Dual Renin-Angiotensin System Blockade in Heart Failure

We wish to comment, specifically, on Dr. Messerli’s remarks about the value of dual renin-angiotensin system blockade in heart failure (1). There are only 2 prospectively designed, adequately sized, and appropriately powered trials that examined the effect of adding an angiotensin receptor blocker to background therapy, including an angiotensin-converting enzyme (ACE) inhibitor, in patients with heart failure. Both showed a statistically significant and clinically meaningful reduction in the primary or coprimary mortality-morbidity composite outcome (2,3). Furthermore, the surrogate benefits of angiotensin receptor blockers added to ACE inhibitors “moved in parallel” with the benefits on clinical outcome (4,5). The mortality/morbidity benefits were seen despite the expected and modest increase in risk of renal dysfunction, hyperkalemia, and hypotension. Regulatory authorities decreed that the benefits outweighed the risks sufficiently to lead to worldwide approval of this combination for symptomatic patients with chronic heart failure and a low left ventricular ejection fraction, with appropriate monitoring to minimize adverse effects (6). International guidelines committees also drew a conclusion that was different from that of Dr. Messerli (7). The most recent guidelines even gave the combination the strongest recommendation (Level of Evidence: A, Class I) to prevent hospital admission for heart failure, a distressing and prognostically important outcome in these higher-risk patients remaining symptomatic despite treatment with an ACE inhibitor (8,9). We believe that patients would be better off if physicians adhere to authoritative guidelines and apply the evidence in practice.

John J. V. McMurray, MD
Christopher B. Granger, MD
Jan Östergren, MD, PhD
Salim Yusuf, MB, DPhil
Marc A. Pfeffer, MD, PhD
*Karl Swedberg, MD, PhD
*University of Glasgow
BHF Glasgow Cardiovascular Research Centre
126 University Place
Glasgow, Scotland G128TA
United Kingdom
E-mail: j.mcmurray@bio.gla.ac.uk

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Dual Renin-Angiotensin System Blockade and Kidney Disease

Based on the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) study dealing with renal outcomes (1), Messerli (2) concluded that albuminuria can no longer be regarded as a valid surrogate end point in renal disease and that dual renin-angiotensin system (RAS) blockade is dead until further notice. Since these interpretations have major importance, a meticulous analysis of the ONTARGET study findings is warranted. The ONTARGET study was conducted in 25,620 participants with low risk of chronic progressive kidney disease, except the 263 patients wrongly enrolled with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m². The mean urinary albumin/creatinine ratio was 0.81 mg/mmol (7.2 mg/g), mean eGFR 73.6 ml/min/1.73 m² with a sustained rate of decline < 1 ml/min/year. The primary renal end point was a composite of any dialysis, doubling of serum creatinine, and death.

The need for dialysis was established arbitrarily without any predetermined protocol, and data were assessed post-hoc with a questionnaire to all sites. Serum creatinine was measured locally, and the local methods were not calibrated to a standard. Change in
creatinine method from Jaffe to enzymatic assays was not accounted for. Doubling of serum creatinine in major renal outcome trials are confirmed by a second measurement of serum creatinine, usually a month later than the first abnormal value (3,4). No such confirmatory measurements were carried out in the ONTARGET study. Single central measures of urinary albumin/creatinine ratio were carried out at baseline, at 2 years, and at the end of the study. Repeated determinations are generally applied in renal outcome trials due to huge variation in this ratio. The ONTARGET study was not powered to detect differences in renal outcomes.

The primary renal outcome was driven by death (approximately 84% of all the events). A secondary renal outcome; any dialysis or doubling of serum creatinine was similar with telmisartan (n=189) and ramipril (n=174), and more frequent with combination therapy (n=212, p=0.038 vs. ramipril, but p=NS vs. telmisartan). In 3 of 165 originally reported cases of dialysis (5), later information revealed that no dialysis took place. In 3 additional cases, no information could be obtained regarding acute (<2 months) or chronic dialysis (>2 months) (n=61 [38.4%] dealt with acute dialysis for various reasons but not for hyperkalemia). Removing acute dialysis from the renal end point led to insignificant differences between the 3 groups. Treatment trials in chronic kidney disease never include acute dialysis in their primary end point (3,4,6,7). The number of patients in chronic dialysis was very low (0.36% to 0.40%) and nearly identical in the 3 arms.

The initial eGFR decline from baseline to 6 weeks was, as expected, significantly bigger during dual RAS blockade. This initial reversible hemodynamic phenomenon is well known, and mainly due to lowering of glomerular capillary hydraulic pressure (8,9). The sustained decline in eGFR (ml/min/year) from 6 weeks to final was 0.27 (ramipril), 0.44 (telmisartan), and 0.53 (combined) (p<0.0001). These sustained reductions in eGFR are less than normally expected due to aging (0.6 to 1.1 ml/min/year).

All groups had a rise from baseline to final in albumin/creatinine ratio: 31% (ramipril), 24% (telmisartan), and 21% (combined). These findings are very surprising since previous studies dealing with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in kidney disease nearly always showed a reduction (10).

The ONTARGET study, investigating RAS blockade in a population with low risk for progressive kidney disease, applying insufficiently measured renal end points, confounded by death and acute dialysis, has resulted in inconclusive evidence and misinterpretation of the role of dual RAS blockade and importance of albuminuria as a valid surrogate end point for renal disease. We echo the final statement in the Lancet editorial on the ONTARGET study: “A properly done prospective trial in patients with advanced proteinuric chronic kidney disease is still needed to answer definitively the question about efficacy of combination therapy to block the RAS on progression of chronic kidney progression” (11). The proposed designed study is ongoing: the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) study (12).

Hans-Henrik Parving, MD
Barry M. Brenner, MD
John J. V. McMurray, MD
Dick de Zeeuw, MD
Steven M. Haffner, MD
Scott D. Solomon, MD

In writing a viewpoint article on dual renin-angiotensin system (RAS) blockade (1), I seem to have inadvertently stepped into a hornet’s nest. The ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) trial, like all studies, can be criticized, and in retrospect there is always “should’ve, would’ve, could’ve.” This is particularly true when findings go against the grain of what is perceived as a major paradigm, namely, albuminuria/proteinuria being synonymous with renal outcome. Clearly, this paradigm was shattered by the ONTARGET study: in patients with relatively low urinary albumin excretion, dual RAS blockade compared with ramipril alone was associated with a decrement in glomerular filtration rate despite less progression in albuminuria. Thus, urinary albumin excretion can no longer be taken as a sign of renal outcome. Similarly, preventing microalbuminuria or the transition from

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Reply

Nish Chaturevedi, MD
Marc A. Pfeffer, MD
*Department of Medical Endocrinology, Rigshospitalet
Blegdamsvej 9, 2100 Ø
Copenhagen
Denmark
E-mail: hhparving@dadlnet.dk
doi:10.1016/j.jacc.2009.02.074