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Effects of bardoxolone methyl on body weight, waist circumference and glycemic control in obese patients with type 2 diabetes mellitus and stage 4 chronic kidney disease

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ABSTRACT

Aims: Obesity is associated with progression of chronic kidney disease (CKD). Treatment with bardoxolone methyl in a multinational phase 3 trial, Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes (BEACON), resulted in increases in estimated glomerular filtration rate (eGFR) with concurrent reductions in body weight. We performed post-hoc analyses to further characterize reductions in body weight with bardoxolone methyl.
Methods: Eligible patients with type 2 diabetes (T2DM) and CKD stage 4 (eGFR 15 to <30 mL/min/1.73 m^2) were randomized 1:1 to receive once-daily oral dose of bardoxolone methyl (20 mg) or placebo.
Results: BEACON enrolled 2185 patients. Patients randomized to bardoxolone methyl experienced significant reductions in body weight from baseline relative to patients randomized to placebo (−5.7 kg; 95% CI: −6.0 to −5.3 kg; $p < 0.001$). In patients randomized to bardoxolone methyl, rate and magnitude of body weight loss were proportional to baseline BMI. Bardoxolone methyl resulted in significant reductions in waist circumference and improved glycemic control.
Conclusions: Bardoxolone methyl resulted in significant weight loss in a generally obese patient population with T2DM and stage 4 CKD, with the magnitude and rate dependent on baseline BMI.

1. Introduction

Obesity increases the risk for type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease, as well as progressive chronic kidney disease.[1,2] Obesity is characterized by changes in adipose tissue including the deposition of fat, enlargement of adipocytes, and a pro-inflammatory phenotype that leads to the development of insulin resistance and metabolic syndrome.[3–5]

Bardoxolone methyl and related analogs have been shown to improve glycemic control, decrease lipid accumulation, and reduce inflammation in multiple animal models of diabetes and obesity,[6–9] while also improving kidney function and preventing structural injury in models of kidney disease.[10–13] Through activation of nuclear factor erythroid-derived 2-related factor 2 (Nrf2) and inhibition of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), bardoxolone methyl up-regulates the antioxidant response and suppresses pro-inflammatory signaling to reduce oxidative stress and inflammation and promote mitochondrial function.[14,15]

Bardoxolone methyl has also been studied in at least seven clinical trials enrolling approximately 2600 patients with type 2 diabetes (T2DM) and CKD. Improvements in kidney function, assessed using measured inulin clearance, measured creatinine clearance, and estimated glomerular filtration rate (eGFR), have been observed consistently with bardoxolone methyl treatment in several clinical trials.[16–19] The largest of these was a multinational, randomized, double-blind, placebo-controlled phase 3 outcomes trial, which enrolled 2185 patients with T2DM and CKD stage 4 [Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: The Occurrence of Renal Events (BEACON)].[18] The BEACON trial was terminated early because of safety concerns, largely driven by a significant increase in heart failure events within the first four weeks of exposure. Patients randomized to bardoxolone methyl experienced significantly improved kidney function. Lower serum creatinine concentrations (corresponding to higher eGFRs), along with lower serum concentrations of urea nitrogen, uric acid, and phosphorus were observed. In concert with improved kidney function, reductions in body weight were also observed in bardoxolone methyl-treated patients. Given that serum creatinine concentration depends on its clearance as well as its generation as a function of skeletal muscle mass[20] and to address the question as to whether the observed decrease in serum creatinine was related to improved GFR versus a loss of muscle mass, we performed post-hoc analyses to further characterize reductions in body weight induced by bardoxolone methyl treatment.

2. Materials and methods

2.1. Study design

The BEACON trial (NCT01351675) was a phase 3, randomized, double-blind, parallel-group, international, multicenter trial of once-daily administration of bardoxolone methyl (20 mg), as compared with placebo. Previous publications describe the BEACON trial design in detail.[18,21] The study protocol was approved by Institutional Review Boards or Ethics Committees at participating sites and all patients provided written informed consent.

BEACON enrolled adults with type 2 diabetes mellitus and stage 4 CKD, corresponding to an eGFR of 15 to <30 mL/min/1.73 m^2. Patients were randomized 1:1 to once-daily administration of bardoxolone methyl or placebo. Patients received background conventional therapy that included inhibitors of the renin–angiotensin–aldosterone system, insulin or other hypoglycemic agents, and, when appropriate, other cardiovascular medications.

Estimated GFR was calculated using serum creatinine and the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. Estimated GFR and vital signs (including body weight and Quételet's (body mass) index (BMI)) were assessed every 4 weeks through Week 12, followed by assessments every 8 weeks thereafter. Waist circumference and hemoglobin A_{1c} (HbA_{1c}) were assessed every 24 weeks. A subset of the patients ($n = 174$, 8%) consented to additional 24-hour urine collections at baseline and Week 4; to assess whether the weight loss was derived from muscle mass or adipose tissue, we examined changes in urinary creatinine excretion over 24 h.

The primary composite endpoint of the trial was the time-to-first event in the composite outcome defined as end-stage renal disease (ESRD; need for maintenance dialysis, kidney transplantation, or renal death) or cardiovascular death. Secondary efficacy outcomes included the change in eGFR, time-to-first hospitalization for heart failure or death due to heart failure, and time-to-first event of a composite consisting of non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, or cardiovascular death.

2.2. Statistical analysis

We analyzed the BEACON population using summary statistics to compare changes in body weight, waist circumference, and HbA_{1c} in patients randomized to bardoxolone methyl or placebo in accordance with the intention-to-treat principle. One-sample (paired) t-tests were used for comparing mean changes to zero and two-sample t-tests were used to compare the difference in means between bardoxolone methyl and placebo groups. Longitudinal analyses of body weight were also used to compare mean changes in body weight between the bardoxolone methyl and placebo groups. As previously described, mixed-effects regression used post-baseline body weight as the response variable; treatment group, time, the interaction of treatment group with time, interaction of baseline body weight with time; and continuous covariates (body weight at baseline, baseline eGFR and urinary albumin-to-creatinine ratio).[18]

3. Results

As previously published, from June 2011 through September 2012, a total of 2185 patients were randomized to receiving either bardoxolone methyl ($n = 1088$) or placebo ($n = 1097$).[18] Previous publications also describe the demographics and baseline characteristics of the patients randomized to bardoxolone methyl versus those randomized to placebo in BEACON,[22] which are summarized in Table 1, along with characteristics of the 174 patients who consented to 24-hour urine collections. The demographics and baseline characteristics for the subset of patients that consented to additional 24-hour urine collections were similar to that of the entire BEACON population and between patients randomized to bardoxolone methyl or placebo.

3.1. Weight

The majority of patients enrolled in BEACON were overweight or obese; 93% of patients had BMI ≥ 25.0 kg/m^2 at baseline. The mean BMI and body weights at baseline were 33.7 ± 7.1 kg/m^2 and 95.1 ± 22.0 kg for patients randomized to bardoxolone methyl ($n = 1088$), and 33.9 ± 7.2 kg/m^2 and 95.3 ± 21.1 kg for patients randomized to placebo ($n = 1097$). As previously reported, patients randomized to bardoxolone methyl experienced a significant reduction in body weight compared to placebo (−5.7 kg [95% CI: −6.0 to −5.3 kg]; $p < 0.001$).[18]

In patients randomized to bardoxolone methyl, the rate and magnitude of body weight loss were proportional to baseline BMI (Fig. 1). Body weight plateaued at 32 weeks in patients within the World Health Organization (WHO) lean and normal BMI groups at baseline (18.5 to 24.9 kg/m^2), while it continued to decline in patients who were overweight (25.0 to 29.9 kg/m^2) or obese (≥30 kg/m^2) at baseline.

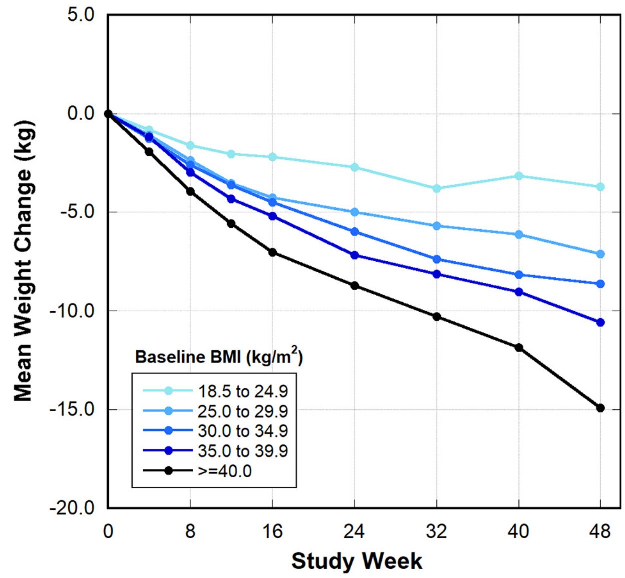

Fig. 1. Changes from baseline in body weight with bardoxolone methyl by baseline BMI. Mean changes from baseline in body weight (kg) for patients randomised to bardoxolone methyl stratified by baseline BMI categories using World Health Organization (WHO) classifications: Underweight (< 18.5 kg/m^2): $n = 0$ (0%); normal weight (18.5 to 24.9 kg/m^2): $n = 78$ (7%); overweight (25.0 to 29.9 kg/m^2): $n = 269$ (24%); class I obesity (30.0 to 34.9 kg/m^2): $n = 334$ (31%); class II obesity (35.0 to 39.9 kg/m^2): $n = 231$ (21%); class III obesity (≥ 40.0 kg/m^2): $n = 175$ (16%).

3.2. Waist circumference

Bardoxolone methyl treatment significantly decreased waist circumference relative to baseline and relative to placebo at Weeks 24 and 48 ($p < 0.01$; Fig. 2, panel A). Bardoxolone methyl-treated patients had mean (±SD) decreases in waist circumference of −4.1 ± 8.0 cm ($n = 622$) at Week 24 and − 6.5 ± 9.3 cm ($n = 239$) at Week 48. In contrast, placebo-treated patients experienced minimal to no change in waist circumference at Week 24 and Week 48 (mean ± SD -0.4 ± 8.4 ($n = 717$) and 0.0 ± 8.6 ($n = 280$) at Weeks 24 and 48, respectively). Similar to changes in body weight, the magnitude of reductions in waist circumference with bardoxolone methyl treatment was proportional to baseline BMI; obese patients experienced more pronounced reductions in waist circumference compared with patients who were not obese (Fig. 2, panel B).

3.3. 24-Hour urinary excretion

As seen in Table 1, the mean baseline BMI and body weight for the subset of patients who consented to additional 24-hour urine collections were similar to that of the entire BEACON population. Accordingly, significant reductions in body weight were observed in patients randomized to bardoxolone methyl at Week 4 (mean ± SD = −0.7 ± 2.0 kg; $p = 0.03$ for bardoxolone methyl versus placebo). Conversely, mean (±SD) 24-hour urinary creatinine excretion with bardoxolone methyl was unchanged from baseline at Week 4 (1134 ± 394 mg versus 1191 ± 339 mg at baseline; $n = 61$) and was not significantly different from changes with placebo (Table 2; $p = 0.33$).

3.4. Hemoglobin A_{1c}

Mean baseline HbA_{1c} was 7.15 ± 1.27% and 7.10 ± 1.17% for patients randomized to bardoxolone methyl and placebo, respectively. Bardoxolone methyl treatment significantly decreased HbA_{1c} relative to baseline at Week 24 (−0.12 ± 1.04; $p = 0.0033$) and at Week 48 (−0.17 ± 1.13%; $p = 0.026$; Table 3); between group differences were also statistically significant at Week 24 and Week 48 (−0.13 ± 1.01, $p = 0.023$ and − 0.25 ± 1.13, $p = 0.014$, respectively), as HbA_{1c}

Table 1
Select demographics and baseline characteristics of BEACON patients.

	Intent-to-treat population		Patients with 24-hr urine collections	
	Placebo ($n = 1097$)	Bardoxolone methyl ($n = 1088$)	Placebo ($n = 87$)	Bardoxolone methyl ($n = 87$)
Age, yr (mean ± SD)	68.2 ± 9.4	68.9 ± 9.7	67.2 ± 10.3	67.8 ± 10.4
Female (n, %)	472 (43)	462 (42)	42 (48)	37 (43)
Race (n, %)				
Caucasian	848 (77)	846 (78)	61 (70)	68 (78)
Black	176 (16)	185 (17)	14 (16)	11 (13)
Other	73 (7)	57 (5)	12 (14)	8 (9)
Weight, kg (mean ± SD)	95.3 ± 21.1	95.1 ± 22.0	95.9 ± 24.1	94.3 ± 20.5
BMI, kg/m^2 (mean ± SD)	33.9 ± 7.2	33.7 ± 7.1	34.3 ± 7.9	33.7 ± 6.4
HbA_{1c}, % (mean ± SD)	7.10 ± 1.17	7.15 ± 1.27	6.97 ± 0.97	7.36 ± 1.54
Serum creatinine, mg/dl (mean ± SD)	2.7 ± 0.6	2.7 ± 0.6	2.8 (0.6)	2.7 (0.5)
eGFR, ml/min/1.73 m^2 (mean ± SD)	22.5 ± 4.6	22.4 ± 4.3	21.8 (4.2)	22.7 (4.3)
UACR, mg/g (geometric mean)	221	210	221	210
Insulin (n, %)	677 (62)	667 (61)	48 (55)	53 (61)

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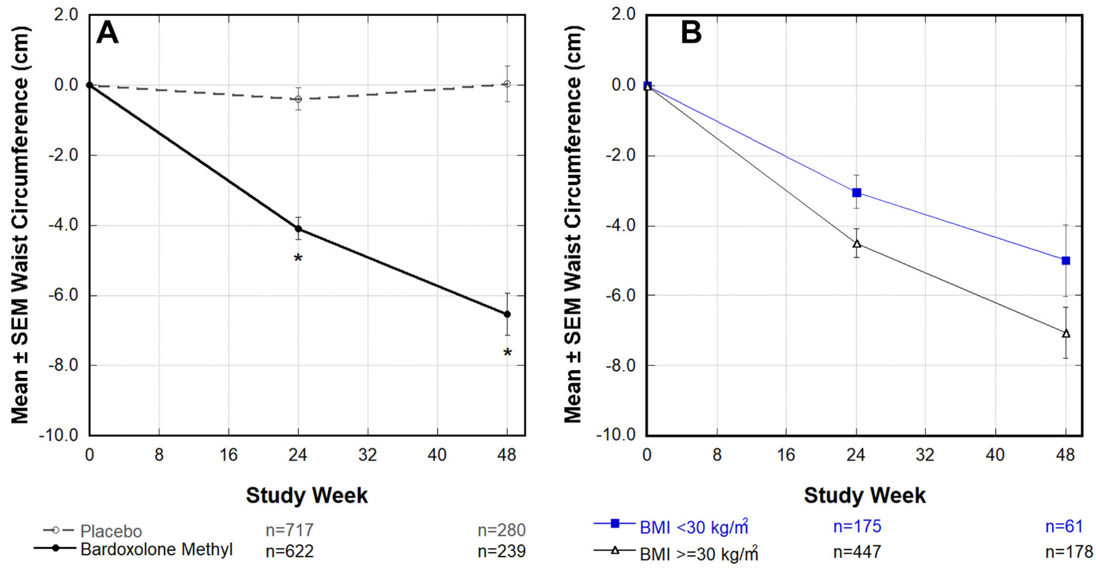

Fig. 2. Changes from baseline in waist circumference. Left. Mean changes (± SEM) from baseline in waist circumference (cm) for patients randomized to bardoxolone methyl or placebo in BEACON. * $p < 0.001$ versus placebo. Right. Mean changes (± SEM) from baseline in waist circumference for patients randomized to bardoxolone methyl stratified by non-obese baseline BMI (< 30 kg/m^2) versus obese baseline BMI (≥ 30 kg/m^2) categories.

values were unchanged in patients randomized to placebo. More importantly, reductions in HbA_{1c} induced by bardoxolone methyl were driven by results in patients with abnormal HbA_{1c} (>7.0%) at baseline; mean changes in HbA_{1c} after 48 weeks of bardoxolone methyl treatment were −0.53 ± 1.47% in patients with baseline $HbA_{1c} > 7.0\%$ (Table 3).

4. Discussion

Bardoxolone methyl treatment resulted in significant reductions in body weight in a generally overweight and obese patient population with T2DM and stage 4 CKD. The magnitude and rate of weight reductions were more pronounced in patients with higher baseline BMI. The loss in body weight was accompanied by a significant reduction in waist circumference, with declines proportional to both baseline body weight and BMI. Moreover, bardoxolone methyl significantly improved glycemic control with results driven by patients with HbA_{1c} above clinical practice guideline recommended targets at baseline. Finally, in a subset of patients who provided timed urine collections, there was no reduction in 24-hour urinary creatinine excretion, suggesting that the loss in body weight was not due to muscle wasting, but rather to loss of adipose tissue, findings consistent with the changes in waist circumference and glycemic control observed in the larger trial population. It is noteworthy that the BEACON trial protocol neither mandated nor recommended any particular diet, exercise or other lifestyle modifications that might account for the observed weight loss.

The trajectory and profile of increases in eGFR following treatment with bardoxolone methyl differ from that of the reductions in body weight; unlike mean changes from baseline in body weight, mean increases in eGFR with bardoxolone methyl were apparent by Week 4 of treatment. In a Japanese trial, bardoxolone methyl significantly increased measured GFR, as assessed by inulin clearance, in patients with T2DM and stage 3 CKD after 16 weeks of treatment compared to placebo,[19] demonstrating that bardoxolone methyl-mediated improvements in eGFR reflect true improvements in measured GFR.

Multiple studies in preclinical models of diabetes and obesity have demonstrated that bardoxolone methyl and its analogs reduce fat production and promote beta-oxidation of lipids to be used as fuel for energy production and reduced food intake.[6] These effects are associated with improved glucose tolerance and insulin sensitivity, reduced body fat, preservation of muscle mass, and increased metabolism and energy expenditure.[6,7,23] Moreover, bardoxolone methyl has also been shown to prevent hypothalamic inflammation, leptin resistance, and body weight gain in mice fed high-fat diets.[24] Although the mechanism of the weight loss associated with bardoxolone methyl treatment in humans is not fully understood, the prevention of leptin signaling impairments, maintenance of energy homeostasis, increased lipolysis of peripheral lipid stores, and improvements in glycemic control observed in preclinical studies may explain the reductions in body weight observed in patients with T2DM and CKD.

Strengths of this trial include a randomized design, a diverse patient population, and high clinical relevance to patients with T2DM and CKD. There was consistency of findings suggesting loss of adipose tissue rather than muscle mass across multiple parameters including body weight, waist circumference, 24-hour urinary creatinine excretion, and HbA_{1c}. While we hypothesized a beneficial effect on body weight and metabolism in bardoxolone methyl-treated patients, the trial was not designed to examine changes in body weight, waist circumference, and glycemic control; thus additional trials may be required to confirm these findings. Assessment of inflammatory markers in future studies may also elucidate how the anti-inflammatory effects of bardoxolone methyl are associated with the changes in body weight and other metabolic parameters.

While the effects on body weight and related parameters with bardoxolone methyl are generally considered beneficial in an obese population with T2DM and CKD, weight loss may be an undesirable effect in some patients. Subgroup analyses suggest that there was very limited loss of body weight in the small fraction of patients who were not overweight or obese. Moreover, the magnitude of weight reduction, trimming of waist circumference, and improvements in glycemic

Table 2
24-Hour urinary creatinine excretion over time and change from baseline.

Urinary creatinine (mg/24 h)	Placebo N = 65	Bardoxolone methyl N = 61
Baseline	1159 ± 471	1191 ± 339
Week 4	1155 ± 457	1134 ± 394
Change from Baseline	−4 ± 327	−57 ± 280

Data are mean values ± SD and only include patients with baseline and Week 4 urinary creatinine values.

Table 3
Change from baseline in hemoglobin A_{1c}.

	Observed HbA_{1c} (%)			Change from baseline (%)	
	Baseline	Week 24	Week 48	Week 24	Week 48
All patients					
Placebo[a]	7.10 ± 1.17 (n = 1097)	7.11 ± 1.29 (n = 721)	7.24 ± 1.44 (n = 275)	0.00 ± 0.99 (p = 0.92)	0.08 ± 1.12 (p = 0.24)
Bardoxolone methyl[a]	7.15 ± 1.27 (n = 1088)	6.96 ± 1.30 (n = 629)	6.90 ± 1.32 (n = 236)	−0.12 ± 1.04 (p = 0.0033)	−0.17 ± 1.13 (p = 0.026)
Difference between treatment groups[b]				−0.13 ± 1.01 (p = 0.023)	−0.25 ± 1.13 (p = 0.014)
Baseline HbA_{1c} > 7.0%					
Placebo[a]	8.10 ± 0.91 (n = 501)	7.90 ± 1.21 (n = 338)	8.07 ± 1.41 (n = 137)	−0.18 ± 1.14 (p = 0.0043)	0.00 ± 1.39 (p = 1.0)
Bardoxolone methyl[a]	8.22 ± 0.98 (n = 509)	7.76 ± 1.32 (n = 283)	7.74 ± 1.44 (n = 100)	−0.44 ± 1.29 (p < 0.001)	−0.53 ± 1.47 (p < 0.001)
Difference between treatment groups[b]				−0.26 ± 1.21 (p = 0.0086)	−0.53 ± 1.42 (p = 0.0051)
Baseline HbA_{1c} ≤ 7.0%					
Placebo[a]	6.25 ± 0.51 (n = 596)	6.42 ± 0.90 (n = 383)	6.41 ± 0.87 (n = 138)	0.16 ± 0.80 (p < 0.001)	0.16 ± 0.76 (p = 0.015)
Bardoxolone methyl[a]	6.21 ± 0.54 (n = 579)	6.31 ± 0.83 (n = 346)	6.28 ± 0.78 (n = 136)	0.14 ± 0.69 (p < 0.001)	0.10 ± 0.70 (p = 0.084)
Difference between treatment groups[b]				0.03 ± 0.75 (p = 0.60)	−0.05 ± 0.73 (p = 0.53)

Data are mean values ± SD.
[a] p-Values comparing values at Week 24 or Week 48 to baseline values within each treatment group.
[b] p-Values comparing the difference in means between the bardoxolone methyl and placebo groups.

control in overweight and obese patients compare favorably to other interventions.

5. Conclusions

In summary, in patients with T2DM and stage 4 CKD, treatment with bardoxolone methyl results in significant loss of body weight, without evidence of muscle wasting. Reductions in waist circumference and improvements in glycemic control suggest generally favorably metabolic effects in overweight and obese persons. If the risk of symptomatic heart failure after treatment initiation can be mitigated by dose titration, dietary salt restriction or other strategies, bardoxolone methyl may prove to be an effective treatment for obesity in patients with T2DM.

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References

1. Stenvinkel P, Zoccali C, Ikizler TA. Obesity in CKD–what should nephrologists know? J Am Soc Nephrol 2013;11(24):1727-36.
2. Kalantar-Zadeh K, Rhee CM, Chou J, et al. The Obesity Paradox in Kidney Disease: How to Reconcile it with Obesity Management. Kidney Int Rep 2017;2(2):271-81.
3. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003;12(112):1821-30.
4. James PT, Rigby N, Leach R. The obesity epidemic, metabolic syndrome and future prevention strategies. Eur J Cardiovasc Prev Rehabil 2004;1(11):3-8.
5. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest 2004;12(114):1752-61.
6. Shin S, Wakabayashi J, Yates MS, et al. Role of Nrf2 in prevention of high-fat diet-induced obesity by synthetic triterpenoid CDDO-Imidazolide. Eur J Pharmacol 2009 (620):138-44.
7. Saha PK, Reddy VT, Konopleva M, et al. The triterpenoid CDDO-Me has potent antidiabetic effects in diet-induced diabetic mice and Leprdb/db mice. J Biol Chem 2010 (285):40581-92.
8. Tanaka Y, Aleksunes LM, Yeager RL, et al. NF-E2-related factor 2 inhibits lipid accumulation and oxidative stress in mice fed a high-fat diet. J Pharmacol Exp Ther 2008;2(325):655-64.
9. Tan Y, Ichikawa T, Li J, et al. Diabetic downregulation of Nrf2 activity via ERK contributes to oxidative stress-induced insulin resistance in cardiac cells in vitro and in vivo. Diabetes 2011;2(60):625-33.
10. Zoja C, Corna D, Locatelli M, et al. Targeting Keap1-Nrf2 Pathway Ameliorates Renal Inflammation and Fibrosis in Mice with Protein-Overload Proteinuria. J Am Soc Nephrol 2010(21):275A.
11. Wu QQ, Wang Y, Senitko M, et al. Bardoxolone Methyl (BARD) ameliorates ischemic AKI and increases expression of protective genes - Nrf2, PPAR{gamma}, and HO-1. Am J Physiol Renal Physiol 2011(300):F1180-92.
12. Tanaka Y, Aleksunes LM, Goedken MJ, et al. Coordinated induction of Nrf2 target genes protects against iron nitrilotriacetate (FeNTA)-induced nephrotoxicity. Toxicol Appl Pharmacol 2008;3(231):364-73.
13. Aleksunes LM, Goedken MJ, Rockwell CE, et al. Transcriptional regulation of renal cytoprotective genes by Nrf2 and its potential use as a therapeutic target to mitigate cisplatin-induced nephrotoxicity. J Pharmacol Exp Ther 2010;1(335):2-12.
14. Sporn MB, Liby KT, Yore MM, et al. New synthetic triterpenoids: potent agents for prevention and treatment of tissue injury caused by inflammatory and oxidative stress. J Nat Prod 2011;3(74):537-45.
15. Ruiz S, Pergola PE, Zager RA, et al. Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int 2013;6(83):1029-41.
16. Pergola P, Krauth M, Huff W, et al. Effect of Bardoxolone on Kidney Function in Patients with T2D and Stage 3b - 4 CKD. Am J Nephrol 2011(33):469-76.
17. Pergola PE, Raskin P, Toto RD, et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N Engl J Med 2011;4(365):327-36.
18. de Zeeuw D, Akizawa T, Audhya P, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. N Engl J Med 2013;26(369):2492-503.
19. Nangaku M, Shimazaki R, Akizawa T. Bardoxolone Methyl Improved GFR Measured by Standard Inulin Clearance: The TSUBAKI Study. J Am Soc Nephrol 2017(28):B1-.
20. Patel SS, Molnar MZ, Tayek JA, et al. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. J Cachexia Sarcopenia Muscle 2013;1(4):19-29.
21. de Zeeuw D, Akizawa T, Agarwal R, et al. Rationale and trial design of Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: the Occurrence of Renal Events (BEACON). Am J Nephrol 2013;3(37):212-22.
22. Lambers Heerspink HJ, Chertow GM, Akizawa T, et al. Baseline characteristics in the Bardoxolone methyl EvAluation in patients with Chronic kidney disease and type 2 diabetes mellitus: the Occurrence of renal eveNts (BEACON) trial. Nephrol Dial Transplant 2013;11(28):2841-50.
23. Dinh CH, Szabo A, Yu Y, et al. Bardoxolone Methyl Prevents Mesenteric Fat Deposition and Inflammation in High-Fat Diet Mice. Sci World J 2015(2015):549352.
24. Camer D, Yu Y, Szabo A, et al. Bardoxolone methyl prevents the development and progression of cardiac and renal pathophysiologies in mice fed a high-fat diet. Chem Biol Interact 2016;243:10-8.