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EDITORIAL

Novel lipid-modifying therapies addressing unmet needs in cardiovascular disease

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Abstract

Cardiovascular disease (CVD) remains a major cause of morbidity and mortality worldwide. Currently, it is well established that dyslipidemia is one of the major risk factors leading to the development of atherosclerosis and CVD. Statins remain the standard-of-care in the treatment of hypercholesterolemia and their use has significantly reduced cardiovascular morbidity and mortality. In addition, recent advances in lipid-modifying therapies, such as the development of proprotein convertase subtilisin/kexin type 9 inhibitors, have further improved cardiovascular outcomes in patients with hypercholesterolemia. However, despite significant progress in the treatment of dyslipidemia, there is still considerable residual risk of recurring cardiovascular events. Furthermore, in some cases, an effective therapy for the identified primary cause of a specific dyslipidemia has not been found up to date. Thus, a number of novel pharmacological interventions are under early human trials, targeting different molecular pathways of lipid formation, regulation and metabolism. This editorial aims to discuss the current clinical and scientific data on new promising lipid-modifying therapies addressing unmet needs in CVD, which may prove beneficial in the near future.

Key words: Lipid-modifying therapies; Cardiovascular disease; Dyslipidemia

Core tip: Despite significant progress in the treatment of dyslipidemia, there is still considerable residual risk of recurring cardiovascular events. Ongoing research has led to the discovery of several different molecules involved in lipid homeostasis, which can serve as possible targets for new lipid-modifying therapies. Novel medications that have

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provided promising results in early human trials include inclisiran, bempedoic acid, seladelpar, CSL-112, apabetalone, volanesorsen, APO(a)-RX, and APO(a)-LRX. Furthermore, several other lipid-lowering agents are being evaluated in ongoing trials. Thus, there is optimism that use of these lipid-lowering medications may in the future lead to a reduction of the residual cardiovascular risk.

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INTRODUCTION

Cardiovascular disease (CVD) has consistently been the leading cause of death in the United States from 1950 through 2014[1]. However, a significant decline in premature mortality due to heart disease is projected through 2030 in United States, attributed mainly to sustained declines in smoking, cholesterol and hypertension, which are major risk factors for CVD, as well as to presumed future advances in medical care and treatment[2].

Undoubtedly, lipid-modifying therapies have played a crucial role in the prevention and treatment of major adverse CV events, improving the CV outcomes of patients with dyslipidemia. Statins are the standard-of-care for the treatment of hypercholesterolemia and their use is supported by extensive evidence demonstrating their effectiveness in lowering low density lipoprotein cholesterol (LDL-C) and in reducing CVD risk in both primary and secondary prevention[3]. Furthermore, statins exert a number of pleiotropic cardioprotective effects, including improved endothelial function, reduced vascular inflammation, and reduced platelet adhesion and thrombosis, which also definitely contribute in the reduction of CVD risk[4]. Another recent success story is the development of monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9), which cause a 54.0%-62.7% incremental reduction in LDL-C levels when administered on top of statins and are associated with a significant reduction of adverse CV events[5,6]. Certainly, several other lipid-modifying therapies are currently being used in everyday clinical practice, such as fibrates, ezetimibe, bile acid sequestrants and niacin.

However, despite the significant progress made in the treatment of dyslipidemia, there is still considerable residual risk of recurring cardiovascular events[7,8]. Our current pharmacological interventions are able to target a finite only number of lipid pathways. For example, up to date, no specific therapy has been found, which would specifically and significantly improve high-density lipoprotein (HDL) functionality and cholesterol efflux capacity (CEC), leading to a reduction of CVD risk. Moreover, there are many rare, yet important, genetic diseases that cause dyslipidemia and hence premature CVD, for which a specific therapy has not yet been found. In addition, intolerance to certain lipid-lowering medications, especially statins, due to side effects (mostly myalgias and weakness), as well as inability to achieve the LDL-C goal despite use of maximally tolerated dose of statins, are factors that undoubtedly contribute to the residual CVD risk[9].

Given the above, extensive research is being conducted for the development of new drugs that would reduce residual CV risk and address other unmet needs in CVD. Thus, this editorial aims to discuss the current clinical and scientific data on new promising lipid-modifying therapies addressing unmet needs in CVD, which may prove beneficial in the near future.

MEDICATIONS THAT DECREASE LDL CHOLESTEROL LEVELS

The direct association between plasma LDL-C concentration and the incidence of CVD has been unequivocally proven in many epidemiological studies. Inclisiran is a new, recently developed agent, which targets PCSK9 *via* a different route, as compared to PCSK9 monoclonal antibodies. Inclisiran, which is administered

subcutaneously, is a chemically synthesized small interfering RNA molecule, which targets the hepatic production of PCSK9, as it affects the degradation of mRNA post-transcription, thus preventing translation of PCSK9[10]. ORION-1 was a phase 2, multicenter, double-blind, placebo-controlled, multiple ascending-dose trial of inclisiran, administered in patients at high risk for CVD with elevated plasma LDL-C concentration. Administration of a single or two doses of inclisiran was associated with marked declines in LDL-C and PCSK9 levels, as compared to placebo. The greatest LDL-C reduction (52.6%) was observed in association with the two-dose 300-mg regimen of inclisiran[11]. An ongoing phase 3 clinical trial, ORION-11, is expected to provide more information about the cardioprotective properties of inclisiran and its long-term safety and efficacy. The results of this trial are expected to be available in late 2019[12].

Undoubtedly, inclisiran is a new promising agent for further reduction of the residual cardiovascular risk in patients with elevated LDL-C. Furthermore, there is optimism that inclisiran only needs to be administered once every 3-6 mo, which would significantly improve compliance and comfort for the patients.

Another novel LDL-C targeting drug, which is currently under clinical trials, is ETC-1002 or bempedoic acid, a dual modulator of hepatic adenosine triphosphate-citrate lyase (ACL) and adenosine monophosphate-activated protein kinase (AMPK). Inhibition of ACL leads to reduced acetyl coenzyme A (CoA) and hence decreased 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which is the molecular target of statins. Adding to that, activation of AMPK leads to an inhibitory phosphorylation of HMG-CoA reductase and to improved glucose regulation[9,13]. In a phase 2a clinical trial, ETC-1002 was shown to be safe and well tolerated and it significantly lowered LDL-C by up to 27% in a dose-dependent manner in patients with hypercholesterolemia[13]. In another phase 2a clinical trial, ETC-1002 not only reduced LDL-C by 43% after 4 wk, but also decreased high sensitivity CRP (hsCRP) by 41% in patients with hypercholesterolemia and type 2 diabetes mellitus without worsening glycemic control[14]. Moreover, ETC-1002 was shown to be effective, causing a significant reduction in LDL-C levels, when administered to patients with statin intolerance or when given as add-on therapy to statin- or ezetimibe-treated patients[15-17].

The results of a phase 3 trial with bempedoic acid (CLEAR Wisdom Trial) were very recently presented at the American College of Cardiology 2019 Scientific Sessions. Bempedoic acid (ETC-1002), added to maximally tolerated statin therapy in patients with hypercholesterolemia and high risk for CVD, lowered LDL-C by 17.4% at 12 wk compared to placebo and maintained significant LDL-C reductions for 52 wk. In addition, bempedoic acid decreased hsCRP by 18.7%. There was no worsening of glycemic control in patients with a history of diabetes and the side effect profile of bempedoic acid was similar to that of placebo. No difference was noted for clinical outcomes, although the trial was not powered for this endpoint[18]. Thus, further outcome studies are required to more definitely assess the role of bempedoic acid in reducing CV risk. Notwithstanding, bempedoic acid may in the future provide an additional therapeutic option to safely lower LDL-C in high CV risk patients with elevated LDL-C treated with maximally tolerated dose of statins and other lipid-modifying therapies.

Peroxisome proliferator-activated receptors (PPARs) are molecular sensors that regulate diverse aspects of lipid metabolism, thus playing a crucial role in lipid homeostasis. Three isotypes of PPARs have been described: α (NR1C1), β/δ (NR1C2) and γ (NR1C3). Fibrates are classical PPARα agonists, whereas thiazolidinediones are potent PPARγ agonists. PPARβ/δ agonists are not currently used in clinical practice; however, they have shown promising results in early clinical trials[19].

Seladelpar or MBX-8025 is a selective PPAR-δ agonist, which has emerged as a promising new agent for the treatment of mixed dyslipidemia. In a multicenter, randomized, double-blind, placebo-controlled study, MBX-8025 was administered to patients with mixed dyslipidemia, alone or in combination with atorvastatin, for 8 wk. In this study, MBX-8025 reduced LDL-C by 18%-43%, triglycerides by 26%-30% and hsCRP by 43%-72%, favorably affecting multiple metabolic parameters. The administration of MBX-8025 was safe and generally well-tolerated[20]. Moreover, MBX-8025 produced substantial reductions in small and very small LDL particles, which translated to reversal of the small dense LDL phenotype in the vast majority of participants[21]. Although these initial results with the use of MBX-8025 appear very promising, further large clinical studies are required to definitely ascertain that the use of MBX-8025 (or another PPARβ/δ agonist) will be truly associated with a reduction in CV risk.

MEDICATIONS THAT INCREASE HDL CHOLESTEROL LEVELS AND/OR FUNCTIONALITY

The inverse association of HDL cholesterol (HDL-C) with future risk of CVD has been unequivocally demonstrated in several epidemiological studies. Although the concept of developing a drug that would raise HDL-C levels and subsequently reduce CV risk exists for many years, no selective HDL-C-raising medication has proven its atheroprotective properties in previous clinical trials. In fact, our current knowledge indicates that HDL functionality plays a much more crucial role in atheroprotection than circulating HDL-C levels[22].

A reconstituted infusible human apolipoprotein A-I (ApoA-I), CSL-112, is under early human trials. In a phase 2a, randomized, double-blind, multicenter, dose-ranging trial, a single intravenous infusion of CSL-112 in patients with stable atherosclerotic disease was shown to be safe and well tolerated. It produced marked and rapid dose-dependent increases in ApoA-I levels (up to 145% increase in the 6.8-g group after 2 h from the time of administration). In addition, total CEC, a key metric of HDL functionality was increased up to 3.1-fold, as compared with placebo[23]. In another phase 2b trial, 4 consecutive weekly infusions of CSL-112, administered to patients with a recent acute myocardial infarction, induced an increase in ApoA-I levels, HDL-C levels, as well as CEC, and preferentially ATP-binding cassette transporter A1 (ABCA1)-dependent CEC, in a dose-dependent manner and with no significant side effects[24]. Given the above, CSL-112 appears to be a very promising new therapeutic intervention for patients with CVD and currently a phase 3 trial is ongoing to assess the potential benefit of CSL-112 in reducing major adverse CV events in patients with acute coronary syndrome. The results of this trial are expected to be available in 2022[25].

Apabetalone or RVX-208 is an orally active small molecule, which increases ApoA-I transcription through an epigenetic mechanism that is mediated by bromodomain and extra-terminal domain (BET) protein 4 (BRD4)[26]. In a multicenter, randomized, double-blind, placebo-controlled study, RVX-208 was administered at varying doses twice daily for 12 wk to statin-treated patients with stable coronary artery disease (CAD). In this study, administration of RVX-208 led to a significant, dose-dependent increase of ApoA-I levels by up to 5.6%. HDL-C levels were also increased by 3.2% to 8.3%, with increasing doses of RVX-208. In addition, there was an increase of the large HDL particles. Transient and reversible elevations in liver transaminases, but with no associated increase in bilirubin levels, were observed in some patients treated with RVX-208[27]. Another study, which retrospectively analyzed the clinical data from two randomized, double-blind, placebo-controlled, similarly designed phase 2b clinical trials of RVX-208 treatment over 6 mo in patients with CAD (SUSTAIN and ASSURE trials), demonstrated a statistically significant increase in HDL-C, ApoA-I, large HDL particles, and average HDL particle size of 7.69%, 10.3%, 30.7%, and 1.16%, respectively, versus placebo. Moreover, a post-hoc analysis showed lower instances of major adverse cardiac events in patients receiving RVX-208[28]. In addition, there is evidence suggesting that RVX-208 may exert some protective effects against the development of type 2 diabetes[29]. Notwithstanding, further studies will be required to better define the role of RVX-208 in the reduction of the risk for CVD.

MEDICATIONS THAT DECREASE TRIGLYCERIDE LEVELS

ApoC-III is another molecule that plays an important regulative role in lipoprotein metabolism. ApoC-III raises plasma triglycerides through inhibition of lipoprotein lipase (LPL), an enzyme essential for the hydrolysis and distribution of triglyceride-rich lipoproteins (TRLs) to extrahepatic tissues, as well as through stimulation of very low-density lipoprotein secretion and *via* prevention of the hepatic clearance of TRL-remnants by the LDL receptor[30]. Elevated plasma triglyceride levels are associated with CVD and clinical studies have clearly shown that non-fasting triglyceride levels are strongly predictive of ischemic events and all-cause mortality, even when differences in plasma HDL-C are taken into account[30]. Epidemiological evidence shows that carriers of loss-of-function mutations of the ApoC-III gene have 39% lower triglycerides, 22% higher HDL-C, and 16% lower LDL-C plasma concentrations. More importantly, their risk of coronary heart disease is reduced by 40%[31].

Given the above, reduction of ApoC-III plasma levels has emerged as a promising therapeutic strategy to decrease risk for CVD. This has led to the development of volanesorsen or ISIS 304801, which is a human antisense oligonucleotide (ASO) that binds to mRNA of the ApoC-III gene and blocks its expression. In a randomized, double-blind, placebo-controlled, dose-ranging, phase 2 study, ISIS 304801,

administered as a single agent to patients with hypertriglyceridemia, produced dose-dependent mean reductions in APOC-III levels of up 79.6% and reductions in triglycerides of up to of 70.9%. No safety concerns related to the use of ISIS 304801 were identified in this study[32]. In another study, volanesorsen (ISIS 304801), administered to patients with hypertriglyceridemia, including familial chylomicronemia syndrome, uniformly lowered ApoC-III on ApoB-100, lipoprotein (a) [Lp(a)] and ApoA-I. Thus, it was suggested that volanesorsen may be a potent agent to reduce triglycerides and CV risk mediated by ApoC-III[33]. In addition, there is evidence that volanesorsen may be an especially useful treatment option for patients with hypertriglyceridemia and type 2 diabetes mellitus, as it improves glucose disposal, insulin sensitivity and various integrative markers of diabetes after short treatment[34]. Given the above, volanesorsen appears to be a novel promising therapy for hypertriglyceridemia, which may also decrease the burden associated with certain genetic diseases causing hypertriglyceridemia, such as the familial chylomicronemia syndrome[35]. Notwithstanding, further investigation on the long-term efficacy and safety of volanesorsen is warranted.

MEDICATIONS THAT DECREASE LIPOPROTEIN (a) LEVELS

There is extensive clinical evidence demonstrating that elevated Lp(a) levels is an independent causative risk factor for CVD and aortic stenosis. Current treatments that are being used to decrease Lp(a) include nicotinic acid, aspirin and, in more severe cases, lipoprotein apheresis. Statins may raise Lp(a) by 10%-20% but are also being used in patients with elevated Lp(a) levels only to decrease LDL-C levels and reduce CVD risk. PCKS9 inhibitors have also been shown to reduce Lp(a) levels by approximately 30%, but up to date they have not been approved for the treatment of high Lp(a) levels[36]. The causality of the relation between Lp(a) and CVD is considered significant and hence the concept of developing drugs that effectively reduce Lp(a) exists for many years. However, it is difficult to target Lp(a), as it has no enzymatic activity and it cannot be feasibly targeted with small molecules or monoclonal antibodies. RNA therapeutics, and specifically ASOs, represent an elegant method to reduce circulating Lp(a). Thus, APO(a)-Rx and APO(a)-LRx were developed, which are ASOs that are administered subcutaneously, inhibiting the synthesis of the atherogenic Apo(a), which is primarily synthesized in the liver[37].

In a randomised, double-blind, placebo-controlled, phase 1 clinical study, participants were treated with a single subcutaneous injection or with six injections of APO(a)-Rx at varying doses. The single injection regimen did not provide any reduction in Lp(a) plasma levels. However, the six injections of APO(a)-Rx resulted in dose-dependent decreases in plasma Lp(a) levels with the highest administered dose of 300 mg being the most effective treatment, as it produced a 77.8%reduction in Lp(a) levels from baseline. Similar reductions were observed in the amount of oxidized phospholipids associated with ApoB-100 and Apo(a). The treatment with APO(a)-Rx was safe and generally well-tolerated, as the most common adverse events were mild injection site reactions[38]. In a phase 2 trial of APO(a)-Rx, which was administered subcutaneously once a week for 12 wk in an ascending-dose design, similar reductions in Lp(a) levels of 66.8%-71.6% were observed[39]. In a phase 1/2a trial of the other developed agent, APO(a)-LRx, the highest administered dose of 40 mg provided a decrease of 92% in Lp(a) levels after six doses in healthy human volunteers. Both agents were also safe[39]. Thus, these new agents targeting the synthesis of Apo(a) may assist clinicians to effectively diminish Lp(a)-mediated cardiovascular risk.

A summary of the mechanisms of action of the aforementioned novel lipid-modifying therapies is shown in Table 1. In addition, the molecular pathways of action and effects of the aforementioned novel lipid-modifying therapies are shown in Figure 1.

ON THE HORIZON

Liver X receptors (LXRs) are members of the nuclear receptor superfamily of DNA-binding transcription factors and act as sensors of cholesterol homeostasis. LXRs mediate physiological responses to cellular and systemic cholesterol overload, including the upregulation of the reverse cholesterol transport (RCT), thus having cardioprotective effects against atherosclerosis. The development of drugs that stimulate LXRs have emerged as a new promising therapeutic intervention[40,41]. There are two isotypes of LXRs; LXRα and LXRβ. XL-652 or BMS-779788 is a partial LXR agonist with LXRβ selectivity. When tested in nonhuman primates, XL-652 appears to

Table 1 Mechanisms of action of novel lipid-modifying therapies addressing unmet needs in cardiovascular disease

Novel pharmacological agent	Mechanism of action
Inclisiran	Small interfering RNA targeting the hepatic synthesis of PCSK9
Bempedoic Acid	Inhibition of hepatic ACL and activation of AMPK
Seladelpar	Selective PPAR-δ agonist
CSL-112	Reconstituted infusible human ApoA-I
Apabetalone	Increase of ApoA-I transcription acting on bromodomain and extra-terminal domain (BET) protein 4 (BRD4)
Volanesorsen	Human ASO inhibiting the expression of mRNA of the ApoC-III gene
APO(a)-Rx and APO(a)-LRx	ASOs inhibiting the synthesis of the apolipoprotein (a)
XL-652	Partial LXR agonist with LXRβ selectivity
Allicin	Upregulation of ABCA1 expression in macrophage-derived foam cells
ACP-501	Recombinant human LCAT

PCSK9: Proprotein convertase subtilisin/kexin type 9; ACL: Adenosine triphosphate-citrate lyase; AMPK: Adenosine monophosphate-activated protein kinase; PPAR: Peroxisome proliferator-activated receptor; ApoA-I: Apolipoprotein A-I; ASO: Antisense oligonucleotide; LXR: Liver X receptor; ABCA1: ATP-binding cassette transporter A1; LCAT: lecithin-cholesterol acyltransferase.

have decreased lipogenic potential, as compared with a full pan agonist, but with similar potency in the induction of genes known to stimulate RCT[42]. XL-652 has also been proven to be safe enough to continue with clinical trials[19].

Another important molecule involved in lipid homeostasis is ABCA1, which has a critical role in modulating efflux of tissue cholesterol and phospholipids into the RCT pathway, thus clearing excess cholesterol from macrophages and preventing atherosclerosis. There is a clinical entity, known as Tangier disease, which is caused by mutations of the ABCA1 gene leading to ABCA1 deficiency[43]. Allicin is a novel anti-atherosclerotic molecule with anti-oxidant and anti-inflammatory properties, which can be extracted from garlic. Allicin has been shown to reduce lipid accumulation through the upregulation of ABCA1 expression in macrophage-derived foam cells[44]. Furthermore, in a randomized, placebo-controlled, clinical trial, the oral administration of a garlic powder tablet, containing 1200 mg of allicin, twice daily for 3 mo, was shown to be superior to placebo in the prevention of carotid intima-media thickness progression in patients with CAD[45]. Another novel promising molecule, which has also been shown in animal studies to up-regulate ABCA1-mediated cholesterol efflux and retard atherosclerosis, is apigenin, a natural flavonoid compound[46]. Thus, given the above, allicin (and possibly apigenin) may be proven useful in the future for the management of CVD and may also potentially have a place in the treatment of patients with Tangier disease with some residual ABCA1 activity.

Lecithin-cholesterol acyltransferase (LCAT) is a key enzyme for the esterification of cholesteryl esters in plasma, promoting also the formation of HDL and enhancing RCT. Mutations in the human LCAT gene underlie either familial LCAT deficiency (FLD) or fish-eye disease (FED)[47]. In this regard, the infusion of recombinant human LCAT is a promising therapeutic option that remains to be explored. In a phase 1b, open-label, single-dose escalation study, a single intravenous infusion of a recombinant human LCAT (ACP-501) had an acceptable safety profile and led to significant dose-proportional increases of both LCAT and HDL-C, as well as to a favorable modification of HDL metabolism. The results of this study provide support for the use of recombinant human LCAT in future clinical trials in patient with CHD and/or FLD[48]. In a first-in-human treatment with enzyme replacement in FLD, ACP-501 infusion therapy improved the anemia, stabilized the renal function, transiently normalized plasma lipids, and favorably modified HDL metabolism. Moreover, ACP-501 therapy was safe and well-tolerated[49]. Hence, the results of these studies are encouraging and support continued development of the recombinant human LCAT therapy.

Last but not least, it should be noted that many other novel lipid-modifying therapies are being currently tested in ongoing trials. These therapies include medications that target protein asialoglycoprotein receptor 1, angiopoietin-related protein 4, desmocollin 1 and many other molecules playing significant roles in lipid homeostasis[50,51].

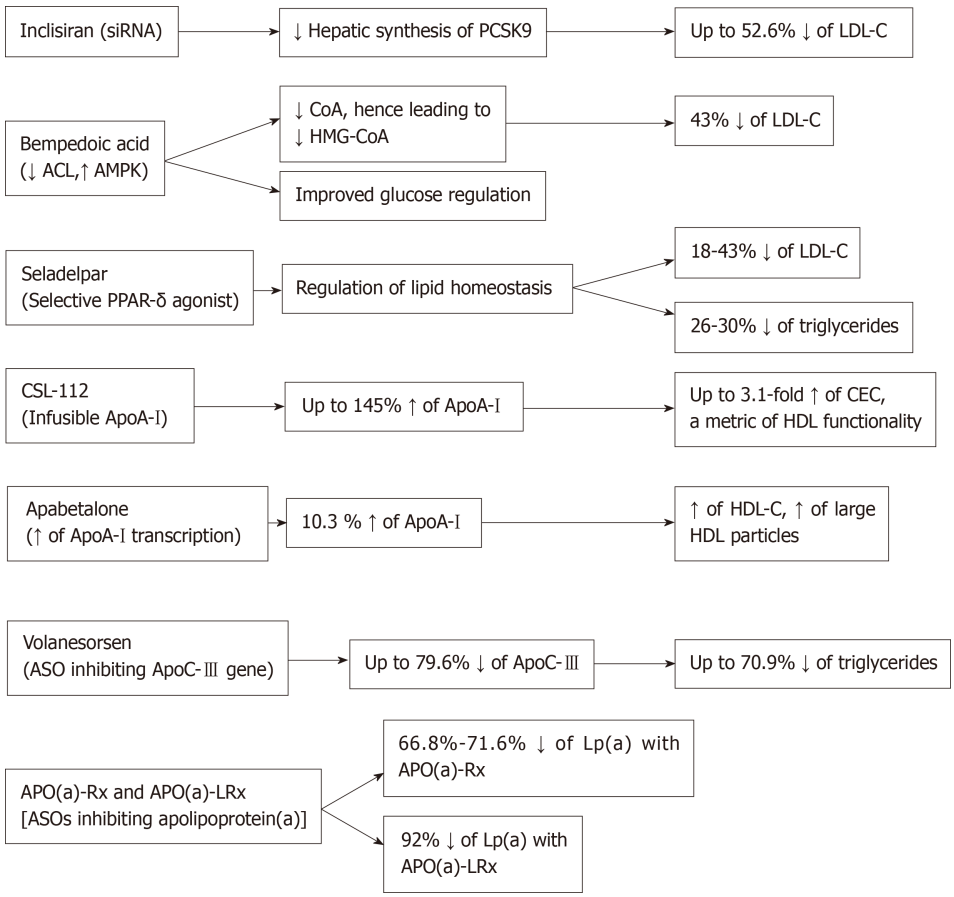

Figure 1 Molecular pathways of action and effects of novel lipid-modifying therapies addressing unmet needs in cardiovascular disease. siRNA: Small interfering RNA; ACL: Adenosine triphosphate-citrate lyase; AMPK: Adenosine monophosphate-activated protein kinase; PPARs: Peroxisome proliferator-activated receptors; Apo: Apolipoprotein; ASO: Antisense oligonucleotide; PCSK9: Proprotein convertase subtilisin/kexin type 9; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA; Lp(a): Lipoprotein (a); LXRs: Liver X receptors; LDL-C: Low-density lipoprotein cholesterol; CEC: Cholesterol efflux capacity.

CONCLUSION

It has been well established that despite the significant progress made in the management of CVD, there are still several unmet needs to be addressed. Currently, various lipid-modifying therapies are being evaluated in ongoing trials, targeting a number of different molecules involved in lipid homeostasis. There is optimism that some of these lipid-modifying therapies will be proven clinically beneficial and will eventually enter everyday clinical practice, hence enhancing the armamentarium for the optimal management of CV risk in dyslipidemic patients. Even if some of these drugs do not succeed in future trials, undoubtedly, we will still be a step forward towards a better understanding of the pathogenesis of atherosclerosis and to creating a better future for our patients, decreasing the risk of CVD.

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REVIEW

Multi-modality imaging in transthyretin amyloid cardiomyopathy

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Abstract

Transthyretin amyloid (TTR) cardiomyopathy is a disease of insidious onset, which is often accompanied by debilitating neurological and/or cardiac complications. The true prevalence is not fully known due to its elusive presentation, being often under-recognized and usually diagnosed only late in its natural history and in older patients. Because of this, effective treatment options are usually precluded by multiple comorbidities and frailty associated with such patients. Therefore, high clinical suspicion with earlier and better detection of this disease is needed. In this review, the novel applications of multimodality imaging in the diagnostic pathway of TTR cardiomyopathy are explored. These include the complimentary roles of transthoracic echocardiography, cardiac magnetic resonance, nuclear scintigraphy and positron emission tomography in quantifying cardiac dysfunction, diagnosis and risk stratification. Recent advances in novel therapeutic options for TTR have further enhanced the importance of a timely and accurate diagnosis of this disease.

Key words: Multimodality imaging; Cardiac amyloidosis; Transthyretin; Echocardiography; Cardiac magnetic resonance; Nuclear imaging

Core tip: Non-invasive diagnosis of transthyretin amyloid (TTR) cardiomyopathy is improving with significant developments in multiple imaging modalities available to date. A greater appreciation of the various strengths and limitations of these imaging modalities is vital, as is high clinical suspicion and timely investigation for the disease, which remains insidious and elusive. This is of particular relevance in light of emerging novel effective therapeutic options. This focused review aims to highlight the role of multimodality imaging in the diagnosis and risk stratification of patients with TTR

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INTRODUCTION

Transthyretin amyloid (TTR) cardiomyopathy is a disease characterized by extracellular accumulation of abnormal amyloid protein fibrils due to autosomal dominant hereditary mutation transmission or from a wild type (acquired) form, previously referred to as senile amyloidosis. Transthyretin is a protein primarily synthesized in the liver and can dissociate, subsequently aggregating to produce amyloid. Distinctively, TTR cardiomyopathy lies in one part of the spectrum of amyloid cardiomyopathy compared to primary systemic amyloidosis or light-chain amyloid (AL) cardiomyopathy, often due to plasma cell dyscrasia.

However, amyloid cardiomyopathy, particularly the TTR subtype, is often under-diagnosed, as patients are often asymptomatic or present with nonspecific symptoms early in the trajectory of the disease. Although certain electrocardiographic markers (*i.e.*, low voltage QRS) may suggest the presence of amyloid cardiomyopathy, these markers are not specific, particularly for TTR[1]. Left ventricular (LV) hypertrophy criteria on electrocardiography has only been observed in 25% of TTR cardiomyopathy[2]. While biomarkers such as natriuretic peptides and troponin may be elevated in TTR cardiomyopathy, inferring worse prognosis, their utility in diagnosis of the disease is limited[3,4]. The diagnostic yield is further challenged by the utility of the gold standard of endomyocardial biopsy, which may be limited by sampling errors in early disease and false positive/negative rates of approximately 10%[5].

Therefore, the true prevalence of TTR cardiomyopathy is not fully known as it is usually diagnosed late in its natural history when the disease is well established. Previous reports using imaging and histological evidence have estimated TTR cardiomyopathy prevalence to be between 0.36% to 25% in different cohorts of elderly patients, including those with aortic stenosis and heart failure with preserved ejection fraction. These have been associated with worse outcomes[6-12]. With that, these observations support the need for higher clinical suspicion and earlier screening and diagnosis of TTR cardiomyopathy with non-invasive imaging modalities.

Indeed, the timely detection of TTR cardiomyopathy may allow earlier implementation of disease-modifying therapy, improving survival. Conventionally, orthotopic liver and/or heart transplantation has been offered to these patients as possible curative treatments, as the misfolded TTR protein is synthesized in the liver[13]. Advanced age at liver transplantation and duration of disease have been associated with increased mortality[13]. Patients are also more likely to be suitable surgical candidates at earlier stages of the disease. Furthermore, recent studies have demonstrated beneficial outcomes in patients with TTR treated with novel medical therapies[14,15]. Published data from the ATTR-ACT trial has shown significant reductions in all-cause mortality in TTR-diagnosed patients treated with Tafamidis, a novel agent with TTR stabilizing properties, along with improvements in cardiovascular-related hospitalizations and quality of life measurements[14]. The authors of this study speculate that treatment with this agent early in the disease course will convey greater benefit, similar to its effect in TTR familial amyloid neuropathy[16]. In a subpopulation of the APOLLO study, the RNA inhibitor, Patisiran, has shown statistically significant improvements in certain exploratory endpoints measuring cardiac function, including natriuretic peptide levels, LV wall thickness and global longitudinal strain[15]. These therapeutic options offer promising solutions and support the need for a timely diagnosis. Otherwise, TTR cardiomyopathy is commonly associated with long-term debilitating neurological and cardiac complications such as arrhythmias and heart failure[17].

With that, this focused review aims to highlight the role of multimodality imaging in the diagnosis and risk stratification of patients with TTR cardiomyopathy.

TRANSTHORACIC ECHOCARDIOGRAPHY

Echocardiography is the primary initial imaging modality performed in the investigation of amyloid cardiomyopathy when clinically suspected. While it is a widely available and inexpensive imaging modality, its ability to differentiate between amyloid cardiomyopathy subtypes is limited and when amyloid cardiomyopathy is suspected based on echocardiography, further investigations are necessary to confirm TTR cardiomyopathy.

Increased LV wall thickness, particularly in the absence of high electrocardiographic voltages, and diastolic dysfunction are among the common early echocardiographic features seen which can raise suspicion of amyloid cardiomyopathy, although the differentials for such features are wide[18,19]. In the later stages of the disease, a restrictive filling pattern and biatrial dilatation may be accompanied by pleural and/or pericardial effusions[19-21]. Although not highly specific, LV wall thickness tends to increase to a greater degree in TTR compared to AL cardiomyopathy[18].

Using myocardial strain analysis, the presence of relative apical sparing of longitudinal strain is very characteristic of amyloid cardiomyopathy and has been demonstrated as a reproducible method of accurately differentiating amyloid cardiomyopathy from other causes of LV hypertrophy. In a study comparing 55 patients with amyloid cardiomyopathy to 30 patients with LV hypertrophy due to due to either hypertrophic cardiomyopathy or aortic stenosis, the presence of relative apical longitudinal strain was 93% sensitive and 82% specific in identifying amyloid cardiomyopathy[22].

This apical sparing pattern of global circumferential strain is usually observed unless severe diastolic dysfunction is present[23]. Furthermore, this imaging technique may better aid the identification of amyloid cardiomyopathy in challenging patient subgroups with mild LV wall thickening and preserved ejection fraction[24]. Despite that, there is limited data on echocardiographic features specific to TTR cardiomyopathy. In a study of biopsy-proven TTR patients using speckle-tracking echocardiography, acquired TTR was characterized by lower LV ejection fraction, as well as lower basal and mid LV radial strain compared to inherited TTR[25].

In addition, only few echocardiographic markers have demonstrated prognostic value specific to TTR cardiomyopathy. Among these, impairment of left atrial function, using conventional and strain-derived speckle-tracking parameters, has been demonstrated in amyloid cardiomyopathy and closely correlates to LV deformation. Acquired TTR was associated with worse left atrial function when compared to inherited TTR or AL[26]. In terms of strain imaging, 4-chamber longitudinal strain was significantly associated with major adverse cardiovascular events in amyloid cardiomyopathy, superior to traditional parameters[27]. Relative apical sparing pattern of global longitudinal strain may indicate worse prognosis, particularly when combined with low LV ejection fraction[28]. In assessing the right ventricle, TAPSE can independently predict major adverse events in amyloid cardiomyopathy patients[29]. Right ventricular dilatation has also been associated with more severe cases of amyloid cardiomyopathy and infers very poor prognosis[30].

BONE SCINTIGRAPHY

In 1975, ^{99m}Tc -methylene diphosphonate accumulation in amyloid cardiomyopathy was reported for the first time[31]. Since then, multiple bone scintigraphy tracers have been tested, although their cellular binding mechanisms are not fully known. Several of these tracers have been predominantly utilized and are described below. Scintigraphy tracer uptake in TTR cardiomyopathy has been suggested as possibly due to the increased number of small microcalcifications seen in the myocardium in TTR[32]. The presence of cardiac tracer uptake confirms amyloid cardiomyopathy but has not been able to exclusively differentiate TTR cardiomyopathy from other subtypes. In addition, the absence of tracer uptake does not rule out amyloid cardiomyopathy.

The authors of a large study of 1217 patients that underwent radionuclide scintigraphy, either ^{99m}Technetium-3,3-disphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), ^{99m}Technetium pyrophosphate (^{99m}Tc-PYP) or ^{99m}Tc-hydroxymehtylene diphosphonate (^{99m}Tc-HMDP) proposed a non-invasive diagnostic criteria for TTR cardiomyopathy[33]. TTR was suggested by a score of 2 or 3 with the use of the Perugini visual score of myocardial radiotracer enhancement (Table 1). Grade 2 or 3 enhancement was shown to be 90% sensitive and 97% specific for TTR cardiomyopathy using this scoring system. Furthermore, when grade 2 or 3 uptake is

combined with absence of monoclonal proteins in serum or urine testing, the diagnostic accuracy improves further. A specificity and positive predictive value of 100% has been demonstrated in this regard. This was consistent among all three of the radiotracers used in the study.

Interestingly, while absence of abnormal cardiac uptake of radionucleotide tracer confers a prognostic benefit, Perugini grade stratification at diagnosis has yet to show prognostic significance in TTR cardiomyopathy[34]. These observations are further supported by a study of a large cohort of patients undergoing scintigraphy for non-cardiac reasons. Of 12521 patients included, myocardial tracer uptake was demonstrated in 0.36%[6].

Despite the added value of nuclear scintigraphy in the diagnostic pathway of amyloid cardiomyopathy, there remains low penetrance and high variability in its utilization[35], thus indicating a greater need for standardization in technique between centres.

^{99m}Tc-DPD scintigraphy

^{99m}Tc-DPD scintigraphy is a highly sensitive technique for imaging TTR cardiomyopathy. In a study utilizing ^{99m}Tc-DPD scintigraphy, all 158 patients with TTR and clinical cardiac involvement demonstrated cardiac tracer uptake[36]. In the diagnosis of TTR cardiomyopathy, a study comparing 15 patients with TTR cardiomyopathy to 10 patients with AL-related cardiomyopathy revealed both sensitivity and specificity of 100% in identifying the TTR cohort using ^{99m}Tc-DPD scintigraphy[37]. Another more recent study comparing a larger group of 45 patients with TTR cardiomyopathy to 34 with AL cardiomyopathy and 15 controls again showed high levels of accuracy with positive and negative predictive values of 88% and 100% using a visual score of ≥ 2[38]. ^{99m}Tc -DPD use as a modality in diagnosing and differentiating TTR from AL cardiomyopathy has also been supported by a study of a small Australian cohort of 13 TTR patients, all showing diagnostic tracer uptake, while 25% of patients with AL-related cardiac involvement showed uptake[39].

^{99m}Tc-DPD has been observed to distribute predominantly in the cardiac septal and basal segments and lowest uptake is found in the apical and apico-antero-lateral segments[40].

Furthermore, reasonable intermodality agreement ^{99m}Tc-DPD has been shown with cardiac magnetic resonance (CMR) in the identification of TTR cardiomyopathy. Significantly improved estimation of cardiac involvement was seen using ^{99m}Tc –DPD scintigraphy when compared to late gadolinium enhancement (LGE) on CMR in a study of 18 patients diagnosed with TTR. These consecutively diagnosed patients had a mean age of 50 years, 56% were female and 56% were asymptomatic[41]. Interestingly, amyloid fibril composition has been shown to affect the result of ^{99m}Tc-DPD scintigraphy. Among 55 biopsy-proven TTR patients, all of those with type A fibrils, and none of those with type B, showed tracer uptake. Type B fibrils were associated with early-onset V30M mutation and in patients carrying the Y114C mutation in inherited TTR, whereas type A was noted in all other mutations currently examined as well as in acquired TTR cardiomyopathy[42].

^{99m}Tc-PYP scintigraphy

^{99m}Tc-PYP is currently the most commonly used form of nuclear scintigraphy. There is growing evidence behind its use of as a cardiac tracer in TTR. In a large multicenter study of 171 patients with CA, 121 due to TTR, ^{99m}Tc-PYP showed 91% sensitivity and 92% specificity in diagnosing TTR cardiomyopathy[43]. Another study demonstrated the ability of ^{99m}Tc -PYP cardiac imaging to distinguish AL from TTR cardiomyopathy with a sensitivity of 97% and specificity of 100% when heart-to-contralateral ratio of > 1.5 was used[44]. Furthermore, ^{99m}Tc-PYP scintigraphy showed reduced uptake in the apical segments of the LV in TTR. This correlates with apical sparing of longitudinal strain seen on echocardiography[45].

In addition, there may be potential to diagnose early TTR cardiomyopathy. An observational study of carriers of inherited TTR mutations included 12 asymptomatic carriers with normal echocardiographic and biochemical parameters. Cardiac ^{99m}Tc-PYP uptake was abnormal by visual scoring, comparing cardiac to bone tracer uptake, in 84%. Grade 2 or 3 tracer avidity, indicating TTR deposition, was seen in 58%[46]. However, serial ^{99m}Tc-PYP scanning has not been shown to track disease progression accurately, as demonstrated in a small study, which showed no significant change in tracer uptake after 18 mo despite obvious clinical progression of disease[47].

POSITRON EMISSION TOMOGRAPHY

Radiolabelled amyloid ligands have previously been developed to investigate for

Table 1 Perugini visual scoring

Score	Cardiac uptake and bone uptake
Score 0	Absent cardiac uptake and normal bone uptake
Score 1	Mild cardiac uptake
Score 2	Moderate cardiac uptake accompanied by attenuated bone uptake
Score 3	Strong cardiac uptake with mild/absent bone uptake

amyloid deposits in the brain in Alzheimer's disease. These tracers have also shown some utility in amyloid cardiomyopathy. Its concomitant use with nuclear scintigraphy aids in confirming localization of tracer uptake in heart. A systematic review of six studies involving the use of positron emission tomography (PET) in amyloid cardiomyopathy, including 98 patients, demonstrated a pooled sensitivity of 95% and specificity of 98% in differentiating amyloid cardiomyopathy from controls[48]. Although the individual studies have been small, due to high levels of accuracy, the use of PET and scintigraphy may potentially aid in screening early phases of TTR cardiomyopathy where structural disease may not be apparent on echocardiography or CMR[49]. This requires further exploration. Evidence of PET studies utilizing various cardiac tracers are described below.

^{11}C-Pittsburgh compound B, a radiotracer commonly used in the investigation of Alzheimer's disease, has the ability to identify amyloid cardiomyopathy due to both type A and type B amyloid fibrils. While this method does not distinguish between TTR and AL, it may help identify certain patients with type B amyloid fibril disease, predominantly V30M mutation-associated TTR cardiomyopathy where ^{99m}Tc-DPD scintigraphy has shown a lack of tracer uptake. However, the mechanism of this is not fully known[42,50]. In addition, the utility of this compound is limited by its very short half-life and difficult production.

^{18}F-florbetaben PET has been shown to help identify patients with amyloid cardiomyopathy, due to TTR or AL. Percentage ^{18}F-florbetaben retention was shown to predict myocardial dysfunction in amyloid cardiomyopathy[51]. In another study of 14 patients, 9 with AL or TTR cardiomyopathy and 5 controls, ^{18}F-florbetapir uptake was seen in all patients with amyloid cardiomyopathy and none of the controls[49]. An autopsy study of 20 patients with autopsy-documented amyloid cardiomyopathy, either due to AL or TTR, and 10 controls, showed binding of ^{18}F-florbetapir, a similar tracer to ^{18}F-florbetaben, in myocardial sections in all amyloid cardiomyopathy patients and in none of the controls[52].

^{18}F-fluorine sodium fluoride is a PET tracer that has been shown, in a small study, to differentiate biopsy-proven TTR from AL cardiomyopathy and controls. Tracer uptake was shown to be present in all of the TTR cardiomyopathy patients and none of either the AL-related patients or controls[53]. This radioisotope was also able to quantify the degree and regional distribution of tracer uptake. However, another report of two patients with TTR cardiomyopathy did not show any uptake of this tracer[54]. The authors hypothesized that specific TTR mutation may influence radioisotope uptake. Therefore, while ^{18}F-fluorine sodium fluoride shows promise as a TTR-specific investigative and disease-monitoring tool, it requires further investigation in larger studies.

CARDIAC COMPUTED TOMOGRAPHY

Currently, there is limited evidence regarding the utility of computed tomography (CT) in diagnosing TTR cardiomyopathy. Myocardial iodine concentration and ratio were increased in amyloid cardiomyopathy and can accurately distinguish amyloid cardiomyopathy from non-amyloid hypertrophic cardiomyopathy and healthy controls with an AUC of 0.99. At a threshold of 0.65, iodine ratio demonstrated a sensitivity of 100% and a specificity of 92% in diagnosing amyloid cardiomyopathy[55]. Myocardial extracellular volume measured using CT has been shown to accurately track laboratory and echocardiographic markers of amyloid cardiomyopathy severity and correlate with bone scintigraphy quantification of amyloid burden[56]. Furthermore, determining the myocardial extracellular volume previously required blood sampling to measure haematocrit level. However, recently, a methodology of calculating the extracellular volume, using a calculation involving the attenuation of blood, has eliminated the need for blood sampling from this process. This improves the feasibility of using CT as a potentially useful imaging modality in amyloid

cardiomyopathy[57].

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) is a useful imaging modality in the diagnosis of amyloid cardiomyopathy. Its utility in assessing abnormal myocardial interstitium was described in 2005[58]. Characteristic features seen in amyloid cardiomyopathy were described as a subendocardial tram-line pattern on LGE imaging which can progress to transmural enhancement in later stages of the disease[59] (Figure 1). Alongside LGE, conventional sequences and non-contrast techniques including native T1 mapping can help diagnose amyloid cardiomyopathy and quantify amyloid burden, although caution should be applied in the setting of ectopic beats, which is not uncommonly associated with amyloid cardiomyopathy, but may result in overlapping blood pool and subsequent false positive diffuse elevation of T1 levels. Cardiac involvement in patients with inherited TTR can be seen in patients without clinical cardiac signs or increased LV wall thickness on CMR, suggesting a potential role in detecting pre-clinical amyloid cardiomyopathy in certain at-risk patients[60].

LATE GADOLINIUM ENHANCEMENT

LGE on CMR has been shown to be of high diagnostic value in amyloid cardiomyopathy and has achieved a diagnostic sensitivity of 85% and specificity of 92% in a meta-analysis of five studies[61]. Transmural pattern of LGE has been shown to be more associated with TTR than AL, although the classically described circumferential subendocardial or transmural LGE is not seen in most patients with amyloid cardiomyopathy. Other findings which are more suggestive of TTR include greater intraventricular septal wall thickness and right ventricular LGE[62]. These investigators also proposed a scoring system, derived from CMR with LGE, which differentiates TTR from AL with 87% sensitivity and 96% specificity[62].

Furthermore, the results of a study by Fontana and colleagues suggested that phase sensitive inversion recovery should replace conventional magnitude inversion recovery for LGE determination in the setting of amyloid cardiomyopathy. Phase sensitive inversion recovery helps to remove the potential confounder of incorrect inversion recovery time selection in diffuse infiltrative disease[63]. Higher proportion of left atrial LGE has been shown to have a strong association with amyloid cardiomyopathy and may help in differentiating amyloid cardiomyopathy from other cardiomyopathies. A sensitivity of 76% and specificity of 94% has been shown where left atrial LGE is > 33%, with significant reduction in left atrial emptying function[64].

However, LGE has some limitations in the investigation of amyloid cardiomyopathy. LGE does not enable assessment of diffuse changes in interstitial space secondary to amyloid deposition or quantitative assessment of expanded interstitium. This is due to inversion time adjustment to the least-enhancing myocardial region. As a result, absence of LGE does not confirm normal myocardium in amyloid cardiomyopathy[65]. Another limitation associated with gadolinium enhancement is the risk of nephropathy. Caution is warranted due to the high prevalence of renal impairment in patients with amyloid cardiomyopathy.

T1 MAPPING

T1 native mapping using non-contrast MRI has shown high levels of diagnostic accuracy in detecting AL cardiomyopathy. In a study of 53 AL amyloidosis patients, 28 patients with confirmed AL cardiomyopathy were compared to 36 healthy controls and 17 patients with aortic stenosis. Accuracy of 92% was seen using a non-contrast T1 cut-off of 1020 ms[66]. Compared to TTR cardiomyopathy, T1 elevations are higher in AL cardiomyopathy but similar diagnostic and disease-tracking performance has been shown in TTR. In TTR, T1 also correlates with left atrial area and with PR interval and QRS duration on electrocardiogram[67]. Quantification methods of myocardial T1, such as weighted mean shortened modified look-locker inversion recovery sequence T1 values have been shown to be significantly higher in amyloid cardiomyopathy when compared to healthy controls[68]. T1 mapping allows detection of diffuse myocardial disease and quantitative assessments, which are limited in LGE imaging[65].

T1 mapping can accurately identify patients with LGE-confirmed cardiac involvement in TTR and correlates well with the degree of amyloid deposition[69]. As a

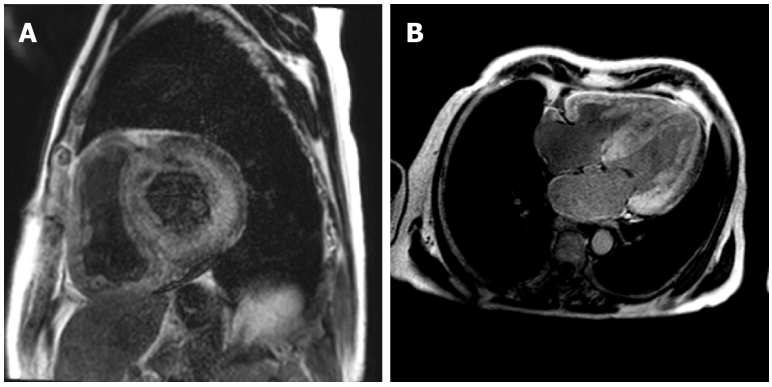

Figure 1 Cardiac magnetic resonance. A, B: Cardiac magnetic resonance demonstrating diffuse, circumferential and near transmural late gadolinium enhancement of the left ventricle in the 4-chamber (A) and short axis views (B), features which are characteristic of amyloid cardiomyopathy.

result, it can help improve detection rates of amyloid cardiomyopathy when used in combination with LGE sequences. It is also a particularly useful tool when contrast is contraindicated due to renal impairment and when LGE artefacts occur due to poor breath-holding and arrhythmias; diagnostic problems commonly seen in these patients.

MYOCARDIAL EXTRACELLULAR VOLUME

Myocardial extracellular volume is another cardiac mapping technique using CMR that is a validated indicator of myocardial fibrosis[70]. It involves T1 mapping acquisitions before and after T1-shortening contrast injection. Both T1 mapping and extracellular volume have recently been shown to perform well as diagnostic techniques in differentiating TTR from other causes of hypertrophic cardiomyopathy[71]. While not a specific feature of amyloid cardiomyopathy, it has been identified as a potential disease-marker to track therapeutic response in the reduction of hepatic amyloid burden following the use of anti-serum amyloid P component antibody in systemic amyloidosis[72].

Extracellular volume correlates with amyloid burden and has been shown to be an independent prognostic factor for survival in TTR cardiomyopathy patients[73]. Furthermore, extracellular volume has been suggested as a more robust marker in TTR cardiomyopathy when compared to T1 mapping as it has shown independent prediction of mortality, where T1 mapping has not[71]. In this regard, T1 mapping and extracellular volume are divergent when comparing TTR to AL cardiomyopathy. Extracellular volume is higher in TTR, reflecting proportionally more amyloid deposition. In contrast, native T1 levels, reflecting both interstitial and cellular changes, are lower in TTR[74]. However, these differing myocardial observations are poorly understood.

OTHER SEQUENCES

CMR-measured longitudinal strain can demonstrate the relative apical sparing and base-to-apex gradient in longitudinal strain, with significantly reduced global longitudinal strain, which is characteristic of amyloid cardiomyopathy[75]. Strain analysis using CMR can help diagnose LGE-positive amyloid cardiomyopathy patients while avoiding the need for contrast medium. Peak circumferential strain level and variability may be more sensitive when compared to LGE imaging in detecting early cardiac involvement in amyloid cardiomyopathy[76]. Basal segments strain parameters can accurately identify cardiac involvement in patients with amyloidosis[77].

Operator-independent heart deformation analysis using CMR has been shown to accurately reproduce radial and circumferential regional myocardial motion patterns, which correlate with feature-tracking indices in amyloid cardiomyopathy[78].

Reduced T2 ratio, comparing the T2 signal intensity of myocardium to skeletal muscle, has shown some utility in amyloid cardiomyopathy diagnosis and can predict mortality[79]. Myocardial oedema, as assessed by T2 mapping, is elevated in both TTR and AL cardiomyopathy, although to a higher degree in AL[80].

CONCLUSION

The use of multi-modality imaging in the diagnosis and management of suspected TTR cardiomyopathy is becoming increasingly accurate and necessary. In light of recent evidence for disease-specific therapeutic agents, high clinical suspicion coupled with earlier utilization of non-invasive imaging modalities are essential for diagnosing this insidious and elusive disease.

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CASE REPORT

Management of atherosclerotic plaque in left internal mammary artery graft five years after angiographic patency: A case report

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Abstract

BACKGROUND

The left internal mammary artery (LIMA) has demonstrated excellent long-term patency rates when used as a bypass conduit with complications usually occurring in the early postoperative period. The rapid development of de-novo atherosclerosis in a previously non-diseased LIMA, subsequently leading to an acute coronary syndrome (ACS) is rarely encountered.

CASE SUMMARY

A 67-year-old man with history of triple coronary artery bypass graft (8 years ago) presented to our hospital with an ACS. He had undergone angiography 5 years ago to investigate episodic chest pain and imaging of the LIMA at the time did not demonstrate the atherosclerotic process. Emergent angiography demonstrated a severe diffuse stenosis in the proximal to mid segment of the LIMA, with embolization of a moderate sized thrombus to the distal skip segment. The LIMA stenosis was characterised by overlying haziness, consistent with acute plaque rupture, associated with residual luminal thrombus. The patient was managed with antithrombotic therapy to reduce the thrombus burden until repeat angiography after 72 h. At repeat angiography, the thrombus burden was substantially reduced at the distal skip segment as well as at the proximal to mid LIMA with the demonstration of multiple plaque cavities. This lesion was predilated and a 2.75 mm × 33 mm everolimus-eluting stent was implanted to a final diameter of 3.0 mm. The patient made a good clinical recovery and was discharged after 6 d.

CONCLUSION

This case highlights the rapid and late development of atherosclerosis in a graft 5 years after documented patency and the importance for consideration of expectant thrombus management.

Key words: Left internal mammary artery graft; Atherosclerosis; Thrombus; Case report

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Core tip: Late complications of the left internal mammary artery (LIMA) graft occur rarely. We present the case of a 67-year-old man with an acute myocardial infarction due to the rapid progression of atherosclerotic plaque in the mid shaft of the IMA, culminating in plaque rupture and thromboembolism. This case highlights the importance of consideration of expectant thrombus management as well as the importance of considering late complication of LIMA graft as a cause of acute coronary syndrome.

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INTRODUCTION

The left internal mammary artery (LIMA) has demonstrated excellent long term patency rates when used as a bypass conduit[1,2]. When vessel occlusion does occur, it is typically associated with the presence of competitive flow from the native circulation leading to atresia, issues relating to surgical technique resulting in distal anastomotic failure or rarely due to dissection (either spontaneous or iatrogenic). The rapid development of de-novo atherosclerosis in a previously non-diseased LIMA, subsequently leading to an acute coronary syndrome (ACS) is rarely encountered. We present the case of a 67-year-old man presenting with an acute myocardial infarction due to the rapid progression of atherosclerotic plaque in the mid shaft of the IMA, culminating in plaque rupture and thromboembolism.

CASE PRESENTATION

Chief complaints

A 67-year-old man presented to the emergency department of our hospital complaining of worsening central chest pain for the duration of 3 h.

History of past illness

The patient had past history of coronary artery bypass graft (8 years ago) LIMA-diagonal to Left Anterior Descending (LAD) artery, free right internal mammary artery (RIMA)-ramus intermedius skip to OM and a left radial artery anastomosed to the PDA and ischaemic cardiomyopathy with moderate segmental systolic dysfunction. He also had history of treated hypertension, dyslipidaemia, rheumatoid arthritis and partial nephrectomy for clear cell carcinoma. His regular medications included aspirin 100 mg daily, atorvastatin 80 mg daily (low density lipoprotein cholesterol 1.7 mmol/L), frusemide 40 mg daily, metoprolol 50 mg twice daily and ramipril 5 mg daily.

Physical and laboratory examinations

The patient's cardiovascular examination revealed his heart sounds were dual with no added murmurs and his chest was clear. Electrocardiogram showed anterolateral ST changes of ischaemia (Figure 1) and troponin elevation to 44 ug/L (reference range < 0.05 ug/L). Full blood picture was normal and biochemistry revealed glomerular filtration rate of 63 mL/min/1.73 m^2 (reference range > 90). C-reactive protein was mildly raised at 6.7 mg/L (reference range < 3.0).

Imaging examinations

A computed tomography aortogram was performed to exclude other differentials for his presentation that revealed no aortic dissection, ulceration or aneurysm apart from scattered small areas of calcified arteriosclerotic plaque. No large central pulmonary embolus was seen either.

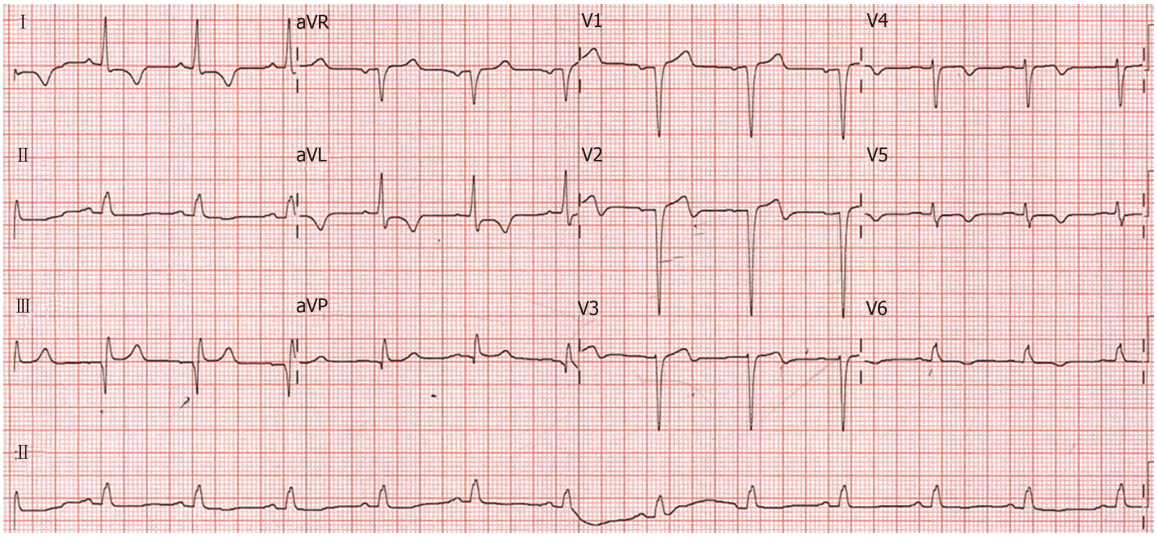

Figure 1 12-lead electrocardiograph at presentation.

Further diagnostic workup

Emergent angiography was organised for this patient due to his clinical picture and raised cardiac markers. Notably, he had undergone angiography 5 years ago to investigate episodic chest pain and imaging of the LIMA at the time did not demonstrate any evidence for atherosclerotic plaque formation (Figure 2A). Angiography demonstrated a severe diffuse stenosis in the proximal to mid segment of the LIMA, with embolization of a moderate sized thrombus to the distal skip segment and anastomosis with the first diagonal branch ("coronary saddle thrombus"). The LIMA stenosis was characterised by overlying haziness, consistent with acute plaque rupture, associated with residual luminal thrombus (Figure 2B).

FINAL DIAGNOSIS

Acute plaque rupture in the LIMA with residual luminal thrombus and distal embolization of the thrombus.

TREATMENT

The patient was managed with intensive antithrombotic therapy initially to reduce the thrombus burden with eptifibatide (10.5 mg/h for 48 h), enoxaparin (1 mg/kg at 80 mg twice daily for 72 h), ticagrelor 90 mg twice daily and aspirin until repeat angiography after 72 h.

At repeat angiography, the thrombus burden was substantially reduced at the distal anastomosis with the diagonal branch and skip graft to LAD. Similarly, the lesion within the proximal to mid LIMA demonstrated marked resolution with the demonstration of multiple plaque cavities and a reduction in overlying thrombus burden (Figure 2C).

This lesion was consequently predilated with 2.5 mm × 15 mm balloon. A 2.75 mm × 33 mm everolimus-eluting stent was implanted with post dilatation to a final diameter of 3.0 mm (Figure 2D).

OUTCOME AND FOLLOW UP

The patient made a good clinical recovery and was discharged after 6 d. On follow-up, he remained well with no further episodes of angina.

DISCUSSION

We describe a case of ACS secondary to atherosclerotic plaque rupture complicated

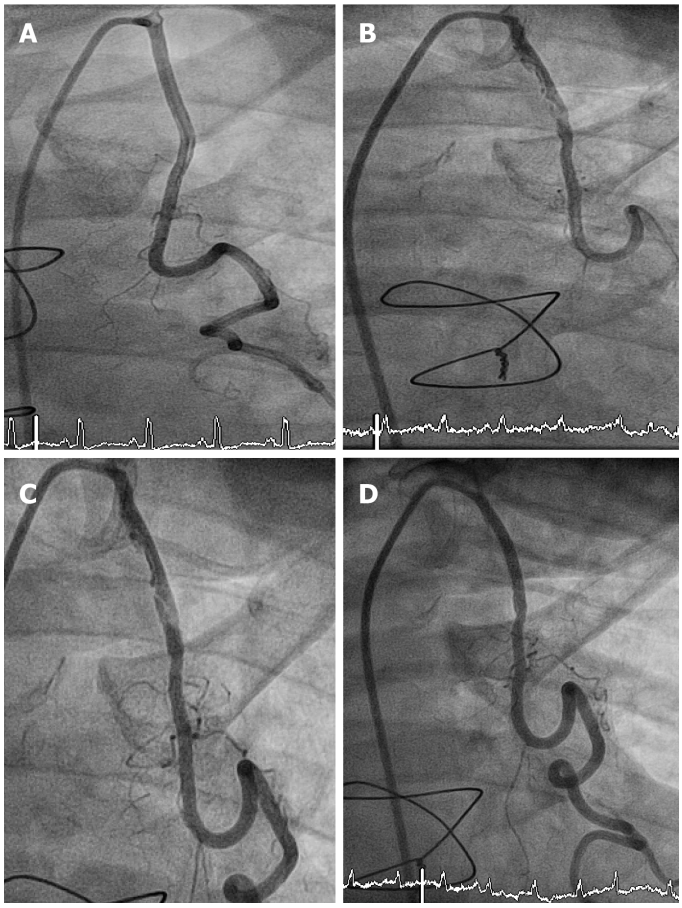

Figure 2 Result of angiography. A: LIMA graft Angiogram performed 5 years prior to the current presentation demonstrates no evidence of atherosclerotic plaque formation; B: Proximal LIMA graft lesion; C: Residual atheroma of the LIMA graft post anti-thrombotic therapy; D: Post stent insertion.

by distal embolization in a LIMA conduit 8 years after surgery and 5 years after angiography revealing a patent graft. Most LIMA occlusions occur in the early postoperative period and are associated with surgical complications such as dissection, hematoma, spasm, or anastomotic stenosis. LIMA-LAD grafts are associated with excellent long-term patency and improved outcomes compared to the saphenous vein grafts. The 10-year patency rate of LIMA grafts is approximately 90% if the graft is patent 1 wk after the procedure[1,2]. Myocardial infarction caused by *de-novo* atherothrombotic disease within the LIMA in the late postoperative period is rare. Our patient's clinical history of dyslipidaemia, hypertension and rheumatoid arthritis increases rate of atherosclerosis progression. Atherosclerotic lesions are also more prone to rupture in patients with rheumatoid arthritis[3].

Atherothrombotic graft occlusion within the IMA itself is rarely described[4,5]. Several unique structural and physiological characteristics protect the LIMA from atherogenesis, which include fewer fenestrations in the endothelial layer, lower intercellular junction permeability, enhanced endothelial expression of anti-thrombotic molecules such as heparin sulfate and tissue plasminogen activator, and higher endothelial nitric oxide production[6].

The most common late complication of LIMA-LAD graft has been dissection, either spontaneous or post intervention, even this is rarely reported in the literature[7]. Spontaneous coronary artery dissection (SCAD) type III was also considered in our case given the appearance of a long lesion with haziness and linear stenosis. However, this was considered less likely due to the appearance of the lesion with multiple plaque cavities and the overlying thrombus.

At the time of angiography, the patient was clinically stable and pain free therefore we elected to defer a percutaneous strategy at the index procedure and use an initial antithrombotic strategy for the following reasons of large thrombus burden, risk of further distal embolization and challenges with protecting both the LAD and diagonal territories. The reduction in thrombus burden would also potentially reduce lumen compression if SCAD were the underlying pathology.

Whilst thrombectomy was considered for acute management, we were dissuaded

by the significant tortuosity of the LIMA (limiting deliverability), concerns regarding the passage of a thrombectomy device into the diagonal vessel could lead to thrombus dislodgment and embolization into the LAD (or vice versa). Whilst SCAD was considered less likely, there remained a risk that wiring the vessel could inadvertently lead to sub-intimal wire passage with consequent distal propagation of the dissection.

At repeat angiography, the thrombus burden was substantially reduced suggesting that this strategy may have mitigated the risk of distal embolization and peri-procedural infarction. Similarly, whilst further imaging with Optical Coherence Tomography (OCT) or Intravascular ultrasonography (IVUS) was considered, we felt the angiographic appearances of the lesion to be sufficiently characteristic of an atherosclerotic process rather than SCAD. In particular, OCT imaging would necessitate pressurized contrast delivery to achieve clearing of the blood pool, hence raising the risk of either propagation of an underlying dissection or hydraulic dissection of the LIMA ostium that such evaluation would be rendered redundant. In addition, there is risk of further extension of SCAD with OCT due to pressurised contrast injection.

The available medical literature comparing the incidence of atheromatous plaque formation with that of SCAD within LIMA conduits is scant, perhaps due to the relative rarity of such events. However, prompt recognition and appropriate management is clearly critical, given the life-threatening nature of such occlusions and the important technical considerations needed to achieve successful reperfusion. Relevant considerations include attention to guiding catheter and coronary wire length (guide catheter shortening and the use of longer length coronary guide wires may be required). The risk of vessel occlusion due to guide wired induced straightening of a tortuous LIMA is a further consideration. This case highlights the rapid development of atherosclerotic disease in a graft 5 years after documented patency and the importance for consideration of expectant thrombus management in a patient with atheromatous plaque rupture of the LIMA graft, to our knowledge; this is the first case in literature describing this strategy.

CONCLUSION

Whilst use of IMA conduits is associated with excellent long-term patency, late atherogenesis complicated by plaque rupture is rarely encountered and the natural history of atheromatous plaque rupture in the LIMA is unknown. Prompt recognition, together with judicious use of antithrombotic and anti-platelet therapy may facilitate optimal percutaneous reperfusion. Confirmatory imaging with IVUS or OCT may provide useful additional lesion definition and help to distinguish between dissection and atheromatous aetiologies.

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