Effects of Dual Blockade of the Renin-Angiotensin System Compared to Single Drug Treatment in Renoprotection for Patients With Diabetes Mellitus Type II and Diabetic Nephropathy

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Abstract
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Methods: Exhaustive search of available medical literature using the search engines, Medline, CINAHL, and Science Citation Index Expanded. Articles were included which used multiple measurements of kidney function and patients with varying levels of kidney function.

Results: After using the exclusion criteria, a collection of articles was narrowed to 6 studies. All articles proved a decrease in proteinuria and short term benefit in renal function. One article demonstrated long term harm to the kidneys.

Conclusion: Dual blockade of RAS reveals short term improvement of renal function which in the long term might have adverse effects on the kidneys. In the future longer term studies should be done to prove or disprove the benefits on kidney health. If dual therapy is beneficial then providers will be able to prescribe ACE-Is and ARBs together to protect the kidneys in DM II patients.

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Effects of Dual Blockade of the Renin-Angiotensin System Compared to Single Drug Treatment in Renoprotection for Patients With Diabetes Mellitus Type II and Diabetic Nephropathy

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Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

[Redacted for privacy]
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**Keywords:** Diabetic nephropathy, angiotensin II type I receptor blocker, angiotensin-converting enzyme inhibitor, and Diabetes Mellitus Type II.
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To my parents: Thank you for your never ending encouragement and confidence in my education and life! You all have given me an amazing foundation to continue building my future on.
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List of Abbreviations

ACE-Is............................angiotensin-converting enzyme inhibitors (also referred to as ACE inhibitors, ACEis, ACEIs)
AER................................................albimn excretion rate
ARBs........................................angiotensin type I receptor antagonists
DM II...........................................Diabetes Mellitus Type II
ESRD...........................................end-stage renal disease
GFR...........................................glomerular filtration rate
RAS...........................................renin-angiotensin system
TGF-β1....................................urinary transforming growth factor β1
UPCr........................................urine protein/creatinine
UPER........................................urinary protein excretion rate
Effects of Dual Blockade of the Renin-Angiotensin System Compared to Single Drug Treatment in Renoprotection for Patients With Diabetes Mellitus Type II and Diabetic Nephropathy

BACKGROUND

Diabetes Mellitus Type II (DM II) is a disease affecting many people and is difficult for patients to manage and live with. Diabetes has become the leading cause of end-stage renal disease (ESRD) in multiple countries, including the United States.\textsuperscript{1-2} Diabetic nephropathy is characterized by persistent proteinuria or microalbuminuria, elevated blood pressure, persistent decline in glomerular filtration rate (GFR), and an increased risk for cardiovascular morbidity and mortality.\textsuperscript{1,3} Typically, proteinuria and hypertension are used as predictors of decreased renal function in DM II patients.\textsuperscript{1,4-5} Proteinuria is also used as a marker of progressive renal insufficiency.\textsuperscript{6} The renin-angiotensin system (RAS) is the key contributor to the development of renal issues in this population. The RAS can be targeted by two different blood pressure medications, angiotensin type I receptor antagonists (ARBs) and angiotensin-converting enzyme inhibitors (ACE-Is). Both act to decrease intraglomerular hypertension and reduce albumin excretion.\textsuperscript{7-8} Hypertension causes thickening of the glomerular basement membrane and glomerulosclerosis, leading to albuminuria.\textsuperscript{7,9} Current guidelines\textsuperscript{10} recommend the use of either blood pressure medication as first-line agents in the treatment of diabetic kidney disease.\textsuperscript{10} ARBs and ACE-Is work to dilate the afferent vessels and efferent vessels of the kidney, respectively. ARBs work against the angiotensin II receptor while ACE-Is limit the conversion of angiotensin I into angiotensin II.\textsuperscript{1,4,8,11-16} Many researchers and providers believe that using both medications in combination might provide more benefit in renoprotection than a single
Angiotensin II also promotes the synthesis of urinary transforming growth factor β1 (TGF-β1). When overproduction of TGF-β1 occurs, an accumulation of protein takes place in the renal system due to the renal tissue fibrosis, hypertrophy, and sclerosis. Lowering local TGF-β1 production might be possible by inhibiting the RAS and thus reducing angiotensin II. Plasma aldosterone with its fibrogenic properties has also been proven to have an effect on increased rate of renal function loss. Preventing death, dialysis, and suffering by avoiding or slowing the progression of kidney disease is the goal of dual blockage of the RAS. If dual blockade of the RAS would show to be valuable in renoprotection then medical providers could aid their patients with keeping their kidneys healthy and thereby prevent suffering.

METHODS
An exhaustive literature search using the Medline, CINAHL, and Science Citation Index / Science Citation Index Expanded for search engines and searching the terms; diabetic nephropathy, angiotensin II type I receptor blocker, angiotensin-converting enzyme inhibitor, and Diabetes Mellitus Type II.

Inclusion criteria for patients included those with DM II with some form of reduced kidney function. The intervention tested was dual blockade of RAS with combination ACE-Is and ARBs. No preference was given to the name brand or generic form of either medication. This was compared to the effects of ACE-I or ARB treatment alone. The desired outcome was improved kidney function. All randomized control trials were considered for this systematic review. Any study that was not randomized was used
only for background information. Studies based in any country, all time periods, and various measurements of kidney function were considered.

Studies were excluded if researchers were only testing monotherapy, if they were not complete or concentrated on blood pressure control. Number of participants was not used to exclude any trials. Any studies that considered nephropathy of a different etiology than DMII were also excluded.

Each article was critically appraised using the critical review form for therapy to measure validity and reveal bias. Six studies were found to be valid and used for this systematic review.

**RESULTS**

The search of three different databases resulted in approximately 60 articles based on terms used. The most prolific database, Medline, produced 43 relevant articles with the keywords used and five of those studies were analyzed for this review. Seven applicable articles were found by CINAHL, but after exclusion criteria were applied only one article was determined to correspond with validity criteria. Science Citation Index / Science Citation Index Expanded generated one article which was a systematic review. A total of 13 studies were used in researching this paper. Six studies were used for their study and results. The remaining articles were used for background information. A summary of all included articles can be found in Table 1. For a synopsis of the studies used for the systematic review, see Table 2: Summary of findings.

In the Krairittichai study\(^\text{17}\), dual therapy with maximal doses of both ARB (telmisartan 80 mg/day) and ACE-I (enalapril 40 mg/day) led to significantly reduced
proteinuria from baseline compared to unchanged proteinuria in ACE therapy alone. Urine protein/creatinine (UPCr) was used as a marker of proteinuria. Although researchers determined that the treatment was safe and well tolerated, GFR fell in both groups and potassium increased in both groups. The study included 80 patients with DM II, hypertension, and UPCR less than 0.5% who had been treated with the maximum ACE-I dosage for 3 months and were recruited from the out-patient department of Rajavithi Hospital in Thailand. The control group remained on ACE-I while the intervention group received maximal ARB in addition to ACE-I for 24 weeks.\textsuperscript{17}

The ONTARGET study\textsuperscript{18} showed greater reduction in proteinuria with dual therapy, but also a larger number of long term adverse effects with dual blockade of the RAS. Increased hypotension was a common side effect with the use of both ACE-Is and ARBs. The study included one of the largest number of participants and longest trial periods, 25 620 individuals age 55 or older with established atherosclerotic vascular disease or with diabetes with end-organ damage monitored for 6 years. Patients were randomized into 3 groups, telmisartan 80 mg /day (ARB), ramipril 10 mg/day (ACE-I), and a combination of both the mentioned maximal dosages. Renal function and proteinuria were measured using serum creatinine, GFR, and urine albumin and these served as surrogate renal endpoints. The primary renal outcomes used as endpoints, dialysis, death, and doubling of serum creatinine were more frequent with the combination of both drugs. The authors of this study believe that their results suggest that proteinuria itself should not be used as a dependable marker of improving renal function since proteinuria showed improvement while kidney function was decreased.\textsuperscript{18}
Matos et al\textsuperscript{7} evaluated 20 hypertensive DM II patients over 40 years of age with non-nephrotic proteinuria in Rio de Janerio, Brazil. Participants were assigned to a random sequence of three treatments periods of 16 weeks each: perindopril 8 mg/day (ACE-I), irbesartan 300 mg/day (ARB), and a combination of both dosages. Multiple labs were measured at the end of each period to monitor renal function, including proteinuria, TGF-β1, plasma renin and aldosterone, blood urea nitrogen (BUN), creatinine, serum proteins, and urinary measurements of sodium, potassium, creatinine, and urea. Matos and his fellow authors noted changes in GFR were not significant with any therapy. Treatment with ARBs and with dual therapy induced similar plasma renin elevation. Plasma aldosterone was reduced only by combination treatment. Reduction in proteinuria with combination therapy was not significantly different than single treatment. TGF-β1 excretion was reduced with both ARB and combination therapy but not ACE-I therapy. The study showed that the combination of both hypertension medications reduced plasma aldosterone, proteinuria and urinary TGF-β1.\textsuperscript{7}

The CALM study\textsuperscript{19} demonstrated reduction in urinary albumin:creatinine ratio with combination treatment was greater than monotherapy. This study measured urinary albumin:creatinine ratios in patients after 12 weeks of monotherapy treatment with candesartan 16 mg/day (ARB) or lisinopril 20mg/day (ACE-I) followed by an additional 12 weeks of either monotherapy or combination treatment. The randomized, double blind, double dummy study took place in 37 tertiary hospitals or primary care centers in four countries (Australia, Denmark, Finland, and Israel). A total of 199 DM II patients aged 30 – 70 years with hypertension and microalbuminuria were used as participants.\textsuperscript{19}
Sengul et al\textsuperscript{20} proved that albumin excretion rate (AER) and thus proteinuria was significantly more reduced with combination therapy. The study included 219 Turkish patients ages 40 – 65 years with DM II, hypertension and microalbuminuria who received lisinopril 20 mg/day (ACE-I) or telmisartan 80mg/day (ARB) for 24 weeks and were then randomized to either continue monotherapy or to be given a combination of both medications for a further 28 weeks.\textsuperscript{20}

Song et al\textsuperscript{21} illustrated no comparable change in plasma/urinary biochemical parameters but the 24-hour urinary protein excretion rate (UPER) was significantly reduced by the combination therapy. TGF-β1 was reduced in all three groups but the most significant change was in the combination therapy group. This study tested 21 Korean DM II patients from 41 years old to 57 years old with hypertension and overt nephropathy, ranging. Each patient participated in three separate 16 week periods of ramipril 10 mg/day (ACE-I), candesartan 16 mg/day (ARB), and combination therapy of half doses of each medication. This is the only article that tested reduced dosages of the medications when participants were given the dual therapy. Proteinuria was shown to be reduced significantly even in low doses with the combination of ACE-Is and ARBs compared to monotherapy.\textsuperscript{21}

\textbf{DISCUSSION}

All studies showed short term improvement in renal function with dual blockade of the RAS in patients with diabetic nephropathy in the short term using proteinuria as the surrogate marker. One study focused on long term effects such as dialysis, death, and doubling of serum creatinine, and thus demonstrated harm to the kidneys even though
there was a decrease in proteinuria. Researchers in this study referenced earlier studies and stated that the benefit of dual therapy might be more pronounced in patients with overt diabetic nephropathy or with specific proteinuric renal diseases.18

Numerous kidney function tests were used and studies were not consistent with one another. Studies used various measurements of proteinuria and renal function. Only one study concentrated on long term renal outcomes. The ONTARGET study18 suggests that proteinuria alone is not an adequate marker of renal function and that major renal outcomes also need to be measured.18 Some of the tests used to measure renal function were UPCr, GFR, serum creatinine, plasma aldosterone, TGF-β1, urinary albumin:creatinine ratio, AER, and UPER. Matos et al7 discovered that dual blockade reduced plasma aldosterone and discussed that this provides further renoprotection.7 Future studies should include more research into plasma aldosterone being a target in the management of diabetic nephropathy. More consistency in kidney function measurements would allow studies to be more easily compared and a clearer understanding of the effects of RAS dual blockade.

The current research is flawed, in that all but one study,18 was done for one year or less thus only one study concentrated on the long term effects of dual blockade of the RAS.

Some studies could not distinguish if the benefit of dual blockade on renoprotection could be attributed to a more effective reduction in blood pressure or to the additive antiproteinuric effect.19 Other studies proved that a minimal and insignificant blood pressure change occurred and consequently direct benefits of combination therapy resulted in reduced proteinuria.7 The Song et al21 study using low-dosages of dual
blockade also aids in distinguishing between blood pressure lowering effects and direct effects on the renal system.21

Recommendations for further studies include longer studies and that studies include numerous and uniform tests to assess kidney function. Most researchers recommend close monitoring of blood pressure, renal function, and plasma potassium when utilizing dual blockade of the RAS.

Many of the researchers set out to prove the benefits of dual therapy. This might have caused some bias when they were analyzing the data or designing their studies.

Limitations of Study

The ONTARGET study18 received consulting and lecture fees and research grants from ARB manufacturing companies.18 This may have served to bias researchers in this study. The Mogensen et al19 and Matos et al7 studies also obtained funding or lecture fees from drug companies.7,19

Discrepancies among the results of the various studies could be attributed to the differences in ethnic profiles of the participants since the studies took place in multiple countries.

Matos et al7 explains that the antiproteinuric effect responds differently based on the underlying renal disease.7 This clarifies why some studies showed a greater or lesser improvement in proteinuria based on the type and degree of nephropathy with which participants had been previously diagnosed.

CONCLUSION

Dual blockade of the RAS seems like a logical treatment plan for renoprotection since simultaneous treatment with both ACE-Is and ARBs would obstruct the synthesis
and activity of angiotensin II. Combination therapy shows short term improvement of renal function but in the long term it might have adverse effects on the kidneys.

In the future longer term studies should be done to prove or disprove the effects on kidney health. If dual therapy is beneficial, then providers will be able to prescribe ACE-Ils and ARBs to protect the kidneys in DM II patients with hypertension and microalbuminuria. The DETAIL and VA NEPHRON-D studies are five year, large scale clinical trials comparing dual blockade of the RAS to monotherapy, but have not been completed. When the results are published this will present more information to medical providers.

More research such as the Song et al study needs to be done to investigate the use of lower dosages in order to prevent adverse effects when testing combination therapy. Also a differentiation of renoprotective and antihypertensive effects of RAS blockade needs further confirmation.
References


Table 1: Summary of Review Articles.

<table>
<thead>
<tr>
<th>Study</th>
<th>Yr. published</th>
<th>Patients/Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krairittichai et al(^1)</td>
<td>2009;92:611-617.</td>
<td>80 pts, DM II, HTN</td>
<td>Dual blockade</td>
<td>ACE alone</td>
<td>Reduced proteinuria more in combo</td>
<td>Randomized,</td>
</tr>
<tr>
<td>Mann et al(^2)</td>
<td>2008;372:547-553.</td>
<td>25,620 Patients 55 years or older with AVD or diabetes with end-organ damage</td>
<td>Dual blockade</td>
<td>Each drug alone</td>
<td>Combo has greater reduction of proteinuria, but overall worsens major renal outcomes</td>
<td>Randomized, double-blind and single-blind study</td>
</tr>
<tr>
<td>Matos et al(^3)</td>
<td>2005;64:180-189.</td>
<td>20 HTN DM II patients with non-nephrotic proteinuria</td>
<td>Dual blockade</td>
<td>Each drug alone</td>
<td>Combo reduces plasma aldosterone, and TGF-β1 (proteinuria)</td>
<td>Randomized, open-label, three-phase, crossover study</td>
</tr>
<tr>
<td>Mogensen et al(^4)</td>
<td>2000;321:1440-1444.</td>
<td>199 patients aged 30 – 75 years</td>
<td>Dual blockade</td>
<td>Each drug alone</td>
<td>Combo therapy beneficial effect on albuminuria</td>
<td>Prospective, randomized, parallel group, double blind</td>
</tr>
<tr>
<td>Sengul et al(^5)</td>
<td>2006;71:210-219.</td>
<td>219 pts, DM II, age 40 – 65, HTN, persistent microalbuminuria</td>
<td>Dual blockade</td>
<td>Each drug alone</td>
<td>Combo had greater reduction in BP and improved AER</td>
<td>Prospective, randomized, parallel group, open-label, crossover</td>
</tr>
<tr>
<td>Song et al(^6)</td>
<td>2006;21:683-689.</td>
<td>21 DM II with overt nephropathy, Koreans 49 +/- 8 years</td>
<td>Dual blockade</td>
<td>16 week ACE alone (ramipril 5mg/day, candesartan 8mg/day)</td>
<td>24-h UPER (urinary protein excretion rate) reduced with combo</td>
<td>Prospective, double-blinded randomized crossover trial</td>
</tr>
</tbody>
</table>
**Table 2: Summary of Findings.**

<table>
<thead>
<tr>
<th>Medication tested for dual blockade</th>
<th>Krairittichai et al&lt;sup&gt;17&lt;/sup&gt;</th>
<th>Mann et al&lt;sup&gt;18&lt;/sup&gt;</th>
<th>Matos et al&lt;sup&gt;7&lt;/sup&gt;</th>
<th>Mogensen et al&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Sengul et al&lt;sup&gt;20&lt;/sup&gt;</th>
<th>Song et al&lt;sup&gt;21&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>telmisartan 80 mg (ARB) and enalapril 40 mg (ACE-I), maximum doses of both</td>
<td>telmisartan 80 mg (ARB) and ramipril 10 mg (ACE-I), maximum doses of both</td>
<td>irbesartan 300 mg (ARB) and perindopril 8 mg (ACE-I), maximum doses of both</td>
<td>candesartan 16 mg (ARB) and lisinopril 20 mg (ACE-I), maximum doses of both</td>
<td>telmisartan 80 mg (ARB) and lisinopril 20 mg (ACE-I), maximum doses of both</td>
<td>candesartan 8 mg (ARB) and ramipril 5 mg (ACE-I), half doses of both (low dose)</td>
<td></td>
</tr>
<tr>
<td>enalapril 40 mg (ACE-I) (maximum dose)</td>
<td>ACE-I and ARB alone (maximum doses)</td>
<td>ACE-I and ARB alone (maximum doses)</td>
<td>ACE-I and ARB alone (maximum doses)</td>
<td>ACE-I and ARB alone (maximum doses)</td>
<td>ACE-I and ARB alone (maximum doses)</td>
<td></td>
</tr>
<tr>
<td>UPCr, proteinuria</td>
<td>Primary: dialysis, death, doubling of serum creatinine Secondary: GFR, proteinuria</td>
<td>Proteinuria, TGF-β1, plasma aldosterone</td>
<td>Proteinuria, urinary albumin: creatinine</td>
<td>Albumin Excretion Rate (AER)</td>
<td>24 hour urinary protein excretion rate (UPER)</td>
<td></td>
</tr>
<tr>
<td>24 weeks (control group: ACE-I, intervention group: combination therapy)</td>
<td>56 months (3 groups: ACE-I, ARB, combination therapy)</td>
<td>48 weeks (three sessions of 16 weeks on each drug)</td>
<td>24 weeks (12 weeks monotherapy, 12 weeks on either monotherapy or combination therapy)</td>
<td>52 weeks (24 weeks on single drug, 28 weeks on monotherapy or combination therapy)</td>
<td>48 weeks (three sessions of 16 weeks on each drug)</td>
<td></td>
</tr>
<tr>
<td>Decrease in UPCr and proteinuria</td>
<td>Decrease in proteinuria and GFR. Increase in dialysis, death, and doubling of serum creatinine.</td>
<td>Decrease in proteinuria, plasma aldosterone, and TGF-β1</td>
<td>Decrease in proteinuria</td>
<td>Improved AER, decrease in blood pressure</td>
<td>Decrease in 24 hour UPER, proteinuria, and TGF-β1</td>
<td></td>
</tr>
</tbody>
</table>