Design of Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D)

Linda F. Fried,* William Duckworth,† Jane Hongyuan Zhang,‡ Theresa O’Connor,‡ Mary Brophy,§ Nicholas Emanuele,¶ Grant D. Huang,‖ Peter A. McCullough,** Paul M. Palevsky,* Stephen Seliger,†† Stuart R. Warren,‡‡ and Peter Peduzzi,‡ for VA NEPHRON-D Investigators

*Veterans Affairs (VA) Pittsburgh Healthcare System and Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; †Carl T. Hayden VA Medical Center, School of Life Sciences, Arizona State University, and Department of Medicine, University of Arizona, Phoenix, Arizona, ‡West Haven VA Cooperative Studies Program Coordinating Center, West Haven, Connecticut; §VA Boston Healthcare System and Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; ¶Hines VA and Department of Medicine, Loyola University Medical Center, Hines Illinois; ‖Cooperative Studies Program Headquarters, VA Office Research and Development, Washington, District of Columbia; **Department of Medicine, William Beaumont Hospital, Royal Oak, Michigan; ††VA Maryland Medical Center and Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, ‡‡VA Cooperative Studies Program Research Pharmacy and University of New Mexico College of Pharmacy, Albuquerque, New Mexico

Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) can slow the progression of diabetic nephropathy. Even with ACEI or ARB treatment, the proportion of patients who progress to end-stage renal disease (ESRD) remains high. Interventions that achieve more complete blockade of the renin–angiotensin system, such as combination ACEI and ARB, might be beneficial. This approach may decrease progression of nondiabetic kidney disease. In diabetic nephropathy, combination therapy decreases proteinuria, but its effect in slowing progression is unknown. In addition, the potential for hyperkalemia may limit the utility of combined therapy in this population. VA NEPHRON-D is a randomized, double-blind, multicenter clinical trial to assess the effect of combination losartan and lisinopril, compared with losartan alone, on the progression of kidney disease in 1850 patients with diabetes and overt proteinuria.

The primary endpoints are time to (1) reduction in estimated GFR (eGFR) of > 50% (if baseline < 60 ml/min/1.73 m²); (2) reduction in eGFR of 30 ml/min/1.73 m² (if baseline ≥ 60 ml/min/1.73 m²); (3) progression to ESRD (need for dialysis, renal transplant, or eGFR < 15 ml/min/1.73 m²); or (4) death. The secondary endpoint is time to change in eGFR or ESRD. Tertiary endpoints are cardiovascular events, slope of change in eGFR, and change in albuminuria at 1 yr. Specific safety endpoints are serious hyperkalemia (potassium > 6 mEq/L, requiring admission, emergency room visit, or dialysis), all-cause mortality, and other serious adverse events.

This paper discusses the design and key methodological issues that arose during the planning of the study.


In 2003, approximately 50% of incident ESRD was due to diabetes; of these cases, 90% were due to type 2 diabetes (1). The overall rate of ESRD secondary to diabetes has risen 68% since 1992 (1). Use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) can slow the progression of diabetic kidney disease. For example, the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study examined losartan versus placebo added to a standard antihypertensive regimen in 1513 individuals with type 2 diabetes and overt nephropathy (2). Losartan decreased the risk of doubling of serum creatinine, ESRD, or death by 16%; decreased the risk of doubling of serum creatinine by 28%; and decreased the risk of ESRD by 25% compared with placebo. In the Irbesartan in Diabetic Nephropathy (IDNT) study, which examined irbesartan versus amlodipine versus placebo in 1715 individuals with overt nephropathy, use of ARBs decreased the risk of doubling of serum creatinine, end-stage renal disease or death by 20%, decreased the risk of doubling of serum creatinine by 33% and decreased the risk of end-stage renal disease by 23% compared with placebo (3). Despite the benefit of ARBs

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Correspondence: Dr. Linda F. Fried, MD, MPH, VA Pittsburgh Healthcare System, University Drive Division, Mailstop 111F-U, Pittsburgh, PA 15240. Phone: 412-360-6181; Fax: 412-360-6908; E-mail: Linda.Fried@va.gov

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in these studies, progression of kidney disease still occurred in approximately 30% of ARB-treated individuals (2,3), highlighting the urgent need for additional therapies to reduce this risk of progression.

Combination ACEI and ARB has been proposed as a potential approach to slow the progression of nephropathy (4). COOPERATE (Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease), a study of 238 individuals with nondiabetic nephropathy (mainly IgA nephropathy) found that combination trandolapril and losartan decreased proteinuria and progression of kidney disease by 50% (5). However, the results of this study have recently been called into question (6,7). The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) study was designed to test the effects of combined ACEI and ARB treatment on cardiovascular disease events in patients at high cardiovascular risk. A recent analysis of renal endpoints was published (8). Their overall findings, that combination ACEI/ARB therapy was no better than monotherapy and may in fact increase risk of certain renal outcomes, needs to be tempered by the fact that only a small subset of their patients had proteinuria and the ONTARGET renal endpoints were all secondary endpoints of the main study. Indeed, in patients with overt diabetic nephropathy in ONTARGET, there was an 8% statistically insignificant benefit with combination therapy. Although combination therapy has been shown in several relatively short trials to decrease proteinuria in individuals with diabetes (9–15), benefits may be limited by a potential increased risk of serious hyperkalemia in these patients (16). These factors all underscore the need for a larger study that examines the long-term effect of combination ACEI and ARB on progression of diabetic nephropathy.

In this article, we describe the key design and methodological issues that arose during the development of a Department of Veterans Affairs (VA) Cooperative Studies Program (CSP)-sponsored study: Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy: VA NEPHRON-D Study: NEPHROpathy iN Diabetes Study (CSP #565).

**Table 1. Inclusion and exclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes, based on clinical diagnosis</td>
</tr>
<tr>
<td>Albuminuria &gt; 300 mg/g creatinine</td>
</tr>
<tr>
<td>Stage 2 or 3 chronic kidney disease (Estimated GFR 30 to &lt; 90 ml/min/1.73 m²)</td>
</tr>
<tr>
<td>Able to give informed consent</td>
</tr>
<tr>
<td>Exclusion criteria</td>
</tr>
<tr>
<td>History of intolerance to ACEI or ARB</td>
</tr>
<tr>
<td>Serum potassium level &gt; 5.5 meq/L</td>
</tr>
<tr>
<td>Receiving sodium polystyrene sulfonate</td>
</tr>
<tr>
<td>Pregnancy, breast-feeding, planning to become pregnant, or sexually active and not using birth control (women)</td>
</tr>
<tr>
<td>Suspected nondiabetic kidney disease</td>
</tr>
<tr>
<td>Receiving renal transplant</td>
</tr>
<tr>
<td>Current use of ACEI/ARB combination</td>
</tr>
<tr>
<td>Current use of lithium</td>
</tr>
<tr>
<td>Severe (end-stage) comorbid disease</td>
</tr>
<tr>
<td>Incarceration</td>
</tr>
<tr>
<td>Age &lt; 18</td>
</tr>
<tr>
<td>Estimated GFR &lt; 30 or ≥90 ml/min/1.73 m²</td>
</tr>
<tr>
<td>HbA1c &gt; 10.5%</td>
</tr>
<tr>
<td>Blood pressure &gt; 180/90</td>
</tr>
<tr>
<td>Patient refusal</td>
</tr>
<tr>
<td>Participation in a concurrent interventional study</td>
</tr>
<tr>
<td>Unwillingness to stop taking proscribed medications⁴</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
⁴For example, nonsteroidal anti-inflammatory medications, potassium sparing diuretics and other medications that block the renin-angiotensin-aldosterone system

**Overview of Study Design**

VA NEPHRON-D is designed as a multicenter, prospective, randomized, parallel group trial to test the efficacy of the combination of an ACEI with an ARB as compared with standard treatment with an ARB alone on the progression of diabetic nephropathy (Figure 1). Participants are individuals with type 2 diabetes with overt nephropathy and an eGFR between 30 and 89.9 ml/min/1.73 m². Specific inclusion and exclusion criteria are listed in Table 1. The inclusion criteria were designed to select a study sample that was as reflective as possible of the larger population of Veterans Health Administration outpatients with type 2 diabetes and nephropathy who would be candidates for ACEI and ARB therapy. The specific study endpoints are listed in Table 2. If individuals meet the primary endpoint as assessed by decline in eGFR, they will continue to receive study medication and will be followed for development of ESRD or death.

All participants will receive open label (unblinded) losartan 100 mg. Individuals who are enrolled in the study and are not currently being treated with losartan 100 mg (either on another ARB or ACEI or no ACEI or ARB) will change to treatment with losartan 50 mg/d. There will not be a washout of prior ACEI or

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**Figure 1. Interventions in the VA Nephron-D study.**

- **Randomization**
- **Losartan + Lisinopril**
  - Lisinopril titrated from 10 to 40 mg
- **Losartan + Placebo**
- **Equivalent titration**
  - Conversion to and titration of losartan to 100 mg/day
- **Follow-up**
  - Every three months - creatinine measured in central laboratory
  - If change in GFR endpoint reached, remain on study medication and followed for ESRD or death

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until the study ends, for up to 5 yr.

**Table 2. Study outcomes**

<table>
<thead>
<tr>
<th>Primary outcome (composite)</th>
<th>Reduction in estimated GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 50% for individuals with a baseline eGFR &lt; 60 ml/min/1.73 m²</td>
</tr>
<tr>
<td></td>
<td>&gt; 30 ml/min/1.73 m² for individuals with a baseline eGFR ≥ 60 ml/min/1.73 m²</td>
</tr>
<tr>
<td>ESRD (permanent need for dialysis, kidney transplantation, or an eGFR &lt; 15 ml/min/1.73 m²)</td>
<td></td>
</tr>
</tbody>
</table>

**Death**

**Secondary outcome (composite)**

Reduction in eGFR

>50% for individuals with a baseline eGFR <60 ml/min/1.73 m²

>30 ml/min/1.73 m² for individuals with a baseline eGFR ≥60 ml/min/1.73 m²

ESRD

Tertiary outcomes

Cardiovascular events (cardiovascular death, myocardial infarction, stroke, hospitalization for congestive heart failure)

Change in albuminuria from randomization to 12 months

Decline in slope of kidney function (eGFR)

Safety outcomes

All-cause mortality

Serious hyperkalemia (potassium >6 meq/L or requiring admission, emergency room visit or dialysis)

Other serious adverse events (hospitalizations, other)

**Methodological Issues**

A number of methodological issues, summarized in Table 3, arose during the design of the current study. They are detailed below.

**Selection of Study Treatments**

**Should Monotherapy Be an ACEI or an ARB?** The initial plan was to use an ACEI as baseline monotherapy and add an ARB/placebo, because ACEI is currently the VA standard of practice. However, scientific reviewers raised the concern that ACEI has not been clearly proven to be effective in delaying progression of nephropathy in type 2 diabetes, as compared with type 1 diabetic nephropathy. An ARB, and in particular an ARB that was FDA approved for type 2 diabetes, was recommended.

ACEI and ARB have been found to be of comparable benefit in heart failure or after myocardial infarction, but some individuals discontinue ACEIs because of their side effects (19,20). The major difference in side effects is due to the development of cough with ACEIs. Of the few studies that directly compared

**ARB medication. Two weeks later, if this dose is tolerated, with no more than a 30% increase in serum creatinine and a potassium level < 5.5 mEq/L, the dose of losartan will be increased to 100 mg/d. The purpose of uniform and unblinded treatment with losartan is twofold: (1) to achieve an accepted standard of care; and (2) to reduce variation in both arms with respect to the pharmacologic blockade of the renin angiotensin system with background medications. If losartan at 100 mg/d is tolerated, the participant will be randomized to receive either blinded study ACEI (lisinopril 10 mg) or matching placebo. Randomization will be stratified by site and within site by baseline albuminuria (<1 versus ≥1 g/g creatinine) and eGFR < 60 ml/min/1.73 m² (stage 3 CKD) versus ≥60 ml/min/1.73 m² (stage 2 CKD). These strata were chosen as both GFR and albuminuria are not only influential independent determinants of progression of kidney disease, but also may modify the effect of ACEI and ARB on progression (5,17). The dose of lisinopril/placebo will be titrated in 2-wk intervals to 20 mg, then to 40 mg/d or maximally tolerated dose. Potassium and creatinine will be assessed after each adjustment. After titration to the highest tolerated ACEI dose, all participants will be followed every 3 months for endpoints and assessment of adverse events until the study ends, for up to 5 yr.

It is anticipated that the most common complication associated with study therapy will be hyperkalemia. The aggressiveness of treatment of hyperkalemia will depend on the degree of elevation and the presence or absence of ECG findings. If during follow-up, a participant’s potassium level increases to >5.0 mEq/L, she or he will be prescribed a low-potassium diet. If the potassium level increases to >5.5 mEq/L, conservative measures, including adjustment in diuretics, administration of chronic alkali supplements, liberalization of salt intake, or chronic use of low-dose sodium polystyrene sulfonate, will be instituted. If the potassium level is > 6.0 mEq/L, the study medications will be stopped until the level decreases to < 5.5 mEq/L. The medication will then be reinstituted at 50% of the prior dose. If the potassium level is > 6.5 mEq/L, study medication will be stopped permanently. If study medications are stopped, individuals will continue to be followed for study endpoints. The study also includes a biorepository of serum, plasma, and urine for samples collected at 1 yr after randomization and a DNA substudy for future studies on factors related to diabetic nephropathy and its complications. The study will be monitored for safety and efficacy by an independent data-monitoring committee.

Sample size was calculated using the method of Lachin and Foulkes (18) for the log rank test and was based on a 5-yr cumulative event rate in the monotherapy arm of 45% (based on event rate in RENAAL [2] and the older age of the VA population, which would be expected to increase the mortality rate), 18% reduction in the cumulative event rate with combination therapy (i.e., 23% reduction in the hazard rate), 85% power, type I error of 5% (2-sided), 10% loss to follow-up, and a 5-yr study with 3 yr of recruitment and minimum 2 yr of follow-up. The target sample size will be 1850 participants and is expected to generate 758 primary events by the end of the study. This sample size will provide 80% power to detect a 16.7% reduction in the cumulative event rate with combination therapy (i.e., 21% reduction in the hazard rate).
the effect of ACEI versus ARB on changes in albumin excretion, most have found that the two are equivalent. Human studies protection was a primary factor in deciding the class of medications to use as monotherapy. Because progression to diabetic nephropathy is a serious condition and there is an effective therapy, the control group should include a therapy that has been shown to be effective (21). Although the planning committee felt that ACEIs and ARBs were likely equally effective in nephroprotection, there were no definitive data to demonstrate equivalence. Therefore, an ARB was selected as the monotherapy treatment for VA NEPHRON-D because it offered the best option from both clinical and scientific standpoints.

**Should There Be Three Arms or Two?** Given the uncertainty of whether there is a difference in the efficacy of ACEI and ARB on progression of kidney disease, the question of whether the study should be a three-arm study (ACEI alone versus ARB alone versus combination) was also considered. This uncertainty could be conceptualized as two study questions: (1) Are ACEI and ARB equivalent treatments? and (2) is combination therapy more effective (superior) than monotherapy for slowing progression of diabetic nephropathy in type 2 diabetics? This conceptualization has implications for sample size requirements. A very large sample size would be required to address equivalence (> 4000 individuals to address the ACEI versus ARB question alone, assuming a 3% difference in proportion reaching endpoint; > 2500 if a 4% difference). Thus, to address both questions in a single trial with equal allocation would require sizing the trial to address the equivalence comparison, which was not feasible and also complicates the trial’s ability to address multiple hypotheses. An alternative would be to use an unbalanced design and to allocate more individuals to the monotherapy arms (equivalence question) and fewer to the combination therapy arm (superiority question). This approach would still require a large sample size and would detract from the more clinically relevant question of whether combination therapy slows the progression of diabetic nephropathy. The study was therefore designed as a two-arm trial to compare ARB to a combination of ARB plus ACEI.

**Endpoints**

<table>
<thead>
<tr>
<th>Table 3. Main methodological issues during design of VA NEPHRON-D</th>
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<tbody>
<tr>
<td><strong>Study treatment</strong></td>
</tr>
<tr>
<td>Should the study be three arms (ACEI vs. ARB vs. both) or two (monotherapy vs. combined therapy)?</td>
</tr>
<tr>
<td>If three arms, should there be equal allocation to the three groups or should the allocation account for the probable smaller difference in ACEI vs. ARB as compared to a monotherapy vs. combined therapy?</td>
</tr>
<tr>
<td>Should the monotherapy be an ACEI or an ARB?</td>
</tr>
<tr>
<td>Management of other care issues</td>
</tr>
<tr>
<td>Should this be part of the study or as part of clinical care and which factors should be part of the study management?</td>
</tr>
<tr>
<td>How should blood pressure be managed?</td>
</tr>
<tr>
<td>How should hyperkalemia be managed?</td>
</tr>
<tr>
<td>Should the primary endpoint include mortality?</td>
</tr>
<tr>
<td>Should doubling of serum creatinine/halving of eGFR be used, or should the endpoint be an absolute decline in kidney function? Does this choice weight the endpoints to individuals with more severe kidney disease at baseline?</td>
</tr>
<tr>
<td>Should cardiovascular events be considered in the primary or secondary endpoints, when IDNT and RENAAL found a nonsignificant 10% reduction in cardiovascular events?</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

versus ARB question alone, assuming a 3% difference in proportion reaching endpoint; > 2500 if a 4% difference). Thus, to address both questions in a single trial with equal allocation would require sizing the trial to address the equivalence comparison, which was not feasible and also complicates the trial’s ability to address multiple hypotheses. An alternative would be to use an unbalanced design and to allocate more individuals to the monotherapy arms (equivalence question) and fewer to the combination therapy arm (superiority question). This approach would still require a large sample size and would detract from the more clinically relevant question of whether combination therapy slows the progression of diabetic nephropathy. The study was therefore designed as a two-arm trial to compare ARB to a combination of ARB plus ACEI.

**Endpoints**

**How Should the Change in Kidney Function Endpoint Be Defined?** The primary and secondary endpoints in this study can be viewed as a combination of a surrogate endpoint (change in kidney function) with harder events (end-stage renal disease or death). The endpoint needed to be one that was feasible for the resources available for a randomized study. To use ESRD or death as an endpoint would require either a very long follow-up or enrollment of only advanced CKD, i.e., those patients that would be expected to could reach ESRD in the time frame of a typical randomized trial. We therefore chose an endpoint that incorporates a decremental change in kidney function. While progression to development of end-stage disease is an endpoint of greater clinical significance to patients than is a decline in kidney function, a progressive decline in kidney function is a prerequisite for this progression to end-stage disease. The composite outcome of doubling of serum.
creatinine, end-stage renal disease or death has become a standard outcome in kidney disease progression studies. Furthermore, the FDA has accepted a doubling in serum creatinine as a surrogate measure of change in renal function. Since serum creatinine is inversely related to eGFR, a doubling of serum creatinine is approximately equivalent to a 50% decline in eGFR (23). To standardize the outcome, serum creatinine will be measured at a central laboratory at the University of Maryland, using an IDMS traceable method. Urine albumin levels will be measured locally.

The upper limit of estimated GFR for inclusion in this study is less than 90 ml/min/1.73m². The range of GFR is somewhat larger than that for RENAAL or IDNT. As a result, participants may be enrolled earlier in their course of disease than those in either the RENAAL or IDNT studies. Since the rate of decline in GFR over time in an individual is relatively constant, inclusion of participants with a higher baseline estimated GFR will decrease the number who would be expected to double their serum creatinine (or halve GFR) over duration of the study. For example, for a person with a baseline eGFR of 80 ml/min/1.73m², the absolute change in eGFR necessary for a 50% decline is 40 ml/min/1.73m² as compared with a decline of only 20 ml/min/1.73m² if the baseline eGFR was 40 ml/min/1.73m². At the same rate of decline of renal function, it would take twice as long for a participant with the higher eGFR to reach this endpoint than one with the lower baseline eGFR. Thus to reach the endpoint during the study time, the participant would either need to be a fast progressor or have a low eGFR at baseline (24).

A wider GFR range enables generalizability to a larger proportion of patients, while still identifying a group at high risk for progression of kidney disease, given presence of overt nephropathy. Since the endpoint of doubling of serum creatinine (halving of eGFR) is an arbitrary cutoff, it was felt that a more appropriate measure of change in renal function would be to include an absolute decline in GFR for those participants with a higher baseline value. A cutoff of 30 ml/min/1.73m², which corresponds to a change in one KDOQI stage of CKD, was chosen. This approach of using different cutoffs for decline in GFR for different baseline is similar to the approach of the Modification of Diet in Renal Disease Study, which had two clinical renal stopping points for decline in GFR (25).

Thus, the composite endpoint includes both end-stage renal disease and GFR change and covers both end-stage and pre-end-stage renal disease. It also increases the event rate and makes the study more feasible. To address the concern that change in kidney function is a surrogate measure, participants will not exit from the study once the eGFR endpoint is reached and will continue to be followed on study medication for development of ESRD or death. However, it is expected that the study endpoint will be driven by change in kidney function.

**Include mortality in the primary endpoint?** Death is included in the composite endpoint because it may be a competing risk for progression of kidney disease and/or development of ESRD. That is, individuals with diabetic kidney disease have an increased mortality and may die before reaching the GFR decline or ESRD endpoints, particularly for the older individual with diabetes (26). If combination therapy alters mortality independent of the effect on progression of kidney disease, it may confound the interpretation of the renal endpoint. However, this view should be balanced against the findings of RENAAL and IDNT where the use of an ARB did not decrease mortality (2,3). One possible reason for the lower effect size observed in RENAAL and IDNT for the primary composite endpoint compared with earlier studies in nondiabetic kidney disease or type 1 diabetes (effect sizes closer to 50%) is the higher mortality in patients with type 2 diabetes (17,27–29).

Including mortality in the composite endpoint increases the potential number of events (increasing power), but if mortality is not impacted by the intervention, the effect size would be smaller (decreasing power). Because the VA population is typ-

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**Table 4. Management of hypertensive medications**

<table>
<thead>
<tr>
<th>Step</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Study medication</td>
<td>Losartan plus lisinopril/placebo</td>
</tr>
<tr>
<td>2: Diuretic</td>
<td>Thiazide, Loop diuretic, Potassium sparing diuretics not allowed</td>
</tr>
<tr>
<td>3*: Non-dihydropyridine calcium channel blocker Beta-blocker</td>
<td>Non-dihydropyridine calcium channel blocker Beta blocker (one not used in step 3)</td>
</tr>
<tr>
<td>4</td>
<td>Clonidine, Alpha blocker, Hydralazine, Minoxidil</td>
</tr>
<tr>
<td>5: Other</td>
<td></td>
</tr>
</tbody>
</table>

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*aAfter step 2, algorithm can be modified to add alpha blocker at step 3 or 4 for prostatic symptoms or isordil/hydralazine for heart failure. 

*bChoice of medications within medication class chosen by site investigator based on Veterans Affairs formulary.

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**Table 5. Effect of combination ACEI/ARB on cardiovascular events**

<table>
<thead>
<tr>
<th>Trial (reference)</th>
<th>N</th>
<th>Population</th>
<th>Treatment</th>
<th>All-cause mortality</th>
<th>Cardiovascular mortality</th>
<th>CHF admission</th>
<th>Composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn et al (30)</td>
<td>2548</td>
<td>CHF with low EF</td>
<td>Valsartan 160 mg bid vs. placebo added onto current ACEI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>HR 1.02 (95% CI, 0.88 to 1.18)</td>
<td>Not stated</td>
<td>Decrease by 27.5% (13.8% vs. 18.2%), P &lt; 0.001</td>
<td>Death, CHF, cardiac arrest with resuscitation, iv inotrope/vasodilator HR 0.87 (95% CI, 0.77 to 0.97)</td>
</tr>
<tr>
<td>CHARM Added (19)</td>
<td>5010</td>
<td>CHF with low EF</td>
<td>Candesartan 32 mg vs. placebo added onto current ACEI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>HR 0.89 (95% CI, 0.77 to 1.02)</td>
<td>0.84 (95% CI, 0.72 to 0.98)</td>
<td>HR 0.83 (95% CI, 0.71 to 0.96), P = 0.014</td>
<td>Cardiovascular death, MI, CHF, stroke HR 0.87 (95% CI, 0.77 to 0.98)</td>
</tr>
<tr>
<td>VALIANT (31)</td>
<td>14,703</td>
<td>Acute MI with clinical heart failure or low EF</td>
<td>Valsartan 160 mg bid vs. captopril 50 mg tid vs. valsartan 80 mg bid plus captopril 50 mg tid</td>
<td>HR 0.98 (97.5% CI, 0.89 to 1.09) for combination vs. captopril</td>
<td>HR 1.00 (97.5% CI, 0.89 to 1.11)</td>
<td>17.1% vs. 19.3% combination therapy vs. captopril, P = 0.005</td>
<td>Cardiovascular death, MI, CHF HR 0.97 (97.5% CI, 0.89 to 1.05)</td>
</tr>
<tr>
<td>ON TARGET (32)</td>
<td>25,560</td>
<td>CVD or diabetes with end-organ damage</td>
<td>Telmisartan 80 mg, ramipril 10 mg, or both</td>
<td>Combination vs. ramipril 1.07 (95% CI, 0.98 to 1.16)</td>
<td>1.04 (95% CI, 0.93 to 1.17)</td>
<td>0.95 (95% CI, 0.82 to 1.10)</td>
<td>Cardiovascular death, MI or stroke: 0.99 (95% CI, 0.92 to 1.07)</td>
</tr>
<tr>
<td>COOPERATE (5)</td>
<td>336</td>
<td>Nondiabetic kidney disease with urine protein &gt; 300 mg/day</td>
<td>Losartan 100 mg vs. trandolapril 3 mg vs. both (same doses)</td>
<td>Only 1 death in study (losartan arm)</td>
<td>Only one death, perhaps ruptured abdominal aortic aneurysm</td>
<td>None reported</td>
<td>Stroke/MI, 1 event in each arm</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio; CI, confidence interval; CHF, chronic heart failure; EF, ejection fraction; MI, myocardial infarction; CVD, chronic vascular disease.

<sup>a</sup>Mean daily dose ACEI was enalapril 17 mg, lisinopril 19 mg, captopril 80 mg, ramipril 6 mg, quinapril 23 mg.

<sup>b</sup>Mean daily dose ACEI was enalapril 17 mg, lisinopril 18 mg, captopril 82 mg, ramipril 7 mg.
ically older, mortality may be greater than prior studies and could be a competing risk. For this reason, mortality was included in the primary endpoint, and renal outcomes alone (change in eGFR and progression to ESRD) make up the secondary endpoint.

Should Cardiovascular Events Be Endpoints? Studies on the effect of monotherapy with ACEI or ARB on the risk of cardiovascular disease in individuals with type 2 diabetes without nephropathy have shown only modest effects on cardiovascular events. In IDNT and RENAAL, ARB use was associated with a 10% decreased risk of the composite outcome of cardiovascular endpoints (2,3). However, losartan decreased the risk of heart failure in RENAAL and IDNT (2,3). Studies of the association of combination ACEI and ARB therapy with cardiovascular events have found mixed results (Table 5). Three large studies examined the efficacy of combination therapy in patients with heart failure. In all three, combination of ACEI/ARB led to a reduction in hospitalization for heart failure (19,30,31), but the combination of ACEI and ARB did not decrease overall mortality compared with monotherapy. Combination therapy with ACEI and ARB did reduce cardiovascular mortality and cardiovascular events in the Candesartan in Heart Failure - Assessment of Reduction in Mortality and Morbidity study, although part of the reduction could be related to the greater reduction in BP that was achieved with combination therapy (31). The ONTARGET study did not find a benefit of combination therapy (Table 5) (32). Importantly, there was a higher risk of hyperkalemia (K+ > 5.5 mEq/L, n = 480, [5.6%] with combination therapy versus 283 [3.3%] with ramipril and 287 [3.4%] with telmisartan).

On the basis of these data, we could not assume a larger effect for combination therapy on a cardiovascular endpoint than what was observed for monotherapy (RENAAL and IDNT (2,3)), that is, 10%. Therefore, our study would be underpowered to detect the expected small effect of combination therapy on cardiovascular outcomes given for the target sample size.

Although cardiovascular events were felt to be an important outcome, collecting sufficiently complete data on these events to allow central adjudication would be costly and increase the workload of site staff. Therefore, a compromise was reached in which local adjudication of cardiovascular events was used, with a prespecified set of criteria for diagnosis. If the event occurred outside of the VA system, the site staff would seek the discharge summary. For VA admissions, these data would be readily available because the VA medical record is completely electronic. Serious adverse event reports will also be used to ascertain completeness of event capture.

In conclusion, VA NEPHRON-D will be a large trial evaluating the safety and efficacy of ACEI/ARB combination compared with ARB alone on progression of diabetic nephropathy. The study began enrollment July 2008.

Appendix
Planning committee members

Linda F. Fried, MD, MPH, VA Pittsburgh Healthcare System/University of Pittsburgh Medical School

William Duckworth, MD, Phoenix, VA/Arizona State University/University of Arizona, Phoenix

Stephen Davis, MD, Vanderbilt University School of Medicine

Nicholas Emanuele, MD, Hines/North Chicago VA and Loyola University Medical Center

Thomas Hostetter, MD, Albert Einstein Medical College

Peter A. McCullough, MD, MPH, William Beaumont Hospital

Paul Palevsky, MD, VA Pittsburgh Healthcare System/University of Pittsburgh Medical School

Mark Pfeffer, MD, PhD, Brigham and Women’s Hospital

Stephen Seliger, MD, MS, VA Maryland Medical Center/University of Maryland School of Medicine

Robert Star, MD, NIDDK

Robert Toto, MD, University of Texas Southwestern Medical Center at Dallas

West Haven Cooperative Studies Coordinating Center, West Haven, CT

Jane Hongyuan Zhang, PhD

Theresa O’Connor, PhD

Peter Peduzzi, PhD

VA Cooperative Studies Program Research Pharmacy, Albuquerque, NM

Stuart Warren, JD, PharmD

MAVERIC Core Laboratory, Boston, MA

Mary Brophy, MD, MPH, VA Boston Healthcare System/Boston University School of Medicine

Health Economics Resource Center (HERC), PAlo Alto, CA

Patricia Sinnott, PT, PhD, MPH

VA Central Office Research and Development

Grant D. Huang, MPH, PhD

Timothy O’Leary, MD, PhD

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References


