Residual cardiovascular disease risk in Heart Failure patients. What is the real role of lipid-lowering therapy?

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Introduction

Heart Failure (HF) is recognized as a clinical condition characterized by debilitating symptoms, poor quality of life, frequent hospital admissions and reduced survival, that also puts a great economic burden to health systems worldwide, as its global prevalence is estimated to be around 2%, with rising trends the last years (1). Coronary heart disease (CAD) is still the most common etiological factor for HF and the main cause of HF with reduced ejection fraction (HFrEF) and one of the main contributors for HF with preserved ejection fraction (HFpEF) (1).

During the last years the main principles and pharmacological targets for the therapy of HFrEF and HFpEF have been described. For HFrEF patients the modulation of five pathways is recommended to improve clinical outcomes, referring to angiotensin 2, norepinephrine, aldosterone, neprilysin and sodium-glucose transport proteins (SGLT) [1]. In the latest 2024 AHA/ ACC [2] and 2023 ESC [3] guidelines various medications have been introduced as first-line (i.e., ARNI/ACE inhibitors, b-blockers, MRA and SGLT2i); and second-line therapies (i.e., iron replacement therapy, ivabradine, omercaptiv mecarbil, vericiguat and hydralazine / nitrate) [4]. Recently the STRONG study [5] underlined the need for early initiation and up-titration of treatment in HF patients for reducing re-hospitalizations, congestion symptoms and improving quality of life. Additionally, the use of N-terminal Brain Natriuretic Peptide (NTproBNP) seems to have the ability to evaluate even oligosymptomatic patients at risk promoting up-titration of medical care (5). However, accumulating evidence suggests that even after introducing all new therapies, residual cardiovascular (CVD) risk exists in HF patients under optimal tolerated medical treatment (1-3). In addition, hyperlipidemia, although not common among non-ischemic HF patients, but still an important determinant of poor prognosis, has not been well studied. Particularly the

role of hypolipidemic medication in the prognosis of HF has rarely been investigated and understood in relevant clinical trials (also considering their large methodological limitations). In this commentary, we aimed to summarize scientific knowledge and highlight clinical considerations regarding the role of hypolipidemic treatment in HF patients.

Hyperlipidemia, and treatment in HF patients

Heart failure, as the final pathway of clinical conditions that cause ventricular pressure or/and volume overload, is accompanied by hypertrophy, inflammation, angiogenesis, and apoptosis [1-3]. Statins may represent a potential treatment strategy for preventing cardiac hypertrophy and improving myocardial revascularization by decreasing nicotinamide adenine dinucleotide phosphate (NADPH) oxidation, activation and increasing NO bioavailability. Thus, statins could be considered as a therapeutical approach that may prevent oxidation and increases relaxation and dilation. However, although statin therapy has proven to be highly effective in primary and secondary prevention of patients with dyslipidemias, studies in HF patients have shown inconclusive results. This is clearer in the cases of advanced HF with deteriorated function of left ventricle and clinical appearance of malnutrition or cachexia. That is the reason lipid management in HF patients takes modest position among all therapeutic tools, as a Class III of recommendation, which means that lipid lowering therapy (LLT) initiation is not recommended in absence of other indications (which in fact refers to only about 30% of all HF patents) [2, 3, 6-9]. This was mainly based on the results of previous large randomized controlled trials (RCT), including patients with HFrEF [7, 8, 10, 11], as well as a meta-analysis of 24 RCTs, that showed insignificant benefit of statin treatment on CVD mortality in patients with HFrEF [9]. However, in the CORONA trial, even with its design limitations, based on retrospective sub-group

analyses, rosuvastatin appeared to provide more CVD benefit in those with higher C-reactive protein (CRP) and lower NTproBNP, sketching the patient who has not yet developed advanced HF [12, 13]. Nearly half of HF patients have HFpEF. Those patients show increased morbidity and mortality, while few pharmacological therapies have shown to improve survival. The pathophysiology of HFpEF is poorly understood but may involve a systemic proinflammatory state. Therefore, statins might improve outcomes in patients with HFpEF, especially in the context of primary and secondary prevention of atherosclerosis [14].

Statin use has been linked with Q10 mitochondrial depletion and muscle fatigue; while it decreases LDL-cholesterol levels leading to increased entry of lipopolysaccharide into cells and increased inflammatory cytokine production [13,15, 16]. Statins are known to suppress the prenylation of Rho protein and its downstream inflammatory cytokine production through NF-kB; thus, the effect of statins on inflammation is likely to vary depending on pathophysiological conditions. Based on pleiotropic effects, statins seem to act as immune suppressive agents and may have beneficial effects on those who have excessive and/or life threatening immune-inflammatory reactions, such as in transplantations or HFpEF [17].

In a metanalysis that included 17 RCTs with 132,538 participants conducted over 4.3 years, statin therapy reduced LDL-cholesterol levels by 0.97 mmol/L (38 mg/dl). Furthermore, numbers of patients experiencing non-fatal hospitalization due to HF were less (RR= 0.90, 95% confidence interval, CI 0.84–0.97) and the composite HF outcome (RR=0.92, 95% CI 0.85–0.99) but not HF death (RR=0.97, 95% CI 0.80–1.17) was also improved. The effect of statins on first non-fatal HF hospitalization was similar whether this was preceded by myocardial infarction or not [9]. Statin use in HF may also have pleiotropic effects as the modulation of Kv1.5 and Kv4.3 channels activity

and the inhibition of sympathetic nerve activity, change myocardial action potential plateau and suppress arrhythmogenesis [15]. Moreover, the lipophilic atorvastatin showed a significant impact on all-cause mortality, left ventricular ejection fraction (LVEF), and hospitalization due to HF; although this was not obvious with hydrophilic rosuvastatin use [18]. Lipophilic statins are to be much more susceptible to drug interactions with many other medications metabolized by the CYP450 system. In two large RCTs rosuvastatin did not reduce the primary composite mortality/ morbidity endpoints in HF patients with or without ischemic heart disease (IHD); although there was no increase in risk, and number of hospitalizations were reduced (8,11,12).

There is some suggestive evidence that statins might reduce muscle strength and alter energy metabolism during aerobic exercise, leading to limited efficacy in HF patients; although its use may preserve or increase lean mass and exercise performance [19]. Statins might also rarely induce inflammatory myopathies characterized by significant elevations of enzymes levels, a myopathic pattern on the electromyogram, and inflammatory infiltrates evident on muscle biopsy, triggering the mitochondrial pathway of apoptosis [14, 20]; although they regulate inflammation and improve cardiac sympathetic activity.

Advanced patient's age and heart failure clinical stage have been related with statin intolerance, while in patients with less advanced HF, statin therapy might be beneficial in reduction of coronary events, whereas in severe HF, it could be too late to for any potential benefits from statin therapy due to progressive loss of pump function. The recent meta-analysis based on the data from 4.2 million statin intolerance patients did not confirm the role of HF on the risk of statin intolerance [21]

PCSK9 is an emerging factor in HF patients, associated with energy metabolism disorders in heart failure [22]. PCSK9 can participate in cardiomyocyte apoptosis through NF-κB signal activation, induce autophagy of primary cardiomyocytes through the reactive oxygen species, and take part in the immune process of tumors. It also participates in platelet activation and thrombosis by binding to platelet CD36 and joins in the process of inflammation through the TLR4/NF-κB signaling pathway. The potential mechanism of PCSK9 regulating energy metabolism in cardiomyocytes during HF is mainly due to energy handling. When cardiomyocytes are exposed to a series of stimulation, the secretion of PCSK9 increases, activates PKB/Akt signal and causes glucose metabolism disorder, affecting the fatty acid β-oxidation and tricarboxylic acid circulation in mitochondria. In addition, the increased PCSK9 can also affect mitochondrial biogenesis, causing energy metabolism disorder of cardiomyocytes [1, 14, 18]. In the BIOSTAT-CHF cohort study [23], circulating PCSK9 was found to be significantly increased in patients with heart failure and positively correlated with the mortality risk. However, in ODYSSEY trial [24] the use of the PCSK9 inhibitor alirocumab in patients with a HF history after an acute coronary event did not show any effectiveness in reducing the risk of major adverse cardiovascular events (MACE) and HF hospitalization. Emerging data in heart transplanted patients revealed that after 3 months of PCSK9 inhibitor initiation, there was an LDL reduced of 51.7% from baseline; while by 9 months, 24 out of 26 patients with available data had a recorded LDL <100 mg/dL; while no known interaction was observed between PCSK9 inhibitors and immunosuppressive medications [25]. Some considerations for the use of the LLT on HF patients came from the so called “cholesterol paradox”; where low serum total cholesterol and lower high-density lipoprotein were associated with poor prognosis in patients with established HF (in

contrast to patients without HF); although this may represent a case of reverse causality. Additionally lower lipid levels are evident in advanced HF patients where hepatic congestion can impair hepatic biosynthesis of cholesterol, while intestinal congestion impairs cholesterol absorption. Thus, cachexia that accompanies advanced right heart failure is correlated with low LDL-C levels, poor nutritional status, and higher N-terminal pro-B-type natriuretic peptide levels. The effect of LVEF on the impact of statin treatment has been illustrated in previous studies, like in the PEARL study; where pitavastatin use had a significant beneficial effect on patients with LVEF above 30% compared with those with LVEF <30%, reflecting the interference of statins with catabolic pathways in advanced HF [26]. On the other hand, lipophilic statin may have a more beneficial effect compared to hydrophilic statins on cardiovascular mortality and morbidity, irrespectively of type of HF and level of LVEF, as it has been illustrated in a metanalysis of 17-studies [27]. New lipid-lowering treatments with bempedoic acid and obicetrapib may have an additive beneficial role in hyperlipidemic patients exhibiting also anti-inflammatory properties in metabolic syndrome, although studies on HF patients are still lacking.

Conclusive remarks

All these considerations may lead to some thoughts that include the fundamental role of lipid levels modification in HF patients in the context of primary and secondary prevention of cardiovascular disease, the avoidance of discontinuation lipid treatment in patients with new diagnosed HF, the awareness that lipids metabolism play a crucial role in energy handling in HF and the acknowledgment that patients in advanced heart failure and cachexia, supportive therapy may not include lipid treatment. In HFpEF

patients, LLT can show beneficial effects in term of secondary and even primary prevention for cardiovascular disease; with again limitations are noted in advanced stages of HFpEF [28]. Additionally, the initiation of new therapies in HF patients like the inhibition of sodium-glucose transport proteins in the nephron, has important effect on the metabolic pattern on those patients modifying residual metabolic risk beyond any lipid-lowering treatment.

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Figure 1

Molecular mechanisms of statin use in HF patients

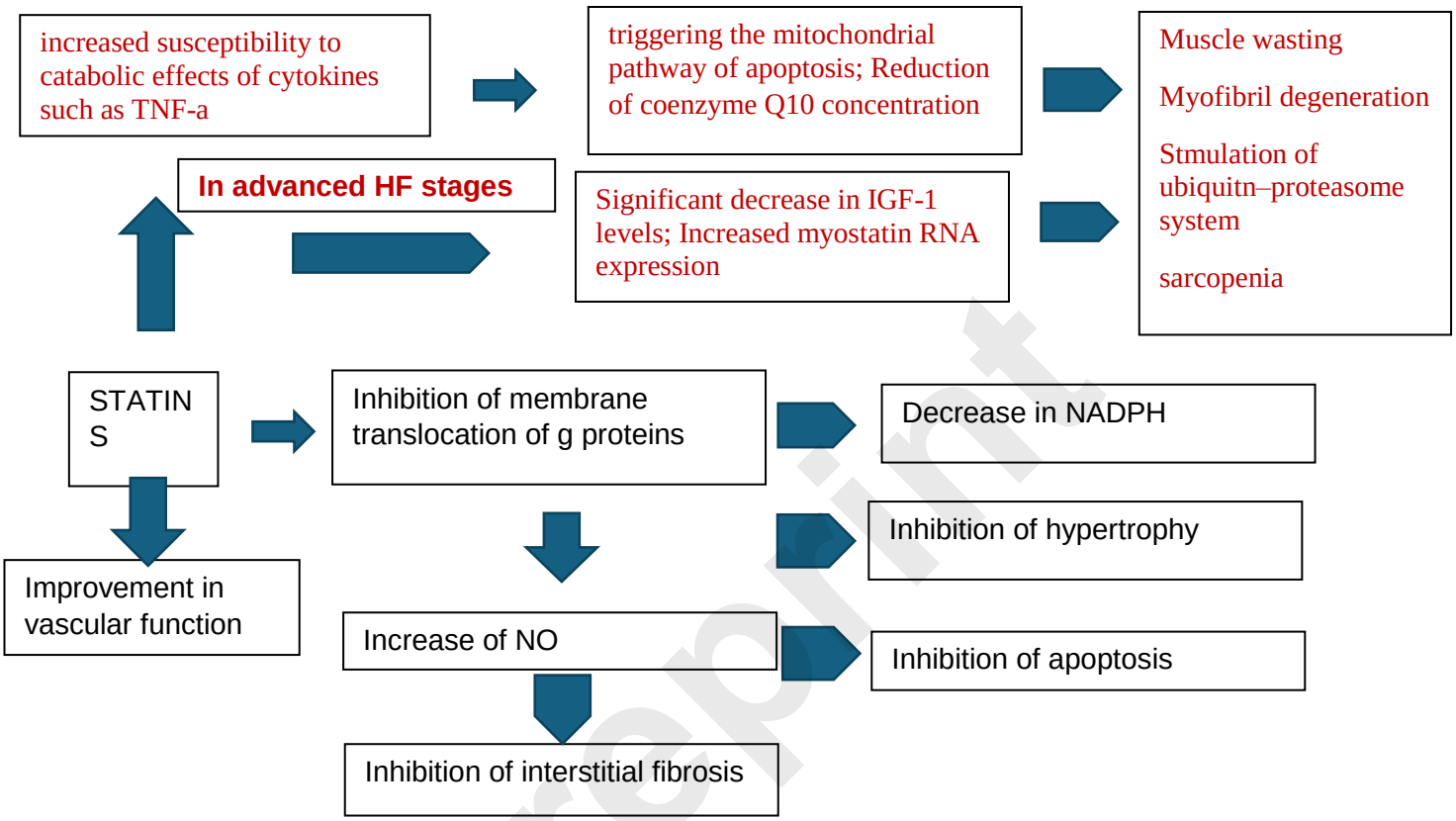

Table Practical Take-Home Message for the use of lipid-lowering therapy in Heart Failure patients

	Potential effects of statins	Indications	Considerations
HFrEF	Decrease of inflammatory markers Increase NO bioavailability Modulate activity of the proteasome; improving cardiac sympathetic activity; Lipophylic may be preferred	Ischemic cardiomyopathy in the terms of secondary prevention Non-ischemic cardiomyopathy in the terms of primary prevention, especially in elevated hs-CRP and lower NtproBNP levels	In advanced HF patients , with cachexia and severe deterioration of clinical status and functional capacity. *Down-titration discontinuation may be considered* ***Risks for:*** increased susceptibility to catabolic effects of cytokines such as TNF-a triggering the mitochondrial pathway of apoptosis- statin-induced depletion of CoQ10
HFpEF	Reduction of inflammation Suppression of immune-inflammatory reactions Reduction of oxidative stress Improvement of endothelium function inhibition of sympathetic nerve activity. Lipophylic may be preferred	Ischemic cardiomyopathy in the terms of secondary prevention Non-ischemic cardiomyopathy in the terms of primary prevention, especially in elevated hs-CRP and lower NtproBNP levels	In advanced HF patients , with cachexia and severe deterioration of clinical status and functional capacity. *Down-titration discontinuation may be considered* ***Risks for:*** increased susceptibility to catabolic effects of cytokines such as TNF-a triggering the mitochondrial pathway of apoptosis- statin-induced depletion of CoQ10

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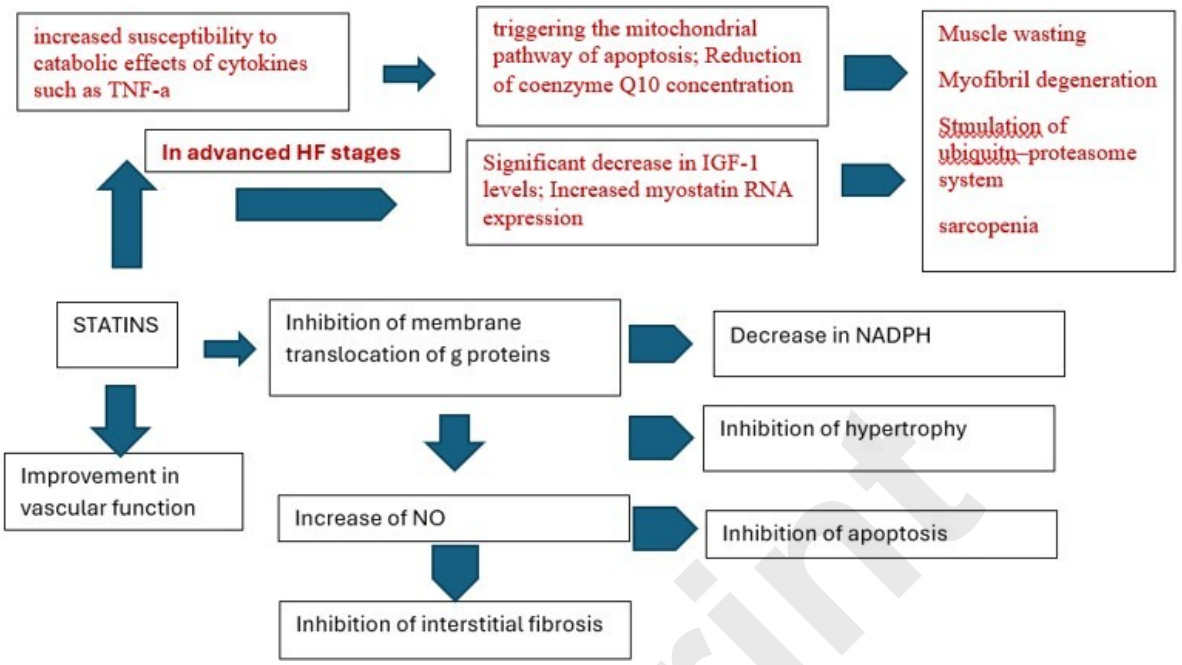

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