

DIS News

College of Health Professions and Biomedical Sciences
Drug Information Service

Literature Highlight: Effect of Telmisartan on Renal Outcomes

The TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) study was a randomized, double-blind, placebo-controlled trial that primarily examined the cardiovascular outcomes associated with the use of telmisartan in patients with cardiovascular disease (CVD). One of the most important secondary outcomes of the TRANSCEND trial were the renal effects of telmisartan. Angiotensin-receptor blockers (ARBs) have been shown to be beneficial to kidney health in large trials of patients with diabetic nephropathy by reducing the rate of dialysis and decreasing the incidence of doubling of serum creatinine (SCr). This article reported on the renal outcomes of telmisartan from the TRANSCEND study.

Five thousand nine hundred and twenty-six patients greater than 55 years old who were intolerant to angiotensin-converting enzyme inhibitors (ACE-Is) with coronary, peripheral, or cerebrovascular disease or diabetes with end organ damage were included. Patients were excluded if they had a known hypersensitivity to ARBs, congestive heart failure (CHF), constrictive pericarditis, syncope of unknown cause within three months of giving informed consent, significant renal disease, or hepatic dysfunction. Eligible patients were randomized to receive either 80 mg of telmisartan or placebo in addition to their regular treatment for 56 months. The primary endpoint was a composite of the first occurrence of dialysis, doubling of SCr, renal transplantation, or death. Secondary endpoints included dialysis, doubling of SCr, change in estimated glomerular filtration rate (GFR), urinary albumin to creatinine ratio (UACR), and progression of proteinuria.

There was no significant difference between telmisartan and placebo in the composite primary outcome; however, significantly more patients in the telmisartan group experienced a doubling of SCr (hazard ratio [HR] 1.59, 95% confidence interval [CI] 1.04-2.41; $p=0.031$). At 56 months, the UACR was sig-

nificantly lower than baseline in the telmisartan group compared to placebo ($p<0.001$). There was also a statistically significant difference in the estimated GFR from baseline to the 56-month measurement. The telmisartan group had a significantly larger decrease in mean GFR than placebo (-3.20 vs. -0.26 mL*(min*1.73m²)⁻¹; $p<0.001$). There are several important limitations when interpreting the results of this study. The inclusion criteria were based on the cardiovascular outcomes for the TRANSCEND trial, limiting the usefulness of the data in exploring the correlation between certain renal outcomes and telmisartan use. Also, the absence of a drug washout period limits the understanding of decrease in GFR; it is unknown if the decreasing trend was transient or indicative of permanent kidney damage. While this study seems to suggest negative renal outcomes with telmisartan, the endpoints have little or poorly understood clinical significance. Doubling of SCr occurred primarily in patients with normal estimated GFR at baseline and never progressed to the need for dialysis. The decrease in GFR at initiation of ARB therapy is expected due to decreasing intraglomerular pressure. The potentially beneficial effects of decreased UACR ratio may only be a function of decreased GFR; it is not understood if this is a clinical benefit.

SUMMARY: Telmisartan does not offer more renal protection than placebo in patients intolerant to ACE inhibitors. Telmisartan should not be used primarily for its renal effects in patients with CVD; however, these findings do not preclude its use for its cardiovascular benefits in patients with CVD who are intolerant to ACE-Is.

Mann JFE, Schmieder RE, Dyal L, et al. Effects of telmisartan on renal outcomes. Ann Intern Med 2009;151:1-10.

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We welcome any comments and suggestions for future newsletter topics.

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Usefulness of Probiotics

The concept of probiotics was first introduced in 1907 by Eli Metchnikoff. Metchnikoff suggested that it was possible to use non-harmful bacteria to replace harmful bacteria in the gut.¹ After studying rural populations in Bulgaria who consumed fermented milk as a staple of their diet, Metchnikoff noticed that these people had long life spans. Metchnikoff suggested that the fermented milk replaced harmful bacteria with lactic acid bacteria and prevented the growth of harmful bacteria.¹ Thus began the interest in what is known as “good” bacteria, leading to the modern definition of probiotics as a “living microorganism which upon ingestion in certain numbers exert health benefits beyond inherent general nutrition”.²

The most commonly studied probiotics belong to the *Lactobacillus* and *Bifidobacterium* species. Other organisms including *Streptococcus thermophilus*, *Saccharomyces boulardii*, *Bacillus cereus*, and *Clostridium butyricum*.² Probiotics have been shown to be beneficial in the treatment and prevention of several diseases.²⁻⁴ Infectious diarrhea and antibiotic-associated diarrhea in adults and children seem to respond favorably to probiotics, and there are several clinical trials backing this claim.² A recent study evaluated the effects of probiotics on the incidence and duration of fever, rhinorrhea, and cough in children 3-5 years of age over the six-month cold and flu season (November to May). Compared to placebo, the incidence of fever was reduced by over 72%, cough by over 62%, and rhinorrhea by over 58% with twice-daily dosing of *L. acidophilus* and *B. animalis*. The duration of symptoms and antibiotic use was also significantly reduced in children treated with probiotics.⁵

Other conditions that may respond to probiotic therapy include irritable bowel syndrome, chronic constipation, travelers diarrhea, *Clostridium difficile* infections, *H. pylori* infections, and vaginitis. There is also some evidence that probiotics are useful in resolving food allergies (lactose intolerance) and eczema, preventing asthma, and may help reduce gastrointestinal and respiratory symptoms in patients with cystic fibrosis.²⁻⁴ It has also been suggested

that probiotics may play a role in the treatment and prevention of some cancers. Probiotics may decrease mutagenic and genotoxic effects in human organs, along with decreasing cancer cell proliferation.³ Probiotics are also being studied as possible adjunctive therapies for the treatment of hypertension and hyperlipidemia. Early evidence suggests that probiotics can help lower blood pressure and lipid levels, but the lack of long-term human studies limits recommending probiotics at this time.⁴

Probiotics are available in a wide variety of forms from yogurt to nutritional supplements.⁶ Probiotics are considered dietary supplements and are not regulated as strictly as medications; therefore, it is important to recommend products from reputable manufacturers to ensure good quality and standardization between batches. Patients with milk allergies or lactose intolerance should check the labels carefully, as some products contain milk protein and lactose. Patients taking probiotics along with antibiotics should separate the products by two hours to avoid reduction of the efficacy of the probiotic by the antibiotic. Probiotics should also be avoided in severely ill patients due to the small risk of infection.⁶

Probiotic research is an ongoing endeavor that may continue to show the positive health effects of these organisms. Probiotics have been proven to be beneficial in treating some gastrointestinal problems and preventing cold and flu symptoms. The use of probiotics in the treatment of other medical conditions is certainly intriguing due to their low risk of adverse effects and ease of use; however, future studies will help define their role and long-term benefits.

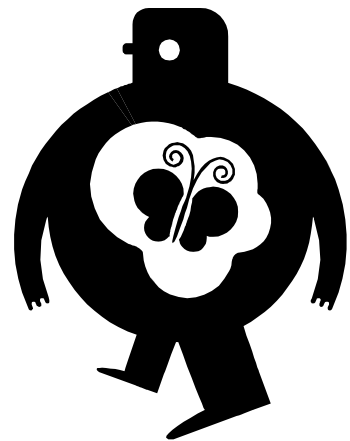
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Low-Dose Naltrexone in Multiple Sclerosis

Multiple sclerosis (MS) is chronic autoimmune disease in which the immune system causes the demyelination of central nervous system (CNS) axons, leading to poor communication between nerves in the spinal cord and brain.¹ The disease progression of MS leads to a variable clinical presentation and can include any of the following symptoms: unilateral numbness or weakness including tingling or pain in one or more extremities, visual disturbances, electric-shock sensations that may occur with certain head movements, tremor, lack of coordination, bladder symptoms, dizziness, and fatigue. MS can present clinically as both a progressive disease in which symptoms become progressively worse or as relapsing-remitting where symptoms come and go. Current treatments for MS encompass both disease-modifying therapy and symptom management. Agents such as baclofen and diazepam are useful in managing spasticity, anticholinergic agents help with bladder symptoms, carbamazepine, phenytoin, or gabapentin help with sensory symptoms, and amantadine, methylphenidate, or dextroamphetamine can help manage fatigue. These treatments, however, have only shown moderate success in controlling MS symptoms.¹

Naltrexone is an opiate antagonist normally used in doses of 50 – 100 mg daily for the treatment of opiate or alcohol addiction.² When naltrexone is given in doses of 5 mg or lower, it becomes an opiate agonist causing a prolonged release of endogenous beta-endorphins (BE), which helps regulate nociception, mood, food intake, and endocrine secretion and have anti-inflammatory activity. Based on anecdotal evidence, low-dose naltrexone (LDN) has been used off-label in patients with MS to treat spasticity, numbness, fatigue, and bladder dysfunction.²

A six-month, phase II, multicenter, open-label trial evaluated the safety and tolerability of LDN in patients with MS.² Markers of efficacy were a secondary objective. Forty patients, 18-65 years of age, with primary progressive MS (PPMS) were enrolled. Patients were also required to have at least one of the following symptoms: spasticity, pain, fa-

tigue, or depression. Patients received a starting naltrexone dose of 2 mg taken nightly for the first month followed by 4 mg nightly for the remainder of the study. The primary endpoints were safety and tolerability of LDN measured by the presence of major and minor adverse events and neurological deterioration. Neurological deterioration was measured by the extended disability standard scale (EDSS). Secondary endpoints included changes in pain (visual analog scale), fatigue (fatigue severity scale), spasticity (Modified Ashworth Scale), and depression (Beck Depression Inventory). Overall, there was no significant change in neurological deficit. Forty-seven percent of patients showed a significant improvement from baseline in spasticity ($p=0.008$), which persisted for one month after naltrexone was stopped. There was no significant improvement in fatigue or depressive symptoms, and pain actually worsened during treatment. Adverse events that occurred most often included irritability ($n=5$), hematological abnormalities ($n=14$), and urinary tract infections (UTIs) ($n=8$). The authors concluded that LDN was well tolerated in patients with PPMS; however, further studies are needed to evaluate naltrexone's potential for efficacy. Limitations to this study include the open-label study design, small number of patients, and lack of a control group.²

A randomized, phase III, placebo-controlled, crossover study assessed the effects of naltrexone on quality of life in patients with MS.³ The results were presented in a poster presentation at the World Congress on Treatment and Research in Multiple Sclerosis. Eighty patients were randomized to receive either 4.5 mg LDN or placebo for eight weeks, followed by a one-week wash-out period prior to crossing over to the other therapy for another eight weeks. Seventy patients completed the trial (nine voluntarily withdrew, one withdrew secondary to an unrelated medical condition) but 10 people were dropped due to incomplete data. LDN significantly improved the mental health component summary score of the quality of life questionnaire (3.3 point difference, $p<0.01$), the mental health inventory (6.0 point difference, $p<0.01$), the pain effects scale (1.6 point difference, $p<0.04$), and the perceived deficits questionnaire (2.4 point difference, $p=0.05$). Naltrexone therapy was well tolerated, and only vivid dreams were

reported during the first week of therapy. The authors concluded that LDN appeared to improve mental, but not physical, quality of life measures in patients with MS.³

LDN exerts its therapeutic effect by causing the prolonged release of endogenous opioids. It may improve mental quality of life and spasticity in patients with MS; however, it does not appear to improve pain or fatigue. Though LDN appears to be helpful at improving some symptoms of MS, more data is needed to determine the clinical effectiveness and long-term safety of LDN therapy in patients with MS.

By Jordan Stone, Pharm. D. Candidate

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Currently the only oral anticoagulant recommended for the prevention of thromboembolism in patients with atrial fibrillation is warfarin. Although effective, warfarin is associated with numerous drug and food interactions, requires routine blood sampling to monitor the therapeutic range, and has a high discontinuation rate. Dabigatran is an oral thrombin inhibitor that is being studied for the prevention of thromboembolism. A randomized, multicenter, open-label study assessed whether dabigatran is a clinically relevant alternative to warfarin in patients with atrial fibrillation.

The study recruited 18,113 patients from 951 clinical centers in 44 countries. Patients greater than 75 years of age (or 65-74 years plus diabetes mellitus, hypertension, or coronary artery disease) with documented atrial fibrillation and at least one of the following were included: previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, or New York Heart Association class II or higher heart failure within six months before screening. Patients with severe heart valve disorder, a previous stroke, increased risk of bleeding, or kidney and liver disease were excluded. Patients were randomized to receive either dabigatran 110 mg or 150 mg twice daily in a blinded fashion or open-label warfarin adjusted to maintain an international normalized ratio (INR) between 2.0 and 3.0. The average follow-up time was two years,

and patients were assessed two weeks after randomization and at months one and three, then every three months in the first year and every four months in the second year. The primary endpoint was stroke or systemic embolism. The primary safety endpoint was major bleeding. Secondary endpoints included, stroke, systemic embolism, death, myocardial infarction (MI), pulmonary embolism (PE), and transient ischemic attack. The authors also specified a primary net clinical benefit outcome which was the composite incidence of stroke, systemic embolism, PE, MI, major bleeding, or death.

The primary outcome occurred in 1.53% of patients per year in the 110 mg dabigatran group, 1.11% of patients per year in the 150 mg dabigatran group, and 1.69% of patients per year in the warfarin group. Both dabigatran groups were considered non-inferior to warfarin ($p < 0.001$); however, 150 mg dabigatran was considered superior to warfarin (relative risk, 0.66; 95% confidence interval, 0.53-0.82; $p < 0.001$). Significantly less major bleeding occurred in the 110 mg dabigatran group compared to warfarin (2.71% vs. 3.36%, $p = 0.003$); however, there was no significant difference in bleeding rate between warfarin and dabigatran 150 mg. Dabigatran 150 mg was also associated with a significantly higher rate of major gastrointestinal bleeding. Side effects for all three groups were similar; however, dyspepsia

occurred more often with dabigatran (5.8% vs. 11.3-11.8%, $p < 0.001$). Overall, there was no significant difference between groups in the net clinical benefit. This study was limited by the potential for bias from the sponsor, which is also the manufacturer of dabigatran. The administration of warfarin in an open-label fashion could also contribute to bias in this study.

SUMMARY: Dabigatran 110 mg is as effective as warfarin at lowering the risk of systemic embolism in patients with atrial fibrillation, with a lower risk of major bleeding. Dabigatran 150 mg is slightly more effective than warfarin with a similar risk of bleeding.

Connolly S, Ezekowitz M, Yusuf P, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Eng J Med 2009;361. Epub August 30, 2009.

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