Thiazide-Type Diuretics and ²-Adrenergic Blockers as First-Line Drug Treatments for Hypertension
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Should β-blockers and diuretics remain as first line therapy for hypertension?

Thiazide-Type Diuretics and β-Adrenergic Blockers as First-Line Drug Treatments for Hypertension

Jeffrey A. Cutler, MD, MPH; Barry R. Davis, MD, PhD

Systemic arterial hypertension affects 72 million US adults and an additional hundreds of millions of persons worldwide. Most of these are candidates for pharmacological treatment to reduce risk of cardiovascular disease (CVD) events, based primarily on a very large body of epidemiological and intervention research in humans. Because of this high prevalence and the cardiovascular consequences of untreated or inadequately treated hypertension, the selection of drugs for initial and continuing, long-term treatment has large public health and economic implications. Fortunately, such decisions and the expert recommendations that seek to guide them can call on evidence from 4 decades of randomized multicenter clinical trials evaluating effects of treatment on clinical CVD. We summarize that evidence in this article, in approximate chronological order, and we comment on the related treatment guidelines. We close with some of the major clinical questions yet to be resolved.

Trials of Blood Pressure Reduction

Before the current era beginning in the early 1990s of emphasis on positive-control trials, which directly compare different drug regimens, there were 3 decades of trials that compared an active regimen with placebo or, in a few cases, “usual care.” For most of this period, the mainstay of treatment was generally a thiazide-type diuretic (hereinafter called thiazides) or, to a lesser extent, a β-adrenergic blocker (termed β-blockers). With few exceptions, these trials, especially those with high statistical power and thiazide-based regimens, showed benefit for CVD outcomes. This evidence, which provided a basis for recommending thiazides or β-blockers as first-step drugs in most editions of US guidelines through 1997, needs to continue to be given due weight in practice and practice guidelines.

The largest and most consistent benefits from the earlier trials were for stroke and (where reported) heart failure. Benefits for coronary heart disease (CHD) were less clear, and commentators frequently speculated that potentially adverse metabolic effects—on potassium (for diuretics), lipids, and glucose—of thiazides and β-blockers were related to this shortfall in reducing CHD outcomes. Two reports in the early 1990s reduced concern about the CHD shortfall considerably. A meta-analysis of essentially all randomized antihypertensive treatment trials with clinical events outcomes, placed in an epidemiological context to address the question of what effects would be expected on the basis of risks of various events at different blood pressure (BP)
levels, showed that treatment significantly reduced nonfatal myocardial infarction (MI) or CHD death (major CHD) by 14%, which represented approximately two thirds of the epidemiological expectation. The authors attributed the shortfall to the short duration of treatment in the trials, averaging 2 to 3 years to CHD events, which was a plausible conclusion. Shortly thereafter, the Systolic Hypertension in the Elderly Program (SHEP) reported that a thiazide-based regimen (using low-dose chlorthalidone) not only reduced fatal and nonfatal stroke by 36% but also lowered major CHD by 27%.

The results of these trials have also provided a basis for guidelines on drug choice through indirect comparisons among trials and groups of trials. Subsequent to SHEP, the similarly designed Systolic Hypertension in Europe (Syst-Eur) trial reported that treatment with a dihydropyridine calcium channel blocker (CCB) as the main drug reduced BP, stroke, and all cardiac events to an extent similar to that in SHEP. However, neither the effects on CHD or heart failure were separately statistically significant. For angiotensin-converting enzyme (ACE) inhibitors, there was no large trial focused on hypertension, but several trials reported that these drugs reduced mortality and morbidity in patients with heart failure and/or CHD; the Studies of Left Ventricular Dysfunction (SOLVD) prevention trial showed that enalapril lowered the risk of MI and overt heart failure in patients with reduced ejection fraction. The size of the heart failure effect was, however, only 20%, in contrast with the 49% benefit in SHEP.

These newer trials provided important added justification for earlier recommendations concerning use of CCBs and ACE inhibitors as first-line drugs in treating hypertension in the 1988 Report of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. However, both JNCV and JNCVI recommended thiazides and β-blockers as preferred initial drugs for antihypertensive treatment. As in the case of ACE inhibitors, the trials of secondary prevention of heart disease continued to play a large role in the thinking about benefits of β-blockers in hypertension.

Despite all of these factors, that is, the weight of the evidence, the consensus incorporated in JNC recommendations, and the low acquisition costs of several generic agents, the use of thiazides and β-blockers to treat hypertension declined dramatically after 1981–1983 through the early 1990s (Figure 1). These trends can be attributed to the following: (1) concerns raised regarding metabolic effects; (2) results of trials that used doses of thiazides much higher than in general use today; and (3) effective marketing of newer patented drugs, in part based on their effects on intermediate markers of various disease processes. Thiazide dosing issues were eventually addressed on the basis of the dose-response curves for BP effects versus potassium depletion, the SHEP trial results, and, most persuasively, by a meta-analysis that separated use of "low-dose" (actually, low-to-moderate dose) from high-dose thiazides among cardiovascular events trials. Nevertheless, it was increasingly recognized that large, direct comparison trials would be needed to provide a solid scientific basis for drug selection. One of the first such trials, and the largest in terms of total study population as well as patients per treatment arm, was the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

The Continuing Case for Thiazide-Type Diuretics

Direct Comparison Trials

ALLHAT: Design and Prespecified Outcomes

ALLHAT was designed to address the issue of which class of drugs should be used for initial therapy for hypertension. It was planned as a practice-based trial to mirror community treatment of hypertension, obtain sufficient patients, and capture the diversity of hypertensive patients (by age, sex,
ethnicity, and diabetic status). More specifically, the study was a randomized, double-blind, multicenter clinical trial, designed to determine whether the incidence of CHD is reduced in high-risk patients with hypertension by a CCB (represented by amlodipine), an ACE inhibitor (represented by lisinopril), or an α-blocker (represented by doxazosin), each compared with diuretic treatment (represented by chlorthalidone).

The overall findings of the trial showed that CHD risk was not improved for any of the 3 newer agents compared with chlorthalidone and should be reasonably extrapolated beyond the exact sample in which it was conducted.

### Table 1. Clinical Outcomes by Antihypertensive Treatment Group

<table>
<thead>
<tr>
<th>Component of secondary outcomes</th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized/fatal</td>
<td>870 (7.7)</td>
<td>706 (12.2)</td>
<td>706 (12.2)</td>
</tr>
<tr>
<td>Angina (hospitalized or treated)</td>
<td>1567 (12.1)</td>
<td>950 (12.6)</td>
<td>950 (12.6)</td>
</tr>
<tr>
<td>Angina (hospitalized)</td>
<td>1078 (8.6)</td>
<td>630 (8.4)</td>
<td>630 (8.4)</td>
</tr>
<tr>
<td>Coronary revascularizations</td>
<td>1113 (9.2)</td>
<td>725 (10.0)</td>
<td>725 (10.0)</td>
</tr>
<tr>
<td>Peripheral arterial disease (hospitalized or treated)</td>
<td>510 (4.1)</td>
<td>265 (3.7)</td>
<td>265 (3.7)</td>
</tr>
</tbody>
</table>

| RR (95% CI)                                      | 1.19 (1.07–1.31) | 1.10 (0.98–1.23) | 1.59 (1.19–2.10) |

**CHD** includes nonfatal MI and fatal CHD; end-stage renal disease: kidney disease death, kidney transplant, or start of chronic renal dialysis; and heart failure: fatal, nonfatal hospitalized, or treated. Adapted from Reference 25, with permission. Copyright 2002, American Medical Association.

**Nonfatal MIs comprise 64% to 66% of the primary outcome.**

**Combined CHD** indicates CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina. Combined CVD indicates CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization).

**Proportional hazards assumption violated; data are RRs from a 2×2 table.**

**BP Differences in ALLHAT**

One of the main criticisms of ALLHAT was that its outcome findings (especially the subgroup findings for stroke) could be explained by observed BP differences among treatment groups. The chlorthalidone-based regimen happened to be the most effective in reducing clinical outcomes and, to a small degree, in BP lowering (Figure 2).

Meta-regressions of effects of BP differences on trial results suggest that they offer a partial explanation, except for heart failure. In ALLHAT, the small differences in achieved mean systolic BP and diastolic BP (<1 mm Hg) between the amlodipine and chlorthalidone groups overall and the lisinopril and chlorthalidone groups in nonblack persons should have had a negligible effect on cardiovascular event rates. In these respective comparisons, the observed rates of heart failure were higher with amlodipine (relative risk [RR]=1.38; 95% CI, 1.25 to 1.52) and lisinopril (RR=1.15; 95% CI, 1.01 to 1.30) than with chlorthalidone.
Extrapolating Findings to Drugs Within a Class
Could the ALLHAT results be extrapolated to other drugs of the same class? For \(\beta\)-blockers, ACE inhibitors, and dihydropyridine CCBs, such extrapolation seems reasonable.\(^{28}\) Data from studies using various thiazide-type diuretics (chlorthalidone, hydrochlorothiazide, indapamide, and bendrofluazide) suggest similar benefits among equivalent doses of all thiazide-type diuretics tested in CVD prevention trials against placebo, usual care, or another drug class.\(^{5,6,8,29–34}\) However, a few studies suggest that the longer duration of action of chlorthalidone may provide some advantage in CVD prevention over hydrochlorothiazide.\(^{22,35}\)

Table 2. Outcomes in the BP Component of ALLHAT by Treatment Group as of February 15, 2000\(^{26}\)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total No. of Patients With Outcomes</th>
<th>4-Year Rate per 100 (SE)</th>
<th>RR (D/C), 95% CI</th>
<th>Z Score</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD (nonfatal MI + fatal CHD)</td>
<td>818</td>
<td>499</td>
<td>7.76 (0.30)</td>
<td>7.91 (0.39)</td>
<td>1.03 (0.92–1.15)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1258</td>
<td>769</td>
<td>10.51 (0.32)</td>
<td>11.04 (0.43)</td>
<td>1.03 (0.94–1.13)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>551</td>
<td>377</td>
<td>4.74 (0.22)</td>
<td>5.60 (0.32)</td>
<td>1.15 (1.01–1.32)</td>
</tr>
<tr>
<td>MI</td>
<td>184</td>
<td>105</td>
<td>1.65 (0.13)</td>
<td>1.76 (0.19)</td>
<td>0.96 (0.76–1.22)</td>
</tr>
<tr>
<td>Definite CHD</td>
<td>57</td>
<td>39</td>
<td>0.54 (0.08)</td>
<td>0.54 (0.10)</td>
<td>1.16 (0.77–1.74)</td>
</tr>
<tr>
<td>Possible CHD</td>
<td>62</td>
<td>43</td>
<td>0.50 (0.08)</td>
<td>0.63 (0.11)</td>
<td>1.17 (0.79–1.73)</td>
</tr>
<tr>
<td>Stroke</td>
<td>92</td>
<td>76</td>
<td>0.79 (0.10)</td>
<td>1.25 (0.16)</td>
<td>1.39 (1.03–1.89)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>59</td>
<td>42</td>
<td>0.60 (0.09)</td>
<td>0.65 (0.11)</td>
<td>1.20 (0.81–1.78)</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>97</td>
<td>72</td>
<td>0.88 (0.10)</td>
<td>1.12 (0.15)</td>
<td>1.25 (0.92–1.70)</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>561</td>
<td>317</td>
<td>4.82 (0.23)</td>
<td>4.72 (0.30)</td>
<td>0.95 (0.83–1.09)</td>
</tr>
<tr>
<td>Cancer</td>
<td>314</td>
<td>162</td>
<td>2.78 (0.18)</td>
<td>2.43 (0.21)</td>
<td>0.87 (0.72–1.05)</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>12</td>
<td>12</td>
<td>0.11 (0.04)</td>
<td>0.24 (0.09)</td>
<td>1.69 (0.76–3.77)</td>
</tr>
<tr>
<td>Accident/suicide/homicide</td>
<td>39</td>
<td>28</td>
<td>0.33 (0.06)</td>
<td>0.40 (0.09)</td>
<td>1.21 (0.75–1.97)</td>
</tr>
<tr>
<td>Other noncardiovascular</td>
<td>196</td>
<td>115</td>
<td>1.75 (0.14)</td>
<td>1.84 (0.19)</td>
<td>0.99 (0.79–1.25)</td>
</tr>
<tr>
<td>Unknown</td>
<td>146</td>
<td>75</td>
<td>1.37 (0.13)</td>
<td>1.18 (0.16)</td>
<td>0.87 (0.66–1.15)</td>
</tr>
<tr>
<td>Combined CHD†</td>
<td>1642</td>
<td>1040</td>
<td>14.87 (0.39)</td>
<td>16.00 (0.53)</td>
<td>1.07 (0.99–1.16)</td>
</tr>
<tr>
<td>Stroke</td>
<td>434</td>
<td>325</td>
<td>4.08 (0.22)</td>
<td>5.49 (0.35)</td>
<td>1.26 (1.01–1.56)</td>
</tr>
<tr>
<td>Combined CVD‡</td>
<td>2829</td>
<td>1947</td>
<td>25.09 (0.48)</td>
<td>28.56 (0.64)</td>
<td>1.20 (1.13–1.27)</td>
</tr>
<tr>
<td>Heart failure (fatal, hospitalized, treated)</td>
<td>546</td>
<td>584</td>
<td>5.35 (0.26)</td>
<td>8.89 (0.42)</td>
<td>1.80 (1.61–2.02)§</td>
</tr>
<tr>
<td>Heart failure (fatal, hospitalized)</td>
<td>440</td>
<td>434</td>
<td>4.41 (0.24)</td>
<td>6.63 (0.37)</td>
<td>1.66 (1.46–1.89)§</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>770</td>
<td>508</td>
<td>7.08 (0.28)</td>
<td>8.02 (0.40)</td>
<td>1.12 (1.00–1.25)</td>
</tr>
<tr>
<td>Hospitalized or treated angina</td>
<td>1227</td>
<td>811</td>
<td>10.81 (0.33)</td>
<td>11.82 (0.45)</td>
<td>1.13 (1.03–1.23)</td>
</tr>
<tr>
<td>Lower-extremity peripheral arterial disease</td>
<td>376</td>
<td>217</td>
<td>3.68 (0.21)</td>
<td>3.49 (0.27)</td>
<td>0.97 (0.82–1.15)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>104</td>
<td>64</td>
<td>1.10 (0.13)</td>
<td>1.08 (0.17)</td>
<td>1.04 (0.76–1.42)</td>
</tr>
</tbody>
</table>

Adapted from Reference 26, with permission from Lippincott Williams & Wilkins. Copyright 2003, American Heart Association.
*To adjust for multiple comparisons, compare the \(P\) value with 0.018 rather than 0.05.
†Combined CHD includes CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina.
‡Combined CVD includes CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized CHF, and peripheral arterial disease (hospitalized, or outpatient revascularization).
§Proportional hazards assumption violated; numbers given are RRs.

Results From Other Trials
After the ALLHAT results appeared, several other active comparator trials were reported. The Second Australian National Blood Pressure Study (ANBP2), a practice-based open-label trial, was the only other large trial besides ALLHAT to compare diuretic-based (hydrochlorothiazide recommended) with ACE inhibitor–based (enalapril recommended) antihypertensive treatment.\(^{34}\) A total of 6083 participants, aged 65 to 84 years, were treated and followed up for a mean of 4.1 years. The primary end point was a composite of all cardiovascular events (including recurrent events, an unusual design) plus all-cause mortality. Cardiovascular events included...
major coronary events, stroke and transient ischemic attacks, heart failure (not otherwise defined), acute occlusion of any other major artery, and dissecting or ruptured aortic aneurysm. The results for the primary end point favored the ACE inhibitor group with marginal significance (RR, 0.89; 95% CI, 0.79 to 1.00; \(P = 0.05\)). The corresponding results with the use of first cardiovascular event had essentially the same RR (\(P = 0.07\)). The RR for heart failure was 0.85 (95% CI, 0.62 to 1.18; \(P = 0.33\)). Frohlich\(^3\) weighed the supposedly conflicting results of ANBP2 and ALLHAT, suggesting possible explanations such as the patients studied (many more black patients in ALLHAT) and the specific drugs used. Additionally, there were almost 8 times as many cardiovascular events in the 2 comparable arms in ALLHAT as in ANBP2, and only ALLHAT was double blind. ANBP2 used a prospective, randomized, open-label, blinded end point (PROBE) design, increasing the potential for bias in the reporting of events (the rates of some outcomes might have been “expected” to be lower with the ACE inhibitor) even though ANBP2 relied on end point committee—adjudicated outcomes. Doses of agents in ANBP2 were left up to the local investigator and were not reported; thus, it is not possible to assess whether appropriate doses of hydrochlorothiazide were used. Even given the possible biases, however, the results of ANBP2 are consistent with those of ALLHAT if the upper confidence limit for the RR in ANBP2 is compared with the estimates of RR in ALLHAT.\(^3\)

The International Nifedipine GITS study [Intervention as a Goal in Hypertension Treatment (INSIGHT)] was the other large trial besides ALLHAT to compare diuretic-based (co-amilozide) with CCB-based (nifedipine) antihypertensive treatment on cardiovascular mortality and morbidity in high-risk patients with hypertension.\(^3\) It was a randomized, double-blind trial in 6321 patients aged 55 to 80 years with hypertension. Patients had at least 1 additional cardiovascular risk factor and were randomly assigned to nifedipine (30 to 60 mg in a long-acting gastrointestinal-transport system [GITS] formulation) or co-amilozide (hydrochlorothiazide 25 to 50 mg plus amiloride). The primary outcome was cardiovascular death, MI, heart failure, or stroke. Primary outcomes occurred in 200 patients (6.3%) in the nifedipine group and in 182 (5.8%) in the co-amilozide group (RR = 1.10; 95% CI, 0.91 to 1.34; \(P = 0.35\)). The CCB was not superior to the diuretic in preventing cardiovascular morbidity and mortality. Nonfatal heart failure was more common in the CCB arm (RR = 2.20; 95% CI, 1.07 to 4.49; \(P = 0.028\)). There were only 3 fatal heart failure events: 2 in the CCB arm and 1 in the diuretic arm.

**Further Details on Heart Failure in ALLHAT**

Another major ALLHAT criticism concerned the heart failure findings. Specifically, were the findings real, and could they be explained by withdrawal from antihypertensive medications, such as diuretics and ACE inhibitors, on entry into ALLHAT? Several articles have addressed these 2 questions in detail.\(^3\) The reliability of the heart failure diagnosis during the trial was examined in depth via the ALLHAT Heart Failure Validation Study (HFVS).\(^4\) This study was designed to validate and elucidate the significance of heart failure events in ALLHAT. This study involved all hospitalized heart failure events and relevant hospital records related to these events. Cardiology fellows, external to ALLHAT and blinded to treatment assignment, centrally abstracted the documentation for each heart failure hospitalization (2778 in 1935 patients; 2 independent reviews per case). ALLHAT and Framingham criteria were assigned by a computer algorithm; the reviewers also rendered a global clinical judgment. Percent agreements with site physician diagnoses were 71%, 80%, and 84% for ALLHAT, Framingham, and reviewers’ judgment, respectively. On the basis of these 3 criteria, RRs (95% CI) for new-onset hospitalized heart failure compared...
with chlorthalidone were, respectively, 1.46 (1.27 to 1.68), 1.42 (1.25 to 1.62), and 1.45 (1.28 to 1.64) for amlodipine; 1.18 (1.02 to 1.28), 1.13 (0.99 to 1.30), and 1.15 (1.01 to 1.32) for lisinopril (Figure 3); and 1.79 (1.51 to 2.11), 1.71 (1.46 to 2.00), and 1.80 (1.55 to 2.10) for doxazosin.40

Although there was early divergence of the heart failure incidence curves in ALLHAT, it continued after the first year for doxazosin and amlodipine versus chlorthalidone. For lisinopril versus chlorthalidone, the curves also separated early but appeared to converge between years 6 and 7.25 Diagnostic analysis revealed that the proportional hazards assumption of constant relative risk over time was not valid.39 A more appropriate model showed that RRs of amlodipine or lisinopril versus chlorthalidone during year 1 were 2.22 (1.69 to 2.91; \( P < .0001 \)) and 2.08 (1.58 to 2.74; \( P < .0001 \)); after year 1, they were 1.22 (1.08 to 1.38; \( P < .0001 \)) and 0.96 (0.85 to 1.10; \( P = .58 \)) (Figure 4).39

In addition, information about previous medication use was collected on the hospitalized and fatal cases of heart failure as a follow-up to the HFVS.41 When case-only design theory was used to assess interactions,42 the analyses did not support an effect of preentry diuretic use on the observed heart failure differences. However, the addition of second- and third-line drugs (≈30% at year 1) probably contributed to the lessening of the divergence starting at 6 to 12 months after randomization. Given these additional examinations, the original conclusions remained the same. Thiazide-type diuretics should be the preferred first-step therapy for prevention of heart failure in high-risk patients with hypertension.

**Diabetes in ALLHAT**

As noted above, the initial ALLHAT reports showed consistent findings for those in the prespecified subgroups with and without a baseline history of diabetes.25,26 A subsequent report on comparisons among the chlorthalidone, amlodipine, and lisinopril arms utilized baseline fasting glucose levels in addition to history to classify participants into those with diabetes, impaired fasting glucose (110 to 125 mg/dL), and fasting normoglycemia. Results were similar in all 3 subgroups, showing, in particular, the superiority of chlorthalidone for heart failure and the absence of any outcome (including end-stage renal disease) for which another arm was superior.43

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**Figure 3.** Incident hospitalized (Hosp) heart failure (HF) outcomes by antihypertensive treatment group (amlodipine/lisinopril vs chlorthalidone).40 *Prespecified end point of treated, hospitalized, or fatal heart failure. Reprinted from Einhorn et al,40 with permission. Copyright 2007, Elsevier.
Among those without diabetes mellitus (DM) at baseline, the mean fasting glucose was \( \approx 93.5 \) mg/dL. Changes in fasting glucose and percentage of incident diabetes mellitus (IDM) at 4 years, although not prespecified outcomes, were +10.8 mg/dL and 11.0% in the chlorthalidone group; +9.3 mg/dL and 9.3% in the amlodipine group, and +6.8 mg/dL and 7.8% in the lisinopril group, respectively. It was observed that these and other metabolic differences did not translate into any overall disadvantage for the diuretic arm during the mean follow-up of 4.9 years (range, 4 to 8 years). Nevertheless, further epidemiological-type analyses were conducted to examine the association of glucose changes with CVD and renal outcomes. There was no significant association of 2-year fasting glucose change with subsequent events, overall or in the chlorthalidone arm separately. In addition, among those who developed IDM by 2 years compared with those who did not, there was no significant increase in subsequent risk for any major disease outcomes except CHD, eg, the RRs for all arms were 1.04 (95% CI, 0.80 to 1.35) for all arms and 0.96 (0.66 to 1.37) for chlorthalidone; for total mortality, they were 1.31 (0.96 to 1.81) and 1.05 (0.66 to 1.67), respectively. For CHD, the risk associated with IDM was 1.64 (1.15 to 2.33) overall but only 1.46 (0.88 to 2.42) in the chlorthalidone arm (Figure 5).

Is this tendency for IDM occurring during low/moderate-dose chlorthalidone treatment to impart less risk for adverse clinical events than during other regimens real? If so, what could be the explanation? First, in the only other long-term follow-up data in treated hypertensive patients that are relatively uncontaminated with concomitant drugs, the findings in the SHEP 14-year extended follow-up study showed a similar phenomenon: a contrast between an increased CVD risk associated with IDM in the placebo arm but not in the chlorthalidone arm. Second, it must be recognized that in a typical hypertensive population, the great majority of IDM that occurs while taking a thiazide is not drug induced but is due to typical causes of type 2 diabetes and therefore would be expected to carry the same risk as any such occurrence. From ALLHAT data on IDM at 4 years, such a fraction can be estimated as 83%, if it is assumed that the CCB is metabolically neutral. If only 1 of 5 cases of IDM in patients prescribed a thiazide is due to the drug but these cases cannot be separated from the majority, the lower risk in such patients would serve to somewhat lower but not eliminate the overall DM-associated risk.

For the reason why thiazide-induced IDM could carry less risk than “naturally occurring” DM, one needs to consider the abundant, but mostly older and often forgotten, literature on potassium depletion and glucose disorders. To the extent that glucose disorders are due to this mechanism, it is plausible that its natural history is quite different. Furthermore, as pointed out in Reference 46, “In the diuretic-treated patient hypokalemia is likely to be intermittent, due to dietary and drug adherence variation, and potassium-sparing therapeutic intervention [which] may also translate to dysglycemia that is intermittent...and thus confer little risk of diabetic complications.”

Network Meta-Analysis
The role of the efficacy of various antihypertensive therapies used as first-line agents in preventing major cardiovascular disease outcomes has been assessed with network meta-analysis. This type of analysis combines direct within-trial, between-drug comparisons with indirect evidence from the other trials. The indirect comparisons, which preserve the within-trial randomized findings, were constructed from trials that had 1 treatment in common.

Data were combined from 42 clinical trials that included 192,478 patients randomized to 7 major treatment strategies.
including placebo. For all outcomes, low-dose diuretics were superior to placebo (Figure 6): CHD (RR, 0.79; 95% CI, 0.69 to 0.92); congestive heart failure (RR, 0.51; 95% CI, 0.42 to 0.62); stroke (RR, 0.71; 0.63 to 0.81); CVD events (RR, 0.76; 95% CI, 0.69 to 0.83); CVD mortality (RR, 0.81; 95% CI, 0.73 to 0.92); and total mortality (RR, 0.90; 95% CI, 0.84 to 0.96). None of the other first-line treatment strategies—β-blockers, ACE inhibitors, CCBs, α-blockers, and angiotensin receptor blockers—was significantly better than low-dose diuretics for any outcome. BP changes were similar between comparison treatments. On the basis of this network meta-analysis, the authors concluded that low-dose diuretics were the most effective first-line treatment for preventing the occurrence of CVD morbidity and mortality.

**JNC7 Recommendations**

In 2003, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High
Blood Pressure (JNC7) issued its recommendations on the basis of the ALLHAT results and other trial evidence that was available at that time. Its major conclusions and recommendations were as follows.

In trials comparing thiazide-type diuretics with other classes of antihypertensive agents, they are (1) well tolerated; (2) effective and relatively safe for the management of hypertension despite potential adverse metabolic effects; and (3) unsurpassed in preventing the cardiovascular complications of hypertension. They are also less expensive and underutilized. The doses of thiazide-type diuretics used in successful morbidity trials of low/moderate-dose diuretics should be used (generally the equivalent of 25 to 50 mg of hydrochlorothiazide or 12.5 to 25 mg of chlorthalidone), although therapy may be initiated at lower doses and titrated to these doses if tolerated.

Figure 6. Network meta-analysis of first-line treatment strategies in randomized controlled clinical trials in hypertension. Asterisks, placed after the closed parentheses of the 95% CI, indicate that β-blockers (P<0.05), angiotensin-converting enzyme inhibitors (P<0.05), calcium channel blockers (P<0.05), and angiotensin receptor blockers (P<0.05) were significantly better than placebo for outcome. α-Blockers were not significantly better than placebo for any outcome (P>0.05). Reprinted from Psaty et al, with permission. Copyright 2003, American Medical Association. All rights reserved.
The algorithm for the treatment of hypertensive patients is to begin with lifestyle modification, and if the BP goal is not achieved, thiazide-type diuretics should be used as initial therapy for most patients, either alone or in combination with 1 of the other classes (ACE inhibitors, angiotensin receptor blockers, β-blockers, CCBs) that have also been shown to reduce 1 or more hypertensive complications in randomized controlled outcome trials (Figure 7). Selection of 1 of these other agents as initial therapy is recommended when a diuretic cannot be used or when a compelling indication is present that requires the use of a specific drug. If the initial drug selected is not tolerated or is contraindicated, then a drug from 1 of the other classes proven to reduce cardiovascular events should be substituted. Because most hypertensive patients will require 2 antihypertensive medications to achieve their BP goals, addition of a second drug from a different class should be initiated when use of a single agent in adequate doses fails to achieve the goal. It is further recommended that patients with stage 2 hypertension be started on 2 drugs initially, 1 of which should be a thiazide.

The Evidence for and Against β-Blockers

The British Medical Research Council (BMRC) trial of treatment of mild hypertension was the first clinical events trial with a β-blocker–based arm (propanolol) in addition to a thiazide arm (bendrofluazide).6 Compared with placebo, only the thiazide significantly reduced stroke, likely as a result of the greater BP reduction than with the β-blocker. Both active treatment arms showed reductions in major cardiovascular events. Along with trials that found improved survival in post-MI patients with β-blockers, this experience was sufficient for guidelines to begin recommending thiazides and β-blockers as relatively equivalent alternatives for initiating treatment. This remained the situation through the 1990s, despite publication of results from the BMRC trial of treatment of hypertension in older adults, the β-blocker arm of which showed no significant reduction in either stroke or CHD events compared with placebo.7 In keeping with practice trends, a cardioselective β-blocker, atenolol, was selected in this trial; in this arm, systolic BP was less well controlled for the first year than in the hydrochlorothiazide arm.

Although 1 observer began questioning the role of the class for first-line treatment,50 during the era of direct comparison trials, the arm representing traditional classes of drugs most often offered participating clinicians a choice of thiazides or β-blockers or selected a β-blocker (most commonly, atenolol) as the comparator. Generally, before 2005 there were few differences for major cardiovascular event rates in individual trials between such regimens and those based on newer classes; an exception was the Losartan Intervention For End point reduction in hypertension (LIFE) trial, in which a composite of stroke, MI, and cardiovascular death was 13% (P=0.02) less frequent in the losartan-based than in the atenolol-based group, owing mostly to an advantage for stroke.51 This small disadvantage for the β-blocker in a special study population selected for left ventricular hypertrophy, in the light of numerous trials not showing such an disadvantage, was not sufficient for the JNC7 group to downgrade the role of β-blockers as alternative first-line drugs.49

The balance of evidence changed substantially with the reporting of results of the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Treatment Arm (ASCOT-BPLA).52 This large open-label trial (PROBE design) compared atenolol-based treatment (bendroflumethiazide as an add-on) with amlodipine-based treatment (perindopril as add-on); it was stopped early because of 11% lower all-cause mortality in the amlodipine group (P=0.02). When the study was terminated early, there was no advantage in this arm for the primary CHD end point (hazard ratio=0.90; P=0.11), and stroke was also significantly reduced, by 23%. This may have been related to the lower mean BP: 2.7/1.9 mm Hg on average, with a greater difference during the first year. Both effects may have in turn been related to the
Figure 8. Outcome data for all β-blockers vs other antihypertensive treatment.53 CONVINCE indicates Controlled Onset Verapamil Investigation of Cardiovascular End Points; ELSA, European Lacidipine Study on Atherosclerosis; HAPPHY, Heart Attack Primary Prevention in Hypertension; INVEST, International Verapamil-Trandolapril Study; MRC, Medical Research Council; NORDIL, Nordic Diltiazem Study; STOP-2, Swedish Trial in Old Patients With Hypertension; and UKPDS, UK Prospective Diabetes Study. Reprinted from Lindholm et al,53 with permission. Copyright 2005, Elsevier.
once daily use of atenolol and/or the relatively low dose of the thiazide added to atenolol when needed for BP control.

After the publication of ASCOT, several meta-analyses were produced that led to recommendations unfavorable to β-blockers (while continuing to acknowledge that evidence on non-atenolol β-blockers in a primary prevention setting is scanty).53,54 Although the trials included differed somewhat between the meta-analyses and the Lindholm article did not address heart failure, they both concluded that β-blockers were less effective than other major antihypertensive classes in preventing stroke (Figure 8). Therefore, the recommendations were to delete β-blockers as a first-line antihypertensive treatment, except in cases in which there are compelling indications, mainly for patients with CHD.

Conclusions
We believe that the JNC7 report came to the proper conclusions about thiazides, on the basis of (1) results of the abundant trials aimed at the effect of BP reduction on clinical events comparing thiazide-based regimens with placebo or lesser treated controls; (2) ALLHAT results in the context of the few other trials evaluating thiazide-based treatment versus another class (trials testing a β-blocker and/or thiazide protocol versus another class are not very informative); and (3) the network meta-analysis by Psaty et al49 that summarized all of this evidence. As noted in JNC7, thiazides (1) are well tolerated, better than other classes in the double-blind setting of ALLHAT, in which a heterogeneous patient population was treated in widely diverse clinical settings; (2) are at least as effective as other classes for BP control in most patients, with the possible exception of younger white men55; (3) are unsurpassed in preventing cardiovascular events and improving survival, including an advantage in prevention of heart failure (in the short term versus ACE inhibitors and in the long term versus CCBs); and (4) have very low acquisition costs. Although frequency of their use in antihypertensive regimens has increased substantially since the ALLHAT and JNC7 publications,56 they are still underutilized, and organized efforts to improve performance in this regard are continuing, most impressively in the Department of Veterans Affairs medical system (William Cushman, MD, personal communication, September 20, 2006).

Some commentators have focused on the small increase in IDM associated with thiazide use while virtually ignoring the advantage for heart failure prevention. This seems backward. Regarding diabetes, naturally occurring disease carries appreciable long-term cardiovascular risk, but it is not clear that thiazide-induced cases do, and they are largely preventable or reversible by management of potassium balance. On the other hand, heart failure imparts high functional impact and mortality risk in the short to medium term. It seems that this benefit should be given considerable weight, except in patients known to be at very low risk of heart failure. Thus, the British recommendation to the effect that thiazides and CCBs are equally desirable choices as first-line drugs in older patients seems ill considered.54

As noted above, the role of other major drug classes (ACE inhibitors, angiotensin receptor blockers, β-blockers, and CCBs) in JNC7 is in cases in which a thiazide is not tolerated or contraindicated, which is an infrequent situation; for listed compelling indications; or in combination treatment, which is likely to be required to control BP in most patients. There is no update of JNC guidelines currently available that might have changed the recommendations regarding β-blockers, but British guidelines have placed them as a lesser choice than the other classes except for compelling indications, ie, situations in which there is another indication for their use. This conclusion seems reasonable to us, even though the data are scant for non-atenolol β-blockers and the evidence for benefit in secondary prevention is much stronger for other β-blockers.57 Interestingly, the parallel situation for ACE inhibitors in younger patients (lack of cardiovascular outcome data) did not deter the British report from recommending them as first choice in this demographic group. Once again, the recommendation seems to turn on effects on dysglycemia without really knowing their importance. However, to our knowledge, there is no reassuring evidence regarding associated risks and mechanisms for β-blockers as exists for thiazides.

Additional Research
Although a strong evidence base exists for a consensus on preferred and other acceptable drug classes for initiating antihypertensive pharmacotherapy, there are several other major research questions for ongoing and needed trials, several of which were highlighted in a report from a 2003 National Heart, Lung, and Blood Institute workshop.58 These include the following: (1) What is the optimal second drug class to add to a thiazide? (2) What goal BP, especially systolic, should be sought for minimizing CVD risk? From the evidence on heart failure in ALLHAT and the importance of the condition generally, we believe that heart failure should be included in any composite primary CVD end point for future hypertension treatment trials.

Acknowledgment
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Disclosures
Dr Davis has served as a consultant for Biomarin, GlaxoSmithKline, Proctor & Gamble, and Takeda Pharmaceutical Company Limited. Dr Cutler has no conflicts of interest.

References


Response to Cutler and Davis

Franz H. Messerli, MD; Sripal Bangalore, MD, MHA; and Stevo Julius, MD

We are delighted that Drs Cutler and Davis find the conclusion of the British guidelines to remove β-blockers from their first-line status in hypertension “reasonable”—a position we have taken a decade ago. Indeed, one may wonder why β-blockers were ever elevated to that status; ever since the MRC trial, every single study comparing β-blockers with either placebo or other therapy has been negative. Never has a drug class been prescribed so much on the basis of so little evidence. In the United States alone, more than 120 million prescriptions for β-blockers were written in 2007. This means that numerous patients still are exposed to the adverse effects, cost, and inconvenience of a drug class without ever having any benefit. We also agree with our colleagues that, on the basis of the ALLHAT study, “thiazide-type diuretics should be the preferred first-step therapy for prevention of heart failure in high-risk patients with hypertension,” although this is true for chlorthalidone only. However, we strongly object to the authors’ suggestion that evidence gained in high-risk patients such as ALLHAT “should be reasonably extrapolated beyond the exact sample in which it was conducted.” That this is pure conjecture and that there is no scientific basis for extrapolation has now been documented by ACCOMPLISH, which now relegates the thiazides to third-line therapy. As to the cost of thiazides, the authors’ own recent ALLHAT analysis showed that amlodipine tended to be preferred on the basis of the fact that it provided a (nonsignificantly) greater survival benefit than the other drugs. This analysis is misleading in that it did not even consider the now generic price of these drugs, nor did it assess cost of new-onset diabetes associated with them. On the basis of our meta-analysis, we estimate that β-blockers and diuretics could account for more than 100 000 cases of new-onset diabetes in the United States every year. Recent data on outcome, cost, and adverse events allow us now to assign antihypertensive drugs to their proper place in the therapeutic arsenal; keeping thiazides or β-blockers as first-line therapy seems to us, as Ralph Waldo Emerson said, “a foolish consistency...the hobgoblin of little minds.”
Should β-blockers and diuretics remain as first-line therapy for hypertension?

Risk/Benefit Assessment of β-Blockers and Diuretics Precludes Their Use for First-Line Therapy in Hypertension

Franz H. Messerli, MD; Sripal Bangalore, MD, MHA; Stevo Julius, MD

In 1977, the first report of the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure was published. On the basis of the available information, the committee suggested an algorithm in which the “first step drugs should usually be a thiazide diuretic.” The algorithm suggested either reserpine, methyldopa, or propranolol as a second step. In 1984, JNC III recommended β-blockers as a class for first-line therapy on an equal basis with the thiazide diuretics. From then on, in all the subsequent JNC reports until JNC 7 in 2003, β-blockers and diuretics remained first-line antihypertensive drugs. JNC 7 suggested that thiazide diuretics should be used as initial therapy in most patients. If these were not tolerated or contraindicated, then a β-blocker, on an equal basis with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor inhibitors, and calcium antagonists, could be substituted. Thus, according to JNC 7, both thiazides and β-blockers are meant to be given to hypertensive patients regardless of their risk factor status and regardless of their concomitant metabolic abnormalities.

Response by Cutler and Davis p 2715

Diabetes and Blood Pressure

Within the same time frame, from 1980 to 2004, the prevalence of diabetes more than doubled in the United States, and almost 10% of people aged >20 years are currently suffering from this disease. Patients with hypertension are known to be at a higher risk of developing new-onset diabetes than are normotensive subjects. In the Atherosclerosis Risk in Communities (ARIC) study, type 2 diabetes was almost twice as likely to develop in hypertensive than in normotensive subjects. In the Women’s Health Study, in a prospective cohort of 38 172 women free of diabetes and cardiovascular disease, baseline blood pressure and blood pressure progression were strong and independent predictors of incident type 2 diabetes. Women with baseline hypertension had a hazard ratio for incident diabetes in the 4-year follow-up of 2.39 (95% CI, 1.95 to 2.93).

Conversely, hypertension is exceedingly common in patients with type 2 diabetes, even in children and adolescents. Upchurch et al reported that 55% of young people had systolic blood pressures >90 percentile at the time of diagnosis of type 2 diabetes. In fact, hypertension at diagnosis was as much as 8 times more common in adolescents with type 2 diabetes compared with those with type 1 diabetes. Thus, hypertension begets type 2 diabetes, and, conversely, diabetes begets hypertension.

New-Onset Diabetes With Thiazide Diuretics

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), about 10% of all patients...
developed new-onset diabetes throughout the 4- to 5-year duration of the study. However, this percentage was between 18% and 40% higher in patients in the chlorthalidone arm than in those in the amldipine and lisinopril arms, respectively.9 In the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE) study,10 hypertensive patients who had never been treated before were randomized to either candesartan-based therapy (plus amlodipine if needed) or thiazide-based therapy (plus atenolol if needed). After only 1 year, 18 patients in the diuretic group fulfilled criteria of the metabolic syndrome, and 9 had developed new-onset diabetes. The corresponding numbers in the candesartan arm were 5 and 1, respectively.

Meta-Analysis of Diuretic-Based Studies
Figure 1 shows the results of a meta-analysis we prepared for this review. We conducted a MEDLINE/PUBMED/EMBASE search of studies using the terms diuretics and hypertension. We limited our search to studies in human subjects and English language in peer-reviewed journals from 1966 to October 2007. All randomized controlled trials of patients with hypertension treated with diuretic therapy with follow-up for at least 1 year and that reported the incidence of new-onset diabetes were included. Statistical analysis was done with the use of standard software (Stata 9.0, Stata Corporation) with the METAN program.11 The pooled effect for each grouping of trials was derived from the point estimate for each separate trial weighted by the inverse of the variance (1/SE²). Heterogeneity was assessed visually with funnel plots, Q (χ²) statistics, and/or I² statistics.12 If trials were homogeneous (P>0.05), a fixed-effect model was used to calculate pooled effect sizes. Otherwise, a random-effect model of DerSimonian and Laird13 was applied to calculate overall differences. Publication bias was estimated with the weighted regression test of Egger.

In the analysis of 6 trials enrolling 30,842 patients with hypertension, diuretics resulted in a 32% increased risk of new-onset diabetes compared with placebo or non–β-blocker antihypertensive agents. Compared with placebo, diuretics resulted in a strong trend toward a 22% increased risk of new-onset diabetes, suggesting that the risk is due to the medication itself. When compared with antihypertensive agents other than β-blockers, diuretics conferred a 35% increased risk of new-onset diabetes. We also performed a meta-regression analysis to evaluate the relationship between follow-up duration of therapy and the risk of new-onset diabetes. The risk of new-onset diabetes increased with increasing duration of diabetic therapy with these agents (Figure 2).
with new-onset diabetes (Figure 3). The risk of new-onset diabetes in any of the aforementioned analyzed studies was new-onset hypertensive agents (Figure 5). Of note, neither in ALLHAT nor increased risk of new-onset diabetes compared with other antihypertensive agents, diuretics, calcium antagonists, β-blockers, and diuretics, respectively, with placebo having a reference value of 1.0 (Figure 6).

**New-Onset Diabetes With β-Blockers**

The prodiabetic effect of the β-blockers has been less well documented. In the ARIC study, hypertensive patients taking β-blockers had a 28% increased risk of developing diabetes compared with those hypertensive subjects who did not take any medication.5

**Meta-Analysis of β-Blocker-Based Studies**

Figures 3 and 4 shows the results of our meta-analysis of all randomized controlled trials enrolling patients with hypertension treated with β-blocker therapy with a follow-up for at least 1 year and that reported the incidence of new-onset diabetes. We conducted a MEDLINE/PUBMED/EMBASE search of studies using the terms adrenergic beta antagonists, beta blockers, and hypertension. We limited our search to studies in human subjects and English language in peer-reviewed journals from 1966 to October 2007. In the analysis of 6 trials enrolling 55,675 patients with hypertension, β-blockers conferred a 32% increased risk of new-onset diabetes compared with placebo or nondiuretic antihypertensive agents. When compared with nondiuretic antihypertensive agents, β-blockers resulted in a 31% increased risk of new-onset diabetes (Figure 3). The risk of new-onset diabetes with β-blockers increased with duration of therapy (Figure 4).

However, in the mixed β-blocker/diuretic trials, in which patients could be randomized to a β-blocker, a diuretic, or their combination, β-blockers/diuretics resulted in an 11% increased risk of new-onset diabetes compared with other antihypertensive agents (Figure 5). Of note, neither in ALLHAT nor in any of the aforementioned analyzed studies was new-onset diabetes a predefined end point. This requires a cautious interpretation of the data.

**Differences Among Antihypertensive Drugs**

The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial14 reported that with regard to metabolic adverse effects, not all β-blockers seem to be created equal. In patients with hypertension and type 2 diabetes who were treated with a blocker of the renin-angiotensin system, the addition of carvedilol, compared with metoprolol, had a favorable effect on glycemic control, insulin resistance, microalbuminuria, and body weight. In a recent thorough and comprehensive network meta-analysis, Elliott and Meyer15 documented the odds ratio of new-onset diabetes to be 0.85, 0.90, 1.05, 1.25, and 1.34 with angiotensin receptor blockers, ACE inhibitors, calcium antagonists, β-blockers, and diuretics, respectively, with placebo having a reference value of 1.0 (Figure 6).

**Does Drug-Associated Diabetes Mellitus Increase Morbidity and Mortality?**

In regard to the clinical significance of drug-associated new-onset diabetes, the ALLHAT investigators attempted to reassure us by stating that “overall these metabolic differences did not translate into more cardiovascular events or into higher all-cause mortality in the chlorthalidone group.” This is a correct but perhaps somewhat myopic statement. We should consider that antihypertensive therapy is lifelong and that a follow-up period of 4 to 6 years, as was the case in ALLHAT, is unlikely to give us any clues regarding the long-term sequelae of the diabetes risk associated with either β-blockers or diuretics.9

Several studies have scrutinized this critical issue, as follows.

1. Verdecchia et al16 reported a 16-year follow-up of almost 800 initially untreated hypertensive patients, 6.5% of whom had diabetes at the onset and 5.8% of whom developed new-onset diabetes throughout the study. Fasting blood sugar at entry and diuretic treatment on follow-up were independent predictors of new-onset diabetes (P<0.0001 and P<0.004, respectively). Compared with subjects who never developed diabetes, the risk for cardiovascular disease during the follow-up was very similar in patients who developed diabetes (odds ratio, 2.92; 95% CI, 1.33 to 6.41; P=0.007) and in the group that had preexisting diabetes (odds ratio, 3.57; 95% CI, 1.65 to 7.73; P=0.001). Patients with new-onset diabetes and those with a previous diagnosis of diabetes were almost 3-fold more likely to develop subsequent cardiovascular disease than those who remained free of diabetes.

2. In a study involving almost 7000 patients, Alderman et al17 showed that cardiovascular disease increased in hypertensive diuretic users who developed hyperglycemia even when blood pressure was well controlled. The authors stated, “Cardiovascular disease incidence has a
3. In the 11,645-patient Multiple Risk Factor Intervention Trial (MRFIT), the occurrence of new-onset diabetes was increased by approximately 30% in diuretic-treated patients and showed an excess mortality risk in the 18-year posttrial follow-up.

4. Almgren et al followed a population sample of 7500 men in which 20.4% of treated hypertensive patients developed diabetes. New-onset diabetes implied a significant increased risk for stroke, myocardial infarction, and mortality (hazard ratio, 1.67, 1.66, and 1.42, respectively). The authors concluded that diabetes in treated hypertensive patients was alarmingly common and carried a high risk for cardiovascular complications and mortality.

5. Aksnes et al, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study, compared patients with diabetes at baseline and new-onset diabetes with patients who did not develop diabetes (5250, 9995, and 1298 patients, respectively). Patients with new-onset diabetes had significantly higher cardiac morbidity, especially more congestive heart failure, than those without diabetes (hazard ratio, 1.43). Patients were followed up for an average of 4.2 years only.

6. In contrast to the aforementioned 5 studies, Kostis et al., in a follow-up of the Systolic Hypertension in the Elderly Program (SHEP), found no significant increase in cardiovascular events in patients who had diabetes associated with chlorthalidone therapy. In fact, these patients had a better prognosis than those who had preexisting diabetes, and diuretic treatment in subjects who had diabetes was strongly associated with lower long-term cardiovascular mortality and total mortality. Thus, at present, the exact clinical significance of diuretic-associated diabetes remains unknown, with 5 studies showing a detrimental outcome and 1 study showing a neutral outcome.

In the present analysis using studies that reported the end point of new-onset diabetes, the risks for other events—all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, and heart failure—are detailed in the Table. Compared with non-β-blocker antihypertensive agents, diuretics did not provide any incremental benefit for the end points of all-cause mortality, cardiovascular mortality, myocardial infarction, and stroke but conferred a 33% reduction in heart failure. The heart failure end point was driven mainly by the study of Aksnes et al.

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**Figure 3.** Relative risk of new-onset diabetes mellitus in studies using β-blockers (BB) against other agents (including placebo). We performed a meta-analysis of all randomized controlled trials of patients on β-blockers for hypertension with follow-up for at least 1 year and that reported the incidence of new-onset diabetes. The sizes of the data markers relate to study sample size and the inverse of the SE of each study. MRC indicates Medical Research Council; MRC-O, Medical Research Council trial of treatment of hypertension in older adults; AASK, African American Study of Kidney Disease and Hypertension; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; and LIFE, Losartan Intervention For End point reduction in hypertension trial. Other abbreviations are as defined in Figure 1 legend.

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**Test(s) of heterogeneity:**

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by the ALLHAT trial. Given the heterogeneity in the definition of heart failure used in various studies, the results should be interpreted with caution. Similarly, compared with nondiuretic antihypertensive agents, β-blocker therapy resulted in an 8% increased risk of all-cause mortality and 30% increased risk of stroke.

Conceivably, new-onset diabetes associated with diuretics and/or β-blockers may be reversible on discontinuation of the offending drug(s). Thus, treatment withdrawal could potentially separate the drug-induced new-onset diabetes from spontaneously occurring new-onset diabetes. However, the

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**Figure 4.** Relative risk of new-onset diabetes mellitus in the studies using β-blockers as a function of follow-up duration. Meta-regression analysis was performed to evaluate the relationship between risk of new-onset diabetes mellitus and the length of follow-up of patients on β-blocker therapy. The diameter of the circles represents the variance of the relative risk of each individual trial. The line represents the regression fit with 95% CI for the effect sizes. Abbreviations are as defined in Figure 1 and Figure 3 legends.

**Figure 5.** Relative risk of new-onset diabetes mellitus in studies using β-blockers (BB) or diuretics (mixed trials) against other agents (including placebo). We performed a meta-analysis of all randomized controlled trials of patients on β-blockers/diuretics for hypertension with follow-up for at least 1 year and that reported the incidence of new-onset diabetes. The sizes of the data markers relate to study sample size and the inverse of the SE of each study. CAPPP indicates Captopril Prevention Project; NORDIL, the Nordic Diltiazem study; and STOP-2, the second Swedish Trial in Old Patients with Hypertension. Other abbreviations are as defined in Figure 1 legend.

**Figure 6.** Risk of new-onset diabetes mellitus with antihypertensive treatment. ARB indicates angiotensin receptor blocker; ACE-I, ACE inhibitor; and CCB, calcium channel blocker. Reprinted from Elliott and Meyer, with permission. Copyright 2007, Lancet.

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<tr>
<td>CAPPP</td>
<td>390/5230</td>
<td>337/5183</td>
<td>1.12 (0.97, 1.29)</td>
</tr>
<tr>
<td>NORDIL</td>
<td>251/5095</td>
<td>216/5059</td>
<td>1.15 (0.97, 1.38)</td>
</tr>
<tr>
<td>STOP2 (vs. ACEi)</td>
<td>97/1961</td>
<td>93/1969</td>
<td>1.05 (0.79, 1.38)</td>
</tr>
<tr>
<td>STOP2 (vs. CCB)</td>
<td>97/1961</td>
<td>95/1965</td>
<td>1.02 (0.78, 1.35)</td>
</tr>
<tr>
<td>Overall</td>
<td>825/14247</td>
<td>741/14176</td>
<td>1.11 (1.01, 1.22)</td>
</tr>
</tbody>
</table>

Test(s) of heterogeneity: l² = 0.69, df = 3, P = 0.875, I² = 0.0% (measured as Tau² = 0.0000).
risk of new-onset diabetes continues to increase with duration of therapy (Figure 4), and diabetes has been identified as a coronary heart disease equivalent. Because antihypertensive therapy is prescribed to prevent coronary heart disease, it seems counterintuitive to select drug classes that indeed have the exact opposite effect, ie, that can induce a coronary risk equivalent.

**Does Concomitant Renin-Angiotensin System Blockade Reduce the Risk of New-Onset Diabetes Associated With Diuretics and β-Blockers?**

Over the past few years, we have come to realize that even patients with uncomplicated hypertension may need ≥2 drugs to bring their blood pressure under control. Because most often diuretics are prescribed in combination with other drugs such as ACE inhibitors or angiotensin receptor blockers, it has been argued that these drugs, by mitigating hypokalemia associated with the thiazides, may abolish some metabolic adverse effects. However, in the International Verapamil-Trandolapril (INVEST) study, the addition of hydrochlorothiazide in a dose-dependent way increased the risk of new-onset diabetes in patients treated with either atenolol or verapamil.22,23 The metabolic effects of the thiazide diuretics in combination with renin-angiotensin system blockade were further investigated in the Study of Trandolapril/Verapamil SR and Insulin Resistance (STAR) study,24 in which patients with the metabolic syndrome were randomized to either verapamil/trandolapril or losartan/hydrochlorothiazide. At the end of 1 year, losartan/hydrochlorothiazide increased plasma glucose significantly more than verapamil/trandolapril after all oral glucose tolerance testing. The differences were more pronounced with high-dose combinations than with low-dose combinations.

Similarly, in the GEMINI study,14 in which all patients were treated with a blocker of the renin-angiotensin system, we observed significant differences in glycylated hemoglobin and insulin resistance between patients on metoprolol and those on carvedilol. Thus, the presence of an ACE inhibitor or an angiotensin receptor blocker did not abolish the effects of β-blockade on metabolic parameters.

Most recently, the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, which compared the fixed combination of benazepril/amldopine with benazepril/hydrochlorothiazide in more than 10 000 patients, was stopped prematurely because of a 20% reduction in cardiovascular mortality in the amlodipine/benazepril arm. Thus the ACCOMPLISH data, in hypertension complicated by multiple risk factors, clearly establishes outcome superiority for a CCB/ACE inhibitor combination over an ACE inhibitor/diuretic combination, thereby relegating the thiazides to third-line therapy.

### Antihypertensive Therapy and Dyslipoproteinemia

The effects of antihypertensive therapy on serum lipids were analyzed by Kasiske et al25 in a meta-analysis of 474 clinical trials in >65 000 patients. Diuretics caused a relative increase in cholesterol levels that was more pronounced with higher doses and worse in black patients than in nonblacks. Chlorthalidone caused a greater increase in low-density lipoprotein cholesterol than did other diuretics. β-Blockers caused an increase in triglyceride levels that was smaller for agents with intrinsic sympathetic activity. A beneficial effect on total cholesterol, low-density lipoprotein cholesterol, and triglycerides was seen with the α-blockers, and a beneficial effect on triglycerides and in diabetic patients on total cholesterol was seen with ACE inhibitors. Calcium antagonists had no effects on lipids. Although, as with new-onset diabetes, the long-term effects of these drug-associated changes are not known, it seems unlikely that the increase in total cholesterol and triglycerides with diuretics and β-blockers, respectively, will be beneficial. In GEMINI, there were distinct differences in total cholesterol and triglycerides between the metoprolol arm and the carvedilol arm, indicating again that blockade of the renin-angiotensin system did not abolish the effect of β-blockers on lipoproteins.14 Signif-

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**Table. Pooled Relative Risk of Cardiovascular Event Based on Our Meta-Analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All-Cause Deaths</th>
<th>Cardiovascular Death</th>
<th>Myocardial Infarction</th>
<th>Heart Failure</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. RR (95% CI)</td>
<td>No. RR (95% CI)</td>
<td>No. RR (95% CI)</td>
<td>No. RR (95% CI)</td>
<td>No. RR (95% CI)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>vs placebo</td>
<td>2 0.90 (0.79–1.02)</td>
<td>2 0.77 (0.63–0.94)</td>
<td>2 0.99 (0.43–2.30)</td>
<td>2 0.99 (0.70–1.41)</td>
</tr>
<tr>
<td></td>
<td>vs others</td>
<td>4 1.02 (0.98–1.06)</td>
<td>4 0.98 (0.91–1.04)</td>
<td>3 1.14 (0.81–1.61)</td>
<td>4 0.67 (0.57–0.79)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>vs placebo</td>
<td>2 1.01 (0.88–1.16)</td>
<td>2 1.00 (0.83–1.20)</td>
<td>2 1.98 (0.53–7.37)</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>vs others</td>
<td>5 1.08 (1.02–1.14)</td>
<td>5 1.13 (0.98–1.31)</td>
<td>3 1.05 (0.94–1.18)</td>
<td>3 1.04 (0.89–1.21)</td>
</tr>
<tr>
<td>Mixed</td>
<td>vs others</td>
<td>4 0.99 (0.92–1.07)</td>
<td>4 1.01 (0.89–1.13)</td>
<td>4 0.94 (0.83–1.06)</td>
<td>4 0.99 (0.84–1.15)</td>
</tr>
</tbody>
</table>

RR indicates relative risk.
icantly more patients had to be started on a statin in the metoprolol arm than in the carvedilol arm.\textsuperscript{14}

**Weight Change and Antihypertensive Therapy**

Sharma et al.\textsuperscript{26} in a systematic analysis of prospective randomized controlled trials, found that \( \beta \)-blockers increased body weight by a median of 1.2 kg; weight gain occurred primarily during the first few months. Of note, not all \( \beta \)-blockers seem to cause weight gain equally. We recently showed no significant weight gain in the GEMINI study in patients on carvedilol, whereas with metoprolol, after 6 months the average weight increased by 1.2 kg.\textsuperscript{27} Recently, Scholze et al.\textsuperscript{28} compared a weight loss regimen with sibutramine in a 16-week, double-blind, placebo-controlled, randomized, multicenter study of 171 obese hypertensive patients who were randomized to 3 different antihypertensive regimens (felodipine/ramipril, verapamil/trandolapril, or metoprolol/hydrochlorothiazide). Overall weight loss and reduction of abdominal obesity were markedly attenuated in the metoprolol/hydrochlorothiazide group compared with the other 2 groups. Similarly, improvement in glucose tolerance and hypertriglyceridemia with weight loss was abrogated in the metoprolol/hydrochlorothiazide cohort compared with the other 2 arms. This would indicate that antihypertensive combination therapy with a renin-angiotensin system blocker and a calcium blocker facilitates weight loss with a sibutramine regimen significantly more than does a \( \beta \)-blocker/diuretic–based regimen. This is further evidence against \( \beta \)-blocker/diuretic treatment for hypertension, especially in the large majority of overweight and obese patients.

**\( \beta \)-Blockade in the Young Hypertensive Patient**

Because numerous studies have shown that the young borderline hypertensive patient is characterized by an elevated cardiac output and an “inappropriately” normal total peripheral resistance, it was thought that \( \beta \)-blockade would be the most “physiological” antihypertensive therapy in this patient population. However, a “normalization” of hemodynamics does not necessarily prevent the transition from borderline to more established hypertension. In addition, the ALPINE study taught us that, if anything, young patients (aged <55 years) were more susceptible to the development of new-onset diabetes with diuretic-based therapy than patients aged >55 years.\textsuperscript{29} Similarly, total cholesterol increased with diuretic therapy in the younger ALPINE study population, whereas it fell in those aged >55 years. Thus, \( \beta \)-blockers are not more beneficial (or less detrimental) in the young than they are in the older patient.

**Other Adverse Effects of \( \beta \)-Blockers and Diuretics**

Neither \( \beta \)-blockers nor diuretics are well tolerated antihypertensive drugs. In most systematic analyses, they fare consistently worse than blockers of the renin-angiotensin system and calcium antagonists. In the Cochrane meta-analysis, the withdrawal rate of patients treated with \( \beta \)-blockers was twice as high as the rate in patients treated with diuretics.\textsuperscript{30} Our analysis allowed us to calculate that for every stroke or heart attack prevented, 3 patients remained impotent and 8 experienced fatigue to the extent that they withdrew from such therapy.\textsuperscript{31} Clearly, this is not an acceptable risk/benefit ratio for a completely asymptomatic disease such as stage 1 hypertension.

The question of nephrotoxicity of long-term thiazide diuretic therapy continues to surface.\textsuperscript{32–35} Because most prospective studies last 6 years at most, solid documents attesting to the safety of diuretic therapy (and of all antihypertensive drugs) are lacking. Similarly, the issue of carcinogenicity with long-term diuretic therapy has not been resolved. We reported in a meta-analysis an association between diuretic use and renal cell carcinoma with a pooled odds ratio of 1.54 in 10 independent case-control studies and 3 cohort studies.\textsuperscript{35} The association between renal cell carcinoma and diuretic therapy remains a concern because the renal tubular cell, ie, the cell that turns cancerous, is also the main target of the diuretic pharmacological effect. Because diuretic-associated carcinogenicity seemed to be cumulative in some studies, it may be yet another reason not to expose young patients to years and decades of thiazide therapy. Clearly, however, the issue of carcinogenicity with hypertension and/or antihypertensive therapy is exceedingly complex, and hasty conclusions should be avoided.

**Morbidity and Mortality Reduction With \( \beta \)-Blockers and Diuretics**

The efficacy of \( \beta \)-blockers in reducing morbidity and mortality in hypertension has come into question recently.\textsuperscript{36–38} Most “evidence” used in current guidelines for hypertension stems from extrapolation from post–myocardial infarction studies or cohorts of hypertensive patients specifically selected for high cardiovascular risk. For many years, extensive marketing efforts by the pharmaceutical industry have planted the seeds of \( \beta \)-blockers being “cardioprotective.” However, in uncomplicated hypertension, particularly in the elderly, outcome data with \( \beta \)-blockers showed either no benefit or even harm.\textsuperscript{37–39}

We are not debating that thiazide diuretics are powerful drugs that repeatedly have been shown to reduce morbidity and mortality in high-risk established essential hypertension such as, for example, in the ALLHAT study. Clearly, in this setting, the benefits of therapy distinctly outweigh the low-grade negative metabolic adverse effects of the thiazides. Thus, unlike with \( \beta \)-blockers, the risk/benefit ratio with thiazide diuretics, specifically chlorthalidone, remains acceptable in such patients, and they should be considered candidates for such therapy. We should also remember that in the elderly, who are exposed to these drugs for a limited time, the metabolic adverse effects may be more acceptable than in the comparatively younger patient. However, in the younger patients with stage 1 hypertension who will be...
placebo in hypertension. Obviously, the myth of universal cardioprotection by β-blockade, a seed initially planted by the pharmaceutical industry, is alive and doing well. This is also documented by the fact that year after year, the β-blocker market has continued to grow, and >100 million prescriptions for β-blockers are written every year in the United States alone, a number that has doubled over the past decade.

Cost-Effectiveness

The compliance of patients with medication depends on multiple factors, including economic costs of the drugs. Previously, the guideline committees endorsed thiazides and β-blockers as first-line agents given the actual cost of medication. However, such an approach does not take into consideration the efficacy and effectiveness of medication. An ideal cost-effectiveness analysis should consider the relative effectiveness of different drugs on clinical outcomes, the direct and indirect costs associated with long-term sequelae with the medications (such as development of diabetes), and the actual cost of the drug itself. Such a formal cost-effectiveness analysis was performed by the National Institute for Health and Clinical Excellence. On the basis of their health-economic model, they concluded that for 65-year-old men and women with an annual cardiovascular disease risk of 2%, heart failure risk of 1%, and diabetes risk of 1.1%, the most cost-effective initial drug in this group was a calcium antagonist.45 β-Blockers were the least cost-effective option. Given the metabolic adverse effects of β-blockers, its direct and indirect costs, and the direct and indirect costs of increased stroke risk in the elderly, β-blockers are not cost-effective for this indication.

Outcome Evidence Versus Surrogate End Point

Glycemia, lipids, and blood pressure are well-known surrogate end points that correlate reasonably well with outcome, ie, morbidity and mortality. However, instances of clear-cut surrogate end point failure have been documented for all 3 of these markers. Thus, the fact that β-blockers and diuretics have a negative impact on glycemia and lipids should be interpreted with caution as long as we have no solid prospective data firmly connecting surrogate end point with outcome.

Conclusions

Under the heading “Bottom Line,” there was an anonymous statement in a widely read medical journal: “It can’t get clearer. Diuretics—the least expensive and most effective agents—should be the first line treatment for almost everyone with hypertension, including patients with diabetes.”46 We beg to differ and think that the time has come to differentiate patients with stage 1 hypertension from those with a more advanced stage of the disease. Because of their inefficacy and multiple adverse effects, β-blockers should no longer be used for initial therapy in hypertension.
In patients with advanced hypertensive cardiovascular disease, the benefits of lowering blood pressure outweigh the small metabolic adverse events associated with diuretics and, in some specific cases, even with β-blockers. However, in uncomplicated hypertension, neither diuretics nor β-blockers are acceptable for first-line treatment. Not quite unexpectedly, Thomas Sydenham’s dictum of primum nil nocere also applies to first-line antihypertensive therapy.

Disclosures
Dr Messerli reports having served as an ad hoc consultant/speaker for the following organizations: Abbott, GSK, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Forest, Sanofii, Mars, and Sanofi. Dr Julius reports having performed as a service as principal investigator for AstraZeneca and Novartis. Dr Bangalore has no disclosures.

References
Response to Messerli et al

Jeffrey A. Cutler, MD, MPH; Barry R. Davis, MD, PhD

The article by Messerli and colleagues argues against first-line diuretic treatment for those with stage I hypertension on the basis of selective evidence from many nonrandomized studies and analyses. The crux of their case gives undue weight to small differences in new-onset diabetes among antihypertensive drug treatments. We disagree with this point for the following reasons: (1) As the authors acknowledge (but fail to incorporate in their conclusions), type 2 diabetes mellitus is a surrogate outcome and is important primarily because of its status as a risk factor, presumably causal, for cardiovascular-renal outcomes. Thiazide-type diuretics have an advantage over other drugs as a first-step treatment for prevention of such outcomes. In ALLHAT, these advantages persisted in subgroups of patients with diabetes or the metabolic syndrome. (2) The cause of the diabetes epidemic is increasing overweight/obesity and physical inactivity. The epidemic can be reversed in the population, and diabetes can be prevented (and treated in its early stage) in the individual by attention to these factors. (3) Most new-onset diabetes in diuretic-treated patients is not diuretic induced. Cases that are can likely be prevented by avoiding significant potassium depletion. There are no direct data on diuretic-induced diabetes and cardiovascular risk. The authors purport to refute JNC7, a broadly based set of consensus, evidence-based guidelines. The process for generating a JNC8 is getting under way, and we are confident that the best evidence will prevail. We have no major disagreement with these authors regarding a secondary role for β-blockers, despite the deficiencies in evidence regarding non-atenolol β-blockers.