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## The Extinguished Beacon of Bardoxolone: Not a Monday Morning Quarterback Story

John A. Tayek, MD<sup>1,\*</sup> and Kamyar Kalantar-Zadeh, MD, MPH, PhD<sup>2,3</sup>

<sup>1</sup>Division of Endocrinology, Harbor-UCLA Medical Center, Torrance, CA

<sup>2</sup>Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology & Hypertension, University of California Irvine Medical Center, Orange, CA

<sup>3</sup>Department of Epidemiology, UCLA Filing School of Public Health, Los Angeles, CA

### Text of the Editorial

The rise and fall of bardoxolone methyl, an oral antioxidant and anti-inflammatory modulator once hoped to be the ultimate silver bullet against diabetic nephropathy, is not a unique story in medicine. What was distinctive in this story, however, was the dramatically high level of enthusiasm about the miraculous effect of the drug after the publication of its Phase II trial in CKD patients, known as the BEAM Study.<sup>1</sup> In the said double-blind, randomized, placebo-controlled trial, 227 diabetic CKD patients (eGFR 20–45 ml/min/1.73 m<sup>2</sup>) who had received placebo or bardoxolone at target doses of 25, 75, or 150 mg daily for 24 weeks, showed significant rise in the mean eGFR of +8.2, +11.4, and +10.4 ml/min/1.73 m<sup>2</sup>, respectively, compared to placebo, and the improvements apparently persisted up to 52 weeks.<sup>1</sup> The main mechanism of action of bardoxolone was believed to be the anti-inflammatory feature that was attributed to the activation of Nrf2, a ubiquitous transcription factor involved in the up-regulation of cytoprotective genes, inhibition of NF-κB, and decreased oxidative stress.<sup>2</sup>

The reported kidney function improvement of bardoxolone was remarkable, but so was the adverse event profile of the drug, which included worsening proteinuria, massive weight loss, muscle spasm, hypomagnesemia, liver function disarrays, and gastrointestinal effects, among others<sup>1</sup> (see Table 1). The calculation of eGFR in the BEAM Study was based on the level of serum creatinine, which is influenced by muscle mass and probably dietary meat intake.<sup>3,4</sup> A dramatic weight loss differential of 10 to 20 lbs. was observed in patients who received bardoxolone vs. placebo; to be exact the bardoxolone weight loss was 7.7 to 10.1 kg, as compared to 2.4 kg in the placebo group.<sup>3,5</sup> In a study, weight loss in diabetics patients reduced serum creatinine from 2.0 to 1.5 mg/dl (p<0.05), and eGFR increased by 13 ml/min.<sup>6</sup> In another study on obesity, an 8% weight loss increased eGFR by 8.9 ml/min by means of reducing serum creatinine.<sup>7</sup> Similarly fasting for Ramadhan increased eGFR likely due to loss of muscle and/or reduction dietary meat intake.<sup>8</sup> In dialysis patients serum creatinine is a robust correlate of muscle mass.<sup>4</sup> In the BEAM Study the 9% loss of weight, and likely skeletal muscle, probably reduced serum creatinine and increased eGFR by 8 to 11 ml/min.<sup>1</sup> The MDRD equation in this study uses serum creatinine, age, sex and race to estimate GFR.<sup>9</sup> Forty-two to 61% of patients on bardoxolone in the BEAM Study had

**Correspondence:** Kamyar Kalantar-Zadeh, MD, MPH, PhD, Harold Simmons Center for Chronic Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, and 1124 West Carson Street, C1-Annex, Torrance, CA 90502, USA, Phone: 310-222-3891, Fax: 310-782-1837, kamkal@ucla.edu.

\*JAT is professor-in-residence of medicine at UCLA David Geffen School of Medicine and attending physician at Harbor-UCLA Medical Center,

muscle spasm reflecting potential muscle loss.<sup>1</sup> Interestingly, the quartile with the greatest increase in eGFR (26.4 ml/min) had the largest weight loss (11.3 kg).<sup>1</sup> Whereas weight reduction should generally be considered favorable in overweight and obese diabetic patients, any unintentional weight loss is inevitably associated with some degree of loss of lean body mass including skeletal muscles.<sup>10, 11</sup> Hence, the said bardoxolone associated weight loss may have led to muscle wasting with a subsequent decline in the serum creatinine level, leading to misleadingly calculated rise in eGFR,<sup>3, 9</sup> not to mention that muscle loss per se may be associated with poor outcomes in both CKD and the general population.<sup>12, 13</sup>

Another dramatic and rather paradoxical complication of bardoxolone was an increase in urinary albumin excretion that paralleled the increase in eGFR in the BEAN Study.<sup>1</sup> Bardoxolone has a similar in structure to cyclopentenone prostaglandins, which can cause renal vasodilatation.<sup>14, 15</sup> It is therefore possible that bardoxolone may have increased the eGFR by causing *afferent* arteriolar dilatation and increasing intra-glomerular pressure. Indeed most of the effect of bardoxolone on the eGFR happened within the first 4 weeks of therapy.<sup>16</sup> This hemodynamic effect is in sharp contradistinction to the ACE inhibitor associated *efferent* arteriolar dilatation and may result in the short-term rise in GFR, which is somewhat similar to what is seen in early stages of diabetic nephropathy, whereas in long-term the glomerular damage from increased intra-glomerular pressure may lead to accelerated decline in renal function.<sup>15</sup> Higher intra-glomerular pressure may also explain the paradoxical increase in albuminuria observed in participants receiving bardoxolone in the BEAN Study.<sup>1</sup> Indeed, the decrease in the eGFR and albuminuria in the intervention groups 4 weeks after the study completion supports the said notion that the effect may have been from hemodynamic rather than anti-inflammatory factors.<sup>15</sup> Hence, bardoxolone could affect glomerular hemodynamics and possibly tubular function, and thus influencing the eGFR without truly improving renal function.

It is important to note that only 42% of patients who were receiving 75 mg per day and 25% of patients who were receiving 150 mg per day bardoxolone in the Phase II BEAM Study were still receiving the assigned dose at the end of the study.<sup>16</sup> This low rate of compliance with the assigned dose was presumably due to an increased incidence of adverse effects and should have warned the investigators and consultants of the Phase III BEACON trial that they inflated adverse events and more unfavorable complications would be expected with a Phase III trial.

The unexplained hypomagnesemia developed in a dose-dependent manner in 26% of bardoxolone-treated patients compared with 5% of patients in the placebo group.<sup>17</sup> Ironically, magnesium has anti-inflammatory and anti-oxidant properties, and it was warned that hypomagnesemia, a predictor of worse CKD progression, might abrogate the long-term beneficial effects of bardoxolone.<sup>17</sup> Other side effects of bardoxolone included gastrointestinal symptoms and liver function abnormalities, as well as muscle spasm.<sup>1</sup> The latter may be reminiscent of structural damage to the muscle fibers and myocytes during the muscle wasting of the observed weight loss. Moreover, among the yet-to-be-reported BEACON study, there were apparently significant number of deaths and heart failure in the bardoxolone group,<sup>18</sup> which may be due to collective effects of the above-mentioned deleterious events or from additional adverse effects of the drug.

In their rush to move forward with the Phase III trial, the investigators argued that no change in 24-hour urinary creatinine excretion was observed after 8 weeks of treatment with bardoxolone in a preliminary study.<sup>19</sup> It was never explained as to why the massive weight loss and the paradoxical increase in proteinuria happened, nor were any of the other side effects adequately examined (Table 1). The investigators chose to ignore these

warnings<sup>3, 5, 15–17</sup> and to proceed with the trial of long-term outcomes (Bardoxolone Methyl Evaluation in Patients with CKD and Type 2 Diabetes: The Occurrence of Renal Events [BEACON]; NCT01351675). Beacon had begun in June 2011, aiming to recruit 2,000 patients with chronic kidney disease or type 2 diabetes and test whether bardoxolone delayed their progression to end-stage renal disease versus placebo, as described in this issue of the *journal*.<sup>18</sup> However, BEACON Study was stopped on the recommendation of its independent data-monitoring committee, which apparently reported the safety imbalance between the active and placebo arms. Reata, the manufacturer of bardoxolone methyl in the USA, has not yet disclosed any detailed information about the nature of the serious adverse events or how many deaths happened in each arm, although these data will eventually be reported. Reata also announced that all other studies of bardoxolone in CKD would also be halted. According to [clinicaltrials.gov](http://clinicaltrials.gov) there were several ongoing phase I or II studies, including a large phase II trial in 180 volunteers to test the effect of bardoxolone on cardiovascular measures. Prior to October 2012, two phase I and three phase II studies have been completed in a total of 474 subjects according to [clinicaltrials.gov](http://clinicaltrials.gov).

Undoubtedly, CKD associated with type 2 diabetes is the leading cause of kidney failure both in the United States and globally. Inflammation and oxidative stress contribute to disease progression. Bardoxolone's effect on diabetic nephropathy was obviously too good to be true, and the adverse event profile was overwhelming. Echoing the righteous criticisms voiced back then<sup>3, 5, 15–17</sup> is not a mere “Monday morning quarterback” story but this is to reiterate that there were legitimate criticisms from experts who were clearly capable of second-guessing adverse outcomes and the high failure likelihood of the BEACON study, given clear data from the BEAM Study. The valuable lesson is that the enthusiasm and hope for ultimate cure of diabetic nephropathy should not cloud our judgment when designing and conducting future trials, or similar negative outcomes can be observed with any trials where the investigator chose to ignore the prior signs and loud warnings.<sup>20</sup>

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**Table 1**

Potential adverse effects of bardoxolone methyl in CKD patients

<b>Adverse effects</b>	<b>Comments</b>
<b>Weight loss</b>	Not clear if fat loss is more or less than muscle loss. May lead to drop in serum creatinine leading to erroneously estimated low eGFR.
<b>Proteinuria</b>	Can be related to hyperfiltration as a results of increases intraglomerular pressure.
<b>Increased GFR</b>	May be similar to hyperfiltration in early diabetic nephropathy, or due to erroneous estimate of GFR related to using serum creatinine
<b>Muscle spasm</b>	May be related to hypomagnesemia or damage to myocytes and muscle wasting
<b>Hypomagnesemia</b>	Apparently no obvious association with potassium disarrays. Impact on QT interval in EKG was not well established
<b>Gastrointestinal effects</b>	Mild to moderate intolerance of undetermined significance but in real world scenario could become a major side effect.
<b>Liver function disorders</b>	Increased level of alanine aminotransferase without further data
<b>Anti-inflammatory effect</b>	Generally is assumed to be a favorable effect, although long-term effects such as increased risk of leukemia or tuberculosis risk is not known
<b>Increased death risk</b>	The main cause of BEACON Study discontinuation. The death etiology is yet to be determined.
<b>(Worsening) heart failure</b>	Not clear whether heart failure can happen as a result of bardoxolone, pending the full disclosure of BEACON data.