Cardiovascular Protection With Antihypertensive Drugs in Dialysis Patients
Systematic Review and Meta-Analysis

Rajiv Agarwal, Arjun D. Sinha

Abstract—Epidemiological studies demonstrate that a lower blood pressure and decline in blood pressure over months or years are associated with higher mortality in dialysis patients. In contrast, randomized, controlled trials lack power to establish benefits of antihypertensive therapy. Patients on long-term dialysis participating in randomized, controlled trials and receiving antihypertensive drug therapy were the subject of this meta-analysis. Outcomes assessed were the hazard ratio of cardiovascular events and all-cause mortality in treated group compared with controls. Among 1202 patients who we identified in 5 studies, the overall benefit of antihypertensive therapy compared with the control or placebo group had a combined hazard ratio for cardiovascular events of 0.69 (95% CI: 0.56 to 0.84) using a fixed-effects model and 0.62 (95% CI: 0.45 to 0.86) using a random-effects model. In a sensitivity analysis, we found that the hypertensive group had a pooled hazard ratio of 0.49 (95% CI: 0.35 to 0.67), but when normotensives were included in the trial, lesser cardiovascular protection was seen (pooled hazard ratio of 0.86 [95% CI: 0.67 to 1.12]). Test for heterogeneity between hypertensive and “normotensive-included” groups was significant ($P < 0.006$). Similar results were seen for risk ratio for death and cardiovascular events. There was evidence of publication bias based on Egger’s test and funnel plot. Randomized trials suggested a benefit of antihypertensive therapy among hemodialysis patients. Adequately powered randomized trials are required to confirm these observations, especially among those with hypertension. (Hypertension. 2009;53:860-866.)

Key Words: systematic review ▪ cardiovascular events ▪ reverse epidemiology ▪ hypertension ▪ hemodialysis ▪ treatment

Hypertension is the third most important cause of global burden of disease in the general population. It trails only childhood and maternal underweight and unsafe sex to account for 64 million disability adjusted life-years and 4.4% of the global disease burden.1 This cardiovascular risk factor was first recognized in cohort studies2 and later supported by clinical trials.3 The vexing observation made by epidemiological studies in hemodialysis patients suggest that low, not high, blood pressure is associated with all-cause mortality.4–9 On the basis of this reverse epidemiology paradox, some have cautioned against lowering blood pressure in patients with hypertension who are on long-term hemodialysis.8

In the last 5 years, several randomized trials have tested the notion of whether antihypertensive therapy based on a variety of antihypertensive drugs, including β-blockers,9 angiotensin-converting enzyme inhibitors,10 and angiotensin receptor blockers,11,12 as well as dihydropyridine calcium channel blockers,13,14 can prevent cardiovascular events. However, these trials have been small, and effect size estimates have sometimes crossed the hazard ratio of 1 to yield statistically insignificant results.

Another important issue that has become evident is that blood pressures obtained before and after dialysis, which are most often used for medical decision-making, may be of limited value in determining the true blood pressure, as measured by interdialytic ambulatory blood pressure monitoring.16 Indeed, current studies often rely solely on blood pressures obtained in the dialysis unit.10–13 Because antihypertensive therapy on average lowers blood pressure in dialysis patients, it may be better to examine the impact of antihypertensive therapy on outcomes rather than examining the extent of blood pressure lowering. Most patients who are treated with antihypertensive drugs have at least some degree of hypertension, and, in fact, most studies deliberately, and rightly so, exclude patients with symptomatic hypotension or very low blood pressure.10–13 However, it is unclear whether the effect estimates may be influenced by inclusion of patients who are not hypertensive on hemodialysis, as has been deliberately done in 3 studies.10–12 The goal of this systematic review was to determine the presence and the magnitude of benefit in treating hemodialysis patients with antihypertensive drugs.

Received December 16, 2008; first decision January 2, 2009; revision accepted February 10, 2009.

From the Division of Nephrology, Department of Medicine, Indiana University School of Medicine (R.A., A.D.S.); and Richard L. Roudebush Veterans’ Affairs Medical Center (R.A.), Indianapolis, Ind.

Correspondence to Rajiv Agarwal, VAMC, 111N, 1481 West 10th St, Indianapolis, IN 46202. E-mail ragarwal@iupui.edu

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Hypertension is available at http://hyper.ahajournals.org DOI: 10.1161/HYPERTENSIONAHA.108.128116
Methods

Data Sources
We searched the PubMed (January 1996 to October 2008) database and the Cochrane Central Register of Controlled Trials (third quarter 2008). The terms “hypertension” and “dialysis” were searched in the title, original title, abstract, MESH headings, heading words, and key word. The result was limited to randomized, controlled trials using a highly sensitive filter. A similar search was performed in EMBASE. To be included in this review, studies had to randomize hemodialysis patients to antihypertensive drugs regardless of the presence or absence of hypertension and to report cardiovascular and/or mortality outcomes. In addition to the above search, we manually reviewed references cited in the retrieved articles and review articles. We also searched the proceedings of the American Society of Nephrology and European Dialysis and Transplantation Association to retrieve unpublished studies.

All of the data were abstracted with a standardized data collection form. From each article included, we abstracted the study design, year, number of included patients, age, cardiovascular event rate and death rate, and treatment characteristics, including the type of drug and duration of use.

Statistical Analysis
Hazard ratios recorded in the reports were log transformed. The SE of these log hazard ratios were calculated from the 95% CIs. Using the inverse of the SE of these hazard ratios, we pooled the hazard ratios between studies with a fixed-effects model. For the sake of comparison, random-effects models are also reported. We used Forest plots to visualize the extent of variation between studies and the I² statistic to quantify heterogeneity between studies. I² values, which range from 0% to 100%, describe the proportion of variation in prevalence estimates that is attributed to between-study variation rather than to sampling error. We obtained the group-specific and overall I² as standard output of the “metan” program. We conducted a sensitivity analysis to test the influence of hypertension status (studies with hypertensive patients only versus those studies that also year, number of included patients, age, cardiovascular event rate and death rate, and treatment characteristics, including the type of drug and duration of use.

Table. Characteristics of Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>BP Medication</th>
<th>Design</th>
<th>Exposure, mo</th>
<th>Normotensives Included</th>
<th>Vintage, y</th>
<th>Age</th>
<th>N</th>
<th>BP Baseline</th>
<th>BP Final</th>
<th>LV Mass Index, g/m²</th>
<th>Deaths</th>
<th>CV Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zannad et al¹¹</td>
<td>2006</td>
<td>Fosinopril</td>
<td>DBRCT</td>
<td>24</td>
<td>Yes</td>
<td>5.3</td>
<td>67</td>
<td>196</td>
<td>146/77</td>
<td>139/76</td>
<td>179</td>
<td>52</td>
<td>67</td>
<td>LVH required for randomization</td>
</tr>
<tr>
<td>Takahashi et al¹²</td>
<td>2006</td>
<td>Candesartan</td>
<td>PROBE</td>
<td>36</td>
<td>Yes</td>
<td>2.74</td>
<td>60</td>
<td>43</td>
<td>153/82</td>
<td>149/80</td>
<td>143.3</td>
<td>0</td>
<td>7</td>
<td>Excluded patients with CVD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nothing</td>
<td>Average exposure</td>
<td>19.4</td>
<td></td>
<td>2.77</td>
<td>62</td>
<td>37</td>
<td>152/85</td>
<td>153/83</td>
<td>152.4</td>
<td>7</td>
<td>17</td>
<td>Primary prevention trial</td>
</tr>
<tr>
<td>Suzuki et al¹³</td>
<td>2008</td>
<td>ARBs</td>
<td>Randomized open</td>
<td>36</td>
<td>No</td>
<td>3.7</td>
<td>59</td>
<td>180</td>
<td>154/81</td>
<td>140/80</td>
<td>25</td>
<td>34</td>
<td>34</td>
<td>Treatment and outcomes not masked</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nothing</td>
<td></td>
<td></td>
<td></td>
<td>3.7</td>
<td>60</td>
<td>180</td>
<td>156/82</td>
<td>140/78</td>
<td>38</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cice et al¹⁰</td>
<td>2003</td>
<td>Carvedilol</td>
<td>DBRCT for 12 mo, then open label</td>
<td>24</td>
<td>Yes</td>
<td>7.1</td>
<td>55</td>
<td>58</td>
<td>134/75</td>
<td>120/70</td>
<td>30</td>
<td>17</td>
<td></td>
<td>Dilated cardiomyopathy required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td>6.8</td>
<td>55</td>
<td>56</td>
<td>135/75</td>
<td>135/76</td>
<td>41</td>
<td>39</td>
<td></td>
<td>All patients on ACE inhibitors or ARBs</td>
</tr>
<tr>
<td>Tepel et al¹⁴</td>
<td>2008</td>
<td>Amlodipine</td>
<td>DBRCT</td>
<td>19</td>
<td>No</td>
<td>2.3</td>
<td>60</td>
<td>123</td>
<td>140/80</td>
<td>130/unchanged</td>
<td>15</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td>1.9</td>
<td>62</td>
<td>128</td>
<td>141/80</td>
<td>140/unchanged</td>
<td>22</td>
<td>32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DBRCT indicates double-blind, randomized, controlled trial; BP, blood pressure; PROBE, prospective randomized, open-label, blinded end point; CV, cardiovascular; CVD, cardiovascular disease; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NA, not available.
Results

A total of 195 studies were obtained from our search, of which 6 studies in adults on hemodialysis were initially identified for this analysis.10–15 One study published in abstract form several years ago was not included in this meta-analysis, given that, despite positive results, the study had not been published. However, inclusion of this study did not materially influence the outcome of this meta-analysis. The causes of exclusion are shown in Figure 1.

The total number of hemodialysis subjects from all of the studies was 1202, and the range of subjects per study was 80 to 397. The study characteristics are shown in the Table.

The hazard ratios for cardiovascular events from the individual studies ranged from 0.29 to 0.93 (Figure 2). No study had a point estimate that suggested harm with treatment. The overall benefit of antihypertensive therapy had a combined hazard ratio of 0.69 (95% CI: 0.56 to 0.84) using an inverse-weighted fixed-effects model and 0.62 (95% CI: 0.45 to 0.86) using a random-effects model. There was substantial heterogeneity between studies with respect to outcomes ($I^2$: 50.4%; $P = 0.073$).

We also calculated the risk ratios for cardiovascular events from the individual studies, which ranged from 0.35 to 1.15 (Figure 3). Based on data provided by the senior author, 1 study had an unadjusted risk ratio estimate that suggested harm with treatment.11 Takahashi et al12 studied primary prevention, whereas Suzuki et al13 and Tepel et al14 did not exclude patients with previous cardiovascular events.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Hazard Ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Death Cardiovascular (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zannad</td>
<td>2006</td>
<td>397</td>
<td>0.93 (0.68, 1.27)</td>
<td>42.48</td>
<td>25.9</td>
</tr>
<tr>
<td>Cice</td>
<td>2003</td>
<td>114</td>
<td>0.76 (0.47, 1.22)</td>
<td>17.76</td>
<td>62.3</td>
</tr>
<tr>
<td>Takahashi-NT</td>
<td>2006</td>
<td>15</td>
<td>0.29 (0.03, 2.78)</td>
<td>0.79</td>
<td>26.7</td>
</tr>
<tr>
<td>I-V Subtotal ($I^2 = 0.0%$, $p = 0.497$)</td>
<td></td>
<td></td>
<td>0.86 (0.67, 1.12)</td>
<td>61.03</td>
<td></td>
</tr>
<tr>
<td>D+L Subtotal</td>
<td></td>
<td></td>
<td>0.86 (0.67, 1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suzuki</td>
<td>2008</td>
<td>360</td>
<td>0.51 (0.33, 0.79)</td>
<td><strong>21.21</strong></td>
<td>17.5</td>
</tr>
<tr>
<td>Tepel</td>
<td>2008</td>
<td>251</td>
<td>0.53 (0.31, 0.92)</td>
<td>13.39</td>
<td>14.7</td>
</tr>
<tr>
<td>Takahashi-HT</td>
<td>2006</td>
<td>65</td>
<td>0.29 (0.11, 0.77)</td>
<td>4.37</td>
<td>30.8</td>
</tr>
<tr>
<td>I-V Subtotal ($I^2 = 0.0%$, $p = 0.551$)</td>
<td></td>
<td></td>
<td>0.49 (0.35, 0.67)</td>
<td>38.97</td>
<td></td>
</tr>
<tr>
<td>D+L Subtotal</td>
<td></td>
<td></td>
<td>0.49 (0.35, 0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensives only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity between groups: $p = 0.006$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-V Overall ($I^2 = 50.4%$, $p = 0.073$)</td>
<td></td>
<td></td>
<td>0.69 (0.56, 0.84)</td>
<td><strong>100.00</strong></td>
<td></td>
</tr>
<tr>
<td>D+L Overall</td>
<td></td>
<td></td>
<td>0.62 (0.45, 0.86)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Forest plot shows the hazard ratios of antihypertensive therapy on cardiovascular events. When studies were divided based on inclusion of normotensive subjects, it was found that those studies that included normotensive subjects did not consistently demonstrate cardiovascular protection, whereas those that included only hypertensive subjects provided significant protection. The test for interaction based on the grouping variable of presence or absence of normotension was significant ($P = 0.006$). There was still significant heterogeneity between studies in hypertensive hemodialysis patients only. This may be because of study design. For example, Takahashi et al12 studied primary prevention, whereas Suzuki et al13 and Tepel et al14 did not exclude patients with previous cardiovascular events.

Included those with normotension) using the metan command of Stata 10.1 (Stata Corp). Publication bias was tested with an Egger’s test19 and the funnel plot20 using metabias and metafunnel programs, respectively, in Stata. Using the metainf program, sensitivity analysis was carried out by excluding 1 trial at a time from pooled effects to determine whether any one study was particularly influential.

<table>
<thead>
<tr>
<th>Antihypertensive therapy of benefit</th>
<th>Antihypertensive therapy harmful</th>
</tr>
</thead>
<tbody>
<tr>
<td>.1</td>
<td>.25</td>
</tr>
<tr>
<td>.5</td>
<td>.75</td>
</tr>
<tr>
<td>1.25</td>
<td>1</td>
</tr>
<tr>
<td>.1</td>
<td>.25</td>
</tr>
<tr>
<td>.5</td>
<td>.75</td>
</tr>
<tr>
<td>1.25</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 3. Earthquake plot shows the risk ratios of antihypertensive therapy on cardiovascular events. When studies were divided based on inclusion of normotensive subjects, it was found that those studies that included normotensive subjects did not consistently demonstrate cardiovascular protection, whereas those that included only hypertensive subjects provided significant protection. The test for interaction based on the grouping variable of presence or absence of normotension was significant ($P = 0.006$). There was still significant heterogeneity between studies in hypertensive hemodialysis patients only. This may be because of study design. For example, Takahashi et al12 studied primary prevention, whereas Suzuki et al13 and Tepel et al14 did not exclude patients with previous cardiovascular events.

Heterogeneity between groups: $p = 0.006$

I-V Overall ($I^2 = 50.4\%$, $p = 0.073$)
D+L Overall

Antihypertensive therapy of benefit
Antihypertensive therapy harmful

862 Hypertension May 2009

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Patients who were normotensive. Cice et al\textsuperscript{10} also had a higher prevalence of left ventricular hypertrophy and excluded patients with symptomatic heart failure. The heterogeneity in hazard ratios is not unexpected, given the differing study designs and populations. The heterogeneous design of these studies is evident from examination of the Table. For example, Zannad et al\textsuperscript{11} required the presence of left ventricular hypertrophy, Cice et al\textsuperscript{10} required symptomatic dilated cardiomyopathy, and Takahashi et al\textsuperscript{12} required an absence of cardiovascular disease for participation in their trials. Zannad et al\textsuperscript{11} had 159 (40\%) of 397 of the patients who were normotensive. Cice et al\textsuperscript{10} required symptomatic dilated cardiomyopathy, whereas the Zannad et al\textsuperscript{11} study was conducted in hemodialysis patients with left ventricular hypertrophy and excluded patients with symptomatic heart failure.

The heterogeneity in hazard ratios is not unexpected, given the differing study designs and populations. The heterogeneous design of these studies is evident from examination of the Table. For example, Zannad et al\textsuperscript{11} required the presence of left ventricular hypertrophy, Cice et al\textsuperscript{10} required symptomatic dilated cardiomyopathy, and Takahashi et al\textsuperscript{12} required an absence of cardiovascular disease for participation in their trials. Zannad et al\textsuperscript{11} had 159 (40\%) of 397 of the patients who were normotensive. Cice et al\textsuperscript{10} also had a substantial but uncertain number of normotensive patients. When studies were divided based on inclusion of normotensive subjects in the randomized group, there was considerable heterogeneity noted between groups (\(P=0.006\) for hazard ratio and \(P=0.029\) for risk ratio of cardiovascular events, but not for all-cause mortality). Although the hypertensive-only group had a pooled hazard ratio of 0.49 (95\% CI: 0.35 to 0.67), the “normotensive-included” group had a pooled hazard ratio of 0.86 (95\% CI: 0.67 to 1.12). Similarly, the hypertensive group had a pooled risk ratio of cardiovascular events of 0.55 (95\% CI: 0.42 to 0.73), and the normotensive-included group had a pooled risk ratio of 0.84 (95\% CI: 0.66 to 1.06).

There was moderate heterogeneity in all-cause mortality between trials (\(I^2 : 50.2\%; \ P=0.09\)), but this was not explained (\(P>0.2\) for group effect) by inclusion or exclusion of normotensive subjects (Figure 4). All-cause mortality was reduced significantly when calculated by the fixed-effects model (risk ratio: 0.79 [95\% CI: 0.65 to 0.96]) but not when estimated by the random-effects model (risk ratio: 0.77 [95\% CI: 0.56 to 1.04]).

The Egger’s publication bias plot showed bias with standardized effect size with a hazard ratio of \(-4.04\) (95\% CI: \(-8.20\) to 0.11; \(P=0.05\)). The funnel plot indicates that studies that may have demonstrated increased hazards with low precision may not have been published (Figure 5).

Performing the meta-analysis after including the unpublished study\textsuperscript{15} did not materially alter the results. Sensitivity analysis to detect undue influence of any 1 study did not reveal the presence of any such evidence.

**Discussion**

In patients on hemodialysis, cohort studies have nearly universally noted an increased risk of mortality with low or declining blood pressure, thus calling into question the wisdom of lowering blood pressure in hemodialysis patients.\textsuperscript{4,6–8} More recently, Tentori et al\textsuperscript{21} reported that achieving the guideline recommended targets in hemodialysis patients was associated with increased mortality. However, some studies have suggested the benefit of blood pressure lowering on longer-term follow up,\textsuperscript{22} which suggests that the instantaneous hazard of mortality may vary with time in this complex group of patients.\textsuperscript{23} However, most studies noted...
above did not distinguish between the benefits of deliberate lowering of blood pressure with antihypertensive drugs versus spontaneous lowering because of intercurrent illnesses.\(^9,24\) Thus, the true benefit or risk of blood pressure lowering is uncertain in this group of patients.

Randomized, controlled trials are the gold standard to establish cause-and-effect relationships. However, when addressing the issue of hypertension in hemodialysis patients, these trials are small and often underpowered. Pooling these estimates may, therefore, yield insights that may offer evidence for controlling hypertension in this population with very high cardiovascular mortality. This meta-analysis pooled the results of 5 published trials to yield effect estimates that suggest a benefit of blood pressure lowering. Repeating the meta-analysis after including the 1 unpublished trial\(^15\) did not materially change the results.

The major finding of this meta-analysis is that the overall benefit of antihypertensive therapy compared with the control (or placebo) group reduced the combined hazard ratio for cardiovascular events by 31% using a fixed-effects model and by 38% using a random-effects model. There was substantial heterogeneity between studies with respect to outcomes. However, when studies were divided based on inclusion of normotensive subjects in the randomized group, it explained most of between-study variance. Heterogeneity between normotensive and hypertensive groups was highly statistically significant (\(P = 0.006\)). Although the hypertensive group had a pooled hazard ratio of 0.49 (95% CI: 0.35 to 0.67), the normotensive group had a pooled hazard ratio of 0.86 (95% CI: 0.67 to 1.12). In fact, even all-cause mortality, an outcome most commonly measured in the observational studies, was not increased with treatment.

The 2 studies that included normotensive patients had quite different study designs compared with those that included only hypertensive patients. The study of Cice et al\(^10\) included symptomatic patients with dilated cardiomyopathy on hemodialysis to address the question of whether treatment with carvedilol would reduce echocardiographic left ventricular dimensions at 1 year; the cardiovascular event rate was a secondary end point. The study of Zannad et al\(^11\) also included those patients who did not become hypotensive on receiving lisinopril between 5 and 20 mg during a run-in period before double-blind randomization. Thus, the question that Zannad et al\(^11\) addressed was whether high-risk hemodialysis patients with left ventricular hypertrophy would benefit from angiotensin-converting enzyme inhibition. Takahashi et al,\(^12\) at our request, provided data stratified by hypertension status. Our meta-analysis suggests that patients with hypertension on hemodialysis may benefit from blood pressure lowering unlike what is suggested by observational studies.

Drugs blocking the renin-angiotensin system may have benefits beyond blood pressure lowering. Similarly, \(\beta\)-blockers may have cardioprotective effects other than their...
effects on blood pressure lowering. Whether the benefits of the antihypertensive drugs used in hemodialysis patients were because of their blood pressure–lowering effects or because of nonhemodynamic actions is difficult to ascertain, because blood pressure was not carefully assessed by ambulatory or home blood pressure monitoring in any of the studies reported. Similarly, the definitions of normotensive and hypertensive categories were as reported by the authors and not by rigorous assessment of interdialytic blood pressures.

A limitation of this meta-analysis is the presence of publication bias. As can be seen from the funnel plot (and supported by the Eggers test), low precision studies with effect estimates that did not show benefit were notably missing. This limitation can be overcome by designing well-powered and executed randomized trials. The trials discussed in this review did not specifically target a lower blood pressure. Although lowering of blood pressure was seen in many trials, we do not know the level to which blood pressure should be lowered in hemodialysis patients. None of these trials used out-of-dialysis unit blood pressure monitoring, which may be better to evaluate the extent of blood pressure lowering. Whether the outcome benefits observed in this meta-analysis were attributable to blood pressure lowering or some nonhemodynamic effects of these drugs is also unclear. This meta-analysis suggests that the presence or absence of hypertension should be considered in designing future randomized trials. Given the limited number of studies, one cannot be certain whether normotensive patients will derive benefits of antihypertensive therapy, should a large trial be performed.

**Perspectives**

The results of this meta-analysis may have therapeutic implications, because patients with hypertension and hemodialysis may not be treated based on current observational studies. Our meta-analysis suggests that these concerns may be misplaced. When therapy is based on blood pressures before and after hemodialysis treatment, it is possible that patients may be suboptimally untreated or treated too aggressively. A simple yet effective strategy and one supported by the American Heart Association is to monitor home blood pressures to assess blood pressure control. Home blood pressure monitoring can improve the achievement of blood pressure targets, has been directly (not inversely) associated with hard outcomes in hemodialysis patients, and, in a clinical trial in hemodialysis patients, is associated with improved blood pressure control. Unfortunately, none of the randomized antihypertensive trials discussed in this review have used ambulatory or home blood pressure–guided antihypertensive therapy. Future trials that use out-of-dialysis unit blood pressure monitoring to direct antihypertensive therapy may better demonstrate the benefit of lowering blood pressure in this high-risk population. The assessment of left ventricular mass and function will further refine cardiovascular risk assessment and the management of hypertension. Until these trials are done, collective evidence from randomized trials suggests that hypertension should be treated among hypertensive patients on hemodialysis.

**Source of Funding**
This work was supported by a grant from the National Institutes of Health (5RO1-DK062030-05).

**Disclosures**
None.

**References**


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*Hypertension*. 2009;53:860-866; originally published online March 9, 2009; doi: 10.1161/HYPERTENSIONAHA.108.128116

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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