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The endothelin pathway: a protective or detrimental target of bardoxolone methyl on cardiac function in patients with advanced chronic kidney disease?

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Abstract

Bardoxolone methyl has been reported to cause detrimental cardiovascular events in the terminated BEACON Phase III human clinical trial via modulation of the renal endothelin pathway. However, the effects of bardoxolone methyl administration on the endothelin pathway in the heart are unknown. Our purpose in this perspective is to highlight the distinctive opposing roles of the renal and heart endothelin pathway in cardiac function. Furthermore, we address the need for further investigation in order to determine if bardoxolone methyl has a protective role in cardiac function through the suppression of the endothelin pathway in the heart.

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The endothelin pathway: a protective or detrimental target of bardoxolone methyl on cardiac function in patients with advanced chronic kidney disease?

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The paradoxical nature of Bardoxolone methyl (BM) has been widely noted in recent scientific literature (Van Laecke, Van Biesen et al. 2014). There are many known anti-inflammatory and anti-oxidative properties of this drug that have shown promise in preclinical studies, including treating complications of diabetes such as retinopathy and nephropathy (Camer, Yu et al. 2014). In addition, phases I and II of human clinical trials in patients with chronic kidney disease found that BM markedly improved kidney function (Pergola, Krauth et al. 2011; Pergola, Raskin et al. 2011). These positive results from the earlier phases led to the BEACON phase III human clinical trial in patients with type 2 diabetes and stage 4 chronic kidney disease (de Zeeuw, Akizawa et al. 2013). However, this trial was terminated due to safety concerns centred on an increased incidence of cardiovascular events in BM treated patients compared to the placebo group (de Zeeuw, Akizawa et al. 2013). This has led to scepticism in the scientific community as to whether BM will ever be used in the future treatment of diseases such as chronic kidney disease.

The mechanisms contributing to the adverse cardiovascular events seen in patients treated with BM in the BEACON trial have since been addressed (Chin, Reisman et al. 2014). It was concluded that the modulation of the endothelin pathway provided an explanation of the mechanisms by which BM caused an increase in cardiovascular events in participants. It was also found that BM was able to suppress the endothelin pathway in the kidneys of chronic kidney disease (CKD) induced rodents and healthy cynomolgus monkeys by reducing the protein expression of the ET_A receptor (Chin, Reisman et al. 2014). In healthy cynomolgus monkeys, BM did not affect ET_B receptor expression (Chin, Reisman et al. 2014). However, in rodents induced with CKD, BM restored ET_B receptor levels to those observed in the control animals (Chin, Reisman et al. 2014). Thus these results are extremely important in trying to explain the detrimental cardiovascular events that occurred in a number of patients taking BM in this human clinical trial. Despite this, there are limitations in the creation of this conclusion, since only the endothelin pathway of kidney tissue and not also cardiac tissue was examined.

It is well established that renal endothelin 1 (ET-1) has several important functions including regulating sodium and water homeostasis, renal blood flow and acid base balance via activation of ET_A and ET_B receptors (Kohan 2006) (Table 1). Furthermore, if the endothelin system is suppressed, such as from being targeted by BM, this balance is disturbed causing fluid retention, which can lead to heart failure (Kohan 2006). However, it is important to note that the endothelin pathway in the heart has a different function to the kidneys. ET-1 in the cardiac muscle promotes cardiac hypertrophy and subsequent heart failure via activation of ET_A receptors (Nasser and El-Mas 2014) (Table 1). Furthermore, both ET_A receptor and combined ET_A/ET_B receptor antagonism has been shown to lower blood pressure, and reduce infarct size in patients with congestive heart failure (Nasser and El-Mas 2014). Thus, suppressing the endothelin pathway in the heart would be protective against adverse cardiovascular vascular events.

In our opinion, due to the differing functions of the endothelin pathway in the kidneys and heart, we feel that more evidence is required to conclude that BM treatment caused adverse cardiovascular events by suppression of the renal endothelin pathway. Future investigation of the effects of BM on cardiac tissue is required in order to determine if BM inhibits ET_A receptors in the heart causing its protection.

Table 1 Summary of endothelin system functions in the kidney and vascular system

	ET-1		ET_A receptors		ET_B receptors
Kidneys	Regulates and homeostasis	sodium and water	Vasoconstrictor and sodium retention effects		Involved in water and sodium reabsorption and inhibiting vasopressin activity
Vascular System	Regulates tone, hypertrophy and blood pressure	vascular cardiac and	Vasoconstrictor (smooth muscle)		Vasoconstrictor (smooth muscle) and vasodilator (endothelial cells)

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