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Editorial commentary: Metabolic effects of cardiovascular medication: Does it matter?

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Cardiovascular disease (CVD) is the leading cause of death worldwide. Due to the development of the public health and care system, there are large declines in CVD mortality in the late 20th century but the CVD mortality is no longer improving in recent years [1]. The CVD mortality improvement relies on several lines of evidence of beneficial drug actions. However, several cardiovascular drugs have been reported to affect the systemic metabolism. In this issue of *Trends in Cardiovascular Medicine*, Fragasso et al. review the metabolic effect of cardiovascular medications to provide useful information for daily clinical practice [2].

Among the cardiovascular drugs, statins are the most well-known for their glucose metabolic effect. Statins are the first-line medication for hyperlipidemia treatment in patients at high CVD risk, and are the most commonly prescribed CVD drugs worldwide. However, growing evidence suggests that statins are associated with an elevated occurrence of new-onset diabetes mellitus (DM). The developing new-onset DM is directly connected with already existing DM risk factors [3]. Atorvastatin, rosuvastatin, and simvastatin have all reported significant increases in new onset of diabetes [4–6]. Despite the diabetogenic effect of statins utilization, the effect on lipid reduction still provides promising cardiovascular protection [7]. Therefore, statin associated new onset DM risk is not considered to be clinically significant and is likely outweighed by benefits of reducing cardiovascular risk.

Some blood pressure lowering drugs impair glucose metabolism, such as beta blockers or diuretics compared to renin–angiotensin–aldosterone system blockade [8,9]. The metabolic effects of different antihypertensive drugs should be considered because not all drugs within the same class have similar effects on insulin sensitivity. This is exemplified by the effects of vasodilating β-blockers failing to worsen insulin resistance and consequently having neutral effects on glycemic control. Furthermore, among beta blockers, carvedilol is found to improve glucose and lipid metabolism and reduce lipid peroxidation [10]. This finding may be related to the alpha adrenoreceptor antagonist activity on glucose metabolism and lipid parameters improvement. It has been reported that selective alpha-1 blocking agents have a benefit on glucose and lipid profiles [11,12]. Thus, the beta blocker action on glucose metabolism should not be considered as class effect because of the diverse pharmacological properties.

Serum free fatty acid (FFA) levels are inversely related to cardiac glucose uptake [13]. High FFA levels alter the metabolism of vascular endothelium leading to premature CVD [14]. Fragasso et al. clarify the fatty acid metabolic effect by cardiovascular drugs [2]. Aspirin, beta blockers, central sympathetic inhibitors, and nicorandil decrease circulating levels of FFA. The decreased arterial FFA concentrations could be a therapeutic option to decrease the failing dependence of cardiac myocytes on FFA and overcome the FFA inhibition of myocardial glucose utilization. For example, the beta blocker carvedilol reduces FFA utilization and provides better glucose utilization in heart failure patients [15]. The myocardial energy change might provide potential mechanisms to explain the reduced cardiac myocyte oxygen consumption and enhanced energy efficacy. Another example is the enhancement of FFA metabolism by nicorandil. The favorable metabolic effects of nicorandil may reduce oxygen free radical production especially on ischemic cardiac myocytes [16].

In conclusion, this review contains convincing but not entirely unexpected evidence that several cardiovascular drugs have metabolic effects and potential influence on CVD. The review article also supports the concept that FFA reduction provides a

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potential therapeutic mechanism for cardiovascular medication. Research in these areas should be able to determine the drug related metabolic effects that influence cardiac metabolism. Physicians should make the cardiovascular drugs more sustainable for CVD patients. More studies are needed to explore the impact of the metabolic effect in CVD patients with diverse metabolic risk factors.

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