Implications of Contemporary Clinical Trials

Effects of Intensive Blood Pressure Control in the Management of Patients With Type 2 Diabetes Mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

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To appreciate the importance of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, one needs to remember that the systolic blood pressure (BP) target currently recommended by major guidelines for diabetic patients, that is, <130 mm Hg, was not based on evidence from large-scale randomized trials. This is shown in Figure 1, which summarizes what was found in trials in which a diabetic group treated with antihypertensive drugs was compared with a group treated with placebo or treated less actively. In all trials except one, the greater systolic BP (SBP) reduction obtained in the actively (or more actively) treated group was associated with a reduction in cardiovascular morbidity and fatal events listed as either a primary or a major secondary end point. However, the absolute in-treatment SBP values always remained >130 mm Hg, except in the Appropriate Blood Pressure Control in Diabetes Study (ABCD) normotensive trial, which consisted of only a few hundred patients and had changes in creatinine clearance as the primary end point. Thus, ACCORD represents the only large-scale randomized trial that provides information on what happens to the cardiovascular risk of diabetic patients when SBP is reduced to <130 mm Hg. Unfortunately, this information is of a negative nature because in ACCORD, the group randomized to a BP control that led to SBP values >120 mm Hg showed an incidence of cardiovascular events that was not significantly reduced compared with the group in which SBP remained >130 mm Hg as a result of randomization to the usual (rather than the tight) BP control treatment strategy. Thus, the message from ACCORD to guidelines and clinical practice is that in diabetic patients it is not necessary to adopt an aggressive BP-lowering strategy because an SBP reduction to the 130- to 140-mm Hg range (for which the beneficial effects are documented) appears to suffice. Indeed, a more aggressive BP-lowering strategy may be detrimental because the ACCORD patients in whom in-treatment SBP was <120 mm Hg had an incidence of serious side effects that was almost 3 times as frequent as that of patients remaining >130 mm Hg.

Does ACCORD provide conclusive evidence on the target SBP to adopt in diabetes mellitus to maximize the BP-related reduction in cardiovascular risk? Without denying its merits (which include a consistent reduction in SBP to levels previously regarded as chimerical), this is not the case for a variety of reasons. First, because cardiovascular morbidity and mortality were substantially less than predicted, ACCORD was somewhat underpowered to show between-group differences. Second, the trial also explored, via a factorial design, the effects of different blood glucose–lowering strategies on outcome and found that, compared with standard treatment, a tight control of glycated hemoglobin was associated with an increased mortality. Even if no interactions between BP and blood glucose were reported, some interference between the 2 treatments cannot be completely ruled out because interaction tests can more sensitively show the existence of an interaction rather than excluding it. Third, the difference in achieved BP between the 2 groups was large (≈14 mm Hg), which leaves the possibility that the group in which SBP was reduced to 119 mm Hg fell in the ascending portion of a J curve for cardiovascular events. That is, SBP values <130 but >120 mm Hg may be associated with a maximal benefit that vanishes when BP is further reduced. A 3-group trial in which data are also collected in patients randomized to achieve an SBP level between 120 and 130 mm Hg might clarify the issue.

A final important problem raised but not conclusively answered by ACCORD is whether the optimal in-treatment SBP is different for different vital organs damaged by hypertension. The reason is that in ACCORD the group in which SBP was more intensively lowered showed a significant reduction in the risk of stroke but not of myocardial infarction. Although the very few strokes occurring in this trial cannot exclude a chance finding, this is in line with results obtained in the “posthoc” analysis of large trials such as Perindopril Progression Against Recurrent

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.110.960120
Stroke (PROGRESS),10 International Verapamil Trandolapril Study (INVEST),11 and Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET).12 In PROGRESS,10 there was a progressive reduction in the recurrence of hemorrhagic and ischemic stroke as SBP was lowered by treatment to <120 mm Hg. In INVEST and ONTARGET,11,12 a progressive reduction of in-treatment SBP toward <120 mm Hg was associated with a progressive reduction in the incidence of stroke, whereas myocardial infarction concomitantly became more frequent. Although comparisons between nonrandomized groups make post hoc analyses scientifically weaker (but in ONTARGET and INVEST, the incidence of stroke and myocardial infarction showed a different behavior in the same initial groups), these data suggest that “the lower the BP, the better” rule may apply to cerebrovascular but not cardiac protection. The same rule may apply also to renal protection because studies on nephropatic patients have shown that the incidence of renal events (end-stage renal disease, dialysis, transplantation, etc) and the effects on markers of renal dysfunction such as reduced glomerular filtration rate, microalbuminuria, and proteinuria undergo a progressive improvement down to very low BP values.13,14 The explanation may lie in the excellent blood flow autoregulation properties of the brain15 and kidney,16 which allows perfusion of these organs to be preserved also at low BP values. It is also possible, however, that because recruitment in INVEST and ONTARGET (but not in PROGRESS) involved mainly individuals with a history of coronary disease, the results of these trials reflect a clinical circumstance in which the mechanisms preserving blood flow at low BP values were selectively impaired in the heart. That cardiac organ damage is associated with an impairment of coronary autoregulation has been shown in a study in which diastolic BP was progressively reduced to 70 mm Hg by infusion of a vasodilator drug. In patients without left ventricular hypertrophy, this reduction did not change coronary blood flow, which in contrast showed a steep progressive fall when BP was reduced to <90 mm Hg in patients with left ventricular hypertrophy (Figure 2).17

If it is true that maximal protection is achieved at BP values lower for the brain than for the heart, then an important question is what BP-lowering strategy should be recommended in clinical practice. One might argue that if an aggressive BP reduction leads to cerebrovascular protection without substantially increasing the risk of coronary events (as suggested by ACCORD), this strategy...
deserves to be adopted anyway. It might also be preferred when the patient faces a much greater risk of a cerebrovascular event than a coronary event. This can be the case in Asian countries because in Asian populations the risk of stroke is much greater than the risk of myocardial infarction.\textsuperscript{18} It can also be the case in patients with a history of stroke because, although these patients have an overall high cardiovascular risk, their risk of stroke recurrence clearly exceeds the risk of a myocardial infarction.\textsuperscript{19–21}

Disclosures

Dr Mancia has received research support from Bayer, Gilead Colorado Inc, and Sanofi Aventis; served as a consultant for Boehringer Ingelheim, Bayer, Daiichi-Sankyo, and Novartis; and been on the speakers’ bureaus for Bayer, Boehringer Ingelheim, Merck Serono, Menarini International, Novartis, Recordati, Sanofi, Sankyo, Servier, and Takeda.

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\textbf{Key Words}: blood pressure ■ clinical trials ■ type 2 diabetes mellitus
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Circulation. 2010;122:847-849
doi: 10.1161/CIRCULATIONAHA.110.960120

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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