



**EDUCATIONAL OBJECTIVE:** Readers will entertain the possibility that striving for a low target blood pressure may not always be beneficial

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# Goal-directed antihypertensive therapy: Lower may not always be better

## ABSTRACT

At least 16 treatment trials have been done in which patients were randomly assigned different blood pressure goals in an attempt to better define specific target pressures. We critically review the data.

## KEY POINTS

Observational data indicate that lower blood pressure is better than higher, and many trials have confirmed that treatment of hypertension is beneficial. Guidelines have set specific goals based on the observational data.

Surprisingly, randomized controlled trials have not shown a lower target to offer significant clinical benefit, and suggest the potential for harm with overly aggressive therapy.

The optimal blood pressure on treatment for an individual patient remains unclear.

A 50-YEAR-OLD AFRICAN AMERICAN WOMAN with type 2 diabetes mellitus, hypertension, hyperlipidemia, and chronic kidney disease presents for a follow-up visit. The patient had been treated with hydrochlorothiazide 25 mg/day and enalapril (Vasotec) 20 mg twice daily until 6 weeks ago. At that time her blood pressure was 160/85 mm Hg, and amlodipine (Norvasc) 10 mg/day was added to her regimen. Her other medications include glipizide (Glucotrol), metformin (Glucophage), lovastatin (Mevacor), fish oils, aspirin, calcium, and vitamin D. Her current blood pressure is 145/80 mm Hg; her serum creatinine level is 1.5 mg/dL, and her urine albumin-to-creatinine ratio is 180 mg/g.

In hypertensive patients who have diabetes or chronic kidney disease, guidelines<sup>1</sup> call for intensification of antihypertensive therapy to reach a goal blood pressure of less than 130/80 mm Hg. What data exist to support these guidelines? And what should the clinician do?

## IS MORE-INTENSE THERAPY IN THE PATIENT'S BEST INTEREST?

Often, clinicians are faced with hypertensive patients whose blood pressure, despite treatment, is higher than the accepted goal. Often, these patients are elderly and are already taking multiple medications that are costly and have significant potential adverse effects. The dilemma is whether to try to reach a target blood pressure listed in a guideline (by increasing the dosage of the current drugs or by adding a drug of a different class) or to “do no harm,” accept the patient’s blood pressure, and keep the regimen the same.<sup>1,2</sup>

The current goal blood pressure is less than 140/90 mm Hg for all but the very elderly, with more intense control recommended for

patients at high risk, ie, those with diabetes mellitus, chronic kidney disease, or atherosclerotic cardiovascular disease.<sup>1</sup>

While it appears to be in the patient's best interests to follow such guidelines, review of available data indicates that this is not necessarily so, and may even be harmful.

### ■ OBSERVATIONAL DATA AND EARLY RANDOMIZED TRIALS

Many observational studies have found that the higher one's blood pressure, the greater one's risk of cardiovascular events and death. Indeed, meta-analyses of these trials, which involved more than 1.5 million people, demonstrate a strong, positive, log-linear relationship between blood pressure and the incidence of cardiovascular disease and death.<sup>3-5</sup>

Further, there is no evidence of a threshold pressure below which the risk is not lower (ie, a "J-point"), starting with 115/75 mm Hg. A J-point may exist for diastolic blood pressure in elderly patients with isolated systolic hypertension<sup>6</sup> and in patients with coronary artery disease.<sup>7</sup> Otherwise, the observation is clear: the lower the blood pressure the better. For every 20 mm Hg lower systolic blood pressure or 10 mm Hg lower diastolic blood pressure, the risk of a cardiovascular event is about 50% less.<sup>4,5</sup>

Observational analyses also show a strong, graded relationship between blood pressure and future end-stage renal disease.<sup>8,9</sup> Post hoc analyses indicate that chronic kidney disease progresses more slowly with lower achieved blood pressures, especially in those with higher degrees of proteinuria.<sup>10-12</sup>

However, observational data do not prove cause and effect, nor do they guarantee similar results with treatment. This requires randomized controlled trials.

### ■ RANDOMIZED TRIALS OF HYPERTENSION TREATMENT

Initial trials were aimed at determining whether hypertension should even be treated. A 1997 meta-analysis of 18 such trials comparing either low-dose diuretic therapy, high-dose diuretic therapy, or beta-blocker therapy with placebo involved 48,000 patients who were followed for an average of 5 years.<sup>13</sup> The

rates of stroke and congestive heart failure were consistently reduced, although only low-dose diuretic therapy reduced the risk of coronary heart disease and death from any cause.

More recent trials enrolled people not considered hypertensive who were randomized to receive either active drugs or placebo, or no treatment. Other trials attempted to assess non-pressure-related effects of specific agents, using other antihypertensive agents in the control group. Still other randomized controlled trials compared one agent or agents with other agents while attempting to attain equivalent blood pressure between groups. Frequently, however, there was some blood pressure difference.

Meta-analyses of most of these trials conclude that the major benefit of antihypertensive therapy—reducing rates of cardiovascular morbidity and mortality—comes from a lower attained blood pressure, irrespective of which agent is used.<sup>14-18</sup> Exceptions exist, however. For example, specific drug classes are indicated after myocardial infarction, and in congestive heart failure and proteinuric chronic kidney disease.<sup>10,19-21</sup>

### ■ 16 TRIALS OF DIFFERENT BLOOD PRESSURE TARGETS

The overriding theme of these observational data is that a lower blood pressure, whether attained naturally or with treatment, is better than a higher one from both the cardiovascular and the renal perspective.

What remains unclear is what blood pressure should be aimed for in a particular patient or group of patients. Is it a specific pressure (eg, 140/90 mm Hg), or does the change from baseline count more? Should other factors such as age or comorbidity alter this number?

Several randomized controlled trials have addressed these questions by targeting different levels of blood pressure. We are aware of at least 16 such trials in adults, including 13 with renal or cardiovascular primary end points and three with surrogate primary end points.

An unavoidable design flaw of all of these trials is their unblinded nature. Consequently, nearly all of them carry a Jadad score (a measure of quality, based on randomization and blinding)<sup>22</sup> of 3 on a scale of 5.

**For every 20 mm Hg lower systolic pressure or 10 mm Hg lower diastolic pressure, the risk of a cardiovascular event is about 50% less**

TABLE 1

**Trials of different blood pressure goals with renal primary end points**

TRIAL	PATIENTS	GOAL BLOOD PRESSURE (BP) (MM HG)	PRESSURE ACHIEVED (MM HG)	RESULTS <sup>a</sup>	COMMENTS
<b>AASK<sup>23</sup></b>	1,094 African Americans with hypertensive nephropathy	MAP ≤ 92 vs 102–107	128/78 vs 141/85	Rate of change of GFR –2.21 vs –1.95 mL/min/1.73 m <sup>2</sup> /year Deaths 8.1% vs 11% <sup>b</sup>	No difference in cardiovascular end points
<b>Toto et al<sup>31</sup></b>	77 with hypertensive nephropathy	DBP 65–80 vs 85–95	133/81 vs 138/87	Rate of change of GFR –0.31 vs –0.05 mL/min/1.73 m <sup>2</sup> /year Deaths 2.4% vs 0% <sup>b</sup>	Small trial
<b>Lewis et al<sup>32</sup></b>	129 with type 1 diabetes mellitus	MAP ≤ 92 vs 100–107	Difference in MAP 6	Rate of change of GFR –4.0 vs –3.0 mL/min/1.73 m <sup>2</sup> /year (6% vs 7%/year)	Significant reduction in proteinuria with strict control Underpowered for primary end point
<b>ABCD Normotensive<sup>33</sup></b>	480 with type 2 diabetes mellitus, DBP 80–90	Decrease in DBP of 10 vs DBP 80–90	128/75 vs 137/81	Change in creatinine clearance (exact numbers not reported) Death 7.6% vs 8.2% <sup>b</sup>	Reduced strokes Nearly half not treated in control group.
<b>ABCD Hypertensive<sup>34</sup></b>	470 with type 2 diabetes mellitus, DBP > 90	DBP < 75 vs 80–90	132/78 vs 137/81	Change in creatinine clearance –3.6 vs –4.98 mL/min/1.73 m <sup>2</sup> /year Death 5.5% vs 10.7%, <i>P</i> = .037 <sup>b</sup>	No difference in cardiovascular end points
<b>ABCD-2V<sup>35</sup></b>	129 with type 2 diabetes mellitus, BP < 140/80–90	DBP < 75 vs no therapy until SBP > 140 or DBP > 90	118/75 vs 124/80	Change in creatinine clearance (exact numbers not reported) Death 1.5% vs 0% <sup>b</sup>	Lower protein excretion with lower blood pressure goal
<b>Schrier et al<sup>36</sup></b>	75 with ADPKD	< 120/80 vs 135–140/85–90	MAP 90 vs 101	Change in creatinine clearance (exact numbers not reported) Death 2.4% vs 2.9% <sup>b</sup>	Greater reduction in left ventricular mass index
<b>MDRD<sup>37,38</sup></b>	840 without diabetes	MAP < 92 (< 98 if > 60 years old) vs < 107 (< 113 if > 60)	Difference in MAP 4.7	Rate of change of GFR –3.7 vs –4.1 mL/min/1.73 m <sup>2</sup> /year	Significant interaction with proteinuria
<b>REIN-2<sup>39</sup></b>	338 without diabetes, with proteinuric nephropathy	<130/80 vs DBP < 90	130/80 vs 134/82	ESRD 23% vs 20% Death 1.2% vs 11.8% <sup>b</sup>	Study terminated early No difference in rate of change of GFR

<sup>a</sup> Except where indicated, none of the differences were statistically significant

<sup>b</sup> Not a primary end point of the trial

All of the trials had a Jadad score (a measure of the quality of clinical trials based on randomization and blinding) of 3 on a scale of 5 except for the ABCD normotensive trial, which had a score of 2.

ADPKD=autosomal dominant polycystic kidney disease; DBP=diastolic blood pressure; ESRD=end-stage renal disease; GFR=glomerular filtration rate; MAP=mean arterial pressure. See text for study names

■ **NINE TRIALS WITH RENAL PRIMARY END POINTS**

Nine of these trials had renal primary end points (TABLE 1).<sup>23-40</sup>

**African American Study of Kidney Disease and Hypertension (AASK)<sup>23</sup>**

**Patients:** 1,094 African Americans with presumed hypertensive renal disease and a measured glomerular filtration rate between 20 and 65 mL/min/1.73 m<sup>2</sup>.

**Randomized blood pressure goals.** Mean arterial pressure 92 mm Hg or less vs 102 to 107 mm Hg.

**Results.** At 4 years, the two groups had average blood pressures of 128/78 and 141/85 mm Hg, respectively. The groups did not differ in the rates of the primary end points—ie, the rate of change in the measured glomerular filtration rate over time or the composite of a 50% reduction in glomerular filtration rate, the onset of end-stage renal disease, or death.

**Comments.** Several issues have been raised about the internal validity of this trial.

So-called hypertensive kidney disease in African Americans (as opposed to European Americans) may be a genetic disorder related to polymorphisms of one or more genes on chromosome 22q. Initial data implicated the MYH9 gene, which encodes non-muscle myosin heavy chain II.<sup>24,25</sup> More recent data implicate the nearby APOL1 gene encoding apolipoprotein L1 as more relevant. These polymorphisms have a much greater prevalence in African Americans and appear responsible for the higher risk of idiopathic focal segmental glomerulosclerosis and HIV-associated nephropathy in this population.<sup>24-26</sup> Therefore, in African Americans, hypertension may in fact be the result of the kidney disease and not its primary cause, which may explain why in this and other African American populations stricter control of blood pressure did not produce a renal benefit.<sup>27,28</sup>

Also, there is the possibility of misclassification bias. A secondary analysis of data obtained by ambulatory monitoring showed that of the 377 participants whose blood pressure appeared to be under control when measured

in the clinic, 70% actually had masked hypertension, ie, uncontrolled hypertension outside the clinic.<sup>29</sup> The real difference in blood pressure between groups may well have been different than that determined in the clinic.

In addition, a prespecified secondary analysis showed no difference in the rates of cardiovascular events and death between the groups.<sup>30</sup> However, the study was not designed to have the statistical power to detect a difference in cardiovascular events. Moreover fewer cardiovascular events occurred than expected, further reducing the study's power to detect a difference.

**Toto et al<sup>31</sup>**

Toto et al reported similar results in an earlier trial in 87 hypertensive patients (77 randomized), predominantly African American, and similar concerns apply.

**Lewis et al<sup>32</sup>**

**Patients:** 129 patients with type 1 diabetes.

**Randomized blood pressure goals.** A mean arterial pressure of either no higher than 92 mm Hg or 100 to 107 mm Hg.

**Results.** At 2 years, despite a difference of 6 mm Hg in mean arterial pressure, the glomerular filtration rate (measured) had declined by the same amount in the two groups. The study was underpowered for this end point. Patients in the group with the lower goal pressure were excreting significantly less protein than those in the other group, but they were received higher doses of an angiotensin-converting enzyme (ACE) inhibitor—in this case, ramipril (Altace).

**The Appropriate Blood Pressure Control in Diabetes (ABCD) trials<sup>33-35</sup>**

**Patients:** 950 patients with type 2 diabetes mellitus and either normal or high blood pressure.

**Randomized blood pressure goals.** Either intensive or moderate therapy (see TABLE 1).

**Results.** At 5 years, creatinine clearance (estimated) had declined by the same amount in the two groups. However, fewer of the hypertensive patients had died in the intensive-therapy group.<sup>34</sup> Similarly, normotensive patients had less progression of albuminuria if treated intensively.<sup>33</sup>

**In African Americans, hypertensive renal disease may be genetic, and the hypertension may be the consequence, not the cause**

In the ABCD Part 2 with Valsartan (ABCD-2V) trial in normotensive patients,<sup>35</sup> therapy with valsartan (Diovan) did not affect creatinine clearance but did reduce albuminuria. However, 75% of the patients in the moderate-treatment group were untreated.

**Schrier et al<sup>36</sup>**

**Patients.** 75 hypertensive patients with autosomal-dominant polycystic kidney disease and left ventricular hypertrophy.

**Randomized blood pressure targets.** Less than 120/80 mm Hg vs 135/85 to 140/90 mm Hg.

**Results.** After 7 years, despite a difference in average mean arterial pressure of 11 mm Hg between the groups (90 vs 101 mm Hg), there was no difference in the rate of decline of creatinine clearance. The left ventricular mass index decreased by 21% in the lower-target group and by 35% in the higher-target group ( $P < .01$ ).

**Modification of Diet in Renal Disease (MDRD) trial<sup>37,38</sup>**

**Patients:** 840 patients whose measured glomerular filtration rate was between 13 and 55 mL/min/1.73 m<sup>2</sup>.

**Randomized blood pressure targets.** A target mean arterial pressure of less than 92 mm Hg vs less than 107 mm Hg.<sup>11,37</sup>

**Results.** After 2.2 years, the mean difference in mean arterial pressure was 4.7 mm Hg. There was, however, no difference in the rate of decline in the glomerular filtration rate.

In a 6-year follow-up, significantly fewer patients in the lower-blood-pressure group reached the end point of end-stage renal disease or the combined end point of end-stage renal disease or death.<sup>38</sup> The rate of death, however, was nearly twice as high in the lower-blood-pressure group (10% vs 6%). The blood pressure and treatment during follow-up were not reported.

**Comments.** Internal validity is an issue, since the blood pressure and therapy during follow-up were unknown, and more patients received ACE inhibitors in the lower-blood-pressure group during the trial. Further, the higher death rate in the lower-blood-pressure group is worrisome.

**The Ramipril Efficacy in Nephropathy (REIN)-2 trial<sup>39</sup>**

**Patients:** 338 nondiabetic patients who had proteinuria and reduced creatinine clearance.

**Treatment and blood pressure goals.** All were treated with ramipril and randomized to intensive (< 130/80 mm Hg) vs standard control (diastolic blood pressure < 90 mm Hg) with therapy based on felodipine (Plendil).

**Results.** The study was terminated early because of futility. Despite a mean difference of 4.1 mm Hg systolic and 2.8 mm Hg diastolic, the groups did not differ in the rate of progression to end-stage renal disease (23% with intensive therapy vs 20% with standard therapy) or in the rate of decline of the measured glomerular filtration rate (0.22 vs 0.24 mL/min/1.73 m<sup>2</sup>/month).

**Comment.** The internal validity of this study can be questioned because of the low separation of achieved blood pressure and because of its early termination.

**No benefit from a lower blood pressure goal in preserving kidney function**

To summarize, these trials all showed no significant benefit from either targeting or achieving lower blood pressure in terms of slowing the decline of kidney function. Overall, they do not define a target and offer little support that a lower goal blood pressure is indicated with respect to the rate of loss of glomerular filtration rate in chronic kidney disease.

However, post hoc analysis of the MDRD trial indicates a statistical interaction between targeted blood pressure and degree of baseline proteinuria. At higher levels of proteinuria ( $\geq 1$  g/day), the group with the lower blood pressure target had better outcomes.

In addition, long-term follow-up (mean of 12.2 years) of the AASK trial, including a 7-year cohort phase with nearly similar blood pressures in both groups, also indicated an interaction with targeted blood pressure and baseline proteinuria.<sup>40</sup> Although the overall analysis was negative, there was a significant reduction in the primary end point in the group originally assigned the low target when analysis was restricted to those in the highest tertile of proteinuria. These and other data<sup>10</sup> suggest that patients with chronic kidney disease and proteinuria may represent a distinct

**When aiming for a target blood pressure, lower is not always better, and it comes at a price**



**TABLE 2**

**Trials of different blood pressure goals with cardiovascular end points**

TRIAL	PATIENTS	GOAL BLOOD PRESSURE (MM HG)	PRESSURE ACHIEVED (MM HG)	RESULTS	COMMENTS
<b>HOT</b> <sup>41</sup>	18,790 with hypertension	≤ 80 vs ≤ 85 vs ≤ 90 diastolic	140/81 vs 141/83 vs 144/85	All myocardial infarctions 2.6 vs 2.7 vs 3.6 events/1,000 patient-years All strokes 3.8 vs 4.7 vs 4.0 All cardiovascular deaths 4.1 vs 3.8 vs 3.7 All deaths 9.0 vs 15.5 vs 15.9 <sup>c</sup>	Poor separation of achieved blood pressures
<b>UKPDS</b> <sup>42,43</sup>	1,148 with type 2 diabetes mellitus	< 150/85 vs < 180/105	144/82 vs 154/87	First clinical end point related to diabetes 50.9 vs 67.4 events/1,000 patient-years <sup>a</sup> Death related to diabetes 13.7 vs 20.3 <sup>b</sup> All-cause death 22.4 vs 27.2	Target in control group was unacceptably high; many patients in the control group were not treated
<b>ACCORD</b> <sup>44</sup>	4,733 with type 2 diabetes mellitus	< 120 vs < 140 systolic	119/64 vs 134/71	Major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death) 1.87% vs 2.09% Deaths 1.28 vs 1.19%/year <sup>c</sup>	Higher rate of severe adverse events in intensive-treatment group
<b>JATOS</b> <sup>45</sup>	4,418 elderly with essential hypertension	< 140 vs 140–160 systolic	136/75 vs 146/78	Composite end point (cardiovascular disease and renal failure) 22.6 vs 22.7 Deaths 2.44% vs 1.9% <sup>c</sup>	

All the trials had a Jadad score (a measure of quality of clinical trials) of 3 on a scale of 5, except for UKPDS, which had a score of 2  
<sup>a</sup>P = .0046; <sup>b</sup>P = .019 <sup>c</sup>Not a primary end point. See text for study names

**Clinic blood pressure may not reflect true blood pressure load in up to one-third of all patients**

subset of chronic kidney disease patients who benefit from more intensive blood-pressure-lowering. However, patients in the REIN-2 trial<sup>34</sup> and the macroalbuminuric patients in the ABCD hypertensive trial<sup>35</sup> did not benefit from a lower targeted blood pressure despite significant proteinuria.

**FOUR TRIALS WITH CARDIOVASCULAR END POINTS**

Four trials have been conducted that had enough power to detect differences in the rates of cardiovascular morbidity and mortality between groups randomized to a lower vs higher blood pressure goal (TABLE 2).<sup>41–45</sup>

**The Hypertension Optimal Treatment (HOT) trial<sup>41</sup>**

**Patients:** 18,790 patients with diastolic blood pressure between 100 and 115 mm Hg.

**Randomized blood pressure goals.** Diastolic pressure of equal to or less than 80, 85, or 90 mm Hg.

**Results.** At an average of 3.8 years, the average blood pressures in the three groups were approximately 140/81, 141/83, and 144/85 mm Hg, respectively. There was no difference between the groups in the rate of the composite primary end point of all myocardial infarctions, all strokes, and cardiovascular death. Any conclusions from this trial were compromised by the small difference in achieved blood pressures between groups.

In the 1,501 patients with diabetes, the incidence of the primary end point was 50% lower with a goal of 80 mm Hg or less than with a goal of 90 mm Hg or less.

**The UK Prospective Diabetes Study (UKPDS)<sup>42,43</sup>**

**Patients:** 1,148 hypertensive patients with type 2 diabetes mellitus.

**Randomized blood pressure goals.** Either “tight control” (aiming for < 150/85 mm Hg) or “less tight control” (aiming for < 180/105 mm Hg).

**Results.** At a median follow-up of 8.4 years, the attained blood pressures were

144/82 vs 154/87 mm Hg. The difference produced significant benefits, including a 24% lower rate of any diabetes-related end point, a 32% lower rate of death due to diabetes, and a nonsignificant 18% lower rate of total mortality—all co-primary end points.

The less-tight-control group had many patients with initial blood pressures below 180/105 mm Hg; hence, over 50% of patients received no antihypertensive therapy at the start of the trial. By the end of the trial 9 years later, 20% had still not been treated. This compares with only 5% of patients in the tight-control group who were not treated with antihypertensives throughout the trial. Therefore, this trial serves as better evidence for treating vs not treating, rather than defining a specific goal.

During a 10-year follow-up, blood pressure differences disappeared within 2 years.<sup>43</sup> There was no legacy effect, as the significant differences noted during the trial were no longer present 10 years later.

**Action to Control Cardiovascular Risk in Diabetes (ACCORD)<sup>44</sup>**

**Patients:** 4,733 patients with type 2 diabetes.

**Randomized blood pressure goals.** Systolic blood pressure lower than either 120 or 140 mm Hg.

**Results.** At 4.7 years, despite a significant difference in mean systolic blood pressure of 14.2 mm Hg after the first year (119.3 vs 133.5 mm Hg), there was no difference in the primary end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. There were fewer strokes in the lower-pressure group but no difference in myocardial infarctions, which were five times more common than strokes. Serious adverse events attributed to antihypertensive treatment occurred more frequently in the intensive-therapy group (3.3% vs 1.3%,  $P < .001$ ).

**Comment.** There were fewer events than expected, possibly limiting the trial's ability to detect a statistical difference. Compared with both the UKPDS and the diabetic population of HOT, ACCORD is much larger and more internally valid (unlike in UKPDS, nearly all patients in both groups were treated, and compared with HOT there was much greater separation of achieved pressure). It is more recent

and better reflects current overall practice. It indicates that when specifically aiming for a target blood pressure, lower is not always better and comes at a price (more severe adverse events).

**Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS)<sup>45</sup>**

**Patients:** 4,418 patients, age 65 to 85 years, with a pretreatment systolic blood pressure above 160 mm Hg.

**Randomized blood pressure goals.** Systolic pressure either lower than 140 mm Hg or 140 to 160 mm Hg.

**Results.** At 2 years, despite a difference of 9.7/3.3 mm Hg, there was no difference in the primary end point (the combined incidence of cerebrovascular disease, cardiac and vascular disease, and renal failure). Fifty-four patients had died in the strict-treatment group and 42 in the mild-treatment group; the difference was not statistically significant.

**Three other trials**

Three other trials<sup>46-48</sup> had surrogate end points, but only one of them reported a composite cardiovascular secondary end point.<sup>46</sup> We will not discuss the other two.<sup>47,48</sup>

**Cardio-Sis.** In the Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica (Cardio-Sis) trial,<sup>46</sup> 1,111 people without diabetes with systolic pressure higher than 150 mm Hg were randomized to tight control (systolic pressure < 130 mm Hg) vs usual control (systolic pressure < 140 mm Hg) and followed for 2 years with electrocardiography to detect left ventricular hypertrophy.

At a median of 2 years, the systolic blood pressure had declined by an average of 3.8 mm Hg more in the tight-control group than in the usual-control group, and the diastolic pressure by an average of 1.5 mm Hg. There was significantly less left ventricular hypertrophy in the tight-control group. The incidence of the secondary end point of a composite of cardiovascular and renal events was also significantly lower. There was no difference individually in the rates of myocardial infarction, stroke, transient ischemic attack, admission for congestive heart failure, or death.

**Much still needs to be learned about the treatment of hypertension**

■ **DISCUSSION: THE DILEMMA OF TREATING AN INDIVIDUAL PATIENT**

These data illustrate the dilemma of treating an individual patient whose blood pressure is not at the currently accepted goal while on multiple antihypertensive medications. According to guidelines, therapy should be intensified in this situation. Observational data show a strong graded relationship between blood pressure and cardiovascular events and death, starting with a blood pressure of 115/75 mm Hg. The observational data relating blood pressure to kidney disease are similar. These data support the guideline recommendations that additional medications should be added to reach the promulgated target. Unfortunately, the targeting trials do not define a target, nor do they support the concept that lower is better.

**Possible explanations for the negative results**

Why does targeting a lower blood pressure not produce the benefit that the observational data lead us to expect?

One possibility is that blood pressure is merely a marker of cardiovascular risk, not a cause of it. This is unlikely, given the temporal relationship, reproducibility, and biologic plausibility that is supported by a very large body of experimental data. However, blood pressure is only one of multiple factors involved in the pathogenesis of vascular and renal disease, and perhaps better attention to other factors such as lipids and smoking may have made the targeting trials underpowered.

Another possibility is that these trials had such strict inclusion and exclusion criteria that they do not represent the general hypertensive population, reducing their external validity.<sup>49</sup> However, the trials generally enrolled populations at higher risk, in which end points were more likely to occur. This would have enhanced the chance to show a positive effect rather than mask it.

It is possible that antihypertensive medications themselves have unwanted side effects that offset their potential benefit. Medication-related side effects could directly contribute to vascular disease despite their beneficial effect of lowering pressure. There could also be re-

duced tissue perfusion due to lower blood pressure per se in the face of a diseased vasculature, with the lower pressure directly contributing to organ dysfunction.

Finally, these trials measured brachial pressures to monitor blood pressure. Brachial pressure does not always correlate with central aortic pressure, which is probably a better marker of the overall pressure burden.<sup>50</sup> It is possible that in these targeting trials, the peripheral blood pressure did not reflect the true central blood pressure and, therefore, significant separation of blood pressures may not have actually occurred.

**Targeted vs achieved blood pressures: Analogies with other markers**

This contradiction is not an exceptional circumstance in medicine.

For example, in chronic kidney disease, a graded observational relationship exists between decreasing levels of hemoglobin and various adverse outcomes.<sup>51-53</sup> However, targeting a more normal level of hemoglobin compared with a lower one has been shown to be detrimental.<sup>54-57</sup> This implies either that anemia is merely a marker of higher risk or, more likely, that the actual measures used to raise the hemoglobin to higher levels are the culprit. Notably, although targeting a higher hemoglobin concentration vs a lower one was detrimental, *achieving* a higher hemoglobin was beneficial within each targeted group.<sup>54,58</sup>

Another example of harm caused by targeting goals based on observational data is tight glucose control, both acutely in the critically ill<sup>59</sup> and chronically in patients with type 2 diabetes.<sup>60</sup> In both cases higher mortality rates ensued.

The same concept may apply to lowering blood pressure. While achieving a lower blood pressure may be more beneficial, targeting a specific goal may be harmful. Given that perhaps 20% of those labeled as hypertensive have resistant hypertension,<sup>61</sup> millions of patients are susceptible to potential harm from targeting a specific goal based solely on observational data. If lower is always better, the randomized trials outlined above should have had more positive outcomes.

It becomes problematic to assign a specific goal for all patients or even groups of patients.

**If lower is always better, the randomized trials should have had more positive outcomes**



The targeting trials do not provide the answer. Based on the observational data it would be optimal to have a blood pressure less than 120/80 mm Hg. This is an observation, not a recommendation. Patients should be assessed on an individual basis, taking into consideration their starting blood pressure, age, medication burden (antihypertensive and otherwise), comorbidities, and ability to comply with a regimen. Given the available data, it is hard to be more specific. In the future it may be possible to identify specific blood pressure targets based on the patient's genetic makeup, but today that is not possible. Even patients with lower initial blood pressure may benefit from therapy,<sup>62,63</sup> and some experts have advocated blood-pressure-lowering in all, irrespective of the baseline value.<sup>14</sup>

**Avoid misclassification**

The first step in treating hypertension should be to avoid misclassification. Make sure the clinic blood pressure is measured correctly, using an appropriately sized cuff, positioning the patient properly, and following all the other recommendations.<sup>64</sup>

However, the clinic blood pressure may not reflect true blood pressure load in up to one-third of all patients.<sup>65</sup> We recommend 24-hour ambulatory blood pressure monitoring<sup>66</sup> or home self-measurement, or both,<sup>67</sup> to better assess true blood pressure burden in several circumstances, including in patients with resistant hypertension (any patient who has not achieved acceptable clinic blood pressure on three or more antihypertensive medications including a diuretic or who requires four or more medications for adequate control), suspicion of white-coat hypertension (or effect), and any patient who has achieved acceptable clinic blood pressure but either has symptoms of hypertension or progressive end-organ damage.

Currently, we base therapy on out-of-office blood pressure (self-measured or by ambulatory monitoring) whenever there is a discrepancy with clinic blood pressure.

Whether therapy should be altered by other less traditional measures of blood pressure such as assessment of central aortic pressure by radial applanation tonometry,<sup>68,69</sup> or 24-hour ambulatory monitoring to assess nighttime blood pressures (specifically, “dip-

ping”),<sup>70</sup> morning surge,<sup>71</sup> or blood pressure variability<sup>72,73</sup> remains unclear and in need of randomized controlled trials.

In any patient requiring blood-pressure-lowering, we recommend lifestyle modifications.<sup>1,2</sup> These include exercise, weight loss, salt and alcohol restriction, evaluation for sleep apnea, and avoidance of medications known to elevate blood pressure such as non-steroidal anti-inflammatory drugs and sympathomimetic decongestants.

**Much needs to be learned**

For the individual patient with unacceptably high blood pressure who is already taking multiple antihypertensive medications of different classes, it is unclear what to do. This type of patient with resistant hypertension would be an excellent candidate for a future targeting trial. Other cardiovascular risk factors should be appropriately addressed, including obesity, lipids, smoking, and poor glycemic control.<sup>74</sup> Each patient should be individually assessed with consideration of both global cardiovascular risk and quality-of-life issues.

Much still needs to be learned about the treatment of hypertension. The facts demonstrate that blood pressure is a strong modifiable risk factor of cardiovascular morbidity and mortality. Lowering it clearly produces benefits. It is unclear what treatment goals should be promulgated by official guidelines for large groups of patients. The resistant case remains a therapeutic dilemma with the potential for harm from overly aggressive treatment. The truly optimal level for an individual patient remains difficult to define. We anxiously await results of ongoing and future targeting trials.

■ **CASE REVISITED**

Regarding the initial case vignette, the patient is clearly not at her recommended goal blood pressure, especially given her high-risk status (diabetes mellitus and chronic kidney disease). Observational data support intensification of therapy, whereas targeting trials are essentially negative and indicate the potential for harm with overly aggressive treatment. Thus, we remain uncertain about what is correct or incorrect in terms of a targeted blood pressure, especially when applied to the individual patient.

**In the future, it may be possible to set specific blood pressure targets based on the patient's genetics—but not yet**

Our approach would be to emphasize lifestyle modifications, to ensure accurate determination of her true blood pressure load (self-measurement at home or ambulatory blood pressure monitor-

ing), to consider secondary causes of hypertension, and to educate the patient about the benefits and consequences of intensifying therapy with the aim of involving her in the decision. ■

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