

Heart medication and metabolism: What physicians should reflect on to keep them in harmony

Cardiovascular diseases are the leading cause of death globally and have been for a long time. This spotlight has ensured that doctors treating patients with heart problems have a wide variety of medications to work with. Most of the time, these medications are used to address direct and immediate problems the heart is dealing with. The catch is that apart from this direct and intended effect, heart medications have additional and easier to overlook effects on the metabolism. A recent review article (1) has described how commonly prescribed heart medications could be making both beneficial and harmful changes in the metabolism of the heart and the rest of the body. These changes are important for physicians to be aware of to make sure that they are doing the most good and the least harm when deciding what medications to prescribe.

Metabolic derangements have long been recognized as playing an important role in the pathophysiology of cardiovascular diseases. Metabolic impairment is not just a feature of the heart, but rather a global issue with important contributions from organs and peripheral tissues. Prescription of cardiac medications is aimed towards the pathophysiological mechanisms underlying the disease process. For instance, inhibition of the renin–angiotensin–aldosterone and sympathetic nervous systems is directed towards ameliorating abnormal neuro-hormonal activation. However, apart from their primary therapeutic actions, these drugs may positively also affect the global and cardiac metabolism. Similarly, a positive ancillary metabolic effect has also been observed with ARNI (angiotensin receptor neprilysin inhibitor), acetylsalicylic acid, trimetazidine, ranolazine, ivabradine, alpha blockers, central sympathetic inhibitors. On the contrary, among the others, thiazide diuretics, mineral corticoid receptor antagonists, calcium channel blockers, unfractionated heparin, direct thrombin inhibitors, specific statins, have all been shown to impair different metabolic functions. In this context it is interesting to note the recent demonstration of the beneficial effect of sodium-glucose transport protein 2 inhibitors (SGLT2i) in diabetic and non-diabetic in cardiac patients, indicating that the cardiovascular effects of these drugs are largely independent from glucose lowering. These findings will necessarily lead to the need to re-consider this class of drugs not as solely a glucose lowering drug but as metabolic cardiovascular drugs.

Overall, it is clear that additional pharmacological actions may be of special interest for both potential beneficial and deleterious effects and should be well understood and known by all providers managing patients with cardiovascular diseases. In table 1 are a few examples of effects from commonly prescribed medications in cardiac patients.

Medications	Metabolic effects
Beta adrenergic receptor blockers	- Reduction of peripheral lipolysis - Reduction of circulating levels of free fatty acids - Increased carbohydrates utilization - Improved insulin sensitivity (carvedilol)
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	- Improved glucose homeostasis - Reduction in the incidence of diabetes
Mineralocorticoid receptor antagonists	- Detrimental effects on glucose and lipid homeostasis by increased cortisol levels through blockade of the glucocorticoid receptors - However, eplerenone appears devoid of metabolic effects
Angiotensin receptor-neprilysin inhibitors	- Improved insulin sensitivity - Greater reduction in HbA1c compared to ACE-inhibitor enalapril
I _r -channel inhibitor (Ivabradine)	- Reduced mitochondrial reactive oxygen species formation - Increased ATP production and calcium retention capacity
Diuretics	- Induced dyslipidemia (thiazide diuretics) - Induced insulin resistance (thiazide diuretics) - Elevated parathyroid hormone level (loop diuretics) - Induced electrolyte depletion (thiazide and loop diuretics) - Activation of neuro-hormonal systems (loop diuretics)
Sodium-glucose cotransporter-2 inhibitors	- Increased glucosuria triggers lipolysis and fatty acid oxidation and ketone body synthesis in the liver - Increased diuresis resulting in reduction in plasma volume and blood pressure
Glucagon-like peptide 1 agonists	- Augmentation of insulin and inhibition of glucagon secretion - Improve insulin resistance - Promote weight loss
Acetylsalicylic acid	- Reduction of circulating FFA, by activating AMP-activated protein kinase - Activation of catabolic pathways (glucose uptake and FFA oxidation) - Inhibition of the transcription factor NF-kappa B (improved glucose tolerance)
Statins	- Pravastatin decreases the risk of development of diabetes - Other statins including simvastatin, atorvastatin, and rosuvastatin increase the risk of development of diabetes - All statins reduce serum testosterone levels
Trimetazidine	- Reduction in fatty acid oxidation - Improved glycolysis and glucose oxidation - Antioxidant activity - Reduced endothelin-1 release
Ranolazine	- Modulation of late sodium current, thereby reducing the accumulation of intracellular Ca⁺⁺ - Increased glucose oxidation - Lowered plasma glucose and HbA1C levels
CPT-1 inhibitors	- Reduction of FFA oxidation - Increased glucose oxidation - Up-regulation of the expression of various enzymes involved in fatty acids beta-oxidation
Vitamin D	- Stimulation of insulin secretion - Improvement in insulin resistance
Psychotropic drugs	- Induced weight gain and insulin resistance - Decreased insulin secretion

Tab. 1. Main metabolic effects of medications used for the treatment of patients with heart failure.
Legend: ACE: angiotensin-converting enzyme; AMP: adenosine monophosphate; ATP: adenosine triphosphate; CPT-I: Carnitine palmitoyl transferase I; FFA: free fatty acids; HbA1c: glycated hemoglobin, NF-kappa B: nuclear factor-kappa B.

In conclusion, most routinely used cardiovascular drugs yield ancillary energy metabolic effects that can either be beneficial or detrimental. Metabolic effects may be peripheral and/or directly influencing cardiac metabolism. Physicians looking after cardiovascular patients should be aware of the ancillary effects of the main drugs used in the daily clinical practice. Some of these metabolic properties may represent a principal effect of single drugs. All these concepts should prompt us to monitor peripheral and cardiac metabolic levels and try to improve them. Evidence-based medicine takes into account the beneficial effects of drugs on hard end-points, obtained by clinical trials of relatively short duration and it cannot be excluded that over longer time periods these beneficial effects of drugs could be either eliminated or reinforced due to their ancillary energy metabolic effects. For these reasons, future trials of cardiovascular drugs should take into account the evaluation of specific action on metabolism in order to better define their prescription in cardiac patients with different metabolic risk profiles.

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