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REVIEW ARTICLE

HDL-Targeted Therapies During Myocardial Infarction

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Abstract

It is now apparent that a variety of deleterious mechanisms intrinsic to myocardial infarction (MI) exists and underlies its high residual lethality. Indeed, despite effective coronary patency therapies, ischemia and reperfusion (I/R) injury accounts for about 50% of the infarcted mass. In this context, recent studies in animal models have demonstrated that coronary reperfusion with high-density lipoproteins (HDL) may reduce MI size in up to 30%. A spectrum of mechanisms mediated by either HDL-related apolipoproteins or phospholipids attenuates myocardial cell death. Hence, promising therapeutic approaches such as infusion of reconstituted HDL particles, new HDL by genomic therapy, or the infusion of apoA-I mimetic peptides have been sought as a way of ensuring protection against I/R injury. In this review, we will explore the limitations and potential therapeutic effects of HDL therapies during the acute phase of MI.

Keywords HDL · Myocardial infarction · Ischemia and reperfusion injury · Genomic therapy · apoA-I mimetics

Introduction

Since its first description in 1929 [1], a vast effort has been undertaken by researchers around the world to clarify the biological actions of a 7–12-nm particle named high-density lipoprotein (HDL). An essential and wide-ranging role has never been questioned since the particle was preserved during 16 million years of human evolution and is conserved in several atherosclerosis-free species. Since the hydrodynamic behavior was the reason for its denomination, several particles are considered together with a broad spectrum of components in their hydrophilic and hydrophobic compartments, i.e., HDL surface and core respectively [2–4]. In fact, the structural conformation of HDL behaves as a nanometric single-layer platform of phospholipids where numerous proteins (up to 96) [5], hundreds of mi-RNAs [4], and over 200 lipid species [6] have mutual interaction. The cholesterol content in lipoprotein (HDL-C), for example, has been used as a marker of the plasma concentration of HDL particles because of certain proportionality between these two variables. In a similar approach, the measurement of apolipoprotein A-I (Apo A-I) in plasma is used as a marker of the concentration of these nanoparticles in the bloodstream. Coherently to this vast number of molecules, there is a broad spectrum of HDL particles and actions, including the attenuation of myocardial infarct (MI) size.

Rapid restoration of blood flow to the ischemic myocardium is the gold standard approach, but allows the development of cellular lesions that may paradoxically reduce the beneficial effects of myocardial reperfusion. In terms of tissue damage, the myocardial ischemia followed by reperfusion represents ~ 50% of the infarcted area which makes this injury of remarkable relevance to the MI patients' therapy [7]. A link between HDL and coronary ischemia/reperfusion (I/R) injury was revealed in the ex vivo isolated Langendorff heart model and was confirmed in in vivo models [8, 9] (Fig. 1). Thus, the potential benefit in restraining the I/R injury also places HDL as a potential therapeutic approach for patients with acute coronary syndrome (ACS).

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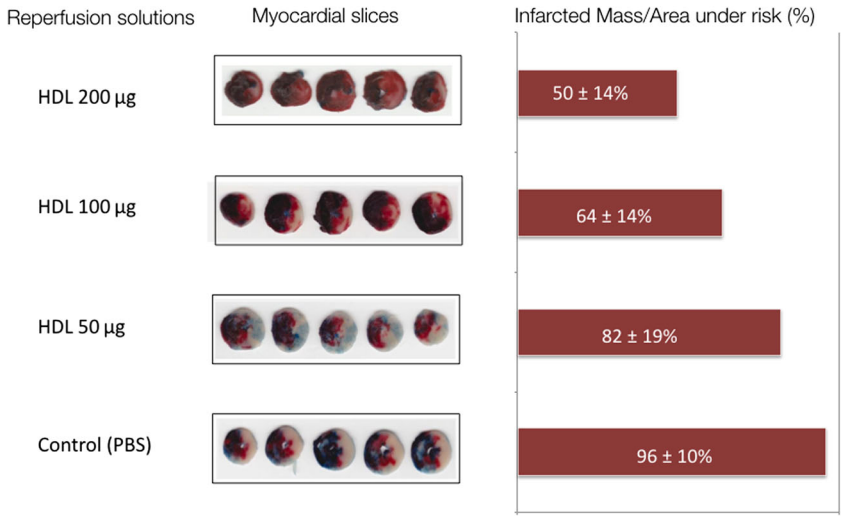

Fig. 1 HDL attenuates reperfusion injury. Hearts isolated from male adult Wistar rats were subjected to 35 min of regional ischemia, followed by 90 min of reperfusion in the Langendorff apparatus. HDL (50, 100, or 200 mg protein/ml) or control (PBS) was administered during the first 7 min of reperfusion. Evans blue was injected to delineate the area at risk (AAR). Infarct size showed as a percentage of AAR. Compared to control, those receiving HDL had a significant and dose-dependent decrease in final infarct size. Data are shown as mean ± SD. HDL, high-density lipoprotein

The main obstacle to the protective role of HDL on I/R injury lies in the fact that the abovementioned acute inflammatory response triggered for tissue repairing may equally induce HDL system dysfunction [10]. In agreement with that, we found that the acute response after MI induces changes in HDL structure, composition, and function and transform HDL into a dysfunctional pro-inflammatory particle [11]. This review is intended to discuss therapeutic strategies aiming at the increase HDL beneficial effect on MI.

Native HDL Alterations During MI

A large number of stimuli, particularly neurohumoral activation, oxidative stress, and inflammation, during the acute phase of MI strongly modify the composition, size, and electrical charge of HDL [12]. HDL reduces the content of cholesterol ester [11, 13, 14] and triglycerides [15] and changes the composition of phospholipids [16], of proteins [17, 18], and possibly of microRNA. Pro-inflammatory proteins, including serum amyloid A, complement 3, and lipopolysaccharide-binding protein, replace those that have anti-oxidant and anti-inflammatory effects [19]. In general, the change in structure modifies HDL binding properties to cellular receptors, enzymes, and transporters [20] and the content changes modify several cell signaling cascades, mostly from anti-inflammatory to pro-inflammatory pathways [21, 22].

In addition to such acute changes, patients presenting with MI generally have a long history of exposure to various risk factors that in turn modify the phenotype and function of HDL [12]. Thus, at the time of coronary occlusion, a predominantly dysfunctional HDL population is very likely to occur. During the acute phase of MI, this dysfunctionality tends to intensify and even generate pathogenic HDL particles. In line with this concept, we recently observed that there is a direct relationship between HDL-C plasma concentration and MI size in patients treated with reperfusion therapy [23]. We also observed that the HDL plasma concentration in the acute phase of MI is inversely related to endothelial function 30 days after the index event [11]. Thus, HDL related to the manifestation of MI, both as cause and as a consequence, is likely to play a pathogenic role in ischemic myocardial tissue and in remote tissues.

This set of evidences seems paradoxical when confronted with studies in animal and cellular models that show beneficial effects of HDL in MI [8, 9]. In fact, these findings seem even contradictory with the proposal of this review. The key element to be considered is that all studies in animal and cellular models used HDL obtained from healthy individuals or artificially reconstituted HDL (rHDL). In fact, when we confronted the effect of healthy HDL with HDL from individuals with MI, we confirmed the opposite effect on the extent of MI [23]. Based on these findings, therapies that may possibly mitigate the pathogenic effect of HDL from MI and provide the beneficial effects of healthy HDL will be discussed below.

Apabetalone in Patients with ACS

Bromodomain and extraterminal (BET) proteins coordinate transcription of the gene by binding to acetylated lysine (Ac) in histones via bromodomains (BD), thus recruiting transcriptional machinery to direct the expression of sensitive BET genes. Chronic and acute inflammation are potent inducers

of BET binding. Apabetalone (RVX-208) selectively inhibits the binding between BET proteins, preferably the BD2 domain of the BRD2 and BRD3 proteins, and the Ac fractions on the histone tails, releasing the chromatin and thereby reducing the effects of transcriptional suppression [24]. As a consequence, the dissociation of the BET protein from the chromatin results in an increase in Apo A-I transcription rate and, therefore, in the plasma level of HDL [24]. In the acute phase of MI, this mechanism is particularly interesting considering that epigenetic stimuli mediated by BET binding may enhance the inflammatory response after MI, particularly interleukin-6 [25].

A post hoc analysis of phase II studies suggested that there was a reduction in the relative risk of major adverse cardiac events in patients with coronary heart disease after apabetalone treatment, particularly in patients with diabetes mellitus or low HDL-C [26]. To confirm this effect, the study Effect of appendixalone on Time to Major Adverse Cardiovascular Events in High-Risk T2DM Subjects With CAD (BETonMACE) was designed and included 2425 patients with a documented ACS 7–90 days prior to screening, who had diabetes mellitus and low HDL-C and were using a maximum tolerated dose of atorvastatin or rosuvastatin. Eligible patients were randomized 1:1 to treatment with apabetalone 100 mg orally twice daily or placebo and the primary end point was the time for the first occurrence of death by cardiovascular disease, nonfatal MI, or stroke. Study enrollment is already completed and the median time between coronary event index and randomization was reported as 34 days [27]. Thus, although promising to prevent the reduction of HDL and the increase in inflammatory response during the acute phase of MI, the myocardial effect of this treatment will not be tested. The study will rather verify whether maintenance of HDL levels in patients with recent ACS may prevent the high rate of recurrence of coronary events.

Statin Therapy and HDL

In the first statin randomized controlled trial (RCT) enrolling patients during the acute phase of ACS, the use of high potency statin slightly reduced the recurrence of acute coronary events [28]. In this study, although the HDL-C levels at admission or after statin therapy were strong predictors of recurrent events, the statin effect on plasma HDL-C concentration was minimal and this effect did not interact with the reduction of events [29].

Cholesterol-efflux capacity is reduced during the acute phase of MI, mainly due to the phenotypic change in HDL [30]. This functional decline of HDL occurs in the first hours after the acute coronary event and persists for up to 3 months [31]. In contrast, even with a modest effect on plasma HDL-C concentration, statins may increase reverse cholesterol transport by increasing macrophage cholesterol efflux, increasing influx of cholesterol to hepatocytes via increased expression of scavenger receptor class B type 1 (SRB1), and about 15% increase in ApoA-I production [32]. Moreover, we found that statins may also increase the cellular efflux of cholesterol via a direct cellular action increasing ATP-binding cassette transporter A1 (ABCA1) expression [33]. In fact, the effect of statins on the expression of ABCA1 and even on the reverse transport of cholesterol, estimated integrally, is proportional to their potency—these effects are markedly more intense with rosuvastatin than with atorvastatin, for example [34]. Thus, the analysis of the statin effect on HDL based on the available clinical studies may be compromised by the difference between the drugs.

We recently reported that post-MI HDL dysfunction is proportional to the increase in inflammatory activity [11]. Studies in our laboratory and others have shown that the early introduction of statins attenuates the increase in inflammatory activity secondary to MI [35]. Thus, albeit not proven, it is plausible that there is greater functional protection in HDL system during MI in patients using high doses of potent statins.

Statins may also change the reverse cholesterol transport by its direct inhibitory effect on cholesteryl ester transfer protein (CETP) synthesis and reduction of the substrate for the exchange of triglycerides by cholesterol ester via CETP, i.e., the very-low-density lipoprotein (VLDL), intermediate-density lipoproteins (IDL), and low-density lipoprotein (LDL) lipoproteins. Approximately 50% of reverse cholesterol transport is performed through the CETP-mediated mechanism whose action transfers HDL ester cholesterol to VLDL and LDL, a potentially atherogenic action. The reduction of CETP activity by statins may then favor the direct transport of cholesterol from HDL to the liver and thus increase the antiatherosclerotic efficacy of reverse cholesterol transport. This hypothesis, however, can be better examined by evaluating clinical trials in which specific CETP inhibitors have been tested in patients with ACS. This topic will be discussed below.

We recently reported the effect of atorvastatin at high doses on 4191 patients with ACS and, in general, atorvastatin did not reduce MACE within 30 days [36]. However, among 2710 patients undergoing PCI, MACE at 30 days was reduced by 28% by atorvastatin treatment (HR 0.72, 95% CI, 0.54–0.96, $p = 0.02$), indicating that if there is a benefit, this is due to mechanisms subsequent to coronary reperfusion. Many mechanisms may explain this effect including the direct cellular effects of statin on the arterial wall or cardiomyocytes. In observational studies, we and others reported that among the patients who had an early reperfusion, the mass of MI was smaller in those using statin [37, 38].

The obvious missing piece in this puzzle is whether or not the action of statins on the HDL system contributes to this post-reperfusion protection effect. Investigation of this issue

is relevant to improve future study designs and to clarify our understanding of the results of ongoing RCTs in which HDL-based therapies are being tested to protect myocardial tissue after MI. It must be borne in mind that reverse causality is a clear possibility, since the functional decline of HDL is proportional to the mass of the MI [30]. Thus, the ongoing RCTs will be the only possible way of clarifying this issue.

CETP Inhibitors and HDL

Although mediation of a bidirectional molar exchange of triglycerides and cholesterol esters between HDL and apo B lipoproteins is its most known action, CETP may also have a prothrombotic action [39] potentially influencing outcome after ACS. Moreover, in MI individuals bearing a high CETP activity, the generation of oxidized HDL is significantly boosted due to the increased transfer of oxidized lipids from apo B–containing lipoproteins, which are more vulnerable to oxidative stress, into HDL [40–42]. In fact, after MI, enhanced CETP activity is independently associated with endothelial dysfunction and recurrence of coronary events [13]. This broad interaction with MI and the effect of markedly elevating plasma HDL-C places CETP inhibition as a promising therapeutic target. In fact, acute stress conditions including ACS are associated with a decrease in CETP activity as systemic inflammation increases [43, 44]. Although it is possible that the inflammation is causing the reduction of CETP as an adaptive response to avoid the increase of the lesions in the acute phase, the modulating effect of CETP on inflammation is also possible. In transgenic mice models expressing the human CETP minigene, Cazita et al. [45] found that the presence of CETP can reduce the production of pro-inflammatory cytokines by macrophages.

Besides the possibility of attenuating some direct deleterious effects of CETP during MI, some indirect effects would be beneficial. A negative association exists between plasma HDL concentration and stress hyperglycemia during MI, which in turn may negatively influence the clinical outcome by a plethora of mechanisms [46, 47]. This effect of HDL is due to the increase in both insulin sensitivity (IS) and secretion [48–50]. In line with this, CETP inhibition reduces blood glucose and increases IS as HDL-C increases [51]. In a mouse model of MI, reconstituted HDL delivered during reperfusion increases myocardial glucose uptake and oxidation, reduces LV infarct size, increases capillary density, and reduces the magnitude of post-ischemic left ventricular dysfunction [52]. From the mechanistic point of view, studies of cellular models indicate that HDL increases insulin sensitivity through the activation of AMP-activated protein kinase (AMPK) in muscle and adipose tissue [48, 53]. In addition, cholesterol efflux via ABCA1 triggers calcium influx, thereby activating calcium/calmodulin-activated protein kinase (CAMKK) [48]. This event also triggers the phosphorylation of AMPK and the consequent translocation of glucose transporter 4 (GLUT4) to the cell membrane [48].

In addition, phenotypic remodeling of HDL after inhibition of CETP during ACS increases its cholesterol efflux capacity 3 to 4 times less than the same inhibition in subjects without acute disease [54–56]. Although there is a clear attenuation of this potential benefit, the improvement of cholesterol efflux may contribute to clinical evolution by the aforementioned arguments.

Pharmacological inhibition of CETP has been repeatedly tested in high-risk individuals but in stable and chronic conditions. The studies were designed to test the pro-atherogenic action hypothesis of CETP and reveal additional therapy to reduce residual cardiovascular risk. In these studies, torcetrapib (Pfizer, USA), dalcetrapib (Roche, Switzerland), anacetrapib (Merck, USA), and evacetrapib (Lilly, USA), all potent CETP inhibitors, were tested. At the time of designing these studies, the current hypothesis was that the association between HDL and cardiovascular disease was based largely on its quantitative aspect, i.e., the higher the plasma HDL-C concentration, the lower the risk. Thus, CETP inhibitors that had the potential to raise plasma HDL-C by more than 100% were considered to be likely to become highly successful therapies. In the first study, torcetrapib increased HDL-C by 72%, but was associated with an excess of deaths attributed to the neurohumoral effects of this drug [57]. The second study with evacetrapib was discontinued due to lack of effects and therefore futility in continuing follow-up [58]. In the latter study, the use of anacetrapib was associated with a 9% reduction in the relative risk of the combined outcome of coronary death, nonfatal myocardial infarction, and coronary revascularization [59]. However, there was an 18% reduction in non-HDL-C which alone could explain the reduction of the primary combined outcome.

The Dal-Outcomes study had as a differential the randomization of 15,871 patients with recent ACS. Patients with appropriate selection criteria were enrolled in a period of 4 to 12 weeks (mean of 8) to assess adherence and allow the metabolic balance time to be reached after the acute coronary event. With this time schedule, much of the potential effect of CETP inhibition in the acute phase of ACS was not tested, but rather the chronic effects in a group of patients with a high recurrence rate of coronary events [60]. HDL-C increased by about 30 to 40% in the dalcetrapib arm, but the study was discontinued due to the absence of clinical benefit. At the end of the day, inhibition of CETP in the acute phase of ACS has never been properly tested and this hypothesis is unlikely to be resolved. Negative or discreetly positive results with the four studies make it unlikely that additional tests will be done in any clinical setting.

Reconstituted HDL Therapies

Reconstituted HDL (rHDL) particles prepared in vitro from purified or recombinant human ApoA-I and phospholipids have been developed as an innovative approach to the management of cardiovascular (CV) disease. Remarkably, rHDL displays all of the major anti-atherogenic activities documented for native HDL, notably cholesterol efflux capacity together with anti-inflammatory, antioxidative, cytoprotective, vasodilatory, anti-infectious, antithrombotic, and antidiabetic activities [61]. Furthermore, a single intravenous injection of rHDL is capable of rapidly raising circulating HDL levels.

Such treatment strategy involves acute administration of rHDL to stabilize plaques in patients with ACS [62] based on the capacity of rHDL to rapidly impact atherosclerotic plaques [63]. After MI, the onset of acute systemic inflammation, which aims to repair the injured heart, may promote the acceleration of atherosclerosis. In fact, ischemic cardiomyocytes induce via sympathetic signaling the release of stem cells and hematopoietic progenitors from bone marrow niches [64]. As a consequence, monocytes infiltrate atherosclerotic lesions, accentuating the inflammation and proteolysis of the extracellular matrix, which increases the instability of the atherosclerotic plaques [65]. In the animal model, infusion of modified ApoA-I-containing rHDLs acutely reduced systemic inflammatory and oxidative activities and the accumulation of macrophages on atherosclerotic plaques [66]. In human subjects, acute reduction in lipid content and inflammatory status of atherosclerotic plaques were documented in patients with peripheral vascular disease following a single infusion of CSL-111, a complex of wild-type human ApoA-I with phosphatidylcholine, at a dose of 80 mg/kg [67].

Almost all prospective randomized studies testing the effect of rHDL on coronary atherosclerotic burden were performed in patients with chronic and stable disease. Earlier studies which employed rHDL containing ApoA-I Milano variant known for its potent atheroprotective properties [68] brought about promising results. Indeed, only five weekly infusions of ETC-216 (a complex of apoA-I Milano with phosphatidylcholine) at a dose of 15 or 45 mg/kg induced a significant reduction in plaque volume of − 4.2% relative to the baseline, but not to placebo, in 57 patients who had ACS, within 14 days before randomization, as assessed by intravascular ultrasound (IVUS) [69]. Strikingly, these promising findings outperformed typical reductions in plaque volume established after statin therapy. In support of these data, four weekly infusions of CSL-111 at a dose of 4 of 40 mg/kg resulted in significant decrease in atheroma volume of − 3.4% as compared to baseline, but not to placebo, in 60 patients with stable coronary disease [70].

Further development of this approach in humans was for a long time hampered by high intervention costs, which result from the large amounts (up to 5 g) of ApoA-I needed per injection [62]. Another limitation involves potential hepatotoxicity due to acute cholesterol removal from hepatocytes as well as to residual cholate used for rHDL assembly [62]. Indeed, administration of CSL-111 at 40 mg/kg was associated with mild, self-limiting transaminase elevation, while the higher dosage of 80 mg/kg was discontinued early because of liver function test abnormalities [70]. These effects were abolished in CSL-112, a more recent rHDL formulation which was well tolerated and not associated with significant alterations in liver or kidney function among patients with acute MI [71].

Several studies performed recently using two different rHDL formulations did not however confirm positive results obtained earlier. Thus, a recent MILANO-PILOT study investigated effects of five weekly infusion of apoA-I Milano HDL formulation MDCO-216 at a dose of 20 mg/kg on coronary atherosclerosis in 120 patients who had an ACS in the last 14 days before randomization [72]. Unexpectedly, HDL-C levels increased post-infusion in placebo patients and decreased with MDCO-216. As a result, MDCO-216 did not produce a significant effect on coronary disease progression measured by IVUS. These results occurred on a background of contemporary therapy involving high-intensity statin use in the post ACS setting. Similarly negative data were obtained in a recent CARAT study in which serial nine-week infusions of CER-001, rHDL formulation containing recombinant human ApoA-I and sphingomyelin, at a dose of 3 mg/kg did not produce a significant effect on coronary disease progression measured by IVUS in 301 ACS patients within 14 days of index event presentation [73, 74].

It appears therefore that rHDL therapy, as it is presently designed, cannot impact clinical events in the setting of contemporary therapy in patients who recently had ACS. These findings did not provide the evidence required to proceed with further development of this approach, nor did they exclude the possibility of benefit in terms of protection of cardiomyocytes from the I/R lesion since the rHDL treatment was administered too late after coronary reperfusion.

There are several possibilities to explain the predominantly negative results of rHDL late administration in ACS and to reconcile positive data obtained earlier with the negative outcome of more recent investigations. First, it is possible that the earlier studies were too small to produce solid data. Indeed, more patients were included in the recent trials of MDCO-216 and CER-001 as compared to the earlier studies of ETC-216 and CSL-111. Furthermore, the effects of rHDL were only significant relative to baseline but not to placebo in the latter studies, thereby undermining their importance.

Second, the clinical setting may represent a key determinant of the outcome of HDL raising. All the trials of rHDL therapy described above were performed in the setting of the late phase after ACS, which is characterized by profound alterations in lipoprotein metabolism and the presence of dysfunctional HDL. There is a possibility that on-treatment HDL particles are dysfunctional in the HDL-raising studies. This

hypothesis is particularly interesting in light of the HDL dysfunctionality under ACS. If infused rHDL particles were rapidly remodeled in the circulation to add to the existing pool of pro-atherogenic HDL, such process would have compromised potential anti-atherogenic effects of the treatment. Indeed, the dose of infused rHDL (up to 6 g) in these trials is markedly lower than the amount of native HDL (about 20 g) that is present in the bloodstream and whose action may be deleterious in either the arterial function [11] or the mass of myocardial infarcted tissue [23].

An interesting possibility involves excessive HDL raising by rHDL administration. Recent epidemiologic findings obtained in the CANHEART study reveal that individuals with high HDL-C levels (> 70 mg/dl in men, >90 mg/dl in women) display increased hazard of non-CV mortality and no beneficial trend in CV mortality [75]. Furthermore, extremely high HDL-C levels were paradoxically associated with elevated mortality as compared to normal HDL-C in both men and women in the Copenhagen City Heart Study and the Copenhagen General Population Study [76]. These data suggest that excessive raising of HDL-C, such as that observed acutely under the action of rHDL or chronically under the action of CETP inhibitors, might be deleterious.

Further along this line, not only the magnitude but equally the mechanism in raising HDL-C can be crucially important for whether or not it brings about CV benefit. The latter may depend on the effect on biologically relevant HDL functions as well as on the action on other aspects of lipoprotein metabolism. It is noteworthy in this regard that rHDL infusions frequently exert hypertriglyceridemic effects, while elevated plasma levels of triglycerides are increasingly recognized as a CV risk factor [77]. Mechanisms of such rHDL-induced hypertriglyceridemia may involve delayed VLDL catabolism secondary to decreased lipoprotein lipase (LPL) activity [78, 79] or to elevated apoC-III levels [63], as well as enhanced hepatic VLDL production [80] secondary to the elevated lipid flux to the liver in the process of randomized controlled trial (RCT) [78]. Arguably, the hypertriglyceridemic effects of rHDL might be deleterious in a setting of ACS already featuring elevated concentrations of triglycerides in the circulation, thereby enhancing such pro-atherogenic alterations. It is interesting in this regard that rHDL-induced elevation of triglycerides is reduced by CETP [78] which activity is inversely related to systemic inflammation [43, 44], thereby suggesting that this metabolic condition might not be optimal for rHDL administration.

Another factor capable of reducing potential benefits of rHDL following ACS is represented by concomitant statin treatment. Indeed, HDL raising was shown to be beneficial only in the absence of statin treatment in a meta-analysis of large-scale clinical trials [81].

Although available data do not support an improvement in anti-atherogenic effect of HDL following rHDL infusion, preliminary data indicated some potential benefit; indeed, the administration of rHDL (CSL112) in ACS patients improved cholesterol efflux capacity [82]. This potential benefit has motivated the ApoA-I Event reducinG in Ischemic Syndromes II (AEGIS-II) trial, which is a phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study enrolling about 17,000 MI patients. The time from symptoms to the treatment is not available so far, but in the study on which this trial was based patients were enrolled up to 7 days after MI [83]. Despite favorable preliminary results, the results of the previous studies using IVUS as the surrogate endpoint and the disproportion between infused rHDL and native HDL (about one third) leave room for the risk of a negative or neutral result.

The vast majority of the evidence in cellular or animal models of MI were focused on the potential benefit of HDL-based therapy in protecting myocardial tissue from I/R damage. In mice, for instance, rHDL delivered during reperfusion increases myocardial glucose uptake and oxidation, reduces LV infarct size and fibrosis, and increases capillary density and post-ischemic left ventricular function [52]. Neither was this assessment done to date in the surrogate endpoints' clinical trials, nor is the AEGIS-II study designed to test this hypothesis. As mentioned above, the I/R injury occurs acutely after reopening of an occluded coronary artery and is responsible to up to 50% of the mass of myocardial tissue injured during MI [7].

In both targets, arterial wall and myocardial tissue, it is fundamental to conceive that the biophysical and molecular characteristics of rHDL may influence its potential clinical benefit. For example, phospholipid content, HDL size, and consequently anti-oxidant capacity are major players in rHDL potential benefit during MI. In addition to that, oxidative changes in ApoA-I may completely change the action of rHDL as it does for native HDL. Myeloperoxidase (MPO) converts ApoA-I tyrosine-192 into 3-chlorotyrosine and methionine-148 into sulfoxide methionine [84–86] and these site-specific changes inhibit ApoA-I binding, diminishing lecithin-cholesterol acyltransferase (LCAT) activation and cholesterol efflux capacity [86].Therapy with rHDL whose composition is resistant to MI-induced dysfunctional oxidation would change intensively the effect during MI. In this context, genetically modified ApoA-I has been developed with change of oxidation-sensitive to oxidation-resistant amino acids in residues with significant functional role [87].

ApoA-I Mimetic Peptides

ApoA-I mimetic peptides are short synthetic peptides that are designed to share the same biological properties as the full-length ApoA-I protein [88]. Because of the relatively high cost to either purify or recombinantly produce the gram quantities of ApoA-I used per dose in HDL therapy, ApoA-I mimetics have been an alternative in making reconstituted lipoprotein particles for HDL therapy. Recently, these peptides have also

been used to create HDL-like particles for the delivery of amphipathic or hydrophobic drugs [89]. These peptides have the theoretical advantage over the full-length protein in that they can be readily modified to enhance both their biological and pharmacokinetic properties. In fact, ApoA-I mimetic peptides made with D-amino acids are resistant to proteolysis and are partially orally available [88].

The first ApoA-I mimetic peptides made were used as probes for understanding the structure of ApoA-I [90] and thus were designed to contain an amphipathic helix, the main secondary structural feature found on ApoA-I [91]. This structural motif, which is an alpha-helix with one side containing hydrophobic amino acids and the other polar or charged amino acids, enables these peptides to bind to lipids and thus form lipoprotein particles. It has also been shown that the amphipathic helix is necessary for these peptides and presumably ApoA-I to efflux cholesterol by the ABCA1 transporter [92, 93], one of the main anti-atherogenic functions of HDL. ApoA-I mimetic peptides, particularly those enriched with phenylalanine in their hydrophobic face, also avidly bind oxidized lipids [94], another potentially important anti-atherogenic function of HDL.

Like rHDL made with the full-length ApoA-I protein, ApoA-I mimetic peptides have been shown to reduce atherosclerosis in a wide variety of animal models [88]. They have also been shown to have benefit in many of other animal disease models, such as in asthma [95], kidney disease [96], Alzheimer's disease [97], and sepsis [98].

Although it is naturally more feasible to use ApoA-I mimetics than rHDL, there is still very little information on the effect of mimetics on MI. In animal models of MI, 37pA, a bihelical amphipathic peptide, reduced I/R injury and improved cardiac function in an isolated heart apparatus [99]. Both isomers, L37pA and D37pA, combined with phospholipid exhibited similar effects to synthetic HDL made with full-length ApoA-I protein. The peptide-lipid complexes significantly reduced post-ischemic cardiac contractile dysfunction and a myocardial necrosis marker compared with saline control group by about 50%, as well as reduce cardiac TNF-α levels. Besides their anti-inflammatory properties, the release of the potent vasodilator prostacyclin after administration of 37pA may also account for some of the beneficial effects of these peptides.

In MI patients, there are 3 published reports of ApoA-I mimetics tested in early-stage clinical trials [100–102], all of them based on the 4F peptide and focused on the change in overall HDL function rather than MI-related outcomes. Both the 4F peptides made with either D or L amino acids were shown to be safe in phase I studies, but only had limited effect in improving HDL function, particularly when given intravenously. It seems, however, that the exposure of the drug in the intestine rather than the plasma concentration may determine their ability to modulate HDL function [100–102]. This has recently been attributed to the fact that this peptide may mediate much of its anti-atherogenic effect by the sequestration of oxidized lipids in the intestine [103]. The current state of development of ApoA-I mimics is preliminary and makes it impossible to draw conclusions about the potential clinical benefit in ACS patients. The greater feasibility for its large-scale use still places it as the most promising among HDL-based therapies. Nevertheless, both mechanistic and clinical studies are needed before considering this therapy a possibility to mitigate residual risk after ACS.

De Novo HDL Generation Via Gene Therapy

Stimulating the de novo production of functional HDL particles with phenotypic characteristics appropriate to a specific clinical condition is one of the possibilities of circumscribing the consistent clinical failure of HDL-raising therapies. In this sense, investigators are focused on using plasmid-DNA-based gene transfer to stimulate and modulate the HDL particle production by the liver [104]. The inherent advantages associated with developing a novel nucleic acid therapy result in a direct, natural replacement for circulating dysfunctional HDL resultant from genetic defects or environmental toxicity and in situ oxidation [105].

Generally, DNA plasmid delivery methods consider either viral or non-viral mediated procedures. Adenoviral vector gene therapy with inclusion of human ApoA-I plasmid inducing hepatocyte-specific expression was tested in mice submitted to ligation of the anterior descending coronary artery. The therapy reduced ventricular remodeling and increased neovascularization in the infarction zone, and systolic and diastolic cardiac function after MI [8]. In addition, this same experimental model demonstrated that ApoA-I gene therapy increases the circulating number and function of endothelial progenitor cells and increased capillary density and relative vascularization in the myocardium [106]. Although these viral methods uniformly provide an effective delivery method and has improved ventricular outcome after MI, they are linked to possible untoward side effects of mutagenesis and tumorigenesis [107], limiting their potential clinical use.

Among non-viral nucleic acid delivery stands an ultrasound-based technology comprised of externally applied ultrasound, i.e., sonoporation. The resultant interaction between acoustic microspheres and the ultrasound radiation forces generates localized, transient "pores" within the vascular endothelial cells resulting in direct parenchymal cellular transfection [108, 109]. Thus, the ability to delivery several DNA plasmids to a local region for transfection presents a novel, effective, and safe option for the site-specific delivery of nucleic acids, including ApoA-I and ABCA1, all leading to the development of a functional HDL molecule. A recent manuscript described the uses of sonoporation to increase serum HDL in rodents using human ApoA-I plasmids and commercial ultrasound systems [110].

The choice of the correct combination of plasmids could define the HDL phenotype that will best suit the MI patient. Inclusion of the apo M plasmid, for example, may possibly potentiate S1P-related effects due to the increase of HDL ability to carry this phospholipid. As commented above, the MPO-mediated changes in ApoA-I tyrosine-192 and methionine-148 residues [84–86] are a strong limitation for any HDL-based therapies during MI. Genetically modified ApoA-I gene has been developed with change of oxidation-sensitive to oxidation-resistant amino acids in these residues [111]. Finally, gene therapy can rapidly deliver a large number of HDL particles de novo, overcoming the substantial dilution limitation between rHDL and native dysfunctional HDL (6:20 g) as in the ongoing studies, such as AEGIS-II. Thus, HDL-based gene therapy with the newer, virus-free approaches should be considered a promising strategy to be investigated in patients with ACS.

Conclusion

This review sought to summarize all available data from animal and cellular models, translational studies in humans, and prospective randomized trials. This joint perspective allowed an overview of the current state of HDL-based therapies for individuals with MI. However, it is important to remember that while mechanistic studies cannot infer directly to the clinical benefit, prospective randomized trials cannot infer in causal mechanisms. The bridge between these findings lies precisely at the edge of scientific development and as such is an evidence in construction. Keeping in mind these potential limitations, natural to any in-depth reviews, some benchmarks can be built.

As a nanoparticle of multiple ligands involved in cardiovascular protection, HDL-based therapy has great potential for clinical use in ACS. Studies in animal and cellular models, mostly based on HDL samples from healthy donors, indicate a broad spectrum of this benefit. In real life, however, the acute coronary event occurs in individuals exposed long to cardiovascular risk factors whose deleterious actions involve the generation of dysfunctional HDL. In addition, acute metabolic, oxidative, and inflammatory changes related to ACS accentuate the HDL dysfunctionality in a lasting way. Thus, paradoxically, one of the greatest benefit potentials of HDL occurs in circumstances where its function is degraded.

Alternatives to overcome this obstacle involve therapies that aim to form or infuse during the acute phase of MI particles of HDL whose phenotype is tailored specifically to the demands of these patients. As mentioned above, the oxidation of apo A-I residues is an important limiting factor for the function of HDL in the acute phase of ACS [86]. Alternatively, the substitution of oxidation-sensitive residues such as tryptophan for phenylalanine was able to maintain intact apo A-I function, adding resistance to oxidative inactivation [111]. The strategy of replacing oxidation-sensitive amino acids with resistant ones has been patented and should be present in future clinical trials [111]. The formation of rHDL with modified Apo A-I may therefore become a beneficial tool for attenuation of I/R lesions in the acute phase of MI. In parallel, in this very same line of action, gene therapy without viral vectors, by sonoporation for example, can generate de novo HDL with the desired characteristics, such as oxidation resistance, within a short time (< 2 h) to be used in the acute phase of MI. Finally, the use of Apo A-I mimetics can equally prevent oxidative modifications and maintain desired effects with intensity even greater than that of native Apo A-I.

In summary, there are several possible alternatives for testing HDL-based therapy in the acute phase of MI. What must be considered is the specific adaptation to the molecular peculiarities of this acute disease and avoiding the extrapolation from studies in stable and chronic patients. As simple as it may seem, we need to keep in mind that functional modulation of HDL is the only alternative to expect the potential benefits related to healthy HDL and required in sick individuals.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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