial

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial studied both the effects of intensive glycemic control and BP lowering in diabetic patients.[9] The BP lowering arm investigated the effects of a fixed combination of perindopril and indapamide on major vascular events. The primary end points were composites of major macrovascular events (death from CV causes, nonfatal MI, or nonfatal stroke) and major microvascular events (new or worsening nephropathy or retinopathy). The mean change in BP over the duration of the trial was significantly decreased in the active BP treatment group compared to placebo (SBP -5.6mmHg, 95% CI 5.2 to 6.0; p<0.0001 and DBP -2.2 mmHg, 95% CI 2.0 to 2.4; p<0.0001), which resulted in a significant reduction in major macrovascular or microvascular events (HR 0.91, 95% CI 0.83 to 1.00; p=0.04). However, the individual microvascular and macrovascular endpoints were only statistically significant when combined, not when separated (macrovascular HR 0.92, 95% CI 0.81 to1.04; p=0.16 and microvascular HR 0.91, 0.80 to1.04; p=0.16). The baseline BP was 145/81 mmHg. At the conclusion of the trial, BP was 136/73 mmHg in the treatment group (which was where subjects in the ACCORD trial started) compared to 140/73 mmHg in the control group.

The lack of linear correlation observed between BP and CV outcomes could be argued based on the differences in patient characteristics between earlier and later studies, as well as the lower target BP values in the newer studies. In the ACCORD trial, subjects were older and 10 years post-diagnosis with DM while the UKPDS study subjects had newly diagnosed DM.[3,7] Also, patients in the ACCORD trial had lower SBP at baseline compared to patients in the UKPDS study (139 mmHg vs. 160 mmHg).[3,7]

Other Trial Data

Similarly, other recent trials showed no difference between intensive SBP control verses moderate control in reducing microvascular and macrovascular complications.[10-12] A subgroup analysis of patients from the International Verapamil SR-Trandolapril (INVEST) study compared the effects of "tight" SBP control (<130 mmHg), "normal" SBP (130-140 mmHg) and "uncontrolled" SBP (>140 mmHg) on CV outcomes in 6400 patients with DM and CAD.[10] The primary endpoint was the first occurrence of all-cause death, nonfatal MI, or nonfatal stroke. The study concluded that tight SBP control did not result in decreased risk of CV events compared to normal SBP control. The event rate was 12.7% in the tight SBP group versus 12.6% in the normal SBP group (HR 1.11, 95% CI 0.93 to 1.11; p=NS).[10] With extended follow-up, the tight control group had a higher mortality rate of 22.8% versus 21.8% in the normal control group (HR 1.05, 95% CI 1.01 to 1.32; p=0.04). These results need to be interpreted carefully because this was a post-hoc analysis based on achieved BP, and mortality was

assessed using the National Death Index. Nevertheless, SBP goals in patients with DM and CAD may need to be re-evaluated. .

The Appropriate Blood Pressure Control in diabetes (ABCD) trial randomized patients to intensive diastolic blood pressure (DBP of 75 mm Hg) vs. moderate DBP control (80-89 mm Hg). The mean BP achieved was 132/78 mm Hg in the intensive group and 138/86 mm Hg in the moderate control group. This trial reported a significant decrease in all cause mortality with intensive BP control (5.5% vs. 10.7%; RR 0.5, 95% CI 0.25 to 1.0; p=0.037). However, there were no significant reductions in the various CV events studied and progression of diabetic retinopathy or neuropathy over a 5 year period.[11] The inconsistencies across the trials may be due to the differences in the baseline CV risk profile of the study subjects enrolled.

The Irbesartan Diabetic Nephropathy (IDNT) trial compared effects of SBP targets of <120 mmHg and ≥120 mmHg on the primary endpoints of all-cause and CV mortality in 1590 patients with type 2 DM. This trial showed an increase in all-cause mortality (28% vs. 12%; RR 3.05, 95% CI 1.80 to 5.17; p<0.0001), and CV mortality (19% vs. 6%; RR 4.06, 95% CI 2.11 to 7.80; p<0.0001) in patients who achieved a SBP <120 mmHg compared to those with a SBP ≥120 mmHg.[12] The results of these studies further support that more intensive SBP control among patients with DM is not associated with improved CV outcomes.

To further determine the optimal target SBP in patients with DM, a recent meta-analysis was conducted.[13] This meta-analysis included randomized controlled trials investigating antihypertensive therapy in patients with type 2 DM or impaired fasting glucose/impaired glucose tolerance with achieved SBP of ≤135 mmHg in the "intensive" BP control group and ≤140 mmHg in the "standard" BP control group. Each trial also had to include a follow-up of at least 1 year and evaluation of macrovascular and microvascular outcomes. A total of 13 randomized controlled trials with a total of 37,736 patients were included in the meta-analysis. The authors assessed trial eligibility and trial bias risk as recommended by the Cochrane Collaboration; of the 13 trials, 9 were considered trials with low risk of bias. Results of the meta-analysis showed a reduction in all-cause mortality in the <135 SBP group (OR 0.87; 95% CI 0.79 to 0.95) but not in the more intensive group of <130 SBP (OR 1.04; 95% CI 0.86 to 1.25). There was also a demonstrated 0.4% absolute risk reduction in stroke (OR 0.83; 95% CI 0.73 to 0.95) with the intensive SBP (≤135 mmHg) versus standard control with the risk continuing to fall with more aggressive control of <130 mmHg. There was no difference between the two groups in CV mortality, MI, and heart failure. In the few studies that reported serious side effects, intensive SBP control was associated with an increased incidence versus standard control (OR 1.20; 95% CI 1.08 to 1.32).[13] There was a greater magnitude of effect in risk reduction of stroke and increase in serious side effects in trials in which the SBP was <130 mmHg, without any additional benefits for other CV outcomes.[13]

Treatment Guidelines

Current guidelines continue to reflect the <130/80 mmHg BP goal for patients with DM based on microvascular benefit despite a lack of evidence for macrovascular events for SBP <130 mmHg. While the upcoming 8th edition of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) guidelines has not yet been published, other guidelines have been updated more recently. The 2011 Canadian Hypertension Education Program (CHEP) guidelines continue to recommend using the <130/80 mmHg BP treatment goal in patients with DM. The authors of the CHEP guidelines are waiting for a more detailed analysis of the ACCORD trial before reconsidering the current BP recommendation. The CHEP guidelines also emphasize that the BP goal used in the ACCORD trial (<120 mmHg) is lower than the current recommendation (<130 mmHg), and that this excessive lowering of BP can lead to increased risk of hypotension and hyperkalemia.[14]

Summary

In conclusion, lowering SBP to the ADA goal of <130 mmHg in patients with DM is associated with a reduction in stroke but not other CV outcomes. Caution should be taken in patients when aggressive therapy to lower SBP to <130 mmHg is likely to cause more harm than benefit. At this time, emphasis should be placed on a multifactorial approach to HTN management in DM which includes: maintaining SBP between 130-139 mmHg while focusing on behavioral modifications (exercise and smoking cessation) and nutritional counseling to reduce long term cardiovascular risks.

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