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## Bardoxolone Methyl in Type 2 Diabetes and Advanced Chronic Kidney Disease

**TO THE EDITOR:** The increased risk of heart failure and cardiovascular events that led to early termination of the BEACON (Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events) trial, reported by de Zeeuw et al. (Dec. 26 issue),<sup>1</sup> may not be due to direct effects of bardoxolone methyl on the cardiovascular system. The transcription factor Nrf2 (nuclear factor [erythroid-derived 2]–related factor 2) is known to regulate the expression of multiple drug-metabolizing enzymes as well as transporters, including ABCC2 (multidrug resistance–associated protein 2),<sup>2</sup> which influences the bioavailability of angiotensin-receptor blockers.<sup>3</sup> Therefore, reduced bioavailability of angiotensin-receptor blockers or angiotensin-converting–enzyme inhibitors (received by approximately 90% of patients in the BEACON trial) because of increased excretion in the bardoxolone methyl group may have led to partial loss of the cardioprotective, renoprotective, and antihypertensive effects of these agents. Nrf2 remains a viable drug target, as evidenced by the approval of BG-12 (dimethyl fumarate) for multiple sclerosis. In contrast to the BEACON trial, the patients enrolled in the two phase 3 trials of BG-12<sup>4,5</sup> were not reported to receive other disease-modifying agents; this minimized the potential for drug–drug interactions. Future trials of Nrf2 activators in patients with chronic diseases who are receiving other agents should address potential drug–drug interactions in the preclinical and phase 2 stages.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** With regard to the article by de Zeeuw et al. and the corresponding editorial by Himmelfarb and Tuttle<sup>1</sup>: the BEACON study involved patients who had type 2 diabetes mellitus and stage 4 chronic kidney disease — a stage in which irreversible damage could be detected in the majority of nephrons. The remaining nephrons in stage 4 chronic kidney disease have hyperfiltration, which increases proteinuria, and any therapy that increases the glomerular filtration rate (GFR) aggravates existing single-nephron hyperfiltration. In the BEAM (52-Week Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes)<sup>2</sup> and BEACON studies, a bardoxolone-induced increase in GFR could explain the increase in proteinuria.

It is feasible that therapy that would decrease single-nephron hyperfiltration could prolong nephron survival. However, combined renin–angiotensin–aldosterone blockade, which decreases single-nephron hyperfiltration, did not show benefit (as shown in the Veterans Affairs Nephropathy in Diabetes [VA NEPHRON-D]<sup>3</sup> trial and the Aliskiren Trial in Type 2 Diabetes Using Cardio-renal Endpoints [ALTITUDE]<sup>4</sup>), perhaps because earlier initiation of such therapy would be necessary (earlier than stage 3a chronic kidney disease).

The decrease of overt proteinuria and preservation of nephrons should be the true therapeutic goal in patients with diabetes and chronic kidney disease, with or without blockade of the renin–angiotensin–aldosterone system.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** Himmelfarb and Tuttle, commenting on the BEACON trial of bardoxolone in diabetic kidney disease, rightly express disappointment at the “failure” of this new treatment. They also note the high rate of failure in phase 3 clinical trials in general, and they argue that better approaches to trial design and execution are needed. Recently, Djulbegovic and colleagues<sup>1</sup> showed that current trial approaches provide the most informative results. These investigators analyzed the outcomes of published and unpublished phase 3 randomized clinical trials during the past 50 years, and they found that just over 50% of these trials showed that the new treatment was better than the standard one. Although this seems disappointing, they show statistically that this modest success rate is the inevitable consequence of pretrial equipoise, and that trials are most informative when they have only a 50% chance of success. Although many aspects of clinical-trial design and dissemination can and should be improved, negative trial results should be lauded as much as positive ones; both advance medical science. It is only trials with poor designs that do not.

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No potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** Chartoumpakis and Sykiotis are correct that investigators who design clinical trials involving patients with chronic diseases should be mindful of the potential for drug–drug interactions. We also agree that Nrf2 activation

remains a viable therapeutic target in chronic kidney disease. However, there is no evidence that the imbalance in adverse effects can be explained by the mechanism they proposed, since the use or nonuse of inhibitors of the renin–angiotensin–aldosterone system did not appear to modify the effects of bardoxolone methyl.

Molnár and colleagues remind readers of the lack of material benefit (i.e., fewer deaths, fewer cardiovascular events, or slowing of progression of chronic kidney disease) associated with the use of dual-agent blockade of the renin–angiotensin–aldosterone system in diabetic kidney disease, as compared with the use of a single agent. We would not prioritize clinical trials of two or more inhibitors of the renin–angiotensin–aldosterone system in chronic kidney disease, with or without bardoxolone methyl, given the available evidence regarding relative safety and efficacy.

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Since publication of their article, the authors report no further potential conflict of interest.

**THE EDITORIALISTS REPLY:** Molnár and colleagues point to glomerular hyperfiltration to explain the results of the BEACON and VA NEPHRON-D trials. They suggest that initiating treatment at earlier stages of disease might increase the chance of therapeutic efficacy. We both served on the data and safety monitoring committee in the VA NEPHRON-D study and were directly involved with the recommendation for early termination because of safety concerns. Since both the BEACON and VA NEPHRON-D trials were terminated early because of adverse safety signals, the efficacy of these approaches has not been completely determined, even in the study populations. It is possible that the safety of the respective therapeutic strategies could be improved by restricting enrollment to patients at an earlier stage of disease and at lower risk for adverse events. A search for therapies that can provide synergistic benefit with moderate inhibition of the renin–angiotensin system is clearly an ongoing high priority for improving outcomes in patients with diabetic kidney disease.

Ellison notes that ethical clinical trials should be testing hypotheses based on equipoise; thus, we should expect approximately 50% of trials to support the null hypothesis, whereby a new treatment will not prove to be better than a standard one. We agree completely with this philosophical premise and recognize that a well-designed and well-conducted “null study” is a successful trial. The treatment of diabetic kidney disease would have greatly advanced over the past several decades if 50% of relevant clinical trials had shown efficacy, which unfortunately has not been the case. Within the framework of equipoise, every effort should be made to maximize patient safety, which should always be the paramount concern in study design. The BEACON trial was terminated early because of strong adverse safety signals in study participants who received baxdaxolone methyl as compared with those who received placebo. The study did not continue long enough to fully determine the efficacy of the drug for slowing the progression of diabetic

kidney disease. We continue to emphasize the need for greater rigor in preclinical testing, careful evaluations of dosing, improved methods for off-target toxicity testing, and biomarker development. We also stress the need for business and regulatory environments that foster innovation. Other authors have also recently called for similar approaches to improving the drug-development process.<sup>1-3</sup>

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Since publication of their article, the authors report no further potential conflict of interest.

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## Overall Survival in Renal-Cell Carcinoma with Pazopanib versus Sunitinib

**TO THE EDITOR:** In the August 22 issue,<sup>1</sup> we reported on a phase 3 trial showing the noninferiority, with respect to progression-free survival, of pazopanib versus sunitinib as first-line treatment for clear-cell, metastatic renal-cell carcinoma, as assessed by independent review. We now report the results of the final analysis of overall survival. Overall survival, a secondary end point, was defined as the time from randomization to death from any cause. The final analysis of overall survival in the intention-to-treat population was to be performed when 650 patients had died or 2 years after the last patient was enrolled. Overall survival was summarized by means of Kaplan–Meier curves and compared with the use of a stratified log-rank test. The strata were baseline Karnofsky performance-status score (70 or 80 vs. 90 or 100 on a scale from 0 to 100, with 100 indicating normal functioning and lower scores indicating increasing disability), baseline level of lactate dehydrogenase (>1.5 vs. ≤1.5 times the upper limit of the normal range), and previous nephrectomy (yes vs. no).

At data cutoff on September 30, 2013, a total

of 334 of 557 patients who were randomly assigned to pazopanib (60%) and 335 of 553 patients who were randomly assigned to sunitinib (61%) had died. Overall survival was similar in the two groups (hazard ratio for death with pazopanib vs. sunitinib, 0.92; 95% confidence interval [CI], 0.79 to 1.06;  $P=0.24$  by a stratified log-rank test) (Fig. 1). Median overall survival was 28.3 months in the pazopanib group (95% CI, 26.0 to 35.5) and 29.1 months in the sunitinib group (95% CI, 25.4 to 33.1).

Subgroup analyses according to Memorial Sloan-Kettering Cancer Center risk criteria<sup>2</sup> showed a median overall survival of 42.5 months among 151 patients who received pazopanib (95% CI, 37.9 to not reached) and 43.6 months among 152 patients who received sunitinib (95% CI, 37.1 to 47.4) in a group of patients with favorable-risk disease (hazard ratio for death with pazopanib, 0.88; 95% CI, 0.63 to 1.21). The median overall survival was 26.9 months among 322 patients who received pazopanib (95% CI, 23.1 to 35.6) and 26.1 months among 328 patients who received sunitinib (95% CI, 20.7 to 31.6) in