Brief Review

Implications of Recently Published Trials of Blood Pressure–Lowering Drugs in Hypertensive or High-Risk Patients

Jan A. Staessen, Tom Richart, Zengwu Wang, Lutgarde Thijs

Abstract—We reviewed 6 recent outcome trials of blood pressure (BP)–lowering drugs in 74,524 randomized hypertensive or high-risk patients. Over interpretation of nonsignificant or marginal probability values in large trials with overlapping end points, exclusion of patients not tolerating or not adhering to experimental treatments, labeling nonsignificant treatment effects as modest, and insufficient information on the quality of the BP measurements or on the BP changes early after randomization raise concern. From a clinical viewpoint, results should not be extrapolated to patients with characteristics dissimilar from those randomized. The benefit beyond BP lowering in cardiovascular prevention is tiny. Dual inhibition of the renin system should only be used in patients at high risk, in whom all drug combinations have been tried and who cannot be controlled by a single renin system inhibitor. Current evidence does not support BP lowering in normotensive patients or the use of renin system inhibitors for prevention of stroke recurrence. Because angiotensin-receptor blockers might offer less protection against myocardial infarction than angiotensin-converting enzyme inhibitors, the latter should remain the preferred renin system inhibitor for cardiovascular prevention in angiotensin-converting enzyme inhibitor-tolerant patients. In 2 trials, in which new-onset diabetes was a predefined end point, 1000 patients had to be treated for 1 year with an angiotensin-receptor blocker instead of placebo to prevent just 2 cases. From a design viewpoint, the time has come to revise the concept of large simple trials and to pursue research questions that serve patient interests more than showing noninferiority or highlight the ancillary qualities of marketable antihypertensive drugs. (Hypertension. 2010;55:819-831.)

Key Words: antihypertensive drugs ■ clinical trials ■ hypertension ■ outcome research ■ primary prevention ■ secondary prevention

The Heart Outcomes Prevention Evaluation (HOPE)1 and the Losartan Intervention for Endpoint Reduction2 studies were forerunners of a new breed of randomized clinical trials in hypertension. They introduced the concept of a large simple trial3 and replaced the previous generation of placebo-controlled trials, which had identified new indications for blood pressure–lowering treatment, such as hypertension in older patients from 60 to 80 years of age.4–7 Most of the large simple trials investigated blockade of the renin system as a way to prevent cardiovascular complications. The purpose of this article was to review recently published outcome trials in hypertensive or high-risk patients,8–27 and to assess their clinical applicability and their implications for the design of future trials. Our review does not include studies on the basis of posttrial monitoring,28 trials with exclusively microvascular end points,29,30 or trials with intermediate or surrogate end points, such as blood pressure,31 brain natriuretic hormone in plasma,32 left ventricular mass,33 or the urinary albumin:creatinine ratio.34

Review of the Evidence

Table 1 summarizes the characteristics of the 6 reviewed trials, in which 74,524 patients were randomly assigned (range: 384516–19 to 25,62020–22). The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)20–22 and the Telmisartan Randomized Assessment Study in Angiotensin-Converting Enzyme (ACE) Intolerant Subjects With Cardiovascular Disease (TRANSCEND)20,27 were not running independently from each other but have to be viewed as 2 complementary studies within a single research program.20 The primary objectives of ONTARGET20–22 were to determine whether the combination of the angiotensin receptor blocker (ARB) telmisartan plus the ACE inhibitor ramipril was more effective in the prevention of cardiovascular and renal
Table 1. Characteristics of Trials

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ACCOMPLISH</th>
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<th>HYVET</th>
<th>ONTARGET</th>
<th>ONTARGET</th>
<th>PRoFEss</th>
<th>TRANSCEND</th>
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<td>NCT00145925</td>
<td>NCT00122811</td>
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<td>NCT00153062</td>
<td>NCT00153101</td>
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<td>Design Degree of blinding</td>
<td>Double</td>
<td>Double</td>
<td>Double</td>
<td>Double</td>
<td>Double</td>
<td>Double</td>
<td>Double</td>
</tr>
<tr>
<td>Primary end point</td>
<td>CVM + MI + A+</td>
<td>CVM + MI + S+</td>
<td>RCA + S</td>
<td>FS + S</td>
<td>CVM + MI + S + HF</td>
<td>FS + S</td>
<td>CVM + MI + S + HF</td>
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<tr>
<td>Sample size assumptions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Predicted/observed end points</td>
<td>1642/1231</td>
<td>2700/1799</td>
<td>420/120</td>
<td>3058/2835</td>
<td>3051/2798</td>
<td>2170/1814</td>
<td>1281/969</td>
</tr>
<tr>
<td>Predicted RRR, %</td>
<td>15</td>
<td>16</td>
<td>35</td>
<td>0</td>
<td>13</td>
<td>25</td>
<td>19</td>
</tr>
<tr>
<td>a/β levels</td>
<td>0.05/0.90</td>
<td>0.05/0.90</td>
<td>0.01/0.90</td>
<td>0.025/0.89*</td>
<td>0.05/0.93*</td>
<td>0.05/0.99</td>
<td>0.05/0.94</td>
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<tr>
<td>No. of randomized patients</td>
<td>11 506</td>
<td>11 140</td>
<td>3845</td>
<td>17 118</td>
<td>17 078</td>
<td>20 332</td>
<td>5926</td>
</tr>
<tr>
<td>Allocated reference/ intervention</td>
<td>5762/5744</td>
<td>5571/5569</td>
<td>1912/1933</td>
<td>8576/8542</td>
<td>8576/8502</td>
<td>10 186/10 146</td>
<td>2972/2954</td>
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<tr>
<td>Screened</td>
<td>13 782</td>
<td>12 877</td>
<td>4761</td>
<td>29 019</td>
<td>29 019</td>
<td>…</td>
<td>6666</td>
</tr>
<tr>
<td>Withdrawn/lost</td>
<td>1754/…</td>
<td>2916/15</td>
<td>1295/17</td>
<td>1059/34†</td>
<td>1599/34†</td>
<td>3687‡/125</td>
<td>1334/18</td>
</tr>
<tr>
<td>Study medication Reference (daily dose in milligrams)§</td>
<td>Benazepril + HCTZ (40 + 12.5 to 25.0)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Ramipril (10)</td>
<td>Ramipril (10)</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Intervention (daily dose in milligrams)§</td>
<td>Benazepril + amlodipine (40 + 5 to 10)</td>
<td>Perindopril + indapamide (2 to 4 + 0.625 to 1.250)</td>
<td>Indapamide, perindopril (1.5/2 to 4)</td>
<td>Telmisartan (80)</td>
<td>Ramipril + telmisartan (10 + 80)</td>
<td>Telmisartan (80)</td>
<td>Telmisartan (80)</td>
</tr>
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<td>Mean characteristics of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>68</td>
<td>66</td>
<td>83</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>SBP/DBP at entry, mm Hg</td>
<td>145/80</td>
<td>145/81</td>
<td>173/91</td>
<td>142/82</td>
<td>142/82</td>
<td>144/84</td>
<td>141/70</td>
</tr>
<tr>
<td>Gradient in SBP/DBP, mm Hg</td>
<td>0.9/1.1</td>
<td>5.6/2.2</td>
<td>15.0/6.1</td>
<td>0.9/0.6</td>
<td>2.4/1.4</td>
<td>3.8/2.0</td>
<td>4.0/2.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.0</td>
<td>28.0</td>
<td>24.7</td>
<td>28.1</td>
<td>28.1</td>
<td>26.8</td>
<td>28.1</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
<td>…</td>
<td>1.0</td>
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<tr>
<td>Blood glucose, mg/dL</td>
<td>127</td>
<td>153</td>
<td>…</td>
<td>121</td>
<td>121</td>
<td>…</td>
<td>117</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>184</td>
<td>201</td>
<td>205</td>
<td>189</td>
<td>191</td>
<td>…</td>
<td>197</td>
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<tr>
<td>Proportion of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>39.5</td>
<td>42.5</td>
<td>60.5</td>
<td>26.8</td>
<td>26.8</td>
<td>36.0</td>
<td>43.0</td>
</tr>
<tr>
<td>Hypertension at entry, treated</td>
<td>100.0 (97.2)</td>
<td>100.0 (98.7)</td>
<td>100.0 (64.7)</td>
<td>68.8 (…)</td>
<td>68.8 (…)</td>
<td>74.0 (…)</td>
<td>76.4 (…)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>11.3</td>
<td>15.1</td>
<td>6.5</td>
<td>12.4</td>
<td>12.7</td>
<td>21.2</td>
<td>9.8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>23.5</td>
<td>12.0</td>
<td>3.1</td>
<td>48.9</td>
<td>48.8</td>
<td>6.7</td>
<td>46.3</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>35.8</td>
<td>…</td>
<td>…</td>
<td>51.3</td>
<td>51.0</td>
<td>…</td>
<td>45.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>13.1</td>
<td>9.2</td>
<td>6.8</td>
<td>20.8§</td>
<td>21.0¶</td>
<td>100.0</td>
<td>22.0§</td>
</tr>
</tbody>
</table>

(Continued)
complications than ramipril alone and to test whether telmisartan was at least as effective as ramipril. This explains the dual entries for ONTARGET in Table 1. The online Data Supplement available at http://hyper.ahajournals.org provides detailed information on the research questions, methods, end points, and outcome results of the 6 reviewed trials over and beyond the information in Table 1 and the evidence reviewed below.

Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ACCOMPLISH</th>
<th>ADVANCE</th>
<th>HYVET</th>
<th>ONTARGET</th>
<th>ONTARGET</th>
<th>PRoFESS</th>
<th>TRANSCEND</th>
</tr>
</thead>
<tbody>
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<td>Diabetes mellitus</td>
<td>60.4</td>
<td>100.0</td>
<td>6.8</td>
<td>37.3</td>
<td>37.3</td>
<td>28.2</td>
<td>35.7</td>
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<td>Renal disease#</td>
<td>6.1</td>
<td>29.3</td>
<td>…</td>
<td>10.8</td>
<td>10.9</td>
<td>…</td>
<td>9.4</td>
</tr>
<tr>
<td>Mean or median follow-up, y</td>
<td>3.0</td>
<td>4.3</td>
<td>1.8</td>
<td>4.7</td>
<td>4.7</td>
<td>2.5</td>
<td>4.7</td>
</tr>
</tbody>
</table>

HCTZ indicates hydrochlorothiazide; RRR, relative risk reduction; SBP/DBP, systolic/diastolic blood pressure; …, the information was unavailable in published reports. End points: A indicates hospitalized angina pectoris; CVM, cardiovascular mortality; FS, fatal stroke; HF, hospitalized heart failure; MI, nonfatal myocardial infarction; MICVE, microvascular events; S, nonfatal stroke; RCA, resuscitated cardiac arrest. Major MICVE in ADVANCE were new or worsening nephropathy (development of macroalbuminuria (>300 mg/g of creatinine), doubling of serum creatinine to a level of ≥2.26 mg/dL (200 μmol/L), need for renal replacement therapy, or death because of renal disease) or retinopathy (development of proliferative retinopathy, macular edema, diabetes-related blindness, or retinal photoocoagulation therapy). Conversion factors: to convert values of serum creatinine to micromoles per liter, multiply by 88.4; to convert values of blood glucose to millimoles per liter, multiply by 0.05551; to convert values of serum total cholesterol to millimoles per liter, multiply by 0.02586.

Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial

European and American guidelines36,37 propose single-pill combinations of antihypertensive drugs as an option to initiate antihypertensive treatment. Whether thiazide diuretics should be included in the combination37 remains controversial. The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) Trial4–12 tested whether treatment with the combination of an ACE inhibitor and a dihydropyridine calcium-channel blocker (CCB) would be more efficacious in reducing cardiovascular events than treatment with an ACE inhibitor plus a thiazide. There were 552 primary-outcome events in the benazepril-amlodipine group (9.6%) and 679 in the benazepril-hydrochlorothiazide group (11.8%), representing a relative risk reduction with benazepril-amlodipine therapy of 19.6% (P < 0.001) but an absolute risk reduction of only 2.2%.

Over the whole duration of the ACCOMPLISH Trial, blood pressure was, on average, 0.9 mm Hg systolic and 1.1 mm Hg diastolic lower (P < 0.001) on the combination with amlodipine. Nevertheless, the ACCOMPLISH investigators proposed benefit “beyond blood pressure lowering.” None of the ACCOMPLISH reports4–12 provided precise information on the blood pressure course during the first 6 months after randomization, when study medications were up-titrated. Blood pressure gradients early in a trial produce Kaplan-Meier estimates that separate soon after randomization and result in persistent benefit for the group with the lower blood pressure, even if subsequent levels are similar across randomized groups.39 Other caveats are the dose40 and the duration of action40 of hydrochlorothiazide. At 12.5 to 25.0 mg/d, hydrochlorothiazide has only half of the blood pressure-lowering effect of amlodipine.
pressure–lowering potency of chlorthalidone. The daily dose of chlorthalidone in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial was 12.5 to 25.0 mg, which would correspond with 25.0 to 50.0 mg of hydrochlorothiazide. Moreover, chlorthalidone (plasma half-life: 60 hours) has a longer duration of action than hydrochlorothiazide (8 to 12 hours). In a randomized crossover trial with 8-week active-treatment periods, chlorthalidone (12.5 mg/d force-titrated to 25.0 mg/d) reduced the nighttime (13.5 versus −6.4 mm Hg; P=0.009) and, therefore, the 24-hour (12.4 versus −7.4 mm Hg; P=0.054) systolic blood pressure more than hydrochlorothiazide (25.0 mg force titrated to 50.0 mg). Amlodipine has a longer duration of action than hydrochlorothiazide, so that blood pressure control is maintained even if 1 daily dose of amlodipine is omitted. Thus, better blood pressure control over the whole day, not translated into a wide separation of the office blood pressure values after the initial titration period, might well explain the ACCOMPLISH results.

**Action in Diabetes and Vascular Disease: Preterax and Diamicron-Controlled Evaluation Trial**

The primary objective of the Action in Diabetes and Vascular Disease: Preterax and Diamicron-Controlled Evaluation Trial (ADVANCE) was to assess the effects of the routine administration of the combination of an ACE inhibitor and a diuretic on vascular events in patients with type 2 diabetes mellitus, irrespective of initial blood pressure levels or background therapies (Table 1).

Compared with patients assigned placebo, those assigned active therapy had a mean reduction in blood pressure of 5.6 mm Hg systolic and 2.2 mm Hg diastolic. There were 861 primary outcome events (macrovascular plus microvascular) in the active-treatment group (15.5%) and 938 in the placebo group (16.8%), resulting in a relative risk reduction by 9% (P=0.04). The separate reductions in macrovascular events (hazard ratio [HR]: 0.92; P=0.16) and microvascular events (HR: 0.91; P=0.16) were similar but nonsignificant. The HRs for all-cause mortality and for coronary events were 0.86 (P=0.03) and 0.86 (P=0.02), respectively. In terms of absolute benefit, the number of patients to be treated for 5 years amounted to 66 (95% CI: 34 to 1068), 79 (95% CI: 43 to 483), or 75 (95% CI: 41 to 453) to prevent 1 vascular event, 1 death, or 1 coronary accident, respectively.

The ADVANCE investigators concluded that the routine administration of a fixed combination of perindopril and indapamide to a broad range of patients with diabetes mellitus had reduced the risks of death and major macrovascular or microvascular complications, irrespective of the initial blood pressure level or ancillary treatment. They extrapolated that if the benefits seen in their trial were applied to just half of the population with diabetes worldwide, >1 million deaths would be avoided over 5 years. For these reasons, they suggested considering such treatment routinely for patients with type 2 diabetes mellitus. These extrapolations certainly need to be tuned down. Indeed, most of the systolic blood pressure gradient seen in the ADVANCE trial was caused by an increase in systolic blood pressure among patients receiving placebo (from 137 to 140 mm Hg) rather than by a decrease in systolic blood pressure among those in the active-treatment group (from 137 to 136 mm Hg). What clinicians should, therefore, remember from the ADVANCE Trial is not to stop antihypertensive therapy in diabetic patients but to intensify treatment until blood pressure control is reached. At entry, treatments were continued at the discretion of the responsible physician, with the exception of ACE inhibitors; participants taking an ACE inhibitor other than perindopril had this treatment withdrawn and were offered substitution with open-label perindopril at a dose of 2 or 4 mg/d. This procedure resulted in an increase in blood pressure at entry into the placebo group (see Figure 1 in Reference 14). Furthermore, ADVANCE did not prove that using combination therapy provides more benefit than the traditional approach of sequentially titrating, rotating, and combining antihypertensive agents of different classes. Finally, the CIs regarding the number of patient years of treatment required to prevent 1 event were wide.

**Prevention Regimen for Effectively Avoiding Second Strokes Trial**

The Prevention Regimen for Effectively Avoiding Second Strokes Trial (PROFESS) involved 20 332 patients who recently had an ischemic stroke. The median interval from stroke to randomization was 15 days. During a mean follow-up of 2.5 years, blood pressure was 3.8 mm Hg systolic and 2.0 mm Hg diastolic lower on telmisartan than on placebo (Table 1). A total of 880 patients (8.7%) in the telmisartan group and 934 patients (9.2%) in the placebo group had a subsequent stroke (HR for telmisartan versus placebo: 0.95; P=0.23). Major cardiovascular events occurred in 1367 patients (13.5%) in the telmisartan group and 1463 patients (14.4%) in the placebo group (HR: 0.94; P=0.11). In an analysis only involving 1141 strokes that occurred 6 months after randomization, stroke recurrence decreased by 12% (95% CI: 1% to 22%; P=0.04).

The PROFESS investigators proposed that randomization of patients soon after the qualifying event might explain the null results of their trial. However, the odds of stroke recurrence were similar in patients randomized within 10 days of the qualifying event (0.92; P=0.19) and in those randomized later (0.93; P=0.18). The P value for interaction was 0.84. In a 2×2 design, all patients randomized to telmisartan or placebo were also allocated antiplatelet drugs. Although the interaction between blood pressure–lowering and antiplatelet treatment was nonsignificant (P=0.35), the PROFESS investigators suggested that background treatment, including statins in 47.4% of patients at entry, might have contributed to the disappointing results of the blood pressure–lowering arm of their trial. The PROFESS results do not support the hypothesis that ARBs might be particularly beneficial in the prevention of stroke, because unopposed stimulation of type 2 or type 4 angiotensin receptors in the ischemic brain might stimulate opening of collaterals and increase neuronal resistance to anoxia.
combination of telmisartan with ramipril was superior to ramipril alone.

Noninferiority of Telmisartan Versus Ramipril
Compared with ramipril, blood pressure was 0.9/0.6 mm Hg lower on telmisartan. The primary outcome occurred in 1412 patients in the ramipril group (16.5%) as compared with 1423 patients in the telmisartan group (16.7%), resulting in an HR of 1.01 ($P=0.83$). The upper boundary of the CI (1.09) was significantly lower than the predefined noninferiority boundary of 1.13 ($P=0.004$; Figure 1). However, the lower boundary of the CI (0.94) indicated that telmisartan was not superior to ramipril. Cough (1.1% versus 4.2%; $P<0.001$) and angioedema (0.1% versus 0.3%; $P=0.01$) occurred less on telmisartan than ramipril, whereas the opposite was the case for hypotensive symptoms (2.6% versus 1.7%; $P<0.001$), but the rate of syncope was the same in the 2 groups (0.2%).

Some experts advocate that noninferiority studies have no ethical justification, because they do not offer any advantage to patients and because they disregard patient interest in favor of commercial incentives to promote new marketable products. Often the premise is that the new treatment might have an advantage, for instance, in terms of fewer adverse effects. That cough and angioedema would be less frequent on telmisartan than on ramipril was predictable and cannot justify the noninferiority approach. Furthermore, noninferiority means comparability within an arbitrary limit ($\Delta$), indicating the tolerable inferiority of the experimental drug versus the standard. There are no fixed rules to determine $\Delta$. In ONTARGET, $\Delta$ was set at the 40th percentile (0.794) of treatment effects in trials comparing outcome on ACE inhibitors versus placebo. This boundary translated into an excess risk for placebo as compared with ramipril of 1.26. A margin of 1.13 ($e^{(\ln(1.26)\times0.49)}$) ensured that telmisartan remained at least half of the effect of ramipril, if the upper limit of the 1-sided 97.5% CI for the HR was less than this value. Consolidated Standards of Reporting Trials guidelines recommend 2-sided tests (Figure 1), but a 1-sided 97.5% CI is equivalent to a 2-sided 95% CI. The significance level required to show noninferiority is open to question.

Telmisartan Plus Ramipril Versus Ramipril Alone
Compared with the ramipril group, blood pressure was 2.4 systolic and 1.4 mm Hg diastolic lower on telmisartan than on the combination. The primary outcome occurred in the combination-therapy group in 1386 patients (16.3%; HR 0.99; $P=0.38$). Hypotensive symptoms (4.8% versus 1.7%; $P<0.001$), syncope (0.3% versus 0.2%; $P=0.03$), and renal dysfunction (13.5% versus 10.2%; $P<0.001$) occurred more frequently on combination therapy. Total mortality was similar on telmisartan compared with ramipril (HR: 0.98; 95% CI: 0.90 to 1.07) but was slightly higher on combination therapy than on ramipril (HR: 1.07; 95% CI: 0.98 to 1.16). For the statement that analyses did not indicate significant differences with respect to any particular cause of death, no data were shown. The main ONTARGET report did not provide any information on the incidence of cancer, a predefined secondary outcome. However, in July

Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial
ONTARGET involved high-risk patients with coronary, peripheral arterial, or cerebrovascular disease or diabetic patients with end-organ damage (Table 1). The trial had 2 objectives (Table 1): to demonstrate the noninferiority of telmisartan compared with ramipril and to test whether the
Table 2. Combined Analyses of TRANSCEND and PRoFESS

<table>
<thead>
<tr>
<th>End Point/Trial</th>
<th>Placebo, n/N (%)</th>
<th>Telmisartan, n/N (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PRoFESS24</td>
<td>1463/10186 (14.4)</td>
<td>1367/10146 (13.5)</td>
<td>0.93 (0.86 to 1.01)</td>
<td>0.067</td>
</tr>
<tr>
<td>TRANSCEND27</td>
<td>504/2972 (17.0)</td>
<td>465/2954 (15.7)</td>
<td>0.91 (0.80 to 1.05)</td>
<td>0.205</td>
</tr>
<tr>
<td>Combined</td>
<td>1967/13158 (14.9)</td>
<td>1832/13100 (14.0)</td>
<td>0.93 (0.86 to 0.99)</td>
<td>0.026</td>
</tr>
<tr>
<td>Combined data ≤6 mo</td>
<td>492/13158 (3.7)</td>
<td>546/13100 (4.2)</td>
<td>1.12 (0.99 to 1.27)</td>
<td>0.075</td>
</tr>
<tr>
<td>Combined data &gt;6 mo</td>
<td>1475/12575 (11.7)</td>
<td>1286/12484 (10.3)</td>
<td>0.86 (0.80 to 0.94)</td>
<td>&lt;0.001</td>
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<tr>
<td>Cardiovascular death, myocardial infarction, stroke</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRoFESS24</td>
<td>1377/10186 (13.5)</td>
<td>1289/10146 (12.7)</td>
<td>0.93 (0.86 to 1.01)</td>
<td>0.086</td>
</tr>
<tr>
<td>TRANSCEND27</td>
<td>440/2972 (14.8)</td>
<td>384/2954 (13.0)</td>
<td>0.86 (0.74 to 1.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>Combined analyses</td>
<td>1817/13158 (13.8)</td>
<td>1673/13100 (12.8)</td>
<td>0.91 (0.85 to 0.98)</td>
<td>0.013</td>
</tr>
<tr>
<td>Combined data ≤6 mo</td>
<td>450/13158 (3.4)</td>
<td>502/13100 (3.8)</td>
<td>1.13 (0.99 to 1.28)</td>
<td>0.074</td>
</tr>
<tr>
<td>Combined data &gt;6 mo</td>
<td>1367/12616 (10.8)</td>
<td>1171/12526 (9.3)</td>
<td>0.85 (0.78 to 0.92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are No. of events/No. randomized (%) unless otherwise specified. This table was reproduced with permission from Reference 27.

2009, in a document submitted to the Food and Drug Administration, Boehringer Ingelheim reported significantly higher HRs for malignancies on the combination of ramipril plus telmisartan than on ramipril alone (for details and reference, see the online Data Supplement).

Renal Outcomes and Left Ventricular Hypertrophy

The secondary renal outcome, dialysis or doubling of serum creatinine, was similar in telmisartan and ramipril (2.21% versus 2.03%; HR: 1.09; P=0.42) but more frequent with combination therapy (2.49%; HR: 1.24; P=0.038).22 Estimated glomerular filtration rate declined less with ramipril compared with telmisartan or combination therapy (~2.82 versus ~4.12 or ~6.11 mL/min per 1.73 m², respectively; P<0.0001). Compared with ramipril, the increase after randomization in the urinary albumin:creatinine ratio (expressed in mg/mmol/L) was less with telmisartan (ratio of last observed versus baseline urinary albumin:creatinine ratio: 1.32 versus 1.25; P=0.033) or with combination therapy (1.32 versus 1.22; P=0.0028).22

In 23 165 ONTARGET patients with an ECG recorded at entry,50 the prevalence of electrocardiographic left ventricular hypertrophy51 at randomization was 12.5%. At 2 and 5 years of follow-up, left ventricular hypertrophy was slightly less frequent on telmisartan (odds ratio: 0.92; P=0.07) and the combination (odds ratio: 0.93; P=0.12) than on ramipril, but the between-group differences were not significant. A small substudy52 of 287 selected patients who underwent MRI at baseline and at 2 years was confirmatory. Decrease in systolic blood pressure was a key determinant (P<0.0001) of the change in left ventricular mass.52

Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease

Patients screened for enrollment in ONTARGET who could not tolerate ACE inhibitors were eligible for randomization in the double-blind TRANSCEND Trial.20,27

Stand-Alone Analysis of TRANSCEND

Compared with placebo, blood pressure was 4.0 mm Hg systolic and 2.2 mm Hg diastolic lower on telmisartan. Hypotensive symptoms were more frequent on telmisartan than on placebo (0.98% versus 0.54%; P=0.049).27 The primary outcome was the same as in ONTARGET21 and occurred in 465 patients (15.7%) of the telmisartan group and in 504 (17.0%) of the placebo group (HR: 0.92; P=0.22).27 The composite secondary end point defined as in HOPE1 occurred in 384 patients (13.0%) on telmisartan and in 440 patients (14.8%) randomized to placebo (HR: 0.76; 95% CI: 0.76 to 1.00).27 The unadjusted P value was 0.048. With adjustment for multiple comparisons and the 87% overlap with the primary end point, it was 0.068. A post hoc analysis involved the primary composite end point as defined in ADVANCE.13,14 It occurred less frequently with telmisartan than with placebo (17.7% versus 19.8%; HR: 0.89; P=0.049).27 There was also a trend in favor of telmisartan in the prevention of myocardial infarction (3.9% versus 5.0%; HR: 0.79; P=0.059).

The prevalence of electrocardiographic left ventricular hypertrophy51 at entry in the 5343 TRANSCEND patients with a baseline ECG was 12.7%.50 It was reduced by telmisartan (10.5% and 9.9% after 2 and 5 years) compared with placebo (12.7% and 12.8% after 2 and 5 years). The odds ratio for the total follow-up on telmisartan versus placebo was 0.79 (P=0.0017). Achieved systolic blood pressure was the main determinant of the incidence or regression of left ventricular hypertrophy during follow-up.50

Combination of TRANSCEND and PRoFESS

In analyses prespecified27 before the completion of PRoFESS24 and TRANSCEND,27 the TRANSCEND investigators pooled the results of these 2 trials (Table 2). In 26 258 randomized patients, the primary (P=0.026) and secondary (P=0.013) composite end points achieved borderline significance. In terms of absolute benefit, ~1000 patients would have to be treated for 1 year with telmisartan to prevent 3 to
4 composite events. While stratifying by time (Table 2), telmisartan had no effect within the first 6 months in both trials, but there was a clear benefit afterward. The PRoFESS report\(^{24}\) proposed noncompliance with the proportional hazards assumption as the justification for this post hoc analysis, which was carried out after inspection of the Kaplan-Meier curves (see Figure 1 in Reference 24). All outcome analyses involved a time-to-event approach and included all randomized patients.\(^{24}\) Thus, for the results from 6 months after randomization, patients who experienced an event earlier were censored at the time of the event and treated in the analysis as if no event had occurred. In PRoFESS alone,\(^{24}\) this approach excluded a total of 673 patients, who experienced stroke recurrence within the first 6 months of randomization.

In summary, combining the results of 2 selected trials does not comply with the principles of a systematic review. Significant \(P\) values in the time-stratified analyses were produced after having looked at the data. Finally, the PRoFESS\(^{24}\) and TRANSCEND\(^{27}\) results challenge the principles of a systematic review.

\[\text{Clinical Implications}\]

The clinical implications evolve mainly around 6 themes: generalizability of the results to the common patient with hypertension, benefit beyond blood pressure lowering in the protection of target organs, use of dual inhibition of the renin system with an ACE inhibitor and an ARB, and the prevention of stroke recurrence, coronary events, and new-onset diabetes mellitus.

\[\text{Generalizability}\]

To minimize the risk of null results at affordable costs, the recently published trials\(^{12,14,21,24,27}\) not only needed to be large and simple but they also required high event rates. The researchers, therefore, recruited high-risk patients with diabetes mellitus, target organ damage, or a previous history of cardiovascular disease (Table 1), whereas such patients were systematically excluded from the earlier generation of placebo-controlled trials\(^{4-7}\) and HYVET.\(^{18}\)

Table 1 lists the number of patients screened and randomized. The PRoFESS report provided no information on the number of patients screened. In ADVANCE,\(^{13,14}\) ONTARGET,\(^{20-22}\) and other trials of ACE inhibitors,\(^{48}\) ACE-intolerant and noncompliant patients were systematically excluded. The patients enrolled in TRANSCEND\(^{20,27}\) were all ACE intolerant, and those noncompliant or experiencing adverse effects when challenged with a daily dose of 80 mg of telmisartan did not qualify for entry. Obviously, results are only applicable to patients with similar characteristics as those enrolled in the trials.

\[\text{Beyond Blood Pressure}\]

Above age 50 years, hypertension is the major cardiovascular risk factor.\(^{53}\) Antihypertensive drugs reverse the risk by interfering with this risk indicator and must, therefore, confer benefit by lowering blood pressure. The relation between cardiovascular complications and blood pressure is continuous without threshold.\(^{54,55}\) Large-scale prospective observational studies\(^{54,55}\) and meta-regression analyses of randomized clinical trials demonstrated that small gradients in the systolic blood pressure can explain cardiovascular outcomes.\(^{56,57}\) This is not only true for stroke,\(^{54,55,58}\) the complication most directly linked to blood pressure, but also for myocardial infarction,\(^{54,55,58,59}\) heart failure,\(^{60}\) and left ventricular hypertrophy.\(^{50,52}\) In meta-regression analyses, 150 000\(^{59}\) to 180 000\(^{60}\) randomized patients, followed up for 3 to 5 years, were required to demonstrate 10% to 15% benefit beyond blood pressure lowering of newer antihypertensive drugs, such as CCBs and ACE inhibitors, in the prevention of stroke\(^{58,61}\) or myocardial infarction.\(^{58,59}\) respectively.

Using the meta-regression equations published in 2001,\(^{56}\) we assessed to what extent recently reported risk ratios differed from the odds of benefit as predicted by gradients in systolic blood pressure (Table 3). The end points considered were cardiovascular mortality, cardiovascular events as defined in HOPE (cardiovascular death plus nonfatal stroke and nonfatal myocardial infarction\(^{1}\)), fatal plus nonfatal stroke (or stroke recurrence in PRoFESS\(^{24}\)), and fatal and nonfatal myocardial infarction. The trials evaluated were ACCOMPLISH,\(^{12}\) ADVANCE,\(^{14}\) PRoFESS,\(^{24}\) ONTARGET,\(^{21}\) and TRANSCEND.\(^{27}\) In general, observed and predicted risks did not significantly differ \((P>0.10)\), indicating that blood pressure gradients are sufficient to explain the outcome results. Table 3 lists differences \((P<0.10)\) between predicted\(^{46}\) and observed risks.\(^{12,14,21,24,27}\) The composite cardiovascular end point was reduced less than predicted in ADVANCE\(^{14}\) and PRoFESS,\(^{24}\) partly because of a shortfall in the reduction of stroke\(^{14}\) or stroke recurrence.\(^{24}\) In ONTARGET,\(^{21}\) telmisartan did not reduce myocardial infarction, whereas in ACCOMPLISH\(^{12}\) the decrease in the composite cardiovascular end point was greater than predicted on the basis of the reported small gradient in systolic blood pressure.

\[\text{Dual Inhibition of the Renin System}\]

In ONTARGET,\(^{21,22,50,52}\) dual inhibition of the renin system with an ACE inhibitor and an ARB, despite a 2.4-mm Hg reduction in systolic blood pressure, did not result in better outcomes but increased adverse events. The ONTARGET results\(^{21,22,50,52}\) were in line with the combined effects of an ARB plus an ACE inhibitor, as compared with an ACE inhibitor alone, in 4 previous trials of patients with left ventricular dysfunction.\(^{62}\) The Combination of Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-Diabetic Renal Disease (COOPERATE) trial has recently been retracted from the published record and can no longer be used as evidence supporting dual inhibition of the renin system by the combination of an ACE inhibitor and an ARB (see the online Data Supplement). Whether these disappointing results would apply equally in terms of hard outcomes to the combination of an ARB with a renin inhibitor, such as aliskiren,\(^{63}\) still remains to be established. For now, there is only positive evidence for blood pressure\(^{31}\) and for soft intermediate endpen...
points in high-risk patients. Taken together, the currently available evidence suggests that dual inhibition of the renin system should only be sparingly and very carefully used in patients at high risk, in whom all drug combinations have been tried and who cannot be controlled by a single renin system inhibitor.

Prevention of Stroke Recurrence

For a better interpretation of the PRoFESS results, we combined the results of 10 trials (11 groups of randomized patients), using methods described in detail elsewhere. Overall, the odds ratio for the prevention of stroke recurrence by blood pressure–lowering therapy was 0.78 ($P=0.0007$; Figure 2). There was significant heterogeneity between studies. The pooled odds ratio was 0.63 ($P=0.0001$) for trials involving diuretics as a component of therapy but only 0.93 ($P=0.086$) for trials in which the mainstay of treatment consisted of inhibition of the renin system by atenolol, perindopril, ramipril, candesartan, or telmisartan. The weighted reduction in systolic blood pressure averaged 9.6 mm Hg in 4 studies of diuretics, 4.0 mm Hg in 6 studies of renin system inhibitors, and 5.1 mm Hg in all studies combined (Figure 2). In metaregression, the weighted correlation coefficient between the odds for stroke recurrence and the blood pressure reduction was $-0.57$ ($P=0.067$). The significant heterogeneity ($P<0.0001$) between diuretics and renin system inhibitors in the prevention of stroke recurrence might, therefore, be explained by the greater blood pressure reduction on treatments including diuretics.

In contrast to the recommendations in some guidelines, the above results do not support the use of renin system inhibitors for the prevention of stroke recurrence. Furthermore, lowering blood pressure in patients with a history of stroke and a normal blood pressure cannot be recommended, because the published results are contradictory. In the PROFESS Trial, 68 822 patients with a systolic pressure at entry of ≤ 135 mm Hg had an odds ratio for stroke recurrence on active treatment versus placebo of 1.04 (95% CI: 0.87 to 1.25; $P=0.63$). Similarly, in the TRANSCEND Trial, 27 1955 patients with a systolic pressure at entry of ≤ 133 mm Hg did not experience benefit from blood pressure–lowering therapy in terms of the primary and secondary composite end points. In contrast, the 913 Poststroke Antihypertensive Treatment Study patients, whose blood pressure at randomization was < 140 mm Hg systolic and 90 mm Hg diastolic, had on treatment with indapamide a 50% lower risk of stroke recurrence (95% CI: −74 to −4; $P=0.03$). 73

Prevention of Coronary Events

The TRANSCEND investigators claimed that the results of their trial, along with those of ONTARGET, should help to dispel concerns that ARBs might not reduce myocardial infarction. The results of TRANSCEND (HR versus placebo: 0.79; 95% CI: 0.62 to 1.01; $P=0.059$) and those of ONTARGET (HR versus ramipril: 1.07; 95% CI: 0.94 to 1.22; estimated $P=0.31$; see also Table 3) do not support this assertion. Several trials suggested that ARBs might protect less against coronary complications than placebo, a β-blocker (atenolol), 2 diuretics, or CCBs (amlodipine). A systematic review of 26 trials compared ACE inhibitors and ARBs with placebo or other drug classes. The prevention of myocardial infarction depended on the reduction in blood pressure for both types of renin system inhibitors, but ACE inhibitors apparently had a blood pressure–independent effect on the prevention of myocardial infarction, which was not present for ARBs (9% versus −8%; $P=0.002$). To our knowledge, a head-to-head comparison of ACE inhibitors versus ARBs for the primary prevention of myocardial infarction is

---

Table 3. Observed Odds Ratios and Odds Ratios Predicted by Between-Group Differences in Systolic Pressure in Trials of Blood Pressure–Lowering Therapies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trial</th>
<th>Patients, n</th>
<th>Events, n (%)</th>
<th>ΔSBP, mm Hg*</th>
<th>Observed Odds Ratio (95% CI)</th>
<th>Predicted Odds Ratio (95% CI)</th>
<th>$P_5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVM</td>
<td>TRANSCEND27</td>
<td>5926</td>
<td>450 (7.6)</td>
<td>4.0</td>
<td>1.03 (0.85 to 1.24)</td>
<td>0.83 (0.73 to 0.95)</td>
<td>0.066</td>
</tr>
<tr>
<td>CVE</td>
<td>ACCOMPLISH12</td>
<td>11 506</td>
<td>652 (5.7)</td>
<td>0.9</td>
<td>0.79 (0.68 to 0.92)</td>
<td>0.93 (0.85 to 1.02)</td>
<td>0.070</td>
</tr>
<tr>
<td>CVE</td>
<td>ADVANCE14</td>
<td>11 140</td>
<td>1000 (9.0)</td>
<td>5.6</td>
<td>0.92 (0.81 to 1.04)</td>
<td>0.74 (0.67 to 0.81)</td>
<td>0.007</td>
</tr>
<tr>
<td>CVE</td>
<td>PRoFESS24</td>
<td>20 332</td>
<td>2666 (13.1)</td>
<td>3.8</td>
<td>0.94 (0.87 to 1.02)</td>
<td>0.80 (0.74 to 0.86)</td>
<td>0.004</td>
</tr>
<tr>
<td>CVE</td>
<td>ONTARGET/combo21</td>
<td>17 078</td>
<td>2400 (14.1)</td>
<td>2.4</td>
<td>1.00 (0.93 to 1.09)</td>
<td>0.88 (0.81 to 0.95)</td>
<td>0.025</td>
</tr>
<tr>
<td>CVA</td>
<td>ADVANCE14</td>
<td>11 140</td>
<td>433 (3.9)</td>
<td>5.6</td>
<td>0.98 (0.81 to 1.18)</td>
<td>0.68 (0.62 to 0.75)</td>
<td>0.0007</td>
</tr>
<tr>
<td>CVA</td>
<td>PRoFESS24</td>
<td>20 332</td>
<td>1814 (8.9)</td>
<td>3.8</td>
<td>0.95 (0.86 to 1.04)</td>
<td>0.74 (0.63 to 0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>MI</td>
<td>ONTARGET/telmisartan21</td>
<td>17 118</td>
<td>853 (5.0)</td>
<td>0.9</td>
<td>1.07 (0.94 to 1.22)</td>
<td>0.93 (0.85 to 1.02)</td>
<td>0.084</td>
</tr>
<tr>
<td>MI</td>
<td>ONTARGET/combo21</td>
<td>11 140</td>
<td>851 (7.6)</td>
<td>2.4</td>
<td>1.08 (0.94 to 1.23)</td>
<td>0.89 (0.77 to 1.03)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*ΔSBP is the difference in systolic pressure (experimental minus control group) as defined in Table 1.
†Data show the observed risk (experimental/control) with 95% CI.
‡Data show the odds ratio (95% CI) predicted by metaregression.
§Data show significance of the difference between observed and predicted odds ratios.
Prevention of Diabetes Mellitus

A network meta-analysis evaluated the incidence of new-onset diabetes mellitus according to the drug class used to initiate blood pressure–lowering therapy (Figure 3).78 With diuretics as the comparator, the odds ratios were 0.57 (P<0.0001) for ARBs; 0.67 (P<0.0001) for ACE inhibitors; 0.75 (P=0.002) for CCBs; 0.77 (P=0.009) for placebo; and 0.90 (P=0.30) for β-blockers. In a prospective observational study of hypertensive patients (median follow-up: 6 years), not confounded by previous treatment, new-onset diabetes mellitus and having diabetes mellitus already at baseline carried similar cardiovascular risk. However, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (follow-up: 4.9 years41,79), the Valsartan Antihypertensive Long-Term Use Evaluation Trial (4.2 years80), and the Anglo-Scandinavian Cardiac Outcomes Trial (5.5 years76) did not report a significantly elevated risk in patients with new-onset diabetes mellitus. Assuming an absolute risk of 10% over 5 years on older drugs and a relative benefit on the newer drugs of 30% (Figure 3), 1000 patients would have to be treated for 1 year with the newer agents to avoid 6 iatrogenic cases of diabetes mellitus. Important caveats in the interpretation of this estimate are that, in most trials included in the network meta-analysis, new-onset diabetes mellitus was not a predefined end point; that follow-up was relatively short; and that, in some trials, the comparator was a diuretic41 or β-blocker.76

In PROFESSION24 and TRANSCEND,27 diabetes was a predefined secondary end point, and the comparator was placebo. In PROFESSION,24 the number of patients who had new-onset diabetes after randomization was 125 of 7360 (1.7%) in the telmisartan group, as compared with 151 of 2149 (7.0%) in the valsartan group. The number of patients who had new-onset diabetes mellitus was significantly lower in the telmisartan group, with an absolute risk difference of 5.3% (95% confidence interval, 4.0% to 6.5%; P<0.001). The rate of new-onset diabetes mellitus was lower in the telmisartan group in both the per-protocol (27 of 7360 [0.4%]) and the intention-to-treat (39 of 7360 [0.5%]) analyses.

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Figure 2. Effects of blood pressure lowering on fatal and nonfatal recurrent stroke. Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. Horizontal lines and diamonds denote the 95% CIs for individual trials and summary statistics, respectively. Pooled estimates were computed from a random-effect model in case of significant heterogeneity and otherwise from fixed-effect models. The vertical dotted line marks the position of the point estimate of the pooled effect size for all trials combined. TIA indicates transient ischemic attack. BP and ΔBP stand for the average blood pressure at randomization and the difference in achieved blood pressure between randomized groups. The individual studies were as follows: Carter’s trial64; the Hypertension-Stroke Cooperative Study (HSCG)65; the Dutch TIA Trial66; the Tenormin After Stroke Trial (TEST)67; the Poststroke Antihypertensive Treatment Study (PATS)68; the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)-Monotherapy (PROGRESS/Per) and combined therapy (PROGRESS/Com) arms; the HOPE study70; Study on Cognition and Prognosis in the Elderly (SCOPE);71 the Felodipine Event Reduction Study (FEVER)72; and the PRoFESS trial.24 For Carter’s trial,64 the blood pressure at randomization was estimated by adding 10 and 5 mm Hg to the qualifying systolic and diastolic levels at entry. Reproduced with permission from Reference 73.
the evidence from recent trials does not change the estimates on the basis of PRoFESS and TRANSCEND. Thus, placebo, did not reduce the incidence of diabetes mellitus as compared with 245 (12.8%) of 1913 in the placebo group (HR: 0.85; 95% CI: 0.71 to 1.02; \( P = 0.081 \)). Estimates on the basis of PROGRESS and TRANSCEND indicate that 1000 patients would need to be treated for 1 year with an ARB instead of a metabolically neutral drug (placebo) to prevent just 2 cases of new-onset diabetes mellitus. However, in both trials, the HRs for new-onset diabetes mellitus cannot be excluded. In the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication Trial, the use of ramipril \( \leq 15 \) mg/d, compared with placebo, did not reduce the incidence of diabetes mellitus among patients with impaired fasting glucose levels. Thus, the evidence from recent trials does not change the conclusion from a systematic review published in 2005 that, currently, no single (antihypertensive) agent can be recommended for the prevention of diabetes mellitus.

**Perspectives**

Without usable and accessible reports, research cannot help clinicians and their patients. Consolidated Standards of Reporting Trials experts might reflect on new guidelines on how changes in a targeted risk factor should be reported in relation to the outcome of interest. In particular, how should blood pressure gradients be reported in trials claiming organ protection beyond blood pressure lowering. Should it be the baseline-adjusted between-group difference between the measurement at the last available visit or before an event, as in the Losartan Intervention for Endpoint Reduction Trial, or should all blood pressure measurements in each patients be accounted for? Blood pressure readings taken shortly before an event are likely to be influenced by the upcoming end point. How can we avoid the fact that blood pressure gradients early in a clinical trial are concealed by over-scaling of graphics? Figure 3 in the Valsartan Antihypertensive Long-Term Use Evaluation report provide examples of how full information can be provided. None of the beyond blood pressure trials reported on the quality of the blood pressure measurements. Digit and number preference in the blood pressure readings were monitored in HYVET and led to the closure of centers not keeping up minimal quality standards. Development and application of more accurate blood pressure measurement technologies, for example, observer bias–free measurements with minimized white-coat effect in the hospital environment or self-measurement combined with telemonitoring, might be envisaged in future trial designs.

With regard to the interpretation of clinical trials, Consolidated Standards of Reporting Trials guidelines (http://www.consort-statement.org) require that the results be discussed taking into account possible sources of bias or imprecision, the dangers associated with the multiplicity of outcomes, and the generalizability (external validity). Biases arise when different stakeholders, including the manufacturers of marketable drugs, assign their own values to the design and interpretation of clinical trials. Sponsors and investigators tend to look for what they would like to see. Overinterpretation of nonsignificant or marginal \( P \) values in large trials with overlapping end points, generalizing beyond selection criteria, and labeling nonsignificant treatment effects as modest do necessarily comply with Consolidated Standards of Reporting Trials guidelines. Clinicians might read such small benefits as effects sufficiently large to change their prescriptions, so that patients might not receive the best possible treatment. Recently, Califf et al made recommendations for how to increase transparency and how to reconcile commercial with societal interests. Among other things, they suggested that long-term efforts should be made to house master databases of clinical trials and their statistical exploitation at nonprofit institutions, for which the primary mission is acting for the common good rather than returning value to shareholders. Perhaps the time has come to revise the concept of large simple trials and to pursue research questions that serve patient care more than showing noninferiority or highlighting the ancillary qualities of marketable antihypertensive drugs.

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Short title: Trials of Blood pressure Lowering Drugs

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Review of the Evidence

Table S1 summarizes the characteristics of the 6 reviewed trials, in which 74,524 patients were randomized (range: 3845 to 25,620). The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)\(^1\-^3\) and the Telmisartan Randomized Assessment Study in Angiotensin-Converting Enzyme (ACE) Intolerant Subjects With Cardiovascular Disease TRANSCEND\(^1\,^4\) were not running independently from each other, but have to be viewed as 2 complementary studies within a single research program.\(^1\) The primary objectives of ONTARGET\(^1\-^3\) were to determine whether the combination of the angiotensin receptor blocker (ARB) telmisartan plus the angiotensin-converting enzyme (ACE) inhibitor ramipril was more effective in the prevention of cardiovascular and renal complications than ramipril alone, and to test whether telmisartan was at least as effective as ramipril. This explains the dual entries for ONTARGET in Table S1.

HYVET

The Hypertension in the Very Elderly Trial (HYVET) was a primary prevention trial, set up with the goal to extend the indication for blood pressure lowering treatment to very elderly hypertensive patients (≥80 years), of whom only 11.8% had a history of previous cardiovascular disease.\(^5\-^8\) The patients were randomized to the diuretic indapamide (sustained release, 1.5 mg/d) or matching placebo. If necessary to achieve a target blood pressure below 150 mm Hg systolic and 80 mm Hg diastolic, the ACE inhibitor perindopril (2 or 4 mg/d), or matching placebo, was added. The primary end point was fatal plus nonfatal stroke.

At 2 years, the blood pressure was on average 15.0 mm Hg systolic and 6.1 mm Hg diastolic lower on active treatment than on placebo.\(^7\) In the intention-to-treat analysis, blood pressure lowering reduced the incidence of complications: fatal combined with nonfatal stroke by 30% (95% confidence interval [CI]: −1 to 51; \(P=0.06\)), fatal stroke by 39% (CI: 1 to 62; \(P=0.05\)), all-cause mortality by 21% (CI: 4 to 35; \(P=0.02\)), cardiovascular mortality by 23% (CI: −1 to 40; \(P=0.06\)), and heart failure by 64% (CI: 42 to 78; \(P<0.001\)). To prevent one death or one stroke, 40 and 94 very elderly had to be treated for 2 years.\(^7\)

ACCOMPLISH

The main research question of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial (ACCOMPLISH)\(^9\-^13\) was whether treatment with the combination of an ACE inhibitor and a dihydropyridine calcium-channel blocker (CCB) would be more effective in reducing cardiovascular events than treatment with an ACE inhibitor plus a thiazide. All 11,506 patients (>55 years\(^11\)) had hypertension and were at high cardiovascular risk, because of a history of hospitalized unstable angina (11.6%), myocardial infarction (23.5%), coronary revascularization (35.8%), stroke (13.0%), renal disease (6.1%), an estimated glomerular filtration of less than 60 mL/min (18.1%), left ventricular hypertrophy (13.2%), or diabetes mellitus (60.4%). Hypertension was a systolic blood pressure of at least 160 mm Hg or the use of antihypertensive drugs.

Patients began treatment with either a combination of 20 mg of benazepril and 5 mg of amlodipine or a combination of 20 mg of benazepril and 12.5 mg of hydrochlorothiazide, once daily. In both treatment groups, 1 month after randomization, the daily dose of benazepril was doubled to 40 mg. Thereafter, investigators could increase the amlodipine dose to 10 mg/d and increase the hydrochlorothiazide dose to 25 mg/d, if necessary, to attain a target blood pressure of less than 140/90 mm Hg (or less than 130/80 mm Hg in patients with diabetes or renal disease). Mean blood pressure after dose adjustment was 131.6/73.3 mm Hg in the benazepril-amlodipine group (n=5463) and 132.5/74.4 mm Hg in the benazepril-hydrochlorothiazide group (n=5474). The mean difference in blood pressure between the 2 groups was 0.9 mm Hg systolic and 1.1 mm Hg diastolic (\(P<0.001\) for both systolic and diastolic blood pressures). Blood pressure control was attained in 75.4% of patients of the benazepril-amlodipine group and in 72.4% of patients of the benazepril-hydrochlorothiazide group.
The primary end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. There were 552 primary outcome events in the benazepril-amlodipine group (9.6%) and 679 in the benazepril-hydrochlorothiazide group (11.8%), representing an absolute risk reduction with benazepril-amlodipine therapy of 2.2% and a relative risk reduction of 19.6% (hazard ratio [HR]: 0.80; CI: 0.72 to 0.90; \( P < 0.001 \)). All components of the primary end point with the exception of resuscitation after sudden cardiac arrest, had HRs of around 0.80, but statistical significance was reached only for fatal combined with nonfatal myocardial infarction (HR: 0.78; CI: 0.62 to 0.99; \( P = 0.04 \)) and for coronary revascularization (HR: 0.86; CI: 0.74 to 1.00; \( P = 0.05 \)). For the secondary end point of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke (the primary end point in the Heart Outcomes Prevention Evaluation study [HOPE]14), the HR was 0.79 (CI: 0.67 to 0.92; \( P = 0.002 \)).

**ADVANCE**

The primary objective of the Action in Diabetes and Vascular disease: preterAx and diamicronN-Controlled Evaluation trial (ADVANCE) was to assess the effects of the routine administration of the combination of an ACE inhibitor and a diuretic on vascular events in patients with type-2 diabetes, irrespective of the initial blood pressure levels or the use of other blood pressure lowering drugs (Table S1).15,16 Potentially eligible participants entered a 6-week prerandomization period, during which they received once daily a fixed combination tablet containing 2 mg perindopril and 0.625 mg indapamide. All other treatments were continued at the discretion of the responsible physician, with the exception of ACE inhibitors; participants taking an ACE inhibitor other than perindopril had this treatment withdrawn and were offered substitution with open-label perindopril at a dose of 2 mg/d or 4 mg/d. Patients who adhered to, and tolerated, the open-label study medication were randomized in a double-blind fashion to the combination of 2 mg perindopril plus 0.625 mg indapamide or matching placebo. The dose of the study medication was doubled 3 months after randomization. The primary end points were composites of major macrovascular and microvascular events. The macrovascular and microvascular composite end points were analyzed jointly and separately. Major macrovascular events were cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Major microvascular events were new or worsening nephropathy (development of macroalbuminuria, doubling of serum creatinine to a level of at least 200 μmol/L, need for renal replacement therapy, or death due to renal disease) or retinopathy (development of proliferative retinopathy, macular edema, diabetes-related blindness, or the need for retinal photocoagulation therapy).16

The mean duration of follow-up was 4.3 years (Table S1). The mean blood pressure at entry was 145 mm Hg systolic and 81 mm Hg diastolic. The entry blood pressure was less than 140 mm Hg systolic and 90 mm Hg diastolic in 41.0% of patients. Compared with patients assigned placebo, those assigned active therapy had a lower blood pressure during follow-up. The difference averaged 5.6 mm Hg systolic and 2.2 mm Hg diastolic. There were 861 primary outcome events (macrovascular plus microvascular) in the active treatment group (15.5%) and 938 in the placebo group (16.8%). The HR for active vs placebo treatment was 0.91 (CI: 0.83 to 1.00; \( P = 0.04 \)). The separate reductions in macrovascular and microvascular events were similar, but on their own did not reach significance. The HR was 0.92 (CI: 0.81 to 1.04; \( P = 0.16 \)) for macrovascular end points and 0.91 (CI: 0.80 to 1.04; \( P = 0.16 \)) for microvascular events. In the active treatment group, 211 cardiovascular deaths occurred (3.8%) and in the placebo group 257 (4.6%), resulting in a HR of 0.82 in favor of active treatment (CI: 0.68 to 0.98; \( P = 0.03 \)). With respect to all-cause mortality, 408 (7.3%) and 471 (8.5%) deaths occurred on active treatment and placebo, respectively, resulting in a HR of 0.86 (CI: 0.75 to 0.98; \( P = 0.03 \)). On active treatment, as compared with placebo, there was a reduced risk of coronary events (468 vs 535; 8.4% vs 9.6%; HR: 0.86; CI: 0.76 to 0.98; \( P = 0.02 \)). According to the ADVANCE investigators, there was no evidence that the effects of the study treatment differed by initial blood pressure level or concomitant use of other treatments at baseline. In terms of absolute benefit, the number of patients to be treated for 5 years amounted to 66 (CI: 34 to 1068), 79 (CI: 43 to 483), or 75 (CI: 41 to 453) to prevent one vascular event, one death, or one coronary accident, respectively.16
**PRoFESS**

The Prevention Regimen For Effectively avoiding Second Strokes trial (PRoFESS)\(^{17-20}\) compared in a double-blind fashion telmisartan (80 mg/d) with placebo, given on top of usual treatment (Table S1). PRoFESS involved 20,332 patients who recently had an ischemic stroke. The time from stroke to randomization was 10 days or less among 8087 patients (39.8%), 11 to 30 days among 5887 patients (29.0%), and more than 30 days among 6314 patients (31.1%). The median interval was 15 days. To be eligible patients had to have at least 2 of the following risk factors: diabetes mellitus, hypertension (blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic), smoking, a body mass index larger than 30 kg/m\(^2\), hyperlipidemia, previous vascular disease, or target organ damage.\(^{17}\) The primary outcome was stroke recurrence. Secondary outcomes were major cardiovascular events (death from cardiovascular causes, recurrent stroke, myocardial infarction, or new or worsening heart failure), and new-onset diabetes.

During a mean follow-up of 2.5 years, blood pressure was 3.8 mm Hg systolic and 2.0 mm Hg diastolic lower on telmisartan than on placebo (Table S1). A total of 880 patients (8.7%) in the telmisartan group and 934 patients (9.2%) in the placebo group had a subsequent stroke (HR for telmisartan: 0.95; CI: 0.86 to 1.04; \(P=0.23\)).\(^{18}\) Major cardiovascular events occurred in 1367 patients (13.5%) in the telmisartan group and 1463 patients (14.4%) in the placebo group (HR: 0.94; CI: 0.87 to 1.01; \(P=0.11\)).

The number of patients who had new-onset diabetes after randomization was 125 of 7360 (1.70%) in the telmisartan group, as compared with 151 of 7283 (2.08%) in the placebo group (HR: 0.82; CI: 0.65 to 1.04; \(P=0.10\)).\(^{18}\)

In an analysis only involving 1141 strokes that occurred 6 months after randomization, stroke recurrence decreased by 12% (CI: 1% to 22%; \(P=0.04\)).\(^{18}\) Furthermore, the odds of stroke recurrence were similar in patients randomized within 10 days of the qualifying event (0.92; CI: 0.81 to 1.04; \(n=8087; \ P=0.19\)) and in those randomized later (0.93; CI: 0.84 to 1.03; \(n=12,201; \ P=0.18\)). The \(P\)-value for interaction was 0.84.\(^{18}\) At entry, 47.4% of PRoFESS patients were taking statins. In a 2 × 2 design, all patients randomized to telmisartan or placebo were also allocated antiplatelet drugs (25 mg aspirin plus 200 mg extended-release dipyridamole, twice daily, vs 75 mg clopidogrel, once daily).\(^{20}\) The interaction between blood pressure lowering and antiplatelet treatment was nonsignificant (\(P=0.35\)).

**ONTARGET**

The ONTARGET trial\(^{1-3}\) involved high-risk patients with coronary, peripheral arterial or cerebrovascular disease or diabetic patients with target organ damage (Table S1). The primary outcome in ONTARGET\(^{1-3}\) was the composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure. The main secondary outcome was a composite of death from cardiovascular causes, myocardial infarction or stroke, which had been the primary end point in the HOPE trial.\(^{14}\) The ONTARGET trial had 2 objectives (Table S1): to demonstrate the noninferiority of telmisartan compared with ramipril and to test whether the combination of telmisartan with ramipril was superior to ramipril alone. After a 3-week, single-blind run-in period, patients underwent double-blind randomization, with 8576 assigned to receive 10 mg of ramipril per day, 8542 assigned to receive 80 mg of telmisartan per day, and 8502 assigned to receive both drugs (combination therapy).\(^2\) A high proportion of the 25,620 randomized patients had previously received statins (61.6% at baseline, changing to 70.6% by the end of the study), antiplatelet therapy (from 80.9% to 77.5%), \(\beta\)-blockers (from 56.9% to 56.9%), or diuretics (from 28.0% to 32.5%).\(^2\)

Median follow-up was 56 months (Table S1).\(^2\) The blood pressure at entry averaged 142/81 mm Hg. Compared with the ramipril group, blood pressure was 0.9/0.6 mm Hg lower on telmisartan and 2.4/1.4 mm Hg lower on the combination. The primary outcome occurred in 1412 patients in the ramipril group (16.5%), as compared with 1423 patients in the telmisartan group (16.7%; HR: 1.01; CI: 0.94 to 1.09).\(^2\) The upper boundary of the CI (1.09) for the relative risk of the primary outcome in the telmisartan group as compared with the ramipril group was significantly lower than the predefined noninferiority boundary of 1.13 (\(P=0.004\)). However, the lower boundary of the CI (0.94) indicated that telmisartan was not superior to ramipril.\(^2\) As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs 4.2%; \(P<0.001\)) and angioedema (0.1% vs 0.3%; \(P=0.01\)) and a higher
rate of hypotensive symptoms (2.6% vs 1.7%; \(P<0.001\)), but the rate of syncope was the same in the 2 groups (0.2%).

In the combination therapy group, the primary outcome occurred in 1386 patients (16.3%; HR: 0.99; CI: 0.92 to 1.07). On the combination, as compared with ramipril, there was an increased risk of hypotensive symptoms (4.8% vs 1.7%; \(P<0.001\)), syncope (0.3% vs 0.2%; \(P=0.03\)), and renal dysfunction (13.5% vs 10.2%; \(P<0.001\)).\(^{2}\) The results for the main secondary outcome, defined as in HOPE,\(^{14}\) were similar to those of the primary outcome. Total mortality was similar in telmisartan compared with ramipril (989 vs 1014 deaths; HR: 0.98; CI: 0.90 to 1.07), but higher in the combination therapy group than in the ramipril group (1065 vs 1014 deaths; HR: 1.07; CI: 0.98 to 1.16), but the difference did not reach statistical significance (\(P=0.11\)).

The secondary renal outcome, dialysis or doubling of serum creatinine, was similar on telmisartan and ramipril (2.21% vs 2.03%; HR: 1.09; CI: 0.89 to 1.34; \(P=0.42\)), but more frequent with combination therapy (2.49%; HR: 1.24; CI: 1.01 to 1.51; \(P=0.038\)).\(^{3}\) Estimated glomerular filtration rate declined less with ramipril compared with telmisartan or combination therapy (\(-2.82\) vs \(-4.12\) or \(-6.11\) ml/min/1.73 m\(^2\), respectively; \(P<0.0001\)).\(^{2}\) Compared with ramipril, the increase after randomization in the urinary albumin:creatinine ratio (UACR), expressed in mg/mmol/L, was less with telmisartan (ratio of last observed vs baseline UACR: 1.32 vs 1.25; \(P=0.033\)) or with combination therapy (1.32 vs 1.22; \(P=0.0028\)).\(^{3}\)

In ONTARGET\(^{21}\) and TRANSCEND,\(^{4}\) electrocardiographic left ventricular hypertrophy (yes/no) was based on one or both of the following criteria: (1) sum of the R wave in lead aVL and the S wave in lead V\(_2\) less than 2.0 mV in women or 2.4 mV in men; or (2) strain pattern in I, II, aVL, or V\(_2\) to V\(_6\). A strain pattern was considered to be present, if there was ST-segment depression of at least 0.5 mm and an inverted T wave in any lead in the direction opposite the polarity of the QRS complex.\(^{21}\) This definition of electrocardiographic left ventricular hypertrophy has been validated in terms of outcome.\(^{22}\) In ONTARGET patients with an electrocardiogram recorded at entry, the prevalence of left ventricular hypertrophy at randomization to ramipril (n=7781), telmisartan (n=7773) or the combination (n=7651) was 12.5%, 12.5% and 12.4%, respectively.\(^{21}\) The prevalence of left ventricular hypertrophy decreased (\(P<0.001\) for all) on ramipril (10.8% and 10.5% at 2 and 5 years), telmisartan (10.0% and 9.7%), and the combination (9.9% and 10.2%). Left ventricular hypertrophy showed a nonsignificant trend to be less frequent with telmisartan than with ramipril (odds ratio [OR]: 0.92; CI: 0.83 to 1.01; \(P=0.07\)). The odds of left ventricular hypertrophy during follow-up were also nonsignificantly lower with the combination compared with ramipril (OR: 0.93; CI: 0.84 to 1.02; \(P=0.12\)). There was no differences in the odds of left ventricular hypertrophy between the telmisartan group and the combination therapy group (OR: 1.01; CI: 0.91 to 1.12).\(^{21}\) A small substudy\(^{23}\) involved 287 patients who underwent MRI at baseline and after 2 years (90, 100, and 97 patients in the ramipril, telmisartan, and combination therapy groups, respectively). The results\(^{23}\) confirmed those of the electrocardiographic study.\(^{21}\) At 2 years, left ventricular mass showed average decreases of 4.8% on ramipril, 3.3% on telmisartan, and 5.8% on combination therapy (\(P<0.0001\) for all).\(^{23}\) There were no significant differences among treatment groups in change in left ventricular mass or in any other cardiac measurement on MRI, except for left ventricular mass indexed to height\(^{2.7}\) for combination therapy vs telmisartan (\(P=0.04\)). When the 3 treatment groups were combined, the key determinants of the decrease in left ventricular mass were the baseline value (slope: 0.126; \(P=0.0001\)), decrease in systolic blood pressure (slope: 0.039 g/m\(^2\).7/mm Hg; \(P<0.0001\)), and history of hypertension (\(P=0.03\)).\(^{23}\)

In July of 2009, Boehringer Ingelheim presented a detailed briefing document about telmisartan to the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration.\(^{24}\) In this document, the sponsor noted imbalances in malignancies in both ONTARGET\(^{21}\) and TRANSCEND.\(^{4}\) In ONTARGET,\(^{21}\) the hazard for malignancies was significantly higher for the combination of telmisartan plus ramipril than ramipril alone, regardless of the presence of malignancies at baseline (824 [9.7%] vs 735 [8.6%]; HR: 1.14; CI: 1.03 to 1.26)).

**TRANSCEND**

Patients screened for enrollment in ONTARGET, who could not tolerate ACE inhibitors (n=6666), entered a 3-week single-blind run-in period involving placebo for 1 week followed by telmisartan 80
mg/d. Of those patients who terminated the run-in period without showing poor compliance or side-effects, 5926 (88.9%) were randomized in a double-blind fashion to receive telmisartan 80 mg/d (n=2954) or placebo (n=2972).

Median follow-up was 56 months (Table S1). The blood pressure at entry averaged 141/70 mm Hg. Compared with placebo, blood pressure was 4.0 mm Hg systolic and 2.2 mm Hg diastolic lower on telmisartan. Hypotensive symptoms were more frequent on telmisartan than on placebo (0.98% vs 0.54%; P=0.049). The primary outcome was the same as in ONTARGET. It occurred in 465 patients (15.7%) of the telmisartan group and in 504 (17.0%) of the placebo group (HR: 0.92; CI: 0.81 to 1.05; P=0.22). The composite secondary end point, defined as in HOPE, occurred in 384 patients (13.0%) on telmisartan and in 440 patients (14.8%) randomized to placebo (HR: 0.76; CI: 0.76 to 1.00). The unadjusted P-value was 0.048. With adjustment for multiple comparisons and the 87% overlap with the primary end point, it was 0.068. In the telmisartan group, 894 patients (30.3%) were hospitalized for a cardiovascular reason, compared with 980 (33.0%) on placebo (HR: 0.92; CI: 0.85 to 0.99; P=0.025).

A post-hoc analysis involved the primary composite end point, as defined in ADVANCE, which included both macrovascular and microvascular events. It occurred less frequently with telmisartan than with placebo (523 [17.7%] vs 587 [19.8%]; HR: 0.89; CI: 0.79 to 1.00; P=0.049). There was a trend favoring telmisartan compared with placebo in the prevention of myocardial infarction (116 [3.9%] vs 147 [5.0%] events; HR: 0.79; CI: 0.62 to 1.01; P=0.059). Total mortality (364 [12.3%] vs 349 [11.7%] deaths; HR: 1.05; CI: 0.91 to 1.22; P=0.49) and cardiovascular mortality (227 [7.7%] vs 223 [7.5%] deaths; HR: 1.03; CI: 0.85 to 1.24; P=0.78) were similar on telmisartan and placebo. New-onset diabetes mellitus was a predefined secondary outcome. The number of patients who had a clinical diagnosis of new-onset diabetes was 209 of 1895 (11.0%) in the telmisartan group, as compared with 245 of 1913 (12.8%) in the placebo group (HR: 0.85; CI: 0.71 to 1.02; P=0.081).

The prevalence of electrocardiographic left ventricular hypertrophy at entry in TRANSCEND was 12.7%. It was reduced by telmisartan (n=2688; 10.5% and 9.9% after 2 and 5 years) compared with placebo (n=2655; 12.7% and 12.8% after 2 and 5 years). The OR for the total follow-up on telmisartan vs placebo was 0.79 (CI: 0.68 to 0.91; P=0.0017). New-onset left ventricular hypertrophy occurred less frequently with telmisartan as compared with placebo (OR: 0.63; CI: 0.51 to 0.79; P=0.0001). The average reduction in systolic blood pressure from entry to follow-up was greater in the patients without than in those with incident left ventricular hypertrophy (4.8 vs 1.8 mm Hg; P<0.0001). In the TRANSCEND patients with electrocardiographic left ventricular hypertrophy at randomization, the frequency of regression was similar on telmisartan and placebo (OR: 0.91; CI: 0.70 to 1.19; P=0.49). In this subgroup, the reduction in systolic blood pressure at follow-up was greater in patients with regression than in those with persistent left ventricular hypertrophy (6.8 vs 3.9 mm Hg; P<0.0001).

In TRANSCEND, the risk of malignancies in patients without cancer at baseline (95% of all patients) was significantly higher for telmisartan than placebo (206 [7.3%] vs 169 [6.0%]; HR: 1.24; CI: 1.01 to 1.52).

COOPERATE

The Combination of Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-Diabetic Renal Disease (COOPERATE) trial involved 263 patients with non-diabetic renal disease enrolled at a single Japanese center. They were randomized to an ARB (losartan, 100 mg/d), an ACE inhibitor (trandolapril, 3 mg/d), or their combination. The primary end point was time to doubling of the serum creatinine concentration or end-stage renal disease. Ten of 85 patients on combination treatment (11%) reached the composite primary endpoint compared with 20 of 85 patients on trandolapril alone (23%; HR: 0.38; CI: 0.18 to 0.63; P=0.018), and 20 of 86 patients on losartan alone (23%; HR: 0.40; CI: 0.17 to 0.69; P=0.016). Side effects occurred with similar frequencies in the 3 randomized groups. According to the COOPERATE investigators, combination treatment safely slowed progression of nondiabetic renal disease compared with monotherapy. However, while attempting to include the COOPERATE data in a meta-analysis, Kunz and colleagues identified several inconsistencies in the published report. An institutional review board then audited the COOPERATE results. The Lancet Editors recently reviewed the conclusions of this investigation and concluded that the COOPERATE trial had to be retracted from the published literature.
References


**TABLE S1 (starts). Characteristics of Trials**

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<tr>
<td><strong>Intervention (daily dose in mg)§</strong></td>
<td>benazepril +amlodipine (40+5 to 10)</td>
<td>perindopril +indapamide (2 to 4+0.625 to 1.250)</td>
<td>indapamide perindopril (80)</td>
<td>telmisartan (80)</td>
<td>ramipril +telmisartan (10+80)</td>
<td>telmisartan (80)</td>
<td>telmisartan (80)</td>
</tr>
</tbody>
</table>

(Continued)
### TABLE S1. Characteristics of Trials (Continued)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ACCOMPLISH</th>
<th>ADVANCE</th>
<th>HYVET</th>
<th>ONTARGET</th>
<th>ONTARGET</th>
<th>PROFESS</th>
<th>TRANSCEND</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean characteristics of patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68</td>
<td>66</td>
<td>83</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>SBP/DBP at entry (mm Hg)</td>
<td>145/80</td>
<td>145/81</td>
<td>173/91</td>
<td>142/82</td>
<td>142/82</td>
<td>144/84</td>
<td>141/70</td>
</tr>
<tr>
<td>Gradient in SBP/DBP (mm Hg)</td>
<td>0.9/1.1</td>
<td>5.6/2.2</td>
<td>15.0/6.1</td>
<td>0.9/0.6</td>
<td>2.4/1.4</td>
<td>3.8/2.0</td>
<td>4.0/2.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.0</td>
<td>28.0</td>
<td>24.7</td>
<td>28.1</td>
<td>28.1</td>
<td>26.8</td>
<td>28.1</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
<td>...</td>
<td>1.0</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>127</td>
<td>153</td>
<td>...</td>
<td>121</td>
<td>121</td>
<td>...</td>
<td>117</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>184</td>
<td>201</td>
<td>205</td>
<td>189</td>
<td>191</td>
<td>...</td>
<td>197</td>
</tr>
<tr>
<td><strong>Proportion of patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>39.5</td>
<td>42.5</td>
<td>60.5</td>
<td>26.8</td>
<td>26.8</td>
<td>36.0</td>
<td>43.0</td>
</tr>
<tr>
<td>Hypertension at entry (treated)</td>
<td>100.0 (97.2)</td>
<td>100.0 (68.7)</td>
<td>100.0 (64.7)</td>
<td>68.8 (...)</td>
<td>68.8 (...)</td>
<td>74.0 (...)</td>
<td>76.4 (...)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>11.3</td>
<td>15.1</td>
<td>6.5</td>
<td>12.4</td>
<td>12.7</td>
<td>21.2</td>
<td>9.8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>23.5</td>
<td>12.0</td>
<td>3.1</td>
<td>48.9</td>
<td>48.8</td>
<td>6.7</td>
<td>46.3</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>35.8</td>
<td>...</td>
<td>...</td>
<td>51.3</td>
<td>51.0</td>
<td>...</td>
<td>45.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>13.1</td>
<td>9.2</td>
<td>6.8</td>
<td>20.8§</td>
<td>21.0¶</td>
<td>100.0</td>
<td>22.0§</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>60.4</td>
<td>100.0</td>
<td>6.8</td>
<td>37.3</td>
<td>37.3</td>
<td>28.2</td>
<td>35.7</td>
</tr>
<tr>
<td>Renal disease#</td>
<td>6.1</td>
<td>29.3 a</td>
<td>...</td>
<td>10.8</td>
<td>10.9</td>
<td>...</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>Mean or median follow-up (years)</strong></td>
<td>3.0</td>
<td>4.3</td>
<td>1.8</td>
<td>4.7</td>
<td>4.7</td>
<td>2.5</td>
<td>4.7</td>
</tr>
</tbody>
</table>

**Abbreviations:**  
HCTZ = hydrochlorothiazide; RRR = relative risk reduction; SBP/DBP = systolic/diastolic blood pressure; ..., the information was unavailable in published reports.

**End points:**  
A, hospitalized angina pectoris; CVM, cardiovascular mortality; FS, fatal stroke; HF, hospitalized heart failure; MI, nonfatal myocardial infarction; MICVE, microvascular events; S, nonfatal stroke; RCA, resuscitated cardiac arrest. Major MICVE in ADVANCE were new or worsening nephropathy (development
of macroalbuminuria (>300 mg/g creatinine), doubling of serum creatinine to a level of ≥2.26 mg/dL (200 μmol/L), need for renal replacement therapy, or death due to renal disease) or retinopathy (development of proliferative retinopathy, macular edema, or diabetes-related blindness, or retinal photocoagulation therapy).

**Conversion factors:** To convert values of serum creatinine to micromoles per liter, multiply by 88.4; to convert values of blood glucose to millimoles per liter, multiply by 0.05551; to convert values of serum total cholesterol to millimoles per liter, multiply by 0.02586.

*Data show a 1-sided $P$-value to test noninferiority (telmisartan vs ramipril) and a 2-sided $P$-value to test superiority (telmisartan plus ramipril vs ramipril alone).

†All but 43 ONTARGET patients were followed up until the end of study or until a primary event.

‡Withdrawals among 14,842 patients at the 2-year follow-up visit.

§A plus sign indicates combination therapy and a backward slash addition of a second study drug.

¶Data show the baseline-adjusted difference in the on-treatment blood pressure (reference minus intervention group).

#Definition of renal disease is as follows: ACCOMPLISH, serum creatinine >1.5 mg/dL (133 μmol/L) in women or >1.7 mg/dL (150 μmol/L) in men or presence of macroalbuminuria (>300 mg/g creatinine or in the presence of an ACE inhibitor or aldosterone receptor blocker >200 mg/g creatinine); ADVANCE, macroalbuminuria (>300 mg/g creatinine) or microalbuminuria (30 to 300 mg/g creatinine); ONTARGET, PRoFESS, and TRANSCEND, microalbuminuria (30 to 300 mg/g creatinine).