Pharmacology & Therapeutics 141 (2014) 79–91

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Statins in heart failure—With preserved and reduced ejection fraction. An update

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ARTICLE INFO

Keywords:
Diastolic function
Heart failure
HMG-CoA reductase inhibitors
Inflammation
Statins
Mortality

ABSTRACT

HMG-CoA reductase inhibitors or statins beyond their lipid lowering properties and mevalonate inhibition exert also their actions through a multiplicity of mechanisms. In heart failure (HF) the inhibition of isoprenoid intermediates and small GTPases, which control cellular function such as cell shape, secretion and proliferation, is of clinical significance. Statins share also the peroxisome proliferator-activated receptor pathway and inactivate extracellular-signal-regulated kinase phosphorylation suppressing inflammatory cascade. By down-regulating Rho/Rho kinase signaling pathways, statins increase the stability of eNOS mRNA and induce activation of eNOS through phosphatidylinositol 3-kinase/Akt/eNOS pathway restoring endothelial function. Statins change also myocardial action potential plateau by modulation of Kv1.5 and Kv4.3 channel activity and inhibit sympathetic nerve activity suppressing arrhythmogenesis. Less documented evidence proposes also that statins have anti-hypertrophic effects – through p21ras/mitogen activated protein kinase pathway – which modulate synthesis of matrix metalloproteinases and procollagen 1 expression affecting interstitial fibrosis and diastolic dysfunction. Clinical studies have partly confirmed the experimental findings and despite current guidelines new evidence supports the notion that statins can be beneficial in some cases of HF. In subjects with diastolic HF, moderately impaired systolic function, low b-type natriuretic peptide levels, exacerbated inflammatory response and mild interstitial fibrosis evidence supports that statins can favorably affect the outcome. Under the lights of this evidence in this review article we discuss the current knowledge on the mechanisms of statins' actions and we link current experimental and clinical data to further understand the possible impact of statins' treatment on HF syndrome.

Contents

1. Introduction

Since 1980 when the first 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor or statin was introduced in clinical practice, statins have been extensively used in the treatment of patients with dyslipidemia as well as of those with coronary artery disease (CAD) (Graham et al., 2007). Importantly, large scale trials and metanalysis have documented their significant benefits in terms of primary and secondary CAD prevention which out-weight any potential side effects (Sacks et al., 1996; Baigent et al., 2010; Mihaylova et al., 2012). Statins' benefits extend, according to recent studies, even in patients with normal or low cholesterol levels and beyond their lipid lowering effects, indicating the multiple protective mechanisms (Tousoulis et al., 2007, 2010, 2012c).

Heart failure (HF) is a complex syndrome with different definitions and its diagnosis is based on a combination of symptoms, clinical signs and imaging or laboratory data (McMurray et al., 2012). Moreover,

Abbreviations: CAD, coronary artery disease; CRP, C reactive protein; EF, ejection fraction; eNOS, endothelial NO synthase; ERK, extracellular-signal-regulated kinase; HF, heart failure; IL-, interleukin; LV, left ventricle; MMPs, matrix metalloproteinases; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NF-κB, nuclear factor Kappa B; PRAP, peroxisome proliferator-activated receptor; TNFα, tumor necrosis factor alpha.

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0163-7258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pharmthera.2013.09.001

different categorization schemes have been used dividing HF in acute or chronic, in systolic or diastolic, and in ischemic or dilated simply reflecting the complexity of the syndrome and the multiplicity of the pathophysiologic mechanisms implicated in the disease development and progression (McMurray et al., 2012). In addition to the diverse pathophysiology of HF the syndrome is also characterized by high morbidity and mortality (Stewart et al., 2001; Jhund et al., 2009; Stewart et al., 2010). Recent treatment advantages such as angiotensin converting enzyme inhibitors and beta blockers have not yet proven their clinical benefit in subjects with diastolic HF.

As the most common cause of HF is CAD (McMurray et al., 2012) and statins have proven their benefits in a wide spectrum of diseases directly or indirectly associated with atherosclerotic cardiovascular disease (Sacks et al., 1996; Tousoulis et al., 2009; Baigent et al., 2010; Tousoulis et al., 2010, 2011; Mihaylova et al., 2012), HMG-CoA reductase inhibitors have been tested in subjects with HF. Interestingly, non-randomized, observational and retrospective early studies in subjects with HF of ischemic and non-ischemic etiology have suggested that statins are associated with improved outcomes (Sola et al., 2006; Krum et al., 2007; Vrtovec et al., 2008). Thereafter, two large scale randomized control trials failed to demonstrate any benefits in mortality of HF patients treated with rosuvastatin (Kjekshus et al., 2007; Tavazzi et al., 2008) and subsequently current HF guidelines do not include recommendations for statin use except from when they are indicated for comorbidities, such as established CAD (McMurray et al., 2012).

Despite the negative results of the randomized control trails and current guidelines, recently new studies and metanalysis have been published. In this review article, after taking into consideration the complexity of HF syndrome which encompasses several different entities and the mechanisms of statins' actions, we discuss the current knowledge concerning the implication of statins in HF.

2. Statins—from mechanisms to actions

The main action of HMG-CoA reductase inhibitors is to modulate serum LDL cholesterol levels through mevalonate inhibition while, a variety of other actions have been identified in HF subjects through different pathways and mechanisms (Figs. 1 and 2) (Table 1).

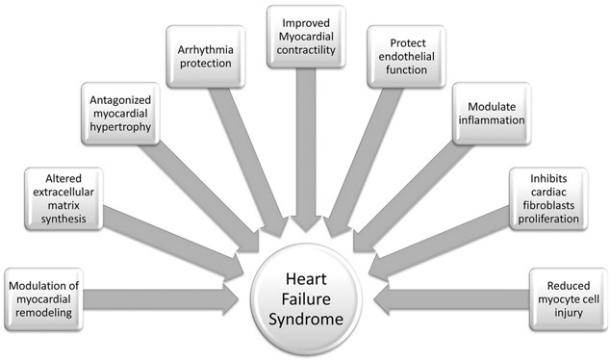

Fig. 2. The figure demonstrates the variety of beneficial effects of statins in subjects with heart failure.

2.1. Lipid lowering mechanisms—the mevalonate pathway

Statins inhibit HMG-CoA reductase. This enzyme catalyzes the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to L-mevalonic acid, which is the rate-limiting step in the cholesterol synthesis pathway. Inhibition of the mevalonate pathway and of cholesterol synthesis triggers an increase in LDL receptor activity by stimulating production of mRNA for LDL receptor in liver (Ma et al., 1986). The induction of LDL receptors is responsible for the observed increase in plasma clearance of LDL cholesterol.

CAD is the cause of approximately two-thirds of cases of systolic HF (McMurray et al., 2012). The beneficial effects of statins-induced LDL reduction are well established in patients with atherosclerosis and CAD (Kjekshus et al., 1997; Sever et al., 2008). Nevertheless, the results from statin treatment, even in ischemic HF cases, are not straightforward and several mechanisms have been proposed for this paradox.

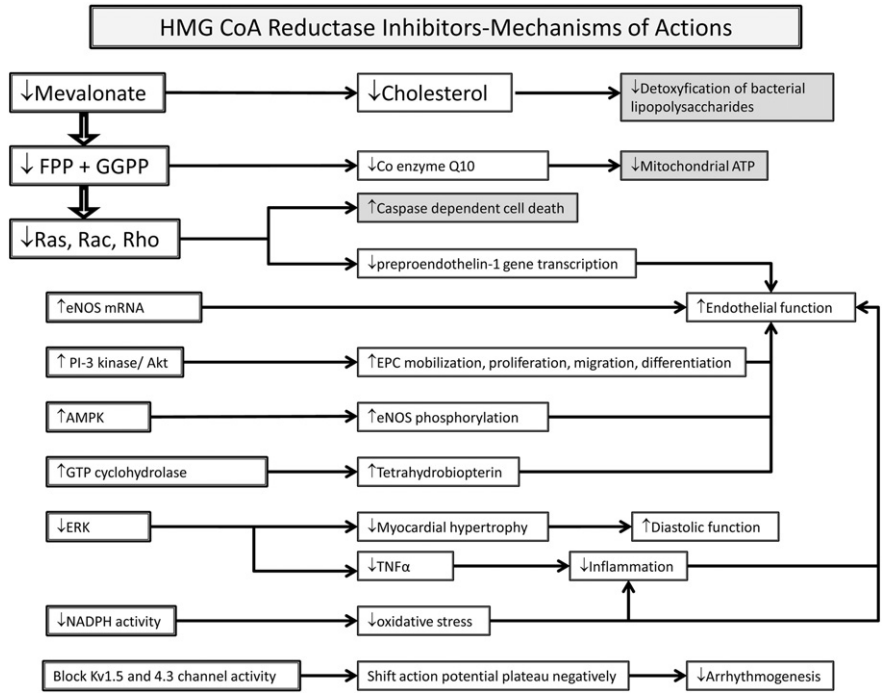

Fig. 1. The figure demonstrates the multiplicity of HMG CoA reductase inhibitors mechanisms and their effects. ↓: decrease; ↑ increase; FPP: farnesyl pyrophosphate: GGPP: geranylgeranyl pyrophosphate; Ras, Rac, Rho; small GTPases; eNOS: endothelial nitric oxide synthase; ATP: adenosine triphosphate; PI-3 kinase: phosphatidylinositol 3-kinase; AMPK: AMP activated protein kinase; GTP: Guanosine triphosphate; NADPH: Nicotinamide adenine dinucleotide phosphate; ERK: extracellular-signal-regulated kinase; Shadow box represents adverse mechanism and actions of HGM CoA reductase inhibitors.