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Contents

Monthly Volume 9 Number 2 February 26, 2017

META-ANALYSIS

CASE REPORT

Contents

World Journal of Cardiology
Volume 9 Number 2 February 26, 2017

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REVIEW

PCSK9 inhibitors: A new era of lipid lowering therapy

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Abstract

Hyperlipidemia is a well-established risk factor for developing cardiovascular disease (CVD). The recent American College of Cardiology and American Heart Association guidelines on lipid management emphasize treatment of individuals at increased risk for developing CVD events with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) at doses proven to reduce CVD events. However, there are limited options for patients who are either intolerant to statin therapy, develop CVD despite being on maximally tolerated statin therapy, or have severe hypercholesterolemia. Recently the Food and Drug Administration approved two novel medications for low-density lipoprotein (LDL)-cholesterol reduction: Evolocumab and Alirocumab. These agents target and inactivate proprotein convertase subtilsin-kexin type 9 (PCSK9), a hepatic protease that attaches and internalizes LDL receptors into lysosomes hence promoting their destruction. By preventing LDL receptor destruction, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone. This review explores PCSK-9 biology and the mechanisms available to alter it; clinical trials targeting PCSK9 activity, and the current state of clinically available inhibitors of PCSK9.

Key words: Hyperlipidemia; Statins; Proprotein convertase subtilsin-kexin type 9

Core tip: Hyperlipidemia is a well-established risk factor for developing cardiovascular disease (CVD). However, there are limited options for patients who are either intolerant to statin therapy, develop CVD despite being on maximally tolerated statin therapy, or have severe hypercholesterolemia. The Food and Drug Administration has approved two novel medications for low-density lipoprotein (LDL)-cholesterol reduction in this patient population: Evolocumab and Alirocumab. These agents target and inactivate proprotein convertase subtilsin-kexin type 9 (PCSK9), a hepatic protease that attaches and internalizes LDL receptors into lysosomes hence promoting their destruction. By preventing LDL receptor destruction, LDL-C levels can be lowered 50%-60% above that achieved by statin therapy alone. PCSK9 inhibitors are

an exciting agent for reducing LDL-C and have ushered in a new era of lipid lowering therapy.

Chaudhary R, Garg J, Shah N, Sumner A. PCSK9 inhibitors: A new era of lipid lowering therapy. *World J Cardiol* 2017; 9(2): 76-91 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i2/76.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i2.76

INTRODUCTION

Hyperlipidemia is a well-established risk factor for developing cardiovascular disease (CVD)[1]. Multiple double blind placebo controlled trials have shown that treatment with HMG CoA Reductase inhibitors (statins) lowers low-density lipoprotein (LDL)-C levels and reduces CVD events in individuals with CVD or those at high risk for developing it[2,3]. However, CVD events continue to occur in some patients on statins, despite receiving maximal tolerated therapy. Other patients develop side effects from statins that limit their use. Hence, newer modalities of treatment to lower LDL-C are needed in clinical practice. Recently the Food and Drug Administration (FDA) approved two medications which target a novel pathway to reduce LDL-C. They are monoclonal antibodies that inactivate proprotein convertase subtilsin-kexin type 9 (PCSK9). This review will explore the biology of PCSK 9, clinical trials targeting PCSK9 activity, and the current state of clinically available inhibitors of PCSK9.

LDL-CHOLESTEROL METABOLISM

LDL-C has been the target of therapy for improving outcomes in patients at high risk for developing CVD and has been considered a surrogate endpoint for clinical events by the FDA[1]. Reviewing LDL cholesterol metabolism is therefore important in understanding therapeutic approaches to treat hyperlipidemia.

The lipid cycle begins with the release of immature very low-density lipoprotein (VLDL) or nascent VLDL from the liver. Nascent VLDL contains apolipoprotein-B100 (apoB-100), apolipoprotein E (apoE), apolipoprotein C1 (apoC1), cholesteryl esters, cholesterol, and triglycerides. While circulating in blood, high-density lipoprotein (HDL) donates apolipoprotein C-Ⅱ (apoC-Ⅱ) to nascent VLDL that leads to its maturation. Mature VLDL interacts with lipoprotein lipase (LPL) in the capillary beds of adipose tissues, cardiac muscle and skeletal muscle cells, which leads to extraction of triglycerides from VLDL for storage or energy production in these tissues. VLDL combines with HDL again and an interchange occurs where apoC-Ⅱ is transferred back to HDL along with phospholipids and triglycerides in exchange for cholesteryl esters *via* cholesterylester-transfer protein (CETP). This exchange and removal of triglycerides leads to conversion of VLDL to intermediate-density lipoprotein (IDL)[4]. Half of IDLs are recognized and endocytosed by liver cells due to apoB-100 and apoE. The remaining IDL lose apoE, and with an increased concentration of cholesterol compared to triglyceride, transform into low-density lipoproteins (LDL). LDL particles thus formed contain apoB-100, which acts as a ligand for binding to LDL receptors (LDLR). Once LDL binds to LDLR, LDL/LDLR complex is internalized by endocytosis into clathrin coated vesicles. In the cytosol, LDL and LDLR separate with recycling of LDLR to the cell surface. LDLR recycling is a continuous process and each receptor recycles up to 150 times after which they are endocytosed and metabolized[5]. Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is involved in intracellular production of cholesterol. This lowers the levels of intracellular cholesterol leading to increased expression of LDLR on cell surfaces causing a reduction in serum LDL-cholesterol[6].

Seidah and colleagues discovered that proprotein convertase subtilisin/kexin type 9 (PCSK9) regulates LDLR degradation and could potentially be a target for modulating LDLR expression and consequently LDL-C levels[7,8]. PCSK9 is a hepatic protease that attaches to and internalizes LDLR into lysosomes hence promoting their destruction[9]. Clinical studies have shown that PCSK9 gain of function mutation is associated with familial hypercholesterolemia and premature CVD[10,11]. Conversely, individuals with loss of function mutations in PCSK9 have been observed to have lower lifetime levels of LDL-C and lower prevalence of CVD[12,13].

Since the discovery of PCSK9, results from preclinical mice studies demonstrated that sterol regulatory element binding protein-2 (SREBP-2) plays a key role in regulating cholesterol metabolism. Low level of intracellular cholesterol activates SREBP-2 and leads to LDLR gene expression. This increases LDLR concentration thus enhancing LDL clearance from circulation[8,14]. At the same time SREBP-2 also induces the expression of PCSK9, which promotes LDLR degradation. Thus, the coordinated interplay of SREBP-2 induced transcription of both LDLR and PCSK9 regulates circulating LDL levels[15,16]. These discoveries resulted in the exploration and development of therapeutic agents to lower LDL levels by targeting PCSK9 activity.

FUNCTIONAL MECHANICS OF PCSK9

Hepatocytes are the predominant site for PCSK9 production, with other sites being intestines and kidneys[17,18]. PCSK9 reduces the number of LDLR in hepatocytes by promoting their metabolism and subsequent degradation[14]. PCSK9 has been shown to act both intracellularly (playing a role as a chaperone) as well as a secreted factor promoting LDLR internalization from the hepatocellular surface. Under normal circumstances, the LDL/LDLR complex is endocytosed by endosomes. The acidic pH of the endosome reduces the affinity of LDL for LDLR with rearrangement of the LDLR's extracellular domain into a hairpin structure, aiding in its recycling

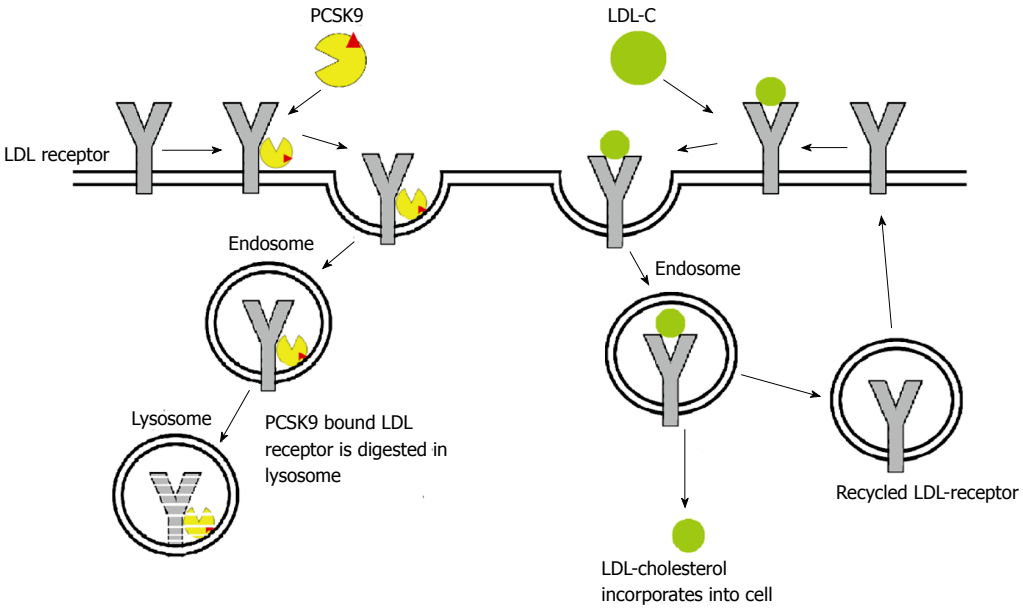

Figure 1 Mechanism and role of PCK9 in low-density lipoprotein-cholesterol metabolism. LDL: Low-density lipoprotein.

back to plasma membrane. PCSK9 binding inhibits this change and locks the LDLR in an open conformation which prevents its recycling. The LDLR is then routed to lysosomes for degradation (Figure 1)[19,20]. The secreted form of PCSK9 circulates in the bloodstream and can be inactivated by cleavage from proprotein convertase. At a molecular level, the secretion of prodomain and catalytically inactive PCSK9 promotes regular degradation of LDLR implying that PCSK9 acts as a chaperone protein rather than an active catalytic enzyme[21,22].

As described above, hepatic expression of PCSK9 and LDLR are closely regulated by SREBP-2 and intracellular levels of cholesterol[23,24]. Lipid lowering therapy with statins[25-27], ezetimibe[28] and bile acid binding resins[29] cause induction of SREBP-2 and hence co-induces both PCSK9 and LDLR. The slight increase in PCSK9 activity seen with statins does not negate their therapeutic effectiveness.

OTHER FUNCTIONS AND LOCATIONS OF PCSK9

Apart from hepatocytes, PCSK9 is also expressed in intestine, central nervous system, and mesenchymal cells of the kidney. *In vitro* studies on human intestinal epithelium have reported recombinant PCSK9 to enhance cholesterol uptake in the human intestinal epithelial cells (Caco-2/15 cell line) *via* the up regulation of the protein expression of NPC1L1 and CD36 (involved in cholesterol absorption in intestinal cells) along with an increased expression of cholesterol transporters[30,31] and reduced cholesterol synthesis (by reducing HMG-CoA reductase activity)[32]. PCSK9 has been shown to have a role in the metabolism of triglycerides and their accumulation in visceral adipose tissue[33]. It also promotes chylomicron secretion and helps regulate enterocyte cholesterol balance[32]. Studies have evaluated PCSK9 and their association with increased susceptibility to hepatitis C viral infection. Labonté *et al*[34] demonstrated a reduced expression of CD81 (CD81 is a co-receptor for Hepatitis C virus infection) by PCSK9 leading to protection against infection by hepatitis C. Therefore, PCSK9 inhibitors (Alirocumab) could increase CD81 expression resulting in greater infectivity. However, *in vitro* and *in vivo* studies in mice showed that PCSK9 did not reduce CD81 expression and had no effect on HCV infectivity. Hence, the literature remains inconclusive about this potential effect of PCSK9 inhibition[34]. Mbikay *et al*[35] demonstrated that PCSK9 inhibition in mouse pancreatic islet β cells led to hypoinsulinemia, hyperglycemia and glucose-intolerance. Additionally the islet cells exhibited signs of malformation, apoptosis and inflammation. Current clinical data has failed to show this as a complication with PCSK9 inhibition.

PCSK9 INHIBITION STRATEGIES

Preclinical studies demonstrate that statin-induced LDL reduction occurs through increased LDLR expression on hepatocytes along with increased LDL turnover, which leads to its enhanced clearance from the circulation. However, statins also induce PCSK9 expression, which dampens the effective LDL clearing by promoting LDLR degradation[23]. Since PCSK9 is expressed both intracellularly and in the circulation, multiple potential targets exist for its inhibition. Various modalities to inhibit PCSK9 have been studied including: (1) inhibition of production by gene silencing through antisense oligonucleotides[36] or small interfering RNA[37]; (2) prevention of PCSK9 binding to LDLR using monoclonal antibodies[38], epidermal growth factor-like repeat A (EGF-A), mimetic peptides[39] or adnectins; and (3) inhibition of PCSK autocatalytic sites.

Gene silencing via antisense oligonucleotides or small interfering RNA

This approach targets intracellular PCSK9 activity by utilizing antisense oligonucleotide to reduce intracellular expression of PCSK9. Preclinical trials on hyperlipidemic mice evaluating two such compounds were promising with a reduction in LDL by 38% at six weeks of therapy while doubling LDLR expression in the liver[38]. However, the phase Ⅰ trials evaluating two of these agents were terminated prematurely and further development of the drug (BMS-84442) was not continued (NCT01082562). Two additional drugs: SPC5001 and SPC4061 showed successful reduction in LDL by 50% during preclinical testing in primates[40]. However, the first phase Ⅰ trial in healthy human subjects and individuals with familial hypercholesterolemia were terminated early (NCT01350960)[41,42]. SPC5001 was seen to cause mild to moderate injection site reactions and renal tubular toxicity[43]. Further development of SPC4061 was discontinued for undisclosed reasons.

Similarly, small interfering RNA (siRNA) administration has been shown to significantly reduce plasma PCSK9 and LDL levels in cynomolgus monkeys[37,38,43]. ALN-PCS is a siRNA, which was tested by delivery through second-generation lipid nanoparticles. In a study by Fitzgerald *et al*[44], ALN-PCS demonstrated a dose dependent reduction in PCSK9 and LDL levels with a reduction of up to 70% in PCSK9 levels and 40% in LDL levels at doses of 0.4 mg/kg. This was the first study to demonstrate intracellular PCSK9 inhibition translated into reduction of circulating LDL levels.

Monoclonal antibodies

Utilization of monoclonal antibodies has been the most effective approach thus far in inhibiting PCSK9 and reducing LDL levels. Currently, at least six monoclonal antibodies (mAb) have been or are being developed and tested: Alirocumab (formerly called SAR236553/REGN727), Evolocumab (formerly called AMG145), RG7652[45], LGT209 (NCT01979601, NCT01859455), 1B20[46] and Bococizumab (formerly called RN316/PF-049 50615). Alirocumab and Evolocumab have recently been approved by the FDA. The major clinical studies leading up to their approval are outlined later in this paper.

Bococizumab is a unique mAb, which utilizes pH sensitive binding to PCSK9 and was developed for a longer serum half-life and duration of action on LDL reduction[47]. In phase Ⅰ studies, single intravenous or subcutaneous dosages significantly reduced LDL in patients with hypercholesterolemia, both with and without concomitant atorvastatin therapy[48]. In a phase Ⅱ trial by Gumbiner *et al*[48], patients on statin therapy not at target LDL-C were enrolled and observed a 60% reduction in LDL-C after 12 wk of therapy. Five phase Ⅲ trials are ongoing for Bococizumab including SPIRE-HF (evaluating the efficacy of this agent in heterozygous familial hypercholesterolemia NCT01968980); SPIRE-HR (NCT01968954) and SPIRE-LDL (NCT01968967) trials are comparing Bococizumab to statin therapy in patients with high atherosclerotic cardiovascular risk with a follow up period of up to 12 wk. SPIRE-1 (NCT01975376) and 2 (NCT01975389) have a follow up period of up to 5 years collecting data on safety and efficacy of this drug[49]. Recently, the preliminary results of a study of Bococizumab delivery using an auto-injector device (SPIRE-AI) reported successfully meeting co-primary endpoints of percent change from baseline in fasting LDL-C at week 12 and the delivery system success rate, defined as the percent of patients whose attempts to operate the pre-filled pen. SPIRE-AI is a 12-wk, double-blind, placebo-controlled, randomized, parallel-group, multicenter, phase Ⅲ clinical trial in 299 patients with hyperlipidemia or mixed dyslipidemia receiving statin therapy and whose LDL-C ⩾ 70 mg/dL and assessed the efficacy, safety, tolerability and subcutaneous administration of Bococizumab 150 mg and 75 mg with a pre-filled pen[50].

Along similar lines, adnectins (also known as monobody) and small peptide inhibitors have been investigated for LDL reduction in phase Ⅰ clinical trials. The results in healthy patients and those with hypercholesterolemia demonstrated a maximal dose related reduction of LDL-C by up to 48%[51]. The advantage of developing adnectins is that they are smaller than mAb, making them cheaper and easier to produce. Their pharmacokinetics have been shown to be favorable with a rapid onset of action in preclinical models, further trials are awaited to see the development of this agent[52].

Inhibition of autocatalytic site

This mechanism as a therapeutic target was first proposed after discovering a loss of function mutation in the autocatalytic cleavage site of PCSK9[53,54]. This approach is still under preclinical investigational phase.

FDA APPROVAL STATUS OF PCSK9 INHIBITORS

The FDA approved Alirocumab (Praluent) in July 2015 for adult patients with heterozygous familial hypercholesterolemia or in patients with clinically significant atherosclerotic CVD requiring additional LDL lowering after being on diet control and maximally tolerated statin therapy. Evolocumab (Repatha) was also approved in August, 2015 for use in adult patients with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical atherosclerotic CVD requiring additional lowering of LDL cholesterol after being on a controlled diet and maximally-tolerated statin therapy.

Alirocumab (status: FDA approved)

Alirocumab has been studied in three phase Ⅰ trials. In two of these trials, healthy volunteers were administered Alirocumab intravenously (n = 40) or subcutaneously (n = 32) which reduced LDL-C in a dose-dependent fashion with a reduction of up to 65% at maximal doses[55]. The

third trial evaluated patients with non-familial hypercholesterolemia on atorvastatin and LDL > 100 mg/dL or with LDL > 130 mg/dL being managed by diet alone. Alirocumab reduced LDL-C up to 65% in patients on statins and up to 60% in patients being managed on diet alone. It was observed that Alirocumab remained effective for a longer period of time in patients not on statins[55].

Three phase Ⅱ trials[56-58] evaluated the efficacy of Alirocumab in patients with familial hypercholesterolemia. Stein *et al*[58] evaluated 77 patients on statin therapy with LDL-C greater than 100 mg/dL and found that Alirocumab reduced LDL-C in a dose-dependent manner by up to 43% with a maximum dosage of 300 mg every 4 wk. However, the reduction was even greater (up to 70%) at a dosage regimen of 150 mg every 2 wk. Additionally, these patients had a significant reduction in apoB levels and non-high density lipoprotein cholesterol and also had increases in HDL. McKenney *et al*[56], in their study of 183 patients confirmed a dose dependent reduction of LDL-C with the most efficacious regimen being 150 mg every 2 wk (with LDL reduction up to 70%). Interestingly, different doses of atorvastatin did not make a significant difference in LDL-C reduction. These results were further corroborated by Roth *et al*[57] in their study of 92 patients with LDL-C > 100 mg/dL. They showed that there was significant and comparable LDL reduction irrespective of the dosage of atorvastatin (10 mg *vs* 80 mg) when added to Alirocumab 150 mg every 2 wk[57].

The phase Ⅲ randomized, double-blinded ODYSSEY trials were designed to evaluate Alirocumab for long-term safety, efficacy and adverse events (Table 1) and include CHOICE Ⅰ, CHOICE Ⅱ, OLE, LONG TERM, COMBO Ⅰ, COMBO Ⅱ, FH Ⅰ, FH Ⅱ, HIGH FH, MONO, ALTERNATIVE, OPTIONS Ⅰ and OPTIONS Ⅱ. The dosage of Alirocumab administered was 150 mg every 2 wk in ODYSSEY LONG TERM and HIGH FH trials and 75 mg (titrated up to 150 mg to reach pre-specified LDL goals) in ODYSSEY ALTERNATIVE, OPTIONS Ⅰ, OPTIONS Ⅱ and COMBO Ⅰ trials.

CHOICE Ⅰ study evaluated Alirocumab *vs* placebo in 803 patients with poorly controlled hypercholesterolemia. Alirocumab reduced LDL by 52% in statin-naïve patients and by 59% in patients on maximally tolerated statins as compared to placebo ($P < 0.001$)[59]. Similarly, COMBO Ⅰ and Ⅱ trials evaluated 316 patients and 720 patients respectively with LDL > 70 mg/dL and high cardiovascular risk on maximally tolerated statin therapy. COMBO Ⅰ showed Alirocumab reduced LDL-C up to 50% (*vs* 2% with placebo) after 24 wk of treatment. COMBO Ⅱ compared ezetimibe to Alirocumab in patients on background statin therapy and found a 50% LDL reduction with Alirocumab *vs* 20% reduction with ezetimibe at 24 wk[60]. OPTIONS Ⅰ trial[61] published in August 2015, randomized 355 patients with hypercholesterolemia and LDL > 70 and found the addition of Alirocumab to atorvastatin had the greatest reduction in LDL as compared to addition of ezetimibe, doubling atorvastatin dose or switching to rosuvastatin. Atorvastatin at 20 mg and 40 mg/d regimens reduced LDL by 44% and 54% with addition of Alirocumab respectively *vs* 21% and 23% with addition of ezetimibe respectively *vs* 5% and 5% with doubling atorvastatin dose respectively compared to 21% with switching to rosuvastatin 40 mg/d. In the OPTIONS Ⅱ trial, rosuvastatin was studied using a similar protocol and showed that the addition of Alirocumab had the most significant reduction in LDL-C after 24 wk of therapy as opposed to addition of ezetimibe or doubling the dose of rosuvastatin[62,63]. Another study evaluating the efficacy of Alirocumab as monotherapy (MONO study)[64] compared to ezetimibe in patients with hypercholesterolemia and moderate cardiovascular risk to monotherapy with Alirocumab and found that Alirocumab reduced LDL-C 47% *vs* 16% by ezetimibe after 24 wk of therapy ($P < 0.0001$).

CHOICE Ⅱ study evaluated Alirocumab in patients intolerant to statin therapy. Two hundred and thirty one patients with a history of statin intolerance were shown to have a 56% reduction in LDL with Alirocumab (*vs* placebo; $P < 0.001$)[59]. Another study evaluating Alirocumab in patients intolerant to statin therapy is the ODYSSEY ALTERNATIVE trial. Three hundred and fourteen patients completed this randomized controlled trial, which compared Alirocumab 75 mg every 2 wk ($n = 126$) to ezetimibe 10 mg/d ($n = 125$) and atorvastatin 20 mg/d ($n = 63$) for 24 wk. At 24 wk, the data showed a 45% reduction in LDL with Alirocumab as opposed to 15% reduction in LDL with ezetimibe. This trial demonstrated fewer skeletal muscle adverse events in the Alirocumab group as compared to atorvastatin arm [32.5% *vs* 46% respectively, HR = 0.61 (0.38-0.99; $P = 0.042$)], with no significant difference when compared to the ezetimibe group (41%) [HR 0.71 (0.47 to 1.06; $P = 0.09$)][65].

Alirocumab has also been shown to be effective in lowering LDL-C in patients with familial hypercholesterolemia. The FH Ⅰ and FH Ⅱ studies evaluated a total of 735 patients ($n = 486$ and 249 respectively) with heterozygous familial hypercholesterolemia inadequately controlled on lipid lowering therapy and found Alirocumab to reduce LDL levels 48.8% (*vs* a 9.1% increase in placebo: FH Ⅰ study) and 48.7% (*vs* 2.8% increase in LDL with placebo: FH Ⅱ study) from baseline[66]. ODYSSEY HIGH FH trial reported 105 patients with familial hypercholesterolemia on maximally tolerated statin therapy and LDL > 160 demonstrating a 46% reduction of LDL (*vs* 7% with placebo) at 24 wk ($P < 0.001$)[67]. OLE trial (NCT01954394) is currently ongoing with results anticipated by June 2017. This trial is recruiting patients with heterozygous familial hypercholesterolemia who have completed one of the other studies and evaluating for safety parameters including adverse events, laboratory data and vital signs.

ODYSSEY LONG TERM trial was recently published and is a 78-wk follow-up of 2341 patients with hypercholesterolemia and LDL > 70 mg/dL on maximally tolerated statins. The patients receiving 150 mg Alirocumab every 2 wk were shown to have a 62% reduction

Table 1 Summary of phase Ⅲ ODYSSEY trials with Alirocumab

Name of trial	Ref. Allocation and blinding	No. of patients	Inclusion criteria	Study arms (with dosing)	Primary end point	Results
LONG TERM (NCT01507831)	Seidah *et al*[7]; Randomized double blinded trial	2341	Either 1 or 2 below and who aren't adequately controlled with their LLT: (1) Patients with heFH with or without CHD or CHD risk equivalents OR (2) Patients with HCL with CHD or CHD risk equivalents	Alirocumab (SC) (n = 1553) *vs* Placebo (SC) (n = 788) both with background LLT	Percentage change in calculated LDL cholesterol level from baseline to week 24	-61.0% change with Alirocumab *vs* +0.8% change with placebo (CI: -64.3 to -59.4; P < 0.001)
FH Ⅰ (NCT01623115)	Kastelein *et al*[66]; Randomized double blinded	486	Patients with heterozygous familial hypercholesterolemia who are not adequately controlled with their lipid-modifying therapy	Alirocumab (SC) *vs* Placebo (SC) both with background LLT	Percent change in calculated LDL-C at week 24	-48.8% for Alirocumab compared with 9.1% for placebo (P < 0.0001)
FH Ⅱ (NCT01709500)	Kastelein *et al*[66]; Randomized double blinded	249	Patients with heFH who are not adequately controlled with their LLT	Alirocumab (SC) *vs* Placebo (SC) both with background LLT	Percent change in LDL-C to week 24	-48.7% for Alirocumab compared with 2.8% for placebo (P < 0.0001)
HIGH FH (NCT01617655)	Kastelein *et al*[67]; Randomized double blinded	107	Patients with heterozygous familial hypercholesterolemia who are not adequately controlled with their lipid-modifying therapy with LDL > 160	Alirocumab (SC) (n = 72) *vs* Placebo (SC) (n = 35) both with background LLT	Percent change in calculated LDL-C at week 24	Percent decrease from baseline was 45.7% *vs* 6.6%, difference 39.1, P < 0.0001 Absolute difference in values of LDL-C at 24 wk 107 mg/dL *vs* 182 mg/dL
COMBO Ⅰ (NCT01644175)	Colhoun *et al*[60]; Randomized double blinded	316	Patients with hypercholesterolemia and estbl CHD or CHD risk equivalents; not controlled with a maximally tolerated LLT, both at stable dose for at least 4 to 6 wk prior to screening	Alirocumab (SC) (n = 205) *vs* Placebo (SC) (n = 106)	Percent change in calculated LDL-C at week 24	-48.2% with Alirocumab (CI: -52.0% to -44.4%) and -2.3% with placebo (CI: -7.6% to 3.1%) for Alirocumab and placebo, respectively, an estimated mean difference of -45.9% (CI: -52.5% to -39.3%) (P < 0.0001)
COMBO Ⅱ (NCT01644188)	Moriarty *et al*[65]; Randomized double blind	720	Patients with hypercholesterolemia and established CHD or CHD risk equivalents who are not adequately controlled with a maximally tolerated daily dose of statin at stable dose for at least 4 wk prior to the screening visit	Alirocumab (SC) + placebo (for ezetimibe) orally + background statin therapy (n = 467) *vs* Placebo (SC) + ezetimibe orally + Background statin therapy (n = 240)	Percent change in calculated LDL-C at week 24	Reductions in LDL-C from baseline were 50.6% ± 1.4% for Alirocumab *vs* 20.7% ± 1.9% for ezetimibe (difference 29.8% ± 2.3%; P < 0.0001)
OPTIONS Ⅰ (NCT01730053)	Robinson *et al*[63]; Randomized double-blinded	355	Patients with prior CV disease + LDL-C ⩾ 70 mg/dL, or CV risk factors + LDL-C ⩾ 100 mg/dL	Alirocumab with atorvastatin 20 mg *vs* Ezetimibe with atorvastatin 20 mg *vs* Atorvastatin 40 mg Alirocumab with atorvastatin 40 mg *vs* ezetimibe with atorvastatin 40 mg *vs* atorvastatin 80 mg *vs* rosuvastatin 20 mg	Percent change in calculated LDL-C to week 24	Percent reduction from baseline 44.1% (Alirocumab) *vs* 20.5% (ezetimibe) *vs* 5.0% (atorvastatin 40); P < 0.0001 Percent reduction from baseline 54% (Alirocumab) *vs* 22.6% (Ezetimibe) *vs* 4.8% (Atorvastatin 80) *vs* 21.4% (rosuvastatin 40); P < 0.0001

OPTIONS Ⅱ	Robinson *et al*[63]; Randomized double-blinded	305	Patients with prior CV disease + LDL-C ⩾ 70 mg/dL, or CV risk factors + LDL-C ⩾ 100 mg/dL	Alirocumab with rosuvastatin 10 mg *vs* ezetimibe with rosuvastatin 10 *vs* rosuvastatin 20	Percent change in calculated LDL-C to wk 24	Percent reduction from baseline 50.6% (Alirocumab) *vs* 14.4% (ezetimibe) *vs* 16.3% (rosuvastatin 20); $P < 0.0001$
				Alirocumab with rosuvastatin 20 mg *vs* ezetimibe with rosuvastatin 20 *vs* Rosuvastatin 40		Percent reduction from baseline 36.3% (Alirocumab) *vs* 11.0% (Ezetimibe) *vs* 20.3% (rosuvastatin 40); $P < 0.0001$
ALTERNATIVE (NCT01709513)	Moriarty *et al*[65]; Randomized double-blinded	314	Primary heFH with moderate, high or very high CV risk and history of statin intolerance	Alirocumab + oral placebo *vs* ezetimibe (10 mg/d) + sc placebo *vs* atorvastatin (20 mg/d) + sc placebo	Percent change in calculated LDL-C to week 24 in intention to treat group	Percent reduction from baseline 45% (Alirocumab) *vs* 14.6% (Ezetimibe) with a mean difference of -30.4%; $P < 0.0001$
CHOICE Ⅰ (NCT01926782)	Stroes *et al*[78]; Randomized, double-blinded	803	Patients not having adequate control of their hypercholesterolemia based on their individual level of CVD risk	Alirocumab at q4 week regimen *vs* Placebo	Percent change in LDL from baseline to week 24 for Alirocumab q4w *vs* placebo in patients with hypercholesterolemia at moderate, high, or very high CVD risk with concomitant statin therapy (n = 547)	LDL was reduced by 58.7% with Alirocumab in patients on maximally tolerated statins ($P < 0.001$)
					Percent change in LDL from baseline to week 24 for Alirocumab q4w *vs* placebo in patients with hypercholesterolemia not on concomitant statin therapy (n = 256)	LDL was reduced by 52.4% with Alirocumab in statin naïve patients *vs* placebo ($P < 0.001$)
CHOICE Ⅱ (NCT02023879)	Stroes *et al*[78]; Randomized, double-blinded	231	Patients with primary hypercholesterolemia (heFH or non-FH) not adequately controlled with their non statin lipid modifying therapy or diet and statin intolerance	Alirocumab (SC) *vs* placebo (SC)	The percent change in LDL-C from baseline to week 24	Alirocumab reduced LDL-C by 56.4% ($P < 0.0001$) *vs* placebo
LONG TERM (NCT01507831)	Robinson *et al*[62]; Randomized, double-blinded	2341	Either A or B below and who are not adequately controlled with their LLT: (1) Patients with heFH with or without established CHD or CHD risk equivalents OR (2) Patients with hypercholesterolemia together with established CHD or CHD risk equivalents	Alirocumab (SC) 150 mg every 2 wk *vs* placebo (SC) every 2 wk	Percentage change in calculated LDL cholesterol level from baseline to week 24, analyzed with the use of an intention-to-treat approach	150 mg Alirocumab every 2 wk had a 62% reduction in LDL as opposed to a 1% increase in LDL with placebo at 24 wk

SC: Subcutaneous; LLT: Lipid lowering therapy; heFH: Heterozygous familial hypercholesterolemia; CHD: Coronary heart disease; HCL: Hypercholesterolemia; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; UA: Unstable angina; HR: Hazards ratio; CI: Confidence interval.

in LDL as opposed to a 1% increase in LDL with placebo at 24 wk. These results persisted at 78 wk. In a post-

hoc analysis, the reduction in LDL was also associated with reduction in the combined end-point of death from coronary artery disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke or unstable angina requiring hospitalization (1.7% with Alirocumab *vs* 3.3% with placebo; HR = 0.52; 95%CI: 0.31-0.9; *P* = 0.02)[68]. The ODYSSEY Outcomes trial (NCT01663402) is ongoing is closed to recruitment, and will assess the effects of Alirocumab on CVD events in 18000 patients on maximally tolerated statin therapy. Results of this trial are expected in February 2018.

Evolocumab (status: FDA approved)

Evolocumab has been studied in two phase Ⅰ studies. Dias *et al*[69] evaluated healthy volunteers in phase Ⅰa and showed a short-term dose-dependent reduction in LDL by up to 65% and after 6 to 8 wk of therapy by up to 75% with a maximally administered dose of 420 mg subcutaneously/intravenously. Phase Ⅰb trial similarly demonstrated up to 75% reduction in LDL as compared to placebo over 1 to 4 wk in healthy volunteers.

Four phase Ⅱ trials were subsequently performed that continued to show the benefits of Evolocumab with a dose-dependent reduction of LDL (maximal dosing up to 420 mg) when added to maximally tolerated statin therapy in patients with hypercholesterolemia (including familial hypercholesterolemia)[70-72]. In LAPLACE-TIMI57 trial[70], Evolocumab was tested at varying doses ranging from 70 to 140 mg every 2 wk or 280 to 420 mg every 4 wk in 631 patients on stable statin therapy and LDL more than 85 mg/dL. LDL reduction up to 65% was observed with the every two-week regimen as compared to approximately 50% LDL reduction with the every 4-wk regimen. Evolocumab has also been studied as monotherapy in 160 patients with hypercholesterolemia and intolerance to statins in the GAUSS trial[73]. At doses of 420 mg every 4 wk, it was shown to reduce LDL by 40% to 50%. Furthermore, addition of ezetimibe reduced LDL by up to 65%. Subsequently, the MENDEL trial[71] showed a similar efficacy in LDL-C lowering when Evolocumab was used as monotherapy in 406 patients with hypercholesterolemia. Based on these trials, the optimal frequency of Evolocumab therapy was determined to be twice monthly to achieve a 50% to 60% reduction in LDL in combination with statins. However, when used as a monotherapy therapy, a frequency of once every 4 wk would be acceptable. Stein *et al*[74] evaluated 8 patients with homozygous familial hypercholesterolemia, and found Evolocumab (at 420 mg every 2 wk) to reduce LDL by approximately 25% *vs* 20% when used every 4 wk.

Evolocumab has further been evaluated in PROFICIO (Program to reduce LDL-C and cardiovascular outcomes following inhibition of PCSK9 in different populations) phase Ⅲ trials (Table 2). The PROFICIO program includes 14 trials where Evolocumab is being evaluated in patients with hyperlipidemia in combination with statins (LAPLACE-2 and YUKAWA-2); hyperlipidemic patients intolerant to statins (GAUSS-2 and GAUSS-3); standalone in hyperlipidemia (MENDEL-2); heterozygous familial hypercholesterolemia (RUTHERFORD-2 and TAUSSIG); homozygous familial hypercholesterolemia (TESLA and TAUSSIG); with primary hyperlipidemia or mixed cholesterol disorder (THOMAS-1 and THOMAS-2: Device trials). Also, long-term safety and efficacy data is being evaluated by the five following studies: DESCARTES; FOURIER; OSLER-2 trial; GLAGOV trial and TAUSSIG study.

In LAPLACE-2 study 1896 patients with fasting LDL ⩾ 150 (when not on statins) or LDL ⩾ 100 (on non-intense regimen of statins) or LDL ⩾ 70 (on intensive statin therapy) were randomized to a daily moderate or high-intensity statin regimen and after 4 wk, further randomized to receive Evolocumab, ezetimibe or placebo. Evolocumab was shown to reduce LDL levels by 66% to 75% (on every 2 wk regimen) and by 63% to 75% (on once monthly regimen) when compared to placebo in moderate- and high intensity statin groups. In moderate and high intensity statin groups, Evolocumab led to significant reduction in absolute LDL values in both regimens of Evolocumab (every 2 wk and monthly). Adverse events reported were comparable in all groups[75]. YUKAWA-2 study showed a similar reduction in LDL in 404 Japanese patients when Evolocumab regimens (140 mg once every 2 wk and 420 mg once a month) were compared to placebo on 2 regimens of low-dose background statin therapy (5 mg/d and 20 mg/d atorvastatin). Interestingly, the reduction in LDL appeared to be similar irrespective of statin dosage (in combination with Evolocumab) and showed a 67% to 76% LDL reduction at 12 wk[76]. MENDEL-2 trial compared the efficacy of Evolocumab with ezetimibe and placebo in 614 patients with LDL between 100 mg/dL and 190 mg/dL and low risk on Framingham scale (⩽ 10%). Evolocumab was shown to reduce LDL by up to 57% more than placebo and 40% more than ezetimibe after 12 wk of therapy[77].

GAUSS-2 trial evaluated 307 patients with statin intolerance and compared the 2 regimens of Evolocumab (140 mg once every 2 wk and 420 mg once a month) to daily oral or subcutaneous placebo (both placebo groups on ezetimibe). At 12 wk, Evolocumab group showed a reduction in LDL by 56% *vs* 39% in the other groups (placebo + ezetimibe arm)[78]. Along similar lines, GAUSS-3 trial evaluated the efficacy of Evolocumab in 218 statin intolerant patients compared to ezetimibe. The initial phase of the study included administration of atorvastatin (20 mg) for 10 wk and placebo randomized in a 1:1 fashion, followed by a 2-wk washout period and crossover to alternate therapy for another 10 wk. The patients who experienced muscle related adverse effects while on statin therapy and not on placebo were further enrolled in the second phase of the study, which was a 24 wk double blinded randomized controlled trial to compare Evolocumab (420 mg/mo divided in 3 doses) with ezetimibe (10 mg/d). At 24 wk, LDL-C was

Table 2 Summary of important phase Ⅲ PROFICIO (Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations) trials with Evolocumab

Name of trial	Ref. Allocation and blinding	No. of patients	Inclusion criteria	Study arms (with dosing)	Primary end point	Results
LAPLACE-2 (NCT01763866)	Robinson *et al*[75]; Randomized double blinded trial	1896	Individuals with LDL > 150 mg/dL (not on statin); or LDL > 100 mg/dL (on non-intensive statin); or LDL ≥ 80 mg/dL (with intensive statin therapy)	Initially randomized to daily moderate or high intensity atorvastatin for 4 wk. Patients were again randomized to Evolocumab (sc) *vs* ezetimibe *vs* placebo	Percentage change in calculated LDL cholesterol level from baseline to week 12	Evolocumab q2w and qmonthly: 63% to 75% reduction in LDL *vs* placebo Ezetimibe 19% to 32% reduction in LDL *vs* placebo
YUKAWA-2 (NCT01953328)	Kiyosue *et al*[76]; Randomized double blinded	404	Japanese patients with LDL > 70 on stable dose statins for > 4 wk and high cardiovascular risk	Initially randomized to daily atorvastatin of 5 mg or 20 mg for 4 wk. They were further randomized to Evolocumab (sc) at q2 week and qmonthly *vs* placebo	Percent change in calculated LDL-C from baseline at week 12	-67.0% to -76% reduction with Evolocumab compared to placebo (P < 0.0001)
GAUSS-2 (NCT01763905)	Stroes *et al*[78]; Randomized double blinded	307	Patients with LDL not at goal according to their cardiovascular risk and not on statin or low dose statin due to history of statin intolerance (> 2 statins) with stable LLT > 4 wk	Evolovumab (SC) at q2 week and qmonthly dosing *vs* Placebo (SC) + Ezetimibe (10 mg/d) daily	Percent change in LDL-C from baseline at the mean of weeks 10 and 12 and at week 12 Change from baseline LDL at week 12	-55.3% to -56.1% for Evolocumab compared with -16.6% to -19.2% for ezetimibe (P < 0.0001) -103.6 to -105.4 (Evolocumab) *vs* -33 to -39 (mg/dL)
MENDEL-2 (NCT01763827	Koren *et al*[77]; Randomized double-blinded	614	NCEP ATP Ⅲ Framingham risk score of < 10% Fasting LDL-C ≥ 100 mg/dL and < 190 mg/dL	Oral placebo to SC placebo; ezetimibe to SC placebo and oral placebo to SC Evolocumab at dosing regimens of 140 mg biweekly and 420 mg monthly	Percent change from baseline in LDL-C level averaged at weeks 10 and 12	Percent LDL change from baseline averaged at weeks 10 and 12 in the: Once per 2 wk arm: -56.9% (with Evolocumab) *vs* -17.5 (with ezetimibe) *vs* -0.4% (placebo) For monthly arm: -58.8% (with evolocumab) *vs* -19.1 (with ezetimibe) *vs* -1.4% (placebo)
					Percent change from baseline in LDL-C level at week 12	Percent LDL change from baseline averaged at weeks 12: Once per 2 wk arm: -57% (with Evolocumab) *vs* -17.8 (with ezetimibe) *vs* 0.1% (placebo) For monthly arm: -56.1% (with Evolocumab) *vs* -18.6 (with ezetimibe) *vs* -1.3% (placebo)
RUTHERFORD-2 (NCT01763918)	Raal *et al*[72]; Randomized double blinded	329	Patients with heterozygous familial hypercholesterolemia who are on stable LLT for 4 wk and LDL > 100 mg/dL	Evolocumab (SC) at 140 mg q2 weeks *vs* placebo SC q2w AND Evolocumab SC qmonthly *vs* Placebo (SC)	Percent change from baseline in LDL-C level averaged at weeks 10 and 12 Percent change from baseline in LDL-C level at week 12	Percent LDL change from baseline averaged at weeks 12 in the: Once per 2 wk arm: -61.2% (with Evolocumab) *vs* -1.1% (with placebo) For monthly arm: -63.3% (with evolocumab) *vs* 2.3% (with placebo) Percent LDL change from baseline averaged at weeks 10 and 12 in the: Once per 2 wk arm: -61.3% (with Evolocumab) *vs* -2% (with placebo) For monthly arm: -55.7% (with Evolocumab) *vs* 5.5% (with placebo)

TESLA (NCT01588496)	Raal *et al*[82]; Randomized double-blinded	50	Homozygous familial hypercholesterolemia, on stable lipid-regulating therapy for at least 4 wk, LDL cholesterol ⩾ 130 mg/dL (3.4 mmol/L); Triglyceride ⩽ 400 mg/dL (4.5 mmol/L); Body weight of ⩾ 40 kg at screening, and not receiving lipoprotein apheresis	Evolocumab (SC) 420 mg every 4 wk *vs* placebo (SC)	Percentage change in ultracentrifugation LDL cholesterol from baseline at week 12 compared with placebo, analyzed by intention-to-treat Percent change from baseline in LDL-C at week 52	Evolocumab significantly reduced ultracentrifugation LDL cholesterol at 12 wk by 30.9% (95%CI: -43.9% to -18.0%; $P < 0.0001$) *vs* placebo
DESCARTES (NCT01516879)	Blom *et al*[80]; Randomized, double-blinded	901	Fasting LDL ⩾ 75 mg/dL and meeting the following on background LLT: (1) < 100 mg/dL for subjects with diagnosed CHD or CHD risk equivalent; (2) < 130 mg/dL for subjects without diagnosed CHD or CHD risk equivalent; (3) on maximal background LLT defined as atorvastatin 80 mg PO QD and ezetimibe 10 mg PO QD Fasting triglycerides ⩽ 400 mg/dL	Evolocumab (SC) 420 mg every 4 wk with diet alone *vs* placebo with diet Evolocumab (SC) 420 mg every 4 wk with diet + atorvastatin 10 mg/d *vs* placebo with diet and atorvastatin 10 mg/d Evolocumab (SC) 420 mg every 4 wk + atorvastatin 80 mg/d *vs* placebo + atorvastatin 80 mg/d Evolocumab (SC) 420 mg every 4 wk + atorvastatin 80 mg/d + ezetimibe 10 mg/d *vs* placebo + atorvastatin 80 mg/d + ezetimibe 10 mg/d		Addition of Evolocumab resulted in LDL reduction by: (1) 51% to 60% in diet alone group; (2) 59% to 64% in patients on 10 mg atorvastatin (3) 51% to 62% in patients on 80 mg atorvastatin (4) 43% to 54% in patients with atorvastatin 80 mg/d and ezetimibe 10 mg/d ($P < 0.001$ for all)

SC: Subcutaneous; LLT: Lipid lowering therapy; heFH: Heterozygous familial hypercholesterolemia; CHD: Coronary heart disease; HCL: Hypercholesterolemia; MACE: Major adverse Cardiovascular Events; MI: Myocardial infarction; UA: Unstable angina; HR: Hazards ratio; CI: Confidence interval.

reduced by 53% with Evolocumab compared to 17% with ezetimibe. Muscle-related side effects were reported in 21% patients on Evolocumab compared to 29% with ezetimibe with stoppage of drug administration due to muscle symptoms in 1% of patients in Evolocumab and 7% of patients on ezetimibe[79].

DESCARTES trial[80] evaluated 901 patients with hyperlipidemia, comparing Evolocumab (420 mg once a month subcutaneous) plus background lipid lowering therapy *vs* placebo plus background lipid lowering therapy for a period of 52 wk. Background lipid lowering therapy included: Diet alone, low intensity atorvastatin (10 mg), high intensity atorvastatin (80 mg) or atorvastatin 80 mg/d. All patients had fasting LDL-C > 75 mg/dL on background lipid lowering therapy. Addition of Evolocumab resulted in LDL reduction by 51% to 60% in diet alone group, 59% to 64% in patients on 10 mg atorvastatin, 51% to 62% in patients on 80 mg atorvastatin and 43% to 54% in patients with atorvastatin 80 mg/d and ezetimibe 10 mg/d ($P < 0.001$ for all).

Evolocumab has also been shown to be efficacious in patients with heterozygous and homozygous familial hypercholesterolemia. In the RUTHERFORD-2 trial, 329 patients with heterozygous familial hypercholesterolemia were randomized to receive Evolocumab (140 and 420 mg respectively) or placebo at two weekly and monthly regimens. Evolocumab showed a significant reduction in LDL with both regimens: 140 mg every 2 wk led to 59.2% reduction (CI: 53.4% to 65.1%) and 420 mg once a month led to LDL reduction by 61.3% (CI: 53.6% to 69%) as compared to placebo after 12 wk ($P < 0.001$ for all)[81]. The TESLA trial examined 50 patients with homozygous familial hypercholesterolemia on stable lipid lowering therapy and evaluated monthly Evolocumab (420 mg) *vs* placebo therapy for 12 wk. Addition of Evolocumab led to a significant reduction in LDL-C by up to 31% (CI: -44% to -18%; $P < 0.0001$)[82].

In the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) 1 and 2 trials 4465 patients were enrolled who had completed 1 of the phase 2 or phase 3 studies of Evolocumab (MENDEL-1, LAPLACE TIMI 57, GAUSS-1, RUTHERFORD-1, YUKAWA-1, MENDEL-2, LAPLACE-2, GAUSS-2, RUTHERFORD-2, DESCARTES, THOMAS-1 or THOMAS-2) and randomized to receive either Evolocumab (420 mg/mo in OSLER-1 and 140 mg every 2 wk or 420 mg once a month in OSLER-2 trial) plus standard therapy ($n = 2976$) or standard therapy ($n = 1489$). The median follow-up was 11.1 mo. This study showed a 61% reduction in LDL-C with Evolocumab compared to standard therapy (95%CI: 59% to 63%; $P < 0.001$). Overall adverse events were in 69% of patients in Evolocumab group compared to 65% in standard therapy group. Of note, the neurocognitive adverse events were low, but were more frequent in Evolocumab group and appeared

to be unrelated to LDL level at the time of treatment. Composite adverse cardiovascular events (all-cause death, coronary events including myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization, cerebrovascular events including stroke or transient ischemic attack, and heart failure requiring hospitalization) were significantly lower in patients with Evolocumab compared to standard therapy (HR = 0.47; 95%CI: 0.28 to 0.78; $P = 0.003$)[83,84].

The TAUSSIG trial (NCT01624142) is evaluating Evolocumab therapy in 300 patients with severe familial hypercholesterolemia to determine its efficacy and side effect profile. The results of this study are anticipated by March 2020. Preliminary results reported by Stein *et al*[74] on 8 patients with LDLR-negative or LDLR defective homozygous familial hypercholesterolemia on stable drug therapy when treated with Evolocumab at 420 mg monthly for ⩾ 12 wk, followed by 420 mg every 2 wk for another 12 wk showed LDL reduction by 14% to 16% at 12 wk with 2 wk and 4 wk dosing regimens respectively with no serious adverse events reported[75]. Finally, the preliminary results of GLAGOV study (NCT01813422) evaluating 950 patients with coronary artery disease on lipid lowering therapy undergoing cardiac catheterization for changes in percentage atheroma volume after 78 wk of Evolocumab therapy met primary and secondary endpoints and final results are to be reported in American Heart Association (AHA) conference in November, 2016.

PHARMACOKINETICS AND PHARMACODYNAMICS

The pharmacokinetic and pharmacodynamics parameters of PCSK9 inhibitors are described below[85,86].

Alirocumab

The time taken to reach maximum serum concentration is 3-7 d with similar serum concentration - time profiles between abdomen, upper arm or thigh as the sites of injection. Steady state concentrations are reached at an average of 3 to 4 doses. The volume of distribution following intravenous administration is 0.04 to 0.05 L/kg. The median half-life (t1/2) observed was between 17 to 20 d at 75 or 150 mg dosing every 2 wk. Alirocumab is eliminated in two phases depending upon its plasma concentration. The predominant mode of elimination at lower concentrations is *via* saturation of the targets (PCSK9) bound to the antibodies; however, at higher concentrations it is primarily through proteolytic pathways[81]. There have been no metabolism studies conducted since it has been previously demonstrated that reticuloendothelial system is responsible for metabolizing antibodies to small peptides and amino acids[87]. The maximum reduction in free plasma PCSK9 levels and LDL was observed within 3 and 15 d respectively, after drug administration with no difference noted between different sites. No dose adjustment is needed for patients with mild or moderately impaired renal or hepatic function. No data are available in patients with severe renal and hepatic impairment.

Evolocumab

The pharmacokinetic and pharmacodynamics properties of Evolocumab[83] demonstrate non-linear pharmacokinetics in absorption at doses below 140 mg; however, between doses of 140 to 420 mg linear pharmacokinetics is observed. The time to reach maximum concentration is 3 to 4 d after a single dose. After a single 420 mg dosage, its volume of distribution has been estimated to be 3.3 L ± 0.5 L. A steady state in serum is observed after about 12 wk of dosing. The t1/2 of Evolocumab is between 11 to 17 d. The maximum reduction of LDL after therapy was similar after dosing of 140 mg every 2 wk or 420 mg once a month with effect within 14 d. Clinical studies have not revealed a difference in pharmacokinetics of Evolocumab in mild or moderate renal and hepatic impairment. However, subjects with severe renal and hepatic impairment have not been studied.

ADVERSE EFFECTS AND CONTRAINDICATIONS

The following side effects have been reported by data gathered from over 7000 patients ($n = 2476$ for Alirocumab and $n = 5416$ for Evolocumab) evaluated in the clinical trials mentioned above. Major side effects observed for Alirocumab and Evolocumab are described below.

Alirocumab

Alirocumab is contraindicated in patients who develop serious hypersensitivity reactions like hypersensitivity vasculitis or allergic reactions requiring hospitalization with its usage. The most common adverse effects observed with Alirocumab include nasopharyngitis (11.3% *vs* 11.1% in placebo), injection site reactions (erythema, itchiness, swelling, pain or tenderness) (7.2% *vs* 5.1% in placebo), influenza (5.7% *vs* 4.6% in placebo), urinary tract infection (4.8% *vs* 4.6% in placebo), diarrhea (4.7% *vs* 4.4% in placebo), bronchitis (4.3% *vs* 3.8% in placebo), myalgia (4.2% *vs* 3.4% in placebo), muscle spasms (3.1% *vs* 2.4% in placebo), sinusitis (3% *vs* 2.7% in placebo), cough (2.5% *vs* 2.3% in placebo), contusion (2.1% *vs* 1.3% in placebo) and musculoskeletal pain (2.1% *vs* 1.6% in placebo). The most common adverse events that lead to drug discontinuation were allergic reactions (0.6% for Alirocumab *vs* 0.2% for placebo) and elevated liver enzymes (0.3% in Alirocumab *vs* < 0.1% in placebo).

Evolocumab

Contraindications for Evolocumab are similar to Alirocumab. The overall incidence of adverse effects with Evolocumab 140 mg every 2 wk as compared to placebo were 43.6% *vs* 41% respectively. The most common adverse effects were nasopharyngitis (5.9% *vs* 4.8% in placebo), upper respiratory tract infection (3.2% *vs* 2.7%

in placebo), back pain (3% *vs* 2.7% in placebo) and nausea (2.1% *vs* 1.8% in placebo). Of note the most common adverse events leading to drug discontinuation include myalgia, nausea and dizziness. Other serious adverse events noted were cardiac disorders in 2.4% individuals including palpitations (0.6% *vs* 0.3% in placebo), angina pectoris (0.3% *vs* 0.2% in placebo), and ventricular extra systoles (0.3% *vs* 0.1% in placebo).

In addition, data from trials evaluating Evolocumab and Alirocumab have shown a higher incidence of cognitive adverse events in patients treated with PCSK9 inhibitors (0.9% *vs* 0.3% for Evolocumab compared to standard care[83] and 1.2% *vs* 0.5% for Alirocumab compared to placebo[69]). It has been suggested that responder and ascertainment bias might have played a role in reporting of adverse cognitive events in the OSLER trial since the adverse events were not related to the degree of LDL-C lowering with no clustering in the LDL-C < 25 mg/dL group relative to the 25-50 mg/dL or > 50 mg/dL groups[88]. However, patients in ODYSSEY LONG TERM trial were blinded to treatment and followed for nearly 18 mo. Also, the neurocognitive adverse events were measured subjectively and not verified by neurocognitive testing. A dedicated study evaluating neurocognitive adverse events with PCSK9 inhibitors is underway: Evaluating PCSK9 Binding anti-Body Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects (EBBINGHAUS) (NCT02207634). It is enrolling individuals without dementia or mild cognitive impairment at baseline randomized in a double-blind, placebo-controlled fashion to evaluate Evolocumab on background statin therapy *vs* statin therapy alone. The primary outcome being measured is Spatial Working Memory test; an assessment of executive function and the results are expected in September 2017.

Another potential and significant complication with drugs that are monoclonal antibodies is the development of anti-drug antibodies that may interfere with clinical efficacy and increase adverse events[89]. This complication has not been reported in the trials to date using PCSK9 inhibitors.

CLINICAL USE OF PCSK9 INHIBITORS

The 2013 American College of Cardiology/American Heart Association recommendations on cholesterol management centered on identifying patients who would have a reduction in CVD events with statin treatment. The focus shifted from treating to a specific LDL-C level, to treating at risk individuals with a treatment (statin) proven to reduce future CVD events. Subsequently, the IMPROVE-IT trial demonstrated that addition of ezetimibe to simvastatin lowers LDL-C more than that achieved by simvastatin alone and that this reduction in LDL-C was associated with a greater reduction in CVD events compared with simvastatin alone[86,90]. This study raises the issue of LDL-C treatment targets with a lower level of LDL-C corresponding to a lower risk of CVD events. The introduction of PCSK9 inhibitors will necessitate re-evaluation of existing cholesterol treatment recommendations.

PCSK9 inhibitors are especially beneficial in the treatment of familial hypercholesterolemic patients who are intolerant to statins or have an elevated LDL-C level despite being on maximally tolerated statin therapy. Intuitively, addition of a PCSK9 inhibitor to low dose statin therapy will be more effective in lowering LDL and avoiding the side effects of statins, since low dose and high dose statin regimens have yielded similar efficacy when combined with PCSK9 inhibitors.

Several potential barriers exist that may impede the widespread use of these medicines. First, statins have a proven effectiveness that has been demonstrated in multiple long-term studies. Statins have been shown to reduce cardiovascular mortality by 30% and incidence of stroke by 20% in multiple long-term studies[91,92]. PCSK9 inhibitors are effective in reducing LDL-C levels but currently lack data demonstrating their use reduces CVD events. Trials evaluating the effect of PCSK9 inhibitors on long-term CVD events, however, are currently underway: FOURIER (Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk; *n* = 22500) for Evolocumab (NCT01764633) and ODYSSEY-OUTCOMES (ODYSSEY outcomes: Evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab SAR236553) (NCT01663402) for Alirocumab. However, their data will not be available until December 2017 (for Alirocumab) and February 2018 (for Evolocumab).

Another potential barrier to widespread use of PCSK9 inhibitors is their cost. The Institute for Clinical and Economic Review (ICER) reported that the number needed to treat for 5 years to avoid one major adverse cardiovascular event (NNT5) is 28. However, a list price of $ 14350 per year generates a cost-effectiveness ratio which far exceeds the accepted threshold of $ 100000/quality-affected life-years[93]. To achieve cost-effectiveness at this threshold would require a price reduction by 60% to 65% of the current price. At the conclusion of their report, the ICER suggested a reduction by 85% to an annual cost of $2177 might be required to avoid excessive cost burdens to the health care system[94]. It should be noted that since there are limited data on clinical adverse cardiovascular events, cost effectiveness data might change once results from ongoing CVD endpoint studies are available.

PCSK9 therapy is a welcome treatment option for statin intolerant patients who require treatment of their hyperlipidemia. It will be important that busy practitioners do not under-prescribe statins nor be dissuaded from attempting to find a dose of and statin agent that is tolerated by the patient because PCSK9 inhibitors are available. Despite these obstacles, PCSK9 inhibitors are an exciting agent for reducing LDL-C hyperlipidemia and have ushered in a new era of lipid lowering therapy.

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REVIEW

Assessment of stable coronary artery disease by cardiovascular magnetic resonance imaging: Current and emerging techniques

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Abstract

Coronary artery disease (CAD) is a leading cause of death and disability worldwide. Cardiovascular magnetic resonance (CMR) is established in clinical practice guidelines with a growing evidence base supporting its use to aid the diagnosis and management of patients with suspected or established CAD. CMR is a multi-parametric imaging modality that yields high spatial resolution images that can be acquired in any plane for the assessment of global and regional cardiac function, myocardial perfusion and viability, tissue characterisation and coronary artery anatomy, all within a single study protocol and without exposure to ionising radiation. Advances in technology and acquisition techniques continue to progress the utility of CMR across a wide spectrum of cardiovascular disease, and the publication of large scale clinical trials continues to strengthen the role of CMR in daily cardiology practice. This article aims to review current practice and explore the future directions of multi-parametric CMR imaging in the investigation of stable CAD.

Key words: Cardiovascular magnetic resonance; Coronary heart disease; Myocardial perfusion; Viability; Prognosis

Core tip: Coronary artery disease (CAD) is a leading cause of death worldwide. Cardiovascular magnetic resonance (CMR) is established in clinical practice guidelines with a growing evidence base supporting its use to aid diagnosis and management of patients with suspected or established CAD. CMR is a multi-parametric imaging modality that yields high spatial resolution images that can be acquired in any plane for assessment of global and regional cardiac function, myocardial perfusion and viability, tissue characterisation and coronary artery anatomy, all within a single study protocol and without exposure to ionising radiation.

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INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death and disability worldwide[1]. Despite major advances in the treatment of CAD resulting in significantly decreased mortality rates, CAD remains the single most common cause of death in the European Union, leading to 19% of deaths in men and 20% of deaths in women[2]; in the United States, CAD causes 1 in every 7 deaths, accounting for 370213 deaths in 2013[3]. The economic health burden of CAD is substantial with an estimated cost of CAD management at €60 billion in the European Union[4], and $182 billion in the United States[3]. Cardiovascular medicine benefits from a myriad of diagnostic methods that can guide intervention and clinical decision-making. Invasive coronary X-ray angiography delineates coronary anatomy in patients presenting with stable chest pain, however there is a low yield of obstructive CAD in those referred, and there are associated risks, albeit low, from major complications and ionising radiation[5]. Furthermore unless measurement of fractional flow reserve (FFR) is performed, routine coronary angiography does not give information on ischaemia burden, which according to current guidelines, is required to guide revascularisation decisions. Non-invasive functional imaging modalities such as single-photon emission computed tomography (SPECT), dobutamine stress echocardiography (DSE), cardiovascular magnetic resonance (CMR) or positron emission tomography (PET) are used to diagnose CAD, guide clinical decision making and confer prognostic information and consequently are well established for these roles in clinical practice guidelines[6,7].

CMR is a unique multi-parametric imaging modality producing high spatial resolution images that can be acquired in any plane for the assessment of global and regional cardiac function, myocardial perfusion and viability, tissue characterisation and proximal coronary artery anatomy, all within a single study and without exposure to ionising radiation (Figure 1). Historically, long scanning times, limited scanner availability and narrow bore sizes restricted the use of CMR, but these issues have been largely resolved, such that CMR has become a first line investigation for suspected stable angina in many centres in the United Kingdom and Europe. Consequently CMR is part of international clinical practice guidelines for the assessment of known and unknown stable CAD and for the identification of those who may benefit from revascularisation[6-9]. This review aims to focus on the current utility of CMR for the diagnosis of suspected stable CAD and potential future developments and applications of CMR in this role.

CMR IN STABLE CAD

A CMR protocol for the investigation of stable CAD will typically take between 30-60 min and involves the acquisition of cine images in multiple planes for the assessment of left ventricular function and volumes, stress and rest myocardial perfusion imaging and late gadolinium enhancement (LGE) imaging for the assessment of myocardial viability and scar quantification (Figure 2).

CMR is the reference standard non-invasive technique for the measurement of left ventricular (LV) and right ventricular (RV) volumes, and ejection fraction, with high intra- and inter-observer reproducibility[10,11]. Steady state free precession cine imaging is typically performed for the assessment of LV function to enable visual assessment of global and regional myocardial function in a similar manner to echocardiography; however there are no limitations due to poor acoustic windows or large body habitus degrading image quality. CMR volumetric analysis is performed by acquiring a stack of contiguous breath held cine images from the base of the heart to the apex; the endocardial and epicardial borders are subsequently contoured giving mass, volumes and function. Thus CMR provides a true 3D analysis of LV and RV function unlike 2D echocardiography that relies on geometric assumptions for volumetric calculations. Furthermore specific myocardial tagging pulse sequences can be performed that enable more detailed assessment of intra-myocardial mechanics beyond ejection fraction, including torsion, twist, strain and strain rates[12]. Additionally, feature tracking is a novel post-processing method of quantitatively assessing strain and strain rate using standard cine images without having to acquire further imaging sequences as is the case with standard CMR tissue tagging[12,13].

DIAGNOSIS OF CAD

Ischaemia detection by CMR is performed using either vasodilator or inotropic stress. Ischaemia detection by CMR is recommended as a first line strategy for investigating suspected angina in patients with an intermediate pre-test likelihood of CAD in both the current European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) guidelines (Table 1)[6,14], whilst the United States guidelines are more conservative and give a grade IIa recommendation for stress perfusion CMR in patients with uninterpretable ECGs or unable to exercise[7].

STRESS PERFUSION CMR

Stress perfusion CMR requires the induction of hyperaemia by a vasodilating agent, and then observation of the passage of a gadolinium based contrast agent (GBCA) through the myocardium to identify perfusion defects. Typically the vasodilating agent used is adenosine though regadenason and less commonly dipyridamole and nicorandil are also

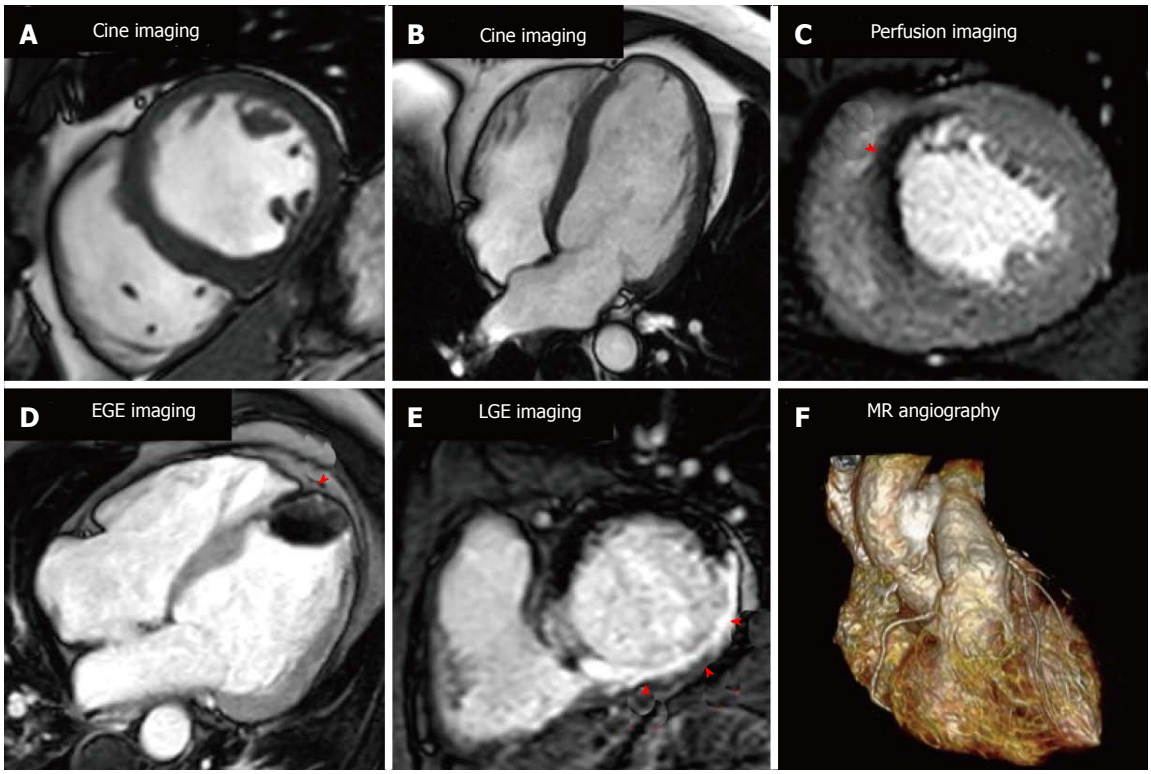

Figure 1 Cardiovascular magnetic resonance imaging techniques. A and B show short axis and 4 chamber cine images respectively for anatomical and functional assessment; C shows stress perfusion with a septal perfusion defect (arrow); D shows early gadolinium enhancement imaging with a large apical thrombus (arrow); E is late gadolinium enhanced imaging with a transmural inferior infarction (arrows); F is 3D whole heart magnetic resonance angiography. LGE: Late gadolinium enhancement; EGE: Early gadolinium enhancement.

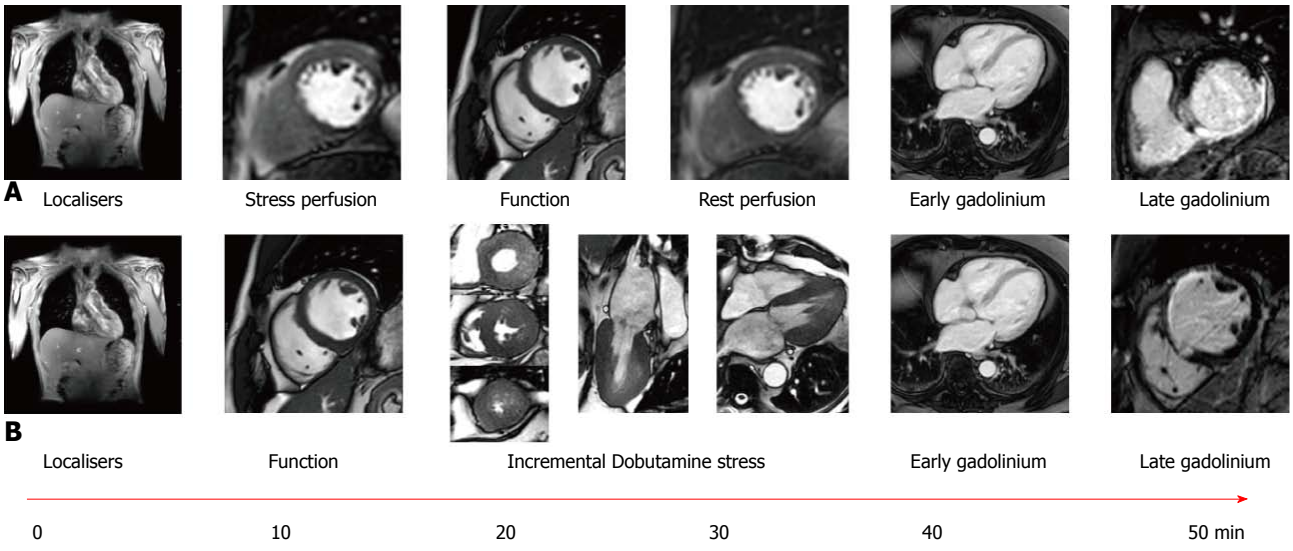

Figure 2 Cardiovascular magnetic resonance multi-parametric protocols for the investigation of suspected coronary artery disease. A shows a typical multi-parametric cardiovascular magnetic resonance protocol for the investigation of stable coronary artery disease with adenosine stress perfusion; and B with incremental dose dobutamine stress.

used. Adenosine produces vasodilatation in most vascular beds, including the coronary circulation, *via* A2A and A2B receptors[15]. Adenosine is given as an intravenous infusion typically at a rate of 140 mcg/kg per minute, though this can be increased if there is no haemodynamic response; the main side effects of adenosine are transient heart block, and bronchospasm can be caused in those with reversible airways disease[15]. Regadenason is a new selective A2A adenosine receptor agonist that is given *via* an intravenous bolus, has less respiratory side effects than adenosine, and has recently been approved by both the FDA and in Europe for this indication[16,17]. The coronary micro-vasculature can dilate up to 4 or 5 times from the resting state to ensure adequate tissue perfusion for example during exercise.

Table 1 European Society of Cardiology and American College of Cardiology Foundation/American Heart Association Recommendations for cardiovascular magnetic resonance in stable coronary artery disease

ESC guidelines	
Suspected/stable coronary artery disease[6]	
In patients with suspected stable coronary artery disease and pretest probability of 15%-85% stress imaging is preferred as the initial test option if local expertise and availability permit	Class Ⅰ
An imaging stress test is recommended in patients with resting ECG abnormalities, which prevent accurate interpretation of ECG changes during stress	Class Ⅰ
CMR should be considered in symptomatic patients with prior revascularisation (PCI or CABG)	Class Ⅱa
Risk stratification is recommended based on clinical assessment and the results of the stress test initially employed for making a diagnosis of stable coronary artery disease	Class Ⅰ
CMR is recommended in the presence of recurrent or new symptoms once instability has been ruled out	Class Ⅰ
In symptomatic patients with revascularised stable coronary artery disease, CMR is indicated rather than stress ECG	Class Ⅰ
CMR is recommended for risk stratification in patients with known stable coronary artery disease and a deterioration in symptoms if the site and extent of ischemia would influence clinical decision making	Class Ⅰ
Recommendations for imaging to determine ischemia to plan revascularisation[6,144]	
An imaging stress test should be considered to assess the functional severity of intermediate lesions on coronary arteriography	Class Ⅱa
To achieve a prognostic benefit by revascularisation in patients with coronary artery disease, ischemia has to be documented by non-invasive imaging	Class Ⅰ
Following MI with multivessel disease, or in whom revascularisation of other vessels is considered, CMR for ischaemia and viability is indicated before or after discharge	Class Ⅰ
Heart failure[8]	
CMR should be considered in patients with HF thought to have CAD, and who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischaemia and viable myocardium	Class Ⅱa
AHA guidelines	
Diagnosis and management of stable coronary artery disease[7]	
CMR can be used for patients with an intermediate (10%-90%) to high (> 90%) pretest probability of obstructive IHD who have an uninterpretable ECG and at least moderate physical functioning or no disabling comorbidity	Class Ⅱa
CMR is reasonable for patients with an intermediate to high pretest probability of IHD who are incapable of at least moderate physical functioning or have disabling comorbidity	Class Ⅱa
Pharmacological stress CMR is reasonable for risk assessment in patients with SIHD who are unable to exercise to an adequate workload regardless of interpretability of ECG	Class Ⅱa
CMR is reasonable in patients with known SIHD who have new or worsening symptoms (not unstable) and who are incapable of at least moderate physical functioning or have disabling comorbidity	Class Ⅱa

ESC: European Society of Cardiology; CMR: Cardiovascular magnetic resonance; ECG: Electrocardiogram; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; AHA: American Heart Association; IHD: Ischemic heart disease; SIHD: Stable ischemic heart disease.

However the microvasculature distal to a stenosed coronary artery is already near-maximally vasodilated at rest and consequently when hyperaemia is provoked a coronary steal effect is caused. GBCAs increase the signal intensity in T1 weighted images and the passage of GBCAs through the myocardium causes healthy myocardium to become brighter while regions of hypoperfusion ("ischaemia") remain dark (Figure 3).

The diagnostic accuracy of stress perfusion CMR for the detection of CAD is well validated. A meta-analysis of 37 studies demonstrated a combined sensitivity of 89% (95%CI: 88%-91%) and specificity of 76% (95%CI: 73%-78%) for perfusion CMR for the diagnosis of CAD[18]. The CE-MARC study (n = 752), the largest prospective randomised single-centre trial of CMR in this context showed superiority of perfusion CMR over SPECT, with a higher sensitivity (87% *vs* 67%, $P < 0.0001$) and negative predictive value (91% *vs* 79%, $P < 0.0001$) but similar specificity (83% *vs* 83% $P = 0.916$) and positive predictive values (77% *vs* 71%, $P = 0.061$)[19,20]. Furthermore in a pre-specified gender sub analysis of CE-MARC, CMR showed similar sensitivity for CAD detection in both males and females, whilst SPECT had significantly lower sensitivity in females compared to males[21].

The multi-centre, multi-vendor MR-IMPACT Ⅱ trial (n = 515) also confirmed CMR's superior sensitivity compared to SPECT (67% *vs* 59%, $P = 0.024$) but with a lower specificity (61% *vs* 72%, $P = 0.038$)[22]; however unlike CE-MARC only the stress/rest perfusion component of the CMR protocol was analysed. CE-MARC included analysis of LGE for scar detection, cine imaging for regional ventricular function and magnetic resonance angiography (MRA) for coronary artery anatomy, and a subsequent sub-analysis of CE-MARC demonstrated the additive diagnostic accuracy of the summation of these components of the multi-parametric protocol[23].

Stress perfusion CMR has also been validated against FFR in a recent meta-analysis with a pooled sensitivity and specificity of 0.90 (95%CI: 0.86-0.93) and 0.87 (95%CI: 0.82-0.90) at the patient level and 0.89 (95%CI: 0.83-0.92) and 0.86 (95%CI: 0.77-0.92) at the coronary artery and territory levels[24]. Furthermore CMR stress perfusion had comparable sensitivity and specificity to cardiac CT and PET in a recent meta-analysis of non-invasive imaging modalities, and was superior to both SPECT and DSE when using FFR as the reference standard[25]. Most trials thus far have excluded patients with arrhythmia amid concerns regarding ECG gating, however the diagnostic accuracy of stress perfusion CMR remains high in suspected CAD patients with AF or

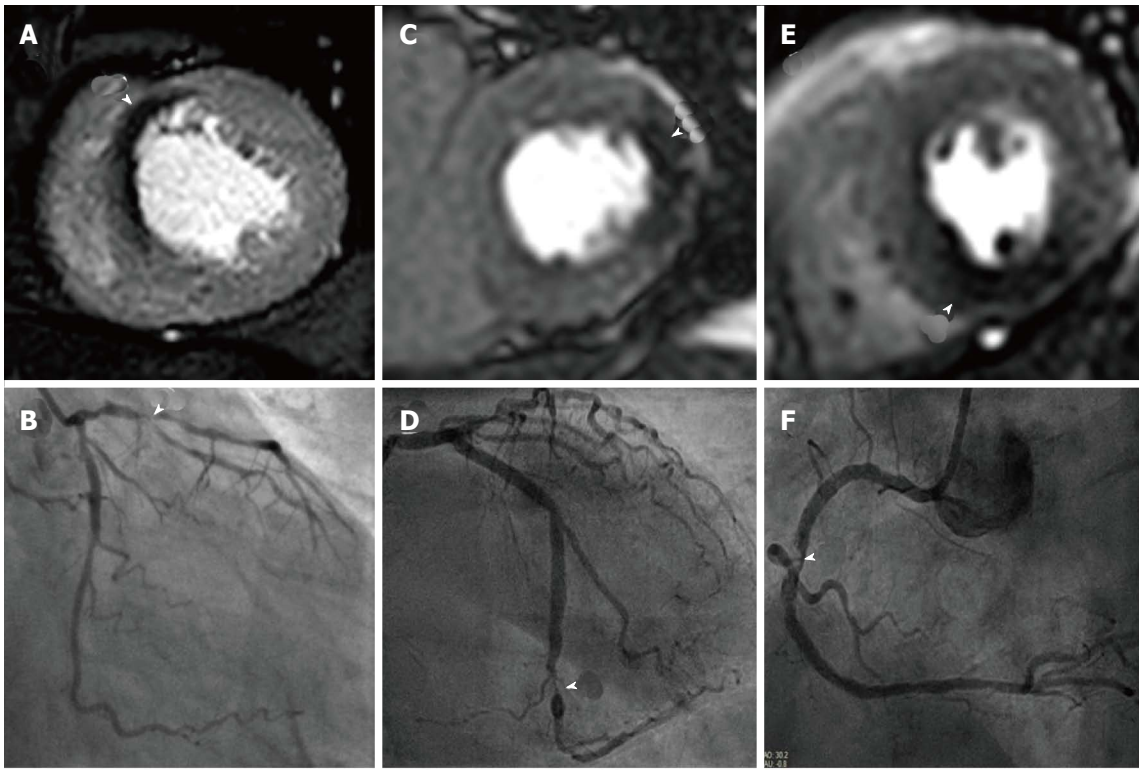

Figure 3 Cardiovascular magnetic resonance perfusion techniques. A is a high spatial resolution *k-t* BLAST stress perfusion CMR study at 3.0T showing an antero-septal perfusion defect with corresponding left anterior descending lesion at angiography in B; C shows a transmural lateral perfusion defect at standard resolution at 1.5T with corresponding circumflex lesion in D; E shows a transmural inferior perfusion defect at standard resolution at 1.5T with corresponding right coronary artery lesion in F. BLAST: Broad-use linear acquisition speed-up technique; CMR: Cardiovascular magnetic resonance.

frequent ectopy (sensitivity 80%, specificity 74%)[26].

1.5T *VS* 3.0T FIELD STRENGTH

Although 1.5T is remains the standard field strength used in clinical CMR, imaging at a higher field strength of 3.0T offers increased signal to noise and contrast to noise ratios thereby giving improved spatial and temporal enhancement[27]. Consequently the diagnostic accuracy of perfusion imaging at 3.0T may be improved, and in a small direct comparison of CMR perfusion at 1.5T, 3.0T (n = 61) showed greater diagnostic accuracy in both single vessel (AUC: 0.89 *vs* 0.70; $P < 0.05$) and multi-vessel disease (AUC: 0.95 *vs* 0.82, $P < 0.05$)[28]. Furthermore, 3.0T has been compared to 1.5T using FFR as reference standard, corroborating it's superior diagnostic accuracy[29,30]. The higher 3.0T field strength does however pose challenges with greater field inhomogeneity, susceptibility artefacts and higher local energy deposition. Also, many implants deemed "MR compatible" at 1.5T cannot be scanned at 3.0T[31]. These issues are however being overcome with improved technology and the use of multi-transmit radiofrequency CMR techniques improving field homogeneity[32].

IMPROVING PERFUSION IMAGING

Currently typical CMR perfusion imaging acquires 3 short axis slices of the left ventricle with an in-plane spatial resolution of 2-3 mm. Developments in CMR technology however now allow faster scan speeds; these novel acquisition techniques allow accelerated data acquisition based on spatio-temporal undersampling (*k-t* SENSE or *k-t* BLAST and highly constrained back projection HYPR, compressed sensing and others)[33]. These faster data acquisition techniques have been applied to achieve in-plane spatial resolution < 2 mm or full-coverage of the LV using 3D whole-heart perfusion imaging. High spatial-resolution imaging offers benefits by significantly reducing dark rim artefacts, as these are directly proportional to voxel size[34]. Moreover there is improved ability to detect sub-endocardial ischaemia which is critical in multi-vessel disease where there is a lack of reference healthy myocardium for comparison[35,36]. High spatial-resolution perfusion CMR has been validated at both 1.5T and 3.0T against quantitative coronary angiography (QCA) with improved diagnostic accuracy at both field strengths compared to standard resolution perfusion imaging[27,36,37]. Furthermore validation against FFR gave sensitivity and specificity to detect stenoses at a threshold of FFR < 0.75 of 0.82 and 0.94 ($P < 0.0001$) respectively, and an area under the curve of 0.92 ($P < 0.0001$)[38].

Conventional stress perfusion CMR is typically acquired in 3 short-axis slices, and thus unlike SPECT does not truly calculate global ischaemia burden. Accelerated acquisition techniques can also be employed to achieve full LV coverage using a 3D whole-heart single shot acquisition.

Such 3D acquisitions can overcome the assumptions made about "missing" myocardium between the slices from conventional 2D multi-slice perfusion imaging. Two studies have validated the feasibility and diagnostic accuracy of 3D stress perfusion CMR against FFR; at 1.5T 3D perfusion demonstrated a sensitivity, specificity and diagnostic accuracy of 90%, 82% and 87% respectively and 91%, 90% and 91% respectively at 3.0T[39,40]. Furthermore in a recent multicentre trial of 3D stress perfusion at 3.0T, sensitivity and specificity were 84.7% and 90.8% relative to the FFR reference[41]. The main motivation for 3D perfusion is to give a more accurate quantification of total myocardial ischaemia burden; evidence from SPECT suggests a prognostic benefit for revascularisation in those with an ischaemia burden > 10%, with an ischaemia burden of 10% conferring a risk of approximately 5% for death or MI per year[42,43]. Ischaemia burden as measured by 3D stress perfusion CMR has been compared to SPECT and showed good correlation (rs = 0.70, $P < 0.001$)[44]. Intriguingly a recent pilot study compared ischaemia burden by high-resolution perfusion (using 3 short axis slices) and 3D perfusion imaging (providing whole heart coverage) suggesting that there was also a good correlation between the techniques (r = 0.72; $P = 0.001$), and that therefore the two methods are potentially interchangeable[45].

QUANTITATIVE PERFUSION

CMR stress perfusion studies are normally reported in a qualitative manner; however this can prove challenging in diffuse or multi-vessel disease where there is no healthy reference myocardium to use as a visual comparator. These situations can introduce subjectivity into the analysis and consequently quantitative measurement techniques have been developed to provide an objective assessment of myocardial blood flow. A number of different methods of quantitative analysis have been assessed with the Fermi deconvolution method showing most accuracy when compared to microspheres in an explanted porcine model at 1.5T and mice at 3.0T[46,47], and when compared to SPECT and with QCA[48]. When compared to angiography with FFR, an MPR threshold of 1.58 detected a stenosis with an FFR < 0.75 with a sensitivity of 0.80, specificity of 0.89 ($P < 0.0001$), and area under the curve of 0.89 ($P < 0.0001$)[38]. Myocardial perfusion reserve derived from quantitative CMR perfusion has also shown good correlation to PET imaging, the imaging modality that is widely regarded as the reference standard non-invasive measure of myocardial blood flow[49,50]. Currently, time consuming post-processing has limited quantitative perfusion methods to a research tool, but automated methods are being developed that may potentially overcome this[51].

DOBUTAMINE STRESS CMR

GBCAs have an excellent safety profile[52], but in patients with poor renal clearance (*e.g.*, on dialysis) there is a risk of nephrogenic systemic fibrosis[53]. In those patients unable to have GBCAs inotropic stress CMR is an alternative. Inotropic stress CMR is typically performed with dobutamine in a similar manner to DSE with inducible regional wall motion abnormalities identified in territories supplied by a stenosed coronary artery at peak stress. Unlike DSE however, DSMR's accuracy is not limited by body habitus or in those with poor acoustic windows and in a single centre study DSMR was shown to have significantly greater diagnostic performance to DSE in this context[54]. However echocardiography in this study was performed without harmonic imaging and contrast agents, so that the performance of DSE is likely to be underreported compared with contemporaneous methods. DSMR has a comparable safety profile to DSE with an event rate of 0.1% for sustained VT and 0.4% for non-sustained VT, and 1.6% for atrial fibrillation; patients thus require close monitoring during scanning and resuscitation equipment needs to be available[55]. DSMR has been shown to have high diagnostic accuracy for the detection of CAD with one meta-analysis of 14 trials showing a pooled sensitivity of 0.83 (95%CI: 0.79-0.88) and specificity of 0.86 (95%CI: 0.81-0.91)[56]; furthermore a single centre trial of DSMR *vs* perfusion CMR showed similar diagnostic accuracy[57]. First-pass perfusion can be performed additionally at peak dobutamine stress to provide incremental diagnostic accuracy[58], and can be a useful adjunct in challenging patient groups such as those with pre-existing wall motion abnormalities or dyssynchrony from left bundle branch block[59].

Exercise is commonly used rather than pharmacological agents as the stressor in echocardiography, and gives useful prognostic information such as workload in metabolic equivalent (METs) in addition to ischaemia testing[60,61]. CMR is limited in this respect due to the need for supine scanning and consistent positioning within the scanner. Recent studies however have assessed the feasibility of exercise stress CMR and showed comparable accuracy to echocardiography, though it has yet to reach mainstream clinical use[62,63]. Promising developments are "steppers" and cycle ergometers that can attach directly to the MRI scanner, and thereby eliminate the need to transfer the patient from the exercise equipment into the scanner[64,65].

Prognosis from stress CMR

Both perfusion CMR and DSMR provide excellent prognostic information, and this has recently been shown in two large meta-analyses. One meta-analysis of 14 studies including 12178 patients showed that a negative stress CMR was associated with a 1.03% annualised event rate, comparable to the normal population[66]. A further meta-analysis of 19 studies including 11636 patients showed a similar annualised event rate of 0.8% for a negative stress CMR over a mean follow up of 32 mo[67]. In a large prospective study of 1229 patients undergoing adenosine stress with a mean follow-up period of 4.2 ± 2.1 years, patients with reversible perfusion deficits had a 3-fold

increased risk of major adverse cardiovascular events, with significantly more cardiac deaths ($P < 0.0001$) and nonfatal myocardial infarctions ($P < 0.001$)[68]. Similarly the data from DSMR mirrors the results of first-pass perfusion CMR with a negative study conferring an equally low annual event rate of 1.3%[66,69]. Recently the five-year outcome data from CE-MARC were published with prognostic data for both CMR and SPECT in the same patient population. The analysis showed that although an abnormal result from both tests was a strong indicator of future major adverse cardiovascular events (MACE), CMR was superior at predicting time to MACE in this population[70]. Furthermore CMR remained the only independent predictor of outcome after adjustment for major cardiovascular risk factors, stratification for initial patient treatment and coronary angiographic findings[70]. These findings likely reflect CMR's overall greater diagnostic accuracy, combined with CMR's higher spatial resolution enabling greater identification of subendocardial scar compared to SPECT[71]; a feature known to confer prognostic significance beyond ejection fraction, and clinical or angiographic features[72].

EARLY AND LATE GADOLINIUM ENHANCEMENT IMAGING

GBCAs have a large molecular weight and cannot penetrate an intact cell membrane; consequently GBCAs are constrained to the extracellular space. In healthy myocardium the extracellular space is limited and contrast enters and clears rapidly. The extracellular space in infarcted myocardium however is substantially increased compared to normal myocardium and is less vascular. Thus in chronic myocardial infarction scar tissue composed of a matrix of collagen fibres has significantly increased extracellular space, leading to GBCA accumulation (slow washout), whilst in acute infarction GBCAs passively diffuse across disrupted myocardial cell membranes and into the intracellular space (greater volume of distribution)[73]. Thus both acute and chronic myocardial infarction retain more GBCAs. Imaged with T1 sensitive acquisition methods, this results in a higher signal.

Early gadolinium enhancement imaging is performed immediately following contrast administration; this allows mainly the visualisation of ventricular thrombi that appear "dark/black" due to a lack of contrast uptake as they are non-vascular (Figure 4). CMR has been shown to be superior to both trans-thoracic echocardiography and trans-oesophageal echocardiography for the identification of ventricular thrombi[74,75]. LGE imaging is performed between 10-20 min after contrast administration, an appropriate inversion time is set to null the normal myocardium and the areas where gadolinium is retained enhances (Figure 4). Typically a stack of short axis slices, a 4-chamber view and VLA are acquired. Alternatively, 3D LGE CMR imaging enables whole heart quantification of scar burden to be acquired in a shorter time period (although with a reduction in image quality), which may provide an alternative for patients that struggle to breath-hold[76,77].

VIABILITY ASSESSMENT

CMR viability assessment using LGE enables the accurate detection, and extent and trans-murality of previous myocardial infarction to be determined, and identifies regions with potential to recover function following revascularisation. Hibernating myocardium is dysfunctional myocardium that has been down-regulated through a process of chronic/repetitive ischaemia and which has the potential for functional recovery when blood flow is restored. LGE imaging detects replacement of normal viable myocytes by focal necrosis or fibrosis with high spatial resolution, and has excellent correlation to histopathology[73]. Furthermore the degree of transmural extent of hyper-enhancement on LGE imaging has a direct association to the potential for functional recovery following revascularisation; Kim *et al*[78] demonstrated that segments with less than 25% hyper-enhancement were most likely to attain functional recovery whilst segments with over 75% hyper-enhancement were unlikely to improve, notably this was irrespective of whether the region was initially hypokinetic, dyskinetic or akinetic. A meta-analysis of 331 patients using 50% trans-murality of hyper-enhancement reported a sensitivity of 95% (95%CI: 93%-97%) and specificity of 51% (40%-62%) for predicting functional recovery[79].

CMR viability assessment is not however limited to just LGE imaging; whilst LGE identifies the transmural extent of scarring, the use of low-dose dobutamine (LDD) identifies the contractile reserve. Myocardium is considered viable if there is a 2 mm or more increase in systolic wall thickening within a segment following administration of LDD (5-10 mcg/kg per minute)[80]. While scar burden on LGE has been shown to be most sensitive method for assessment for functional recovery compared to LDD and diastolic wall thickness[81], LDD CMR offers higher specificity and PPV for prediction of functional recovery (91% and 93%, respectively)[79]. Consequently a stepwise approach utilising LGE first followed by LDD if the trans-mural extent of LGE in the territory of the diseased coronary is between 1%-50% has been proposed[82]. Recently both tissue tagging and feature tracking have been used to give quantitative viability assessment with LDD and have been suggested as possible methods to reduce reliance on operator experience in what is currently a qualitative method of assessment[83-85].

LGE imaging has a grade A recommendation to determine myocardial viability prior to revascularisation in the ACCF/AHA/SCMR appropriate use guidelines[86], though viability assessment by LGE is currently not recommended for this indication in ESC or US practice guidelines for management of stable CAD or coronary revascularisation[6,7,9,87]. The utility of viability assessment has been questioned recently following the results of the STICH trial and the subsequently published viability sub-study that showed no mortality benefit from re-

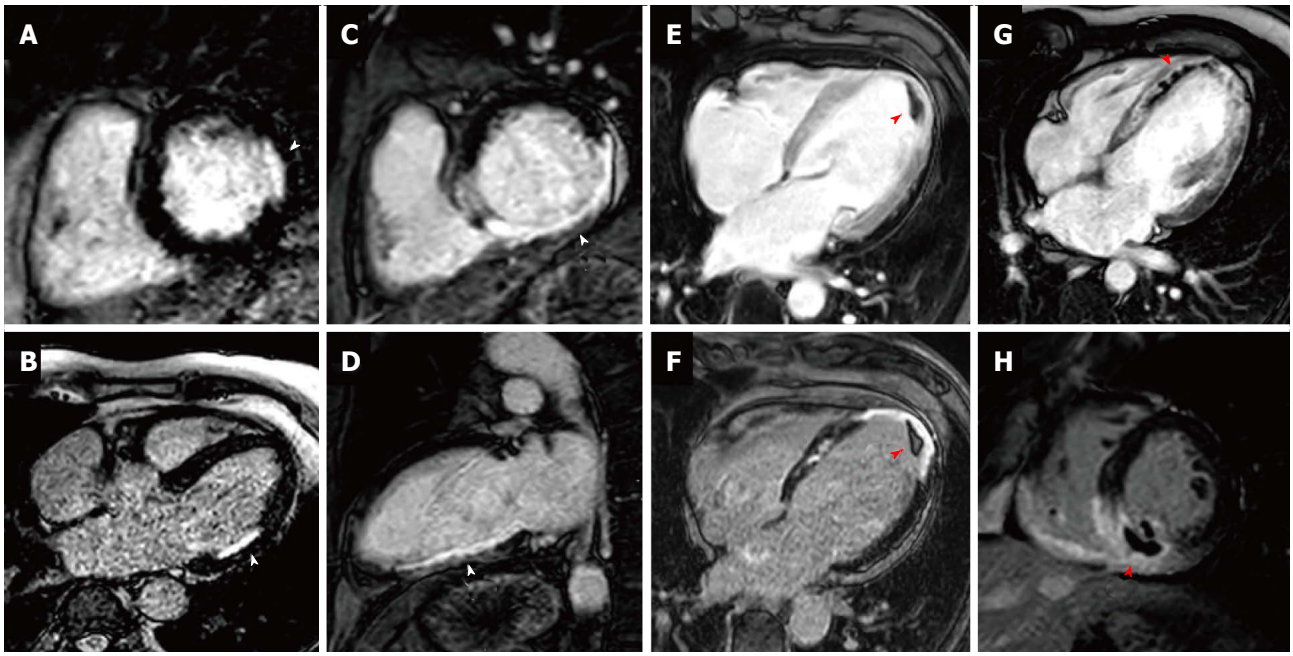

Figure 4 Early and late gadolinium enhancement. A and B show a lateral sub-endocardial infarction on short axis and 4 chamber LGE respectively; C and D show a full thickness inferior infarction on LGE imaging on short axis and VLA respectively; E and F show EGE and LGE imaging respectively of a full thickness apical infarction with an apical thrombus appearing black (highlighted by red arrow); G shows an extensive acute antero-apical infarction with a core of microvascular obstruction visible within the hyperenhancement on EGE (red arrow); H shows an acute inferior wall infarction with MVO and extension into the right ventricle on LGE (red arrow) imaging. LGE: Late gadolinium enhancement; EGE: Early gadolinium enhancement; MVO: Mitral orifice.

vascularisation following viability assessment[88,89]. This is contrary to prior observational data in large meta-analyses including over 3000 patients with viability; revascularisation was associated with 79.6% reduction in annual mortality ($P < 0.0001$) compared with medical treatment[90,91] and presence of dysfunctional viable myocardium by LGE-CMR without revascularisation is an independent predictor of mortality in patients with ischemic LV dysfunction[92]. Questions have been asked however whether the STICH sub-study results would have been different if CMR had been used rather than SPECT, and consequently in Europe the third highest indication for CMR remains the assessment of viability[93].

SCAR BEYOND VIABILITY ASSESSMENT

In addition to identifying viable myocardium, the presence and extent of LGE provides valuable prognostic information, and the extent of scar burden by LGE is readily quantified and reproducible on CMR[94]. Impairment of left ventricular ejection fraction is well recognized as an independent risk factor in those with coronary artery disease[8,95]; LGE can provide additive prognostication in these patients and a recent study of 1560 patients established that the presence of scar by LGE irrespective of LVEF identified those at risk of increased mortality[96]. Furthermore a meta-analysis showed that the presence of LGE increases the risk of death by 4.77% and MACE by 3.9% and that each gram of scar measured by LGE increased the hazards of death and MACE by 4% and 5%, respectively[97]. Additionally the identification of previously unrecognized MI by LGE confers a significantly increased risk of both mortality and MACE[72,98].

The extent of scar burden by LGE in patients with ischaemic heart disease has also been identified in a number of studies to be an independent predictor of ventricular arrhythmias in patients with internal cardiac defibrillators (ICD)[99-101], and a recent meta-analysis of 1105 patients with ICDs determined that the extent of LGE was predictive of ventricular arrhythmia whilst LVEF was not[102]. Additionally in a high risk cohort of patients with a mean LVEF of 35% being considered for ICD implantation, LGE demonstrated that significant scarring (> 5% LV) in patients with LVEF > 30%, conferred a risk similar to those with LVEF $\leqslant$ 30%[103]. Equally, in patients with LVEF $\leqslant$ 30%, minimal or no scar burden established a lower risk cohort similar to those with LVEF > 30%[103]. Other studies have identified the presence of a "grey zone" on LGE imaging, a heterogeneous region of viable and non-viable myocardium at the infarct periphery, as predictive of VT[104,105].

LGE and quantification of scar burden has also been used to predict responsiveness to cardiac resynchronization therapy (CRT)[106], and identification of scarring in the pacing region of the LV lead has been associated with non-response to device therapy[107,108]. In a similar method to imaging the coronary artery anatomy, coronary venous anatomy can be reliably demonstrated using GBCAs, which can potentially aid planning of device implantation[109]. The combination of coronary venous imaging, assessment of ventricular function and LGE may be a useful adjunct in the management of patients with ischaemic cardiomyopathy being considered for CRT, as well as risk stratifying those being considered for

defibrillator therapy.

COST EFFECTIVENESS

The economic burden of CAD is enormous with £6.8 billion spent in 2012 in the United Kingdom; in the United States over 15 million people have CAD costing the US economy $108.9 billion/year[110,111]. Cost effectiveness analyses help to inform optimal management pathways in order to maximise health care benefit within the constraints of limited resources. In the United States a low yield has been reported at diagnostic angiography with just over 40% of patients referred having obstructive CAD[5]. CMR can act as a potential gatekeeper to invasive coronary angiography in order to reduce downstream costs as well as reduce risk from unnecessary invasive assessments.

Health economic analyses based on the CE-MARC dataset identified that despite the higher initial cost of CMR to SPECT, the superior diagnostic accuracy of CMR lead to an overall greater cost effectiveness in models of the United Kingdom, German and Swiss healthcare systems[112-114]. A study of 1158 German patients being investigated for suspected CAD were randomised to either DSMR prior to angiography or direct to angiography; DSMR prior to invasive angiography led to a saving of 12466€ of hospital costs per life year, furthermore this cost saving was maintained through a median period of 7.9 years follow-up[115].

In a cost analysis comparing CMR and X-ray angiography *vs* angiography and FFR to determine the need for revascularisation, CMR and angiography was more cost-effective below a CAD prevalence of 62%, 65%, 83% and 82% for the Swiss, German, United Kingdom, and the United States health care systems, respectively[116]. These studies confirm that as well as the established high diagnostic accuracy, CMR is also a financially advantageous investigative strategy in patients with CAD.

RECENTLY PUBLISHED AND FUTURE STUDIES

Studies thus far have predominantly focused on the diagnostic accuracy of CMR; forthcoming multi-centre clinical effectiveness trials are however focused on evaluating clinical pathways to improve patient outcomes. The recently published CE-MARC 2 trial is a prospective, multi-centre, 3-arm parallel group, randomised controlled trial comparing multi-parametric CMR *vs* UK NICE CG95 guidance[14] *vs* AHA/ACCF SPECT appropriate-use criteria[117] to investigate patients with suspected CAD (pre-test likelihood 10%-90%) requiring further investigation[118,119]. The primary outcome measure was FFR defined unnecessary angiography (FFR > 0.8) with the important safety secondary outcome measure of MACE at 1 and 3 years. CE-MARC 2 showed overall that CMR guided care resulted in significantly reduced rates of unnecessary angiography at 12 mo compared to routine guideline directed care[119].

Contemporary registry data from the United States suggests roughly 12%-26% of elective PCI are deemed inappropriate with considerable variation in practice between sites[120,121]. Both FAME and DEFER showed improved outcomes using FFR guided revascularisation based on ischaemia detection, compared to reliance on visual assessment at angiography[122,123]. These trials would suggest that a better way of selecting patients prior to invasive revascularisation procedures is required. CMR offers a non-invasive ischaemia assessment and the MR-INFORM trial aims to establish if perfusion CMR could act as a non-invasive surrogate to FFR to determine the need for revascularisation in patients with stable CAD[124]. MR-INFORM is a multi-centre, non-inferiority study comparing adenosine perfusion CMR *vs* angiography with FFR measurement to guide revascularisation decisions in patients with stable angina and moderate to high probability of CAD; the primary endpoint is the occurrence of MACE at one year. The trial has completed recruitment and is expected to report in 2017.

The prognostic benefit of revascularisation in stable coronary artery disease is a topic of debate; both the COURAGE trial and BARI-2D failed to show any prognostic benefit of revascularisation over optimal medical therapy (OMT) in patients with stable CAD[125,126]. Determination of extent of ischaemia in both these 2 trials was however limited; in COURAGE only 33% of patients had moderate/severe ischaemia and moreover around 40% had < 5% ischaemia[127]. In both trials however those with a higher residual ischaemia burden had a worse prognosis[127-129]. The ISCHEMIA trial aims to test the hypothesis that a routine invasive strategy with early cardiac catheterisation and revascularisation plus OMT is superior to a conservative management strategy of OMT for patients with moderate or severe ischemia[42]. The trial aims to recruit over 8000 patients worldwide with ischaemia determined by non-invasive imaging (CMR, stress echocardiography, SPECT) with a primary endpoint of time to cardiovascular death or non-fatal myocardial infarction.

Coronary artery evaluation

Coronary MRA (CMRA) allows the non-invasive anatomical assessment of coronary arteries; currently clinical indications are limited to the detection of aberrant origin of coronary arteries, coronary ectasia and/or aneurysms (class Ⅰ indication) and evaluation of bypass grafts (class Ⅱ indication)[130,131]. CMRA for diagnosis of CAD is not presently part of routine clinical practice. The initial multi-centre experience using CMRA in this context showed interpretable image quality in 84% of proximal and middle coronary artery segments, though with a specificity of 42%; CMRA did however exclude triple-vessel disease and left main coronary artery stenosis with a negative predictive value of 100%[132]. Progress in CMRA techniques have improved significantly however, and a recent multi-centre study showed that CMRA at 1.5T detects significant

CAD with a sensitivity of 88% and specificity of 72% and a negative predictive value of 88%[133]. Furthermore one study showed in a direct comparison between CMRA and CT coronary angiography (CTCA) there was no significant difference between coronary imaging at 3.0T and 64-slice CTCA for the detection of CAD with a sensitivity of 87% *vs* 90% ($P = 0.16$) and specificity of 77% *vs* 83% ($P = 0.06$) respectively[134].

Currently CMRA techniques are time consuming and there are questions over the incremental diagnostic merit they provide in addition to established perfusion protocols; the CE-MARC study found no additional diagnostic benefit by including CMRA into a full multi-parametric protocol *vs* the perfusion/LV function/LGE combination (overall accuracy 84.6% *vs* 84.2% ($P = 0.5316$)[23]. Moreover there was no significant improvement in diagnostic accuracy when CMRA was added to perfusion imaging at 1.5T and compared to FFR as the reference standard[135].

FUTURE DIRECTIONS

T1 mapping

Native T1, T1 mapping, and extra cellular volume fraction quantification are novel methods for CMR tissue characterisation. These techniques are currently research tools that have shown promise for diagnosis and prognostication in acute coronary syndromes and other rare disease processes (*e.g.*, Amyloid and Fabry's disease), presently however they do not have an established role in the diagnosis or management of stable ischaemic heart disease[136,137]. Post myocardial infarction however a role for these imaging "biomarkers" is being established in predicting both prognosis and adverse LV remodelling[138,139].

Blood oxygen level dependent

CMR uses the paramagnetic properties of deoxyhaemoglobin as an endogenous contrast agent; increasing deoxyhaemoglobin content leads to a reduction of signal intensity on T2 or T2* weighted images[140]. The magnitude of the BOLD effect depends on the static magnetic field strength, with an exponential increase at 3.0T from 1.5T; consequently most studies have used 3.0T. Thus far BOLD has shown good correlation with QCA and conventional CMR perfusion imaging, but studies are generally small and single centre, limiting its clinical validation[141,142].

Finally hyperpolarised CMR is making the transition from animal studies to human applications. Hyperpolarisation methods artificially increase the number of molecules in one orientation resulting in a significant increase in MR signal; combined with ^{13}C enriched metabolic tracers enable real time imaging of *in vivo* substrate metabolism, coronary angiography and quantitative perfusion imaging[143]. The results of human hyperpolarisation studies are eagerly awaited.

CONCLUSION

Over the last decade the evidence base for the diagnostic accuracy of CMR for the investigation of stable coronary artery disease has been confirmed through the publication of large-scale clinical trials and meta-analyses, and CMR is now firmly established in clinical practice guidelines. CMR enables assessment of cardiac dimensions, function, ischaemia, scar burden and tissue viability in a single study without exposure to ionising radiation. CMR also offers prognostic information with a normal stress CMR associated with a < 1% risk of death or MI at 2 years, whilst the presence of LGE confers added prognostication above and beyond simple LV ejection fraction. New technical developments continue apace and ongoing large clinical trials will further clarify the role of CMR in routine clinical practice and guide the future development of international guidelines.

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REVIEW

Cardiovascular magnetic resonance imaging assessment of outcomes in acute myocardial infarction

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Abstract

Cardiovascular magnetic resonance (CMR) imaging uniquely characterizes myocardial and microvascular injury in acute myocardial infarction (AMI), providing powerful surrogate markers of outcomes. The last 10 years have seen an exponential increase in AMI studies utilizing CMR based endpoints. This article provides a contemporary, comprehensive review of the powerful role of CMR imaging in the assessment of outcomes in AMI. The theory, assessment techniques, chronology, importance in predicting left ventricular function and remodelling, and prognostic value of each CMR surrogate marker is described in detail. Major studies illustrating the importance of the markers are summarized, providing an up to date review of the literature base in CMR imaging in AMI.

Key words: Myocardial infarction; Infarct; Cardiovascular magnetic resonance; Left ventricular remodelling; Prognosis

Core tip: Cardiovascular magnetic resonance (CMR) imaging uniquely characterizes myocardial and microvascular injury in acute myocardial infarction (AMI). Contrast-enhanced CMR offers robust, validated and reproducible surrogate markers, providing an accurate representation of pathophysiology, assessment of myocardial function and injury, and predictive value for medium to long-term LV function, remodelling and prognosis following primary percutaneous coronary intervention for STEMI. These qualities significantly increase the statistical power of studies using CMR endpoints and has resulted in an exponential increase in AMI studies utilizing CMR based endpoints. An understanding of the role of CMR in the assessment of outcomes in AMI is of key importance not only to interventional and imaging cardiologists, but to the cardiology community as a whole.

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INTRODUCTION

Cardiovascular magnetic resonance (CMR) imaging uniquely characterises myocardial and microvascular injury in acute myocardial infarction (AMI), providing powerful surrogate markers of outcomes. The last 10 years have seen an exponential increase in studies utilising CMR based endpoints in patients with AMI undergoing primary percutaneous intervention. This article provides a contemporary, comprehensive review of the powerful role of CMR imaging in the assessment of outcomes in AMI. The theory, assessment techniques, chronology, importance in predicting left ventricular function and remodelling, and prognostic value of each CMR surrogate marker is described in detail. Major studies illustrating the importance of the markers are summarised, providing an up to date review of the literature base in CMR imaging in AMI.

MARKERS OF OUTCOMES FOLLOWING PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN AMI

Prognostic studies using clinical outcomes, in particular mortality require large sample sizes. Surrogate biomarkers of outcome are directly measured alternative endpoints used as a substitute for biological processes and clinical outcomes[1,2]. CMR imaging uniquely characterises myocardial and microvascular injury in AMI due to its accuracy, reliability and validity (Figure 1)[2-4]. This significantly increases the statistical power of studies, allowing sample size requirements to be reduced. CMR data are strong surrogate markers of outcome following primary percutaneous coronary intervention (PPCI) in acute ST-segment elevation MI.

LV EJECTION FRACTION AND VOLUMES IN AMI

Background

In the medium-term following STEMI, LV end-diastolic volume (LVEDV) increases, LV end-systolic volume (LVESV) decreases[5-7] and there can be compensatory hypertrophy of remote myocardium[8,9] in order to preserve stroke volume and ejection fraction (LVEF). Adverse remodelling results from an inability of the heart to maintain geometry post MI in the context of large infarcts and increased wall stresses[10,11]. An increase in LVEDVI > 20%[12,13] and increase in LVESVI > 15%[14] at follow-up are the most commonly used criteria for adverse remodelling.

CMR assessment of LV volumes and ejection fraction

CMR is the gold standard modality for the assessment of ventricular function and volumes. It has higher spatial resolution than single-photon emission computed tomography (SPECT) (approximately 1.8 mm × 1.8 mm × 8 mm *vs* 10 mm × 10 mm × 10 mm)[15], and suffers from little subjectivity or reliance on patient body habitus[16].

Volumes and mass are assessed on analysis of a 3D cine stack of short-axis biventricular contiguous slices. Modern cine sequences use breath-hold, electrocardiographic-gated, segmented steady-state free precession (SSFP) to produce high spatial resolution images with excellent myocardium-blood contrast. Regional systolic function can alternatively be assessed using wall motion scoring[17].

CMR studies have demonstrated that recovery of LVEF occurs relatively early post STEMI. Ripa showed that improvement in LVEF and systolic wall thickening occurred by 1 mo, with no further change at 6 mo[5]. The majority of improvement in LVEF occurred between day 2 and 1 wk in the study by Mather[18], with a final increase by 3 mo. Beek showed that 55% of segments with initially impaired systolic wall thickness improved at 13-wk[19]. Ganame *et al*[20] and Dall'Armelina *et al*[21] however showed that LVEF underwent no significant change by 6 and 12 mo post PPCI respectively. This may be because their subjects sustained less myocardial damage, represented by relatively preserved LVEF and thus lower potential for improvement[21].

Volumetric changes occur more slowly. Ripa *et al*[5] showed a continued increase in LVEDV and reduction in LVESV until 6 mo. Engblom *et al*[7] demonstrated similar sequelae to 12-mo. Ganame showed progressive significant changes in LVEDV and LVESV and resulting LV sphericity at all timepoints to 12 mo[20]. These studies have important implications for optimising timing of follow-up CMR studies assessing remodelling.

The degree of impairment of LVEF and changes in volume depend on a number of CMR-based markers including infarct size (IS)[22], microvascular obstruction (MVO)[23,24], intramyocardial haemorrhage (IMH)[25] and myocardial salvage [non-infarcted proportion of ischaemic area at risk (AAR)][26,27]. Anterior STEMI results in larger IS and lower LVEF due to the greater ischaemic AAR[28].

Prognostic importance of LVEF and volumes in AMI

Norris *et al*[29] and White *et al*[30] first illustrated the prognostic importance of LVEF (strongest independent predictor of survival at 3.5 years) and LVESV (only independent predictor of long-term mortality at 6 years) respectively, using invasive ventriculography. Burns first demonstrated the prognostic importance of LVEF and LV volumes and their strong correlation with each other, using radionucletide analysis[31].

A large evidence base has emerged for the prognostic impact of impaired systolic function based on reduced CMR-derived LVEF (Table 1).

In addition to LVEF-based global systolic function, Bodi demonstrated that the number of dysfunctional segments on CMR at 1-wk post STEMI was an independent predictor of combined MACE at a median follow-up of 553 d[38]. The evidence base for the prognostic importance of LV volumes is largely historical, based on large echocardiographic

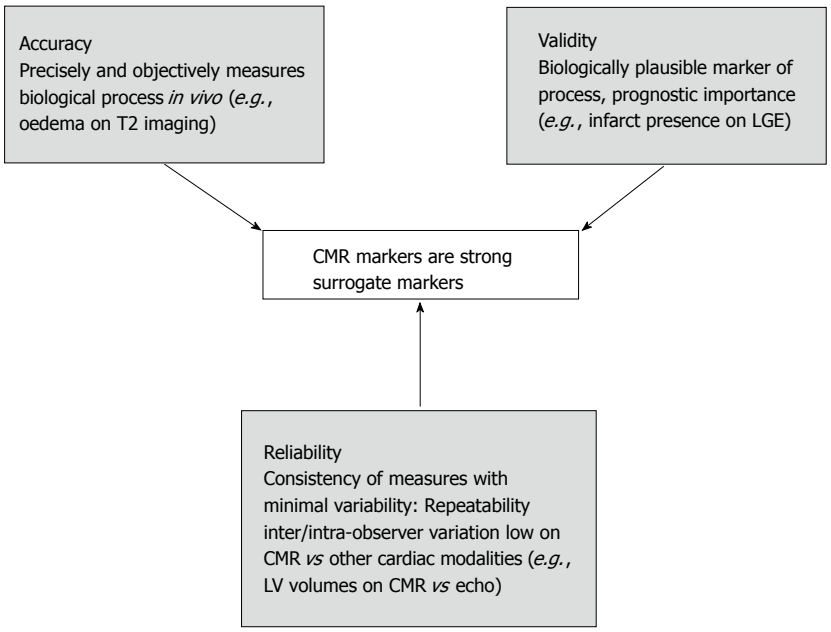

Figure 1 Cardiovascular magnetic resonance markers are ideal surrogate biomarkers for the assessment of revascularisation in acute myocardial infarction[2-4]. CMR: Cardiovascular magnetic resonance; AMI: Acute myocardial infarction; LGE: Late gadolinium enhancement.

Table 1 Cardiovascular magnetic resonance studies illustrating the prognostic importance of left ventricular ejection fraction in acute myocardial infarction

Ref.	Year	*n*	CMR time	Main findings	Follow-up
El Aidi *et al*[32]	2014	25497	N/A	Meta analysis of prognostic value of CMR surrogate markers. LVEF was only IP for MACE (HR 1.05 per -5%)	N/A
Husser *et al*[33]	2012	304	7 d	LVEF was IP for MACE (HR 0.95 for each +1% LVEF)	140 wk
Eitel *et al*[34]	2011	208	3 d	LVEF was IP for MACE (HR 0.95 for each +1% LVEF)	18.5 mo
Amabile *et al*[35]	2010	114	6 d	LVEF was IP for MACE (HR 0.96 for each +1% LVEF)	12 mo
de Waha *et al*[36]	2010	438	3 d	LVEF was IP for MACE (OR 1.63) and all-cause mortality (OR 2.51)	19 mo
Cochet *et al*[37]	2009	127	3-7 d	LVEF of < 40% was IP for MACE (OR 1.20)	12 mo
Hombach *et al*[6]	2005	110	6 d	LVEF was IP for 9 mo MACE (P = 0.006)	225 d

CMR time: Mean/median time of CMR post acute STEMI; MACE: Major adverse cardiovascular events; IP: Independent predictor; LVEF: Left ventricular ejection fraction; CMR: Cardiovascular magnetic resonance; N/A: Not available.

Table 2 Studies illustrating the prognostic importance of left ventricular volumes and adverse left ventricular remodelling in acute myocardial infarction

Ref.	Year	*n*	Modality	Main findings	Follow-up
Ahn *et al*[13]	2013	135	Echo	Adverse LV remodelling (> 20% inc. LVEDV) at 6 mo was IP 3 yr MACE. MACE rate approximately 25% in patients with adverse LV remodelling *vs* approximately 6% in non-remodelled patients	981 d
Hombach *et al*[6]	2005	110	CMR	Baseline LVEDV was IP for MACE (P = 0.038)	225 d
St John Sutton *et al*[39]	2003	512	Echo	Percentage change in LV area (surrogate for LV volume) between baseline echo and follow-up at 12 mo was IP for ventricular ectopy and VT	24 mo
Bolognese *et al*[12]	2002	284	Echo	Baseline LVESV was IP for cardiac death and MACE. Components of MACE higher in patients with adverse remodelling (> 20% inc. LVEDV: Mortality 14% *vs* 5%, MACE 18% *vs* 10%)	5 yr
Otterstad *et al*[40]	2001	712	Echo	Increase in LVESV between acute scan at 7 d and echo at 3 mo strongest IP for MACE	24 mo
St John Sutton *et al*[41]	1994	512	Echo	LV end-diastolic area (RR 1.1) and LV end-systolic area (RR 1.1) on baseline echo, and %-change in LV area at 12 mo echo (RR 1.55) were strongest IPs for MACE	12 mo
White *et al*[30]	1987	605	LV gram	LVESV of LV gram at 4 wk was strongest IP of long-term mortality (P < 0.0001)	78 mo

MACE: Major adverse cardiovascular events; IP: Independent predictor; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; Modality: Modality of LV volume assessment (CMR: Cardiovascular MRI; Echo: Echocardiography; LV gram: LV contrast angiography).

and radionucleotide studies, demonstrating the negative prognostic impact of ventricular dilatation and remodelling as summarised in Table 2.

Negative LV remodelling has demonstrated prognostic importance in two studies, based on the cut-off of LVEDVI dilation of > 20% at 6-mo follow-up[12,13].

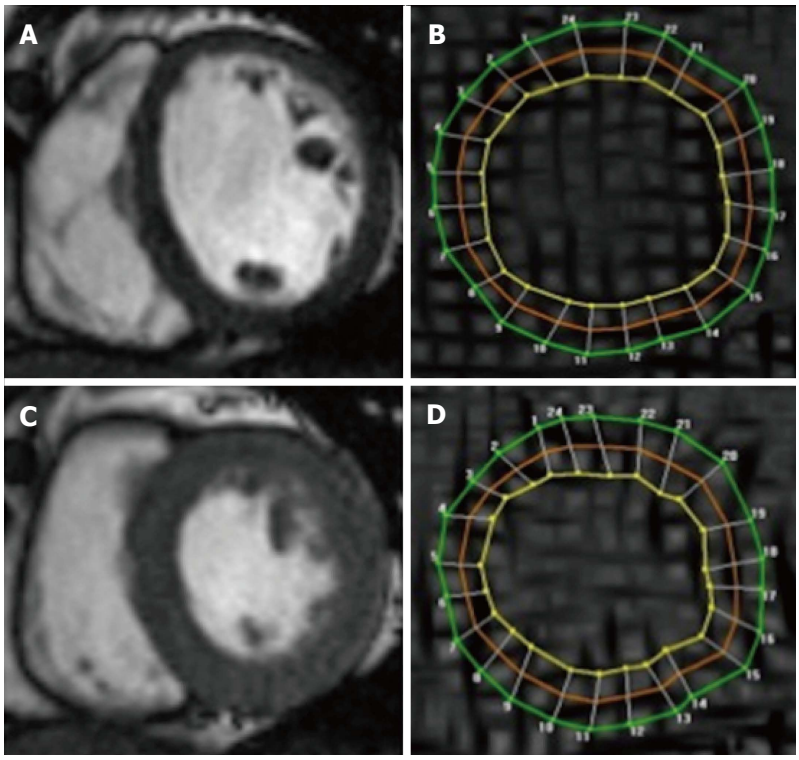

Figure 2 Cardiovascular magnetic resonance assessment of strain using tissue tagging. Cine SSFP images in end-diastole (A) and end-systole (C), with corresponding Spatial Modulation of Motion (SPAMM) tagged images (B and D). Grid lines (tags) are visible and contours drawn at 3 myocardial levels [green (epicardial), red (mid myocardial), yellow (endocardial)] allow tracking of myocardial motion and strain (circumferential), here using Harmonic Phase Analysis.

Recently, left ventricular global performance index has been proposed as a CMR marker of cardiac performance, incorporating LVEF, LV volumes and mass. It has been assessed in one study in STEMI and correlated strongly with IS, MSI, MVO and IMH extent, and had incremental prognostic value to LVEF in predicting 12-mo MACE[42]. Further work is needed to investigate its prognostic value in STEMI.

MYOCARDIAL STRAIN IN AMI

CMR-measured myocardial strain (tissue deformity) is the gold standard non-invasive measure of systolic and diastolic myocardial function[43]. Circumferential strain (Ecc) describes shortening of fibres (contraction) in a short-axis plane tangential to the epicardium; longitudinal strain (Ell) describes shortening in the long axis, and radial strain (Err) describes lengthening (thickening) of fibres towards the centre of the ventricle. Torsion is wringing of the ventricle caused by clockwise rotation at the base, and anticlockwise at the apex.

Strain offers greater accuracy in detecting myocardial dysfunction compared with global (LVEF) and regional (visual wall-motion scoring, segmental wall thickening)[44] measures.

CMR assessment of myocardial strain

In 1989, Axel *et al*[45] developed a T1 spoiled gradient echo sequence, creating "tags" formed by saturation of thin myocardial lines running in perpendicular directions in-plane to form a myocardial grid. These lines act as tissue markers, tracking myocardial deformation as shown in Figure 2. Peak systolic strain and peak diastolic strain rate (relaxation rate of strain) provide very sensitive measures of systolic and diastolic function respectively. Its accuracy has been validated on comparison with sonomicrometry[46,47]. Harmonic Phase Analysis (HARP) is currently the most widely used CMR strain method[48].

Feature tracking (FT) has been introduced as an alternative method to tagging for assessing strain on CMR. FT tracks anatomical features of interest along contour lines on routinely acquired SSFP cine images analogous to echocardiographic Speckle Tracking, obviating the need for additional tagging sequences[49]. FT-derived strain has been compared to tagging in acute STEMI and shown greater feasibility, accuracy and observer agreement[50] and remains an exciting prospect.

CMR LV strain as a predictor of LV function and remodelling in AMI

Strain could improve our understanding of the mechanics underlying LV dysfunction associated with prognostic CMR surrogate markers of myocardial damage in STEMI (*e.g.*, MVO, IMH, oedema).

Systolic function is also in remote (non-infarcted) segments, and LV mechanics outside of the infarct zone are also affected during infarction and contribute to remodelling[44,51,52]. MVO had the highest predictive value for persistent dysfunction on circumferential strain at 7-mo post STEMI and may result in systolic dysfunction due to direct mechanical effects (myocardial stiffness)[53]. Baseline segmental circumferential strain was the strongest predictor of segmental functional recovery at 3-mo in a model containing infarct transmurality and MVO[54]. FT-derived global circumferential strain assessed acutely post PPCI was recently shown to correlated strongly with

Table 3 Studies illustrating the prognostic importance of left ventricular strain in acute myocardial infarction

Ref.	Year	*n*	Modality	Main findings	Follow-up
Ersbøll *et al*[56]	2014	1048	TTE	(E-prime divided by peak early diastolic strain rate) strongest IP of MACE and death	29 mo
Ersbøll *et al*[57]	2013	849	TTE	GLS was IP of MACE	30 mo
Hung *et al*[58]	2010	610	TTE	GLS and strain-rate, and GCS and strain-rate IPs for MACE in model with WMS, LVEF	25 mo
Antoni *et al*[59]	2010	659	TTE	GLS (HR 1.2) was IP of mortality. LVEF, wall-motion score and Tissue Doppler mitral valve inflow not	21 mo

TTE: Transthoracic echocardiography; GLS: Global longitudinal strain; MACE: Major adverse cardiovascular events; IP: Independent predictor; HR: Hazard ratio; LVEF: Left ventricular ejection fraction.

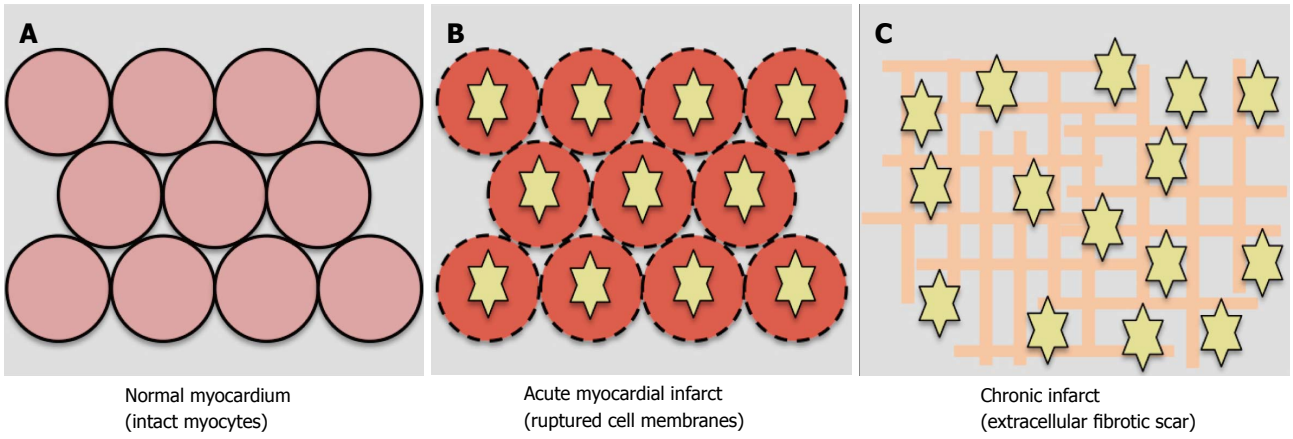

Figure 3 Mechanism of late gadolinium enhancement. Gadolinium is extracellular. A: In normal myocardium, gadolinium washes out approximately 10 min post administration and there is no late gadolinium enhancement (LGE); B: In acute infarct, gadolinium (yellow stars) enters ruptured cell membranes and causes LGE; C: In chronic infarct, LGE results from increased extracellular space due to fibrotic scar deposition.

acute IS on late gadolinium enhancement (LGE) imaging (r = 0.75) and final LVEF at 6 mo (r = -0.71). Global circumferential strain was a stronger predictor of functional recovery (LVEF > 50%) at 6 mo than global longitudinal strain, age, diabetes and baseline LVEF, and was of similar predictive value to acute IS [AUC 0.86 (Ecc) *vs* 0.92 (IS)][55].

Prognostic importance of LV strain in AMI

The evidence base for the prognostic importance of LV strain post STEMI is currently based on echocardiographic studies demonstrating that global longitudinal predicts medium and long-term using Speckle Tracking analysis as summarised in Table 3.

INFARCT SIZE IN AMI

Background

The "ischaemic cascade" is the sequence of patho-physiological effects developing immediately following coronary occlusion. Aerobic respiration loses efficiency resulting in cellular oedema. With increasing ischaemic time, cell membranes rupture. Following healing, necrotic cells are replaced by extracellular collagen deposition (scar). The acute and chronic phases are characterised by increased myocardial extracellular volume[60-62].

CMR assessment of IS in AMI

Gadolinium contrast agents are large extracellular molecules (Figure 3). Infarct can be visualised on T1-weighted imaging approximately 10 min after intravenous contrast administration, known as LGE imaging.

In acute infarct, LGE results from gadolinium entering ruptured cell membranes. In chronic infarction, LGE results from increased extracellular space due to collagen deposition and prolonged washout due to reduced capillary density within myocardium[60,63]. Gadolinium shortens T1, causing infarcted myocardium to appear bright, and normal myocardium to appears black (Figure 4)[63,64]. Normal myocardium is progressively nulled using the appropriate inversion time to provide optimal contrast between infarct and normal myocardium.

Typically, a high spatial resolution of approximately 1.4 mm × 1.6 mm × 6-8 mm is achieved[15]. IS is typically expressed as a percentage of total LV mass. Delineation of infarct can be performed visually (manual quantification)[6,9,22], however most groups use semi-automated methods to reduce observer variability. These include enhancing myocardium exceeding a pre-defined signal intensity (SI) threshold, typically > 2-6 standard deviations above that of remote (non-infarcted) myocardium[2,65]. Currently, the semi-automated full-width at half-maximum (FWHM) method is commonly used[66-70], defining infarct as myocardium with SI > 50% of the peak SI in the infarct core. Amado demonstrated that FWHM had the highest interobserver agreement and closest correlation with TTC-stained infarct in a dog model of acute infarction (r^2 = 0.94), compared with standard

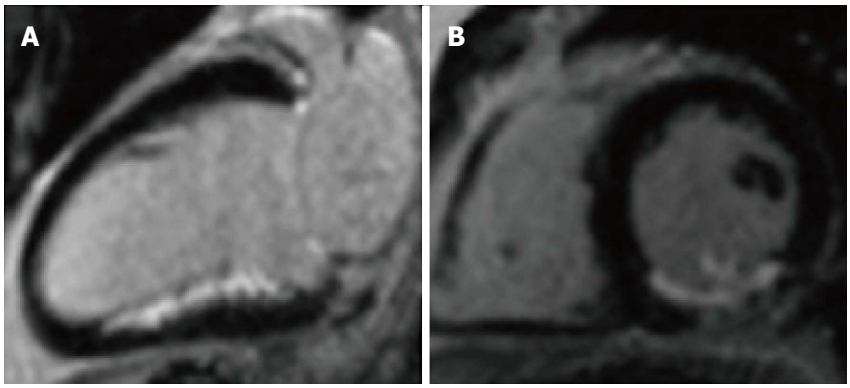

Figure 4 Late gadolinium enhancement of acute infarct. Infarct appears white (enhanced) in the inferior wall, with unaffected myocardium black (nulled). A: 2-chamber long-axis view; B: Short-axis view, mid ventricular level. The posteromedial papillary muscle is also infarcted in the short-axis view.

Table 4 Temporal changes in cardiovascular magnetic resonance-derived infarct size in acute myocardial infarction

Ref.	Year	*n*	CMR times post STEMI	Relative LGE IS reduction	LGE method	Main findings
Carrick *et al*[74]	2016	30	8 h → 3 d → 10 d → 7 mo	26%	Automated	Significant decrease d3 to d10 (20% ± 13% to 14% ± 10% LV mass). No change at 7 mo
Dall'Armelina *et al*[21]	2011	30	2 d → 6 mo	22%	> 2SD	IS reduced at times from 27% ± 15% LV mass 24 h post PPCI, to 21% ± 11% at 6 mo
Mather *et al*[18]	2011	48	2 d → 1 wk → 30 d → 3 mo	37%	> 2SD	27% IS drop between d2 and d7 post PPCI, no change at 3 mo
Ganame *et al*[20]	2011	58	3 d → 4 mo → 12 mo	45%	Manual	33% decrease IS d3 and 4 mo then no further decrease at 12 mo
Ibrahim *et al*[9]	2010	17	1 d → 1 wk → 1 mo → 6 mo	37%	Manual	34% reduction in IS from d2 to 1 wk, then no further change at 1 and 6 mo
Engblom *et al*[7]	2009	22	1 d → 1 wk → 12 mo	40%	Automated	28% reduction in IS between d1 and 1 wk
Ripa *et al*[5]	2007	58	2 d → 1 mo → 6 mo	30%	Manual	14% % reduction in IS from d2 to 1 mo
Hombach *et al*[6]	2005	110	6 d → 9 mo	28%	Manual	28% reduction in IS from d6 to 9 mo

LGE method: SD: Standard deviations; Total LGE IS Overest: Relative overestimation of final IS (last timepoint) on acute CMR; CMR: Cardiovascular magnetic resonance; LGE: Late gadolinium enhancement; IS: Infarct size; PPCI: Primary percutaneous coronary intervention.

deviation methods[66]. This may be because FWHM is less prone to IS overestimation in the presence of oedema, and partial volume effects giving rise to intermediate signal intensities[18,71]. Comparing techniques in STEMI patients showed that FWHM quantification had the lowest intraobserver and interobserver variability, and greatest agreement with LVEF[72].

CMR measurement of IS on LGE is well validated[63,64]. Kim demonstrated that IS in dog myocardium on *ex-vivo* CMR corresponded closely with IS derived from tetrazolium (TTC) staining (r = 0.99)[15,64]. LGE has higher sensitivity for infarct detection compared with SPECT. In an experimental model of MI, CMR LGE detected 92% of all segments with subendocardial infarction (< 50% transmurality) compared with only 28% with SPECT[15]. In patients with MI, SPECT only detects approximately 50% of the infarcts seen on LGE. The superior sensitivity is due to the increased spatial resolution and reproducibility of CMR[60].

Since gadolinium is distributed throughout the extracellular space, gadolinium contrast agents are not specific to necrosis. Acutely, the area of LGE detects not only necrotic cells but also the increased (oedematous) interstitium surrouding viable cells, and thus can overestimate true IS. Studies of IS chronology in humans corroborate this (Table 4). Indeed, severely dysfunctional segments with minimal myocardial salvage early post STEMI can show significant functional improvement at follow-up[73].

The majority of IS reduction occurs relatively early post STEMI, particularly by 1 wk. Indeed IS assessed at 1 wk has been shown to closely correlate with final IS[7,9,18]. Overestimation of necrosis by LGE-derived IS early post STEMI is due to a combination of oedema, infarct resorption and partial volume effects. Oedema results in an overestimation of LGE IS due to increased extracellular water content and thus volume of distribution of contrast agent[66,75].

Infarct resorption results from the healing process where collagenous scar tissue is produced to provide stability and tensile strength to necrotic myocardium[7,11]. This was confirmed in a canine model where a 3.4-fold decrease in infarct volume was seen between day 3 and 8-wk post infarct on *ex-vivo* LGE and TTC-stained slices[64]. The degree of infarct resorption has been shown to be proportional to initial IS (r = 0.65) and presence of LV remodelling (r = 0.41)[10]. The greater degree of infarct resorption relative to total myocardial

Table 5 Cardiovascular magnetic resonance studies illustrating importance of segmental late gadolinium enhancement extent and functional recovery in acute myocardial infarction

Ref.	Year	*n*	LGE method	Cutoff (LGE)	Main findings	Time of CMR 1	Time of CMR 2
Khan *et al*[85]	2016		FWHM	50% SEE	SEE strong predictor or segmental functional improvement (AUC 0.840) and normalisation (AUC 0.887)	2 d	9 mo
Wong *et al*[54]	2014	45	FWHM	50% SEE	Inverse relationship between TEE and likelihood of functional recovery on WMS at 24 wk (area under curve 0.68)	8 d	13 wk
Natale *et al*[86]	2011	46	2SD	50% TEE	Inverse relationship TEE and likelihood of functional recovery on SWT (93% sens, 75% spec)	5 d	20 wk
Engblom *et al*[7]	2008	22	Manual	50% TEE	Inverse relationship between TEE and functional recovery on WMS	7 d	24 wk
Shapiro *et al*[87]	2007	17	Manual	50% SEE	Inverse relationship between TEE and likelihood of functional recovery on WMS at 26 wk. Odds-ratio of functional recovery 0.2 with each SEE quartile	6 d	26 wk
Kitagawa *et al*[88]	2007	18	2SD	50% TEE	Inverse relationship between TEE and functional recovery. 31% segments > 50% TEE still improved	5 d	39 wk
Janssen *et al*[89]	2006	67	Manual	50% TEE	Inverse relationship between TEE and functional recovery on WMS at 12w (51%-75%: 39% segments improved, 76%+: 21% improved)	4 d	12 wk
Motoyasu *et al*[90]	2004	23	2SD	50% TEE	Inverse relationship between SEE and functional recovery on SWT	25 d	24 wk
Beek *et al*[19]	2003	30	6SD	50% SEE	Inverse relationship between SEE and functional recovery on WMS	7 d	13 wk

WMS: Wall motion scoring; SWT: Systolic wall thickening; TEE: Transmural extent of enhancement; SEE: Segmental extent of enhancement; SD: Standard deviations.

Table 6 Cardiovascular magnetic resonance studies illustrating importance of infarct size on left ventricular function and remodelling in acute myocardial infarction

Ref.	Year	*n*	LGE method	Main findings	Time post STEMI of predictive CMR	Follow-up
Ahn *et al*[13]	2013	135	Manual	IS strongest IP of LVR in model with LVEF and MI location	7 d	6 mo (echocardiogram)
Husser *et al*[33]	2012	304	> 2SD	IS IP of LVR in model incl. LVEF, IS, LV vols, MVO	6 d	189 d
Monmeneu *et al*[91]	2012	118	> 2SD	No. segments > 50% transmurality IP for LVR	6 d	6 mo
Ezekowicz *et al*[92]	2010	64	Manual	IS strongest IP of LVEF in model with MVO, troponins	7 d	3 mo
Ganame *et al*[25]	2009	98	Manual	IS strongest IP of LVR (>> MVO, AAR, Troponin-I)	2 d	6 mo
Bodi *et al*[93]	2009	214	> 2SD	Extent of transmural necrosis (no. segments > 50% TEE) strongest IP for LV recovery (+ > 5% LVEF)	7 d	6 mo
Wu *et al*[94]	2008	122	Manual	IS extent only IP for LVEF and LVR	2 d	4 mo
Hombach *et al*[6]	2005	110	Manual	IS extent IP of LVR in model with MVO, % transmurality	6 d	225 d

IS: Infarct size; IP: Independent predictor; LVR: LV remodelling; LVEDVI: Left-ventricular end-diastolic volume index; LVEDVI: Left-ventricular end-systolic volume index; LVEF: Left ventricular ejection fraction; MVO: Microvascular obstruction; SD: Standard deviation.

mass and volume results in an inability to maintain LV geometry in light of mechanical stresses post STEMI, resulting in adverse LV remodelling and sphericity[10,76].

Factors known to affect IS include AAR extent[77-79]; collateral flow to the AAR[79,80]; MVO[81]; time to reperfusion[82] and hyperglycaemia[83].

CMR IS as a predictor of LV function and remodelling in AMI

Segmental function: Kim illustrated in stable patients awaiting revascularisation, that LGE transmurality strongly predicted recovery of systolic function in dysfunctional segments. Only 2% of segments with > 75% transmurality improved after revascularisation[84]. Segmental extent of LGE has also been shown to negatively predict functional recovery in dysfunctional segments following PPCI for acute STEMI, as summarised in Table 5.

Global function: IS is a powerful independent predictor of global LV function and adverse LV remodelling in the medium to long-term post STEMI as summarised in Table 6.

Prognostic importance of CMR-derived IS in AMI

The goal of STEMI management is early reperfusion in order to minimise IS and thus maximise myocardial salvage[95]. There is a strong evidence base for the prognostic importance of CMR-derived IS post STEMI, as summarised in Table 7. IS strongly predicts medium to long-term clinical outcomes.

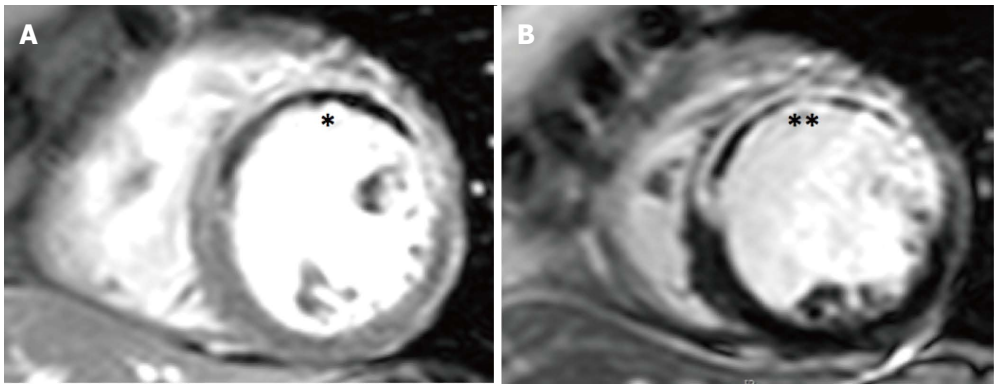

Figure 5 Early and late microvascular obstruction on cardiovascular magnetic resonance. A: Early gadolinium imaging at 1-min post contrast with hypoperfusion in anteroseptal, anterior and anterolateral segments, consistent with early MVO (E-MVO, *); B: Corresponding late gadolinium image showing transmural infarction with a hypointense late MVO core (L-MVO, **) co-localising with E-MVO. MVO: Microvascular obstruction.

Table 7 Cardiovascular magnetic resonance studies illustrating the prognostic importance of infarct in acute myocardial infarction

Ref.	Year	*n*	LGE method	Main findings	CMR timepoint	Follow-up
Husser *et al*[96]	2013	250	> 2SD	Extent of transmural infarction (no. of segments > 50% transmurality) only IP for MACE at 6 mo	7 d	163 wk
Izquierdo *et al*[97]	2013	440	> 2SD	IS was IP for AACEs (arrhythmic cardiac events: Sudden death, VT, VF, ICD shock) in model including LVEF, hypertension	7 d	123 wk
Eitel *et al*[34]	2011	208	> 5SD	IS was IP of MACE at 19 mo in model including MVO, LVEF, MSI, Killip, TIMI post-PPCI	3 d	18.5 mo
Miszalski-Jamka *et al*[98]	2010	77	Manual	LV transmurality index IP (HR 1.03) and IS (HR 1.03) IPs for MACE in a model containing RVEF and RV IS	"3-5 d"	1150 d
Larose *et al*[67]	2010	103	FWHM	IS strongest IP for MACE (HR 1.36) in model containing LVEF, CK. LGE > 23% had HR 6.1 for MACE	4.5 h	2 yr
Bodi *et al*[38]	2009	214	> 2SD	Extent of transmural infarction (no. of segments > 50% transmurality) IP for MACE (HR 1.35 if > 5 segs)	7 d	553 d
Wu *et al*[99]	2008	122	Manual	IS only IP of 2 yr MACE in model containing LVEF, LVESVI	2 d	538 d

LGE: Late gadolinium enhancement; FWHM: Full-width half-maximum; SD: Standard deviations; MACE: Major adverse cardiovascular events; LVEF: Left ventricular ejection fraction; PPCI: Primary percutaneous coronary intervention; LGE method (LGE quantification method): SD: Standard deviations; FWHM: Full-width half-maximum.

MVO IN AMI

Background

Despite prompt IRA recanalization, perfusion of the microcirculatory bed does not always ensue. Histopathogical studies have demonstrated that the infarct core (endocardial) perishes first as necrosis spreads transmurally towards the epicardium. This is known as the "wavefront theory"[100]. At the infarct core, necrosis occurs rapidly with myocardial and capillary endothelial cells perishing simultaneously. Capillaries can become obstructed by cellular debris, resulting in non-perfusion of the infarct core, despite IRA patency[101]. This is known as MVO and can be indicated at angiography, as "no reflow"[101].

CMR assessment of MVO in AMI

Three CMR methods demonstrate MVO (Figure 5). MVO extent is typically expressed as a percentage of LV mass: (1) Qualitative first-pass rest perfusion. A modified version involves quantification of myocardial blood flow (SI-time curve) and time to 50% of maximal SI[102,103]; (2) Hypoperfusion on inversion recovery images between 1-3 min post contrast. A fixed inversion time of approximately 440 ms nulls MVO and retains intermediate signal in normal myocardium. This is known as "early MVO (E-MVO)"[28,104]; and (3) Hypointensity within infarct core on LGE due to absence contrast perfusion, known as "late MVO (L-MVO)". L-MVO occurs in upto 60% of patients on CMR within the first week post STEMI[5,6,18,20]. This is the preferred method of MVO demonstration in contemporary clinical practice and research.

L-MVO extent is maximal at 48 h post infarct[8,18], and then decreases. It exists for at least 1 wk, and for up to 1 mo[8,18] and then resolves in the medium-term in humans (Table 8). Animal models corroborate these findings[105,106].

The extent of MVO on CMR has been shown to correlate with IS[82,94,107,108], oedema, IMH, TIMI-flow pre PCI[35,109] and time to reperfusion[35,82,110].

CMR MVO as a predictor of LV function and remodelling in AMI

L-MVO is a strong independent predictor of medium-term LV function and adverse remodelling (Table 9). It

Table 8 Temporal changes in cardiovascular magnetic resonance late microvascular obstruction in acute myocardial infarction

Ref.	Year	*n*	CMR timepoints	LGE method	Main findings
Carrick *et al*[74]	2016	30	8 h → 3 d → 10 d → 7 mo	Auto	L-MVO in 20%, peaked early at 8 h and stable at d3. Decreased by d10, absent at 7 mo
Mather *et al*[18]	2011	48	2 d → 1 wk → 30 d → 3 mo	> 2SD	L-MVO in 60%, peak at d2. Decrease at subsequent points. L-MVO absent at 3 mo
Ganame *et al*[20]	2011	58	3 d → 4 mo → 12 mo	Manual	L-MVO in 64%. L-MVO absent at 4 mo
Ripa *et al*[5]	2007	58	2 d → 6 mo	Manual	L-MVO in 42%. L-MVO absent at 6 mo
Hombach *et al*[6]	2005	110	6 d → 9 mo	Manual	46% had L-MVO (2.8% LV mass, 16% of IS) on acute CMR. L-MVO absent at 6 mo

MVO: Microvascular obstruction; LGE method: SD: Standard deviations; IS: Infarct size; LV: Left ventricle; CMR: Cardiovascular magnetic resonance.

Table 9 Cardiovascular magnetic resonance studies illustrating the importance of late microvascular obstruction on left ventricular function and remodelling in acute myocardial infarction

Ref.	Year	*n*	LGE method	Main findings	Time post STEMI of predictive CMR	Follow-up
Kidambi *et al*[115]	2013	39	> 2SD	L-MVO only IP of impaired infarct strain. Model with IS, TIMI flow, diabetes, transmurality	3 d	3 mo
Wong *et al*[103]	2012	40	Manual	L-MVO extent only IP for LVEF at 3 mo in model including E-MVO, IS and myocardial blood flow on perfusion	3 d	3 mo
Ezekowitz *et al*[92]	2010	64	Manual	L-MVO extent was IP of LVEF in model with IS and NT-proBNP	7 d	4 mo
Weir *et al*[112]	2010	100	Manual	L-MVO extent was only IP of LVR in model with TIMI post PCI, E-MVO, IS	4 d	6 mo
Ganame *et al*[25]	2009	98	Manual	L-MVO extent was IP of LVR in model with IS, troponin-I, TTR	2 d	6 mo
Nijveldt *et al*[111]	2008	60	Manual	L-MVO presence strongest IP of LVEF change and LVR in model with TTR, IS, LVEF, E-MVO	5 d	4 mo
Hombach *et al*[6]	2005	110	Manual	L-MVO extent IP for LVR in model with baseline IS, infarct transmurality	6 d	225 d

MVO: Microvascular obstruction; IS: Infarct size; IP: Independent predictor; TTR: Time to revascularisation; LVR: Left ventricular remodelling; LVEF: Left ventricular ejection fraction; LVEDVI: Left-ventricular end diastolic volume index; LVESVI: Left-ventricular end systolic volume index.

is likely that this is because L-MVO reflects more severe microvascular and myocardial damage than E-MVO[28,36]. In most studies demonstrating the independent predictive value of L-MVO on LV function and remodelling, E-MVO was not a predictor[103,111,112]. L-MVO was a predictor independent of baseline IS[6,20,92,111-113]. Monocyte recruitment, crucial in cellular debris removal and scar formation, is impaired in areas of L-MVO in rat myocardium and may contribute to the adverse remodelling[114].

Prognostic importance of CMR MVO in AMI

An increasing evidence base demonstrates the strong medium-term prognostic value of L-MVO following STEMI, independent of IS and LVEF[6,36,37,116] (Table 10). The 2 studies featuring both L-MVO and E-MVO showed that L-MVO was a stronger prognostic indicator[36,37]. Regenfus *et al*[117] demonstrated that L-MVO was the strongest IP of long-term combined MACE at 6 years follow-up in a model including CMR-assessed LVEF and IS (HR 3.9), providing incremental prognostic value over traditional CMR markers of myocardial damage. A meta-analysis[118] (8 studies, *n* = 1025) demonstrated that L-MVO presence was the strongest independent predictor of medium-term combined MACE (HR 3.7) and cardiovascular death (HR 13.2) at 2 years independent of IS and LV volumes.

The strong adverse prognostic value of L-MVO may be due to its negative effects on LV function, wall thickness and stiffness, and remodelling, and subsequent risk of heart failure and arrhythmias[6,20,92,111-113].

IMH IN AMI

Background

IMH is a reperfusion injury occurring when restored blood flow into damaged capillaries extravasates erythrocytes into myocardium[121,122]. CMR-derived IMH was first described in reperfused canine myocardium on *ex-vivo* T2-weighted spin-echo (T2w-TSE) imaging with excellent agreement with histology (r = 0.96 for IMH extent)[123].

CMR assessment of IMH in AMI

Paramagnetic haemoglobin breakdown products shorten T2 relaxation times[123,124]. IMH is seen as hypointense zones within hyperintense oedematous myocardium on T2w-TSE sequences. It shows good histological correlation in canine myocardium (*ex-vivo* MRI, r = 0.96)[123] and in an human autopsy case series (*in-vivo* MRI, r = 0.97)[124].

Table 10 Cardiovascular magnetic resonance studies illustrating the prognostic importance of late microvascular obstruction in acute myocardial infarction

Ref.	Year	*n*	LGE method	Main findings	Time of prognostic CMR post STEMI	Follow-up
Regenfus *et al*[117]	2015	249	Manual	L-MVO extent strongest IP for MACE in model including IS, LVEF, TIMI pre and post PPCI and no. diseased vessels	3.7 d	72 mo
Eitel *et al*[119]	2014	738	> 5SD	Largest multicentre study of L-MVO in PPCI. L-MVO > 1.4% LVM and TIMI risk score only IPs of combined MACE. Adding L-MVO to model with clinical predictors, LVEF and IS increased c-statistic	7 d	6 mo
de Waha *et al*[120]	2012	438	Manual	L-MVO extent IP for combined MACE in model including IS, LV volumes (only other IP was LVEF). L-MVO/IS strongest IP in model including L-MVO extent, LVEF, IS, LV volumes	3 d	19 mo
de Waha *et al*[36]	2010	438	Manual	Presence and extent of L-MVO were strongest IPs for MACE and mortality in models with IS, LVEF, ST-res, TIMI-flow post PCI. E-MVO was not an IP	3 d	19 mo
Cochet *et al*[37]	2009	184	Manual	L-MVO strongest IP for MACE, in models including GRACE score, IS, LVEF. L-MVO stronger IP than E-MVO (OR 8.7 *vs* 2.5)	"3-7 d"	12 mo
Bruder *et al*[116]	2008	143	Manual	Only extent of L-MVO > 0.5% LV mass was IP for MACE; model included IS, LVEF, age, DM, sex	4.5 d	12 mo
Hombach *et al*[6]	2005	110	Manual	L-MVO IP for MACE (P = 0.04) in model including LV end-diastolic volume and LVEF	6 d	268 d

MVO: Microvascular obstruction; LVEF: Left ventricular ejection fraction; IS: Infarct size; PCI: Percutaneous coronary intervention; MACE: Major adverse cardiovascular events; IP: Independent predictor.

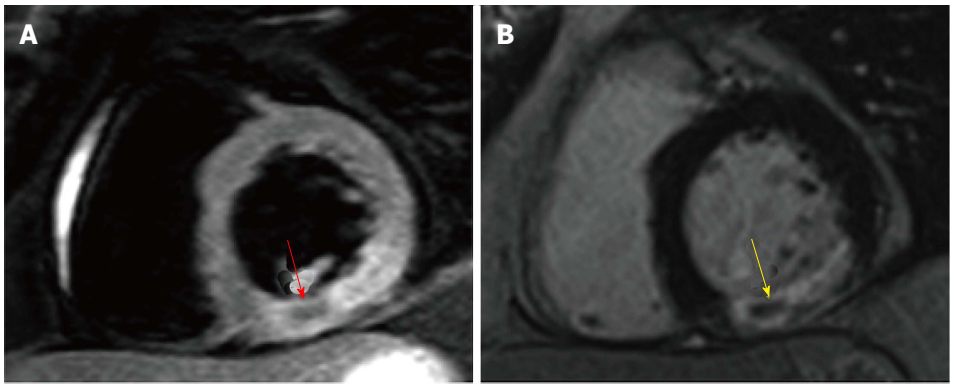

Figure 6 Intramyocardial haemorrhage on cardiovascular magnetic resonance. A: T2-weighted spin-echo image with hypointensity corresponding with IMH within the hyperintense oedematous region in the inferior wall (red arrow); B: Corresponding LGE image showing co-localisation of IMH and L-MVO (yellow arrow). IMH: Intramyocardial haemorrhage; LGE: Late gadolinium enhancement; MVO: Microvascular obstruction.

IMH occurs exclusively in areas of L-MVO (r^2 for co-localisation approximately 0.9) (Figure 6)[25,33,125,126].

Newer sequences based on direct quantification of T2 and T2*[74,126-129] allow IMH to be quantified without the limitations of T2w-TSE imaging. Initial studies have been promising and shown that these sequences are reproducible and appear more sensitive and accurate than T2w-TSE for IMH detection[126,130,131]. O'Regan *et al*[126] showed that T2* had 100% sensitivity for IMH detection compared to 90% for T2w-TSE, where the "gold standard" was co-localisation with L-MVO. In canines, T2* in haemorrhagic infarcts closely correlates with iron levels on spectrometry, and T2*-detected IMH co-localises with iron deposition on Perl's staining[132] and extravasated erythrocytes on Haematoxylin-Eosin staining[128]. In pigs, regions of IMH on T2* imaging showed vessel degeneration and iron deposition[8].

There is a paucity of data on temporal changes in CMR-detected IMH. Mather *et al*[18] showed that IMH on T2w-TSE was present in 33% of patients, with maximal extent at 48 h post PPCI and progressively resolution by 3 mo. Carrick *et al*[74] recently demonstrated that the incidence and extent of IMH on T2* increased between 8 h and 3 d post PPCI. Its extent was significantly lower at 10 d and was seen in only 13% of patients at 7 mo. The authors also found that MVO was present in all patients with IMH, and its extent peaked earlier at 8 h suggesting that IMH is an ensuing reperfusion injury in regions of MVO.

CMR IMH as a predictor of LV function and remodelling in AMI

There is a small evidence base demonstrating that IMH is a strong univariate predictor of medium-term impaired LV function and remodelling, however multivariate analysis reveals mixed results, with some studies suggesting no incremental predictive value of IMH over MVO and IS (Table 11).

Table 11 Cardiovascular magnetic resonance studies illustrating the importance of intramyocardial haemorrhage on left ventricular function and remodelling in acute myocardial infarction

Ref.	Year	*n*	IMH CMR method	Main findings	CMR time post MI	Mean/median F/U CMR
Carrick *et al*[74]	2016	245	T2*	IMH strongest IP for LVR. IMH associated with lower LVEF and greater volumes	3 d	7 mo
Kidambi *et al*[115]	2013	39	T2w-TSE and T2*	IMH associated with attenuation of follow-up infarct strain	3 d	3 mo
Husser *et al*[33]	2012	304	T2w-TSE	IMH strongest IP for LVR in model with LVEF, IS, LV vol, L-MVO	6 d	189 d
Mather *et al*[131]	2011	48	T2w-TSE and T2*	IMH strongest IP of LVR in model with IS, LVEF, LVESV, E-MVO, MSI	2 d	3 mo
Beek *et al*[24]	2010	45	T2w-TSE	IMH was a univariate predictor of LVEF. However no prognostic significance beyond baseline LVEF and MVO in predicting final LVEF	5 d	4 mo
Bekkers *et al*[121]	2010	90	T2w-TSE	Acute MSI and LVEF increase at follow-up lowest if IMH present. But IMH no prognostic significance beyond MVO in predicting LVEF	5 d	103 d
O'Regan *et al*[126]	2010	50	T2*	IMH presence univariate predictor of LVEF and LV volumes. However only IS independently predicted LVEF	3 d	N/A
Ganame *et al*[25]	2009	98	T2w-TSE	IMH extent strongest IP of LVR in model with IS, E-MVO, Troponin-I, AAR, TTR, IS	2 d	4 mo

IS: Infarct size; IP: Independent predictor; LVR: Left ventricular remodelling; MVO: Microvascular obstruction; LVEF: Left ventricular ejection fraction; LVESVI: Left-ventricular end systolic volume index; T2w-TSE: T2-weighted turbo spin-echo; AAR: Area at risk; MSI: Myocardial salvage index; N/A: Not applicable.

Prognostic importance of CMR IMH in AMI

Multivariate analyses including IMH as a prognostic indicator also show mixed results. Amabile *et al*[133] demonstrated that IMH on T2w-TSE at 4 d post STEMI was the strongest independent predictor of MACE at 1-year (HR 2.8) in a model including LVEF, ST-resolution and L-MVO. Husser *et al*[33] showed that only LVEF and IMH extent on T2w-TSE independently predicted MACE at 140 wk follow-up in a model containing LV volumes, AAR, IS and L-MVO. However IMH and MVO extent showed strong correlation (r = 0.95) and adding T2w imaging to a model containing LGE and cine imaging did not improve the predictive power for MACE, supporting a strong concordance of IMH and MVO. Eitel *et al*[125] demonstrated that IMH presence on T2w-TSE and LVEF < 53% were the only CMR independent predictors of MACE at 6 mo in a model with lone MVO. Carrick *et al*[74] recently demonstrated that IMH on T2* mapping was the strongest independent predictor of cardiac death and heart failure hospitalisation at 830 d follow-up. In their multivariate model, L-MVO was not a predictor suggesting that IMH reflects extreme microvascular injury.

ISCHAEMIC AAR AND MYOCARDIAL SALVAGE IN AMI

Background

Oedema is seen in acute cardiac inflammation. In STEMI, it signifies reversible myocardial injury in the ischaemic cascade. The area of oedematous myocardium defines the ischaemic AAR supplied by the occluded IRA[61,134].

CMR assessment of AAR and MSI in AMI

The T2 (transverse) relaxation time is increased by regional water content[135]. T2w-TSE sequences illustrate oedema as hyperintensity[134] and are currently the mainstay of CMR oedema imaging. Most commonly used is the black-blood T2-weighted short-tau inversion-recovery sequence (T2w-STIR). This uses two initial inversion pulses to null moving blood. This is followed by a third inversion pulse, which nulls tissues with short T1 times (fat) to provide high contrast between blood (nulled) and myocardium[134,136]. T2w imaging of myocardial oedema is well-validated in animal studies assessing myocardial water volume on histological assessment[137] and fluorescent microspheres[77]. T2w oedema assessment is well-validated with SPECT[138-140] and angiographic markers of AAR (BARI[141], APPROACHp[142] scoring). AAR on T2w can be assessed accurately for upto 1-wk post-PPCI unlike SPECT, which requires radionucleotide administration during coronary occlusion and has higher spatial resolution and thus ability to detect subendocardial injury[138].

However T2w-TSE imaging has inherent disadvantages that can compromise image quality and oedema detection. Upto 30% of datasets are non-analysable in studies[24,143,144]. New T2w sequences have been studied, with encouraging results (Figure 7).

The aim of prompt reperfusion is to limit IS by minimizing the conversion of reversibly injured myocardial cells (AAR) into necrotic, infarcted tissue (IS)[95,156]. Anterior STEMI typically results in larger IS due to the larger coronary bed supplied by the left anterior descending artery[14,80,82]. Hence a more accurate assessment of revascularisation strategies can be provided by adjusting IS for the AAR. The resulting myocardial salvage index (MSI) defines the proportion of reversibly injured tissue (AAR) that does not progress to infarction (IS, Equation 1, Figure 8). MSI is expressed as percentage of the initial AAR [0% is no salvage, 100% is complete salvage (aborted

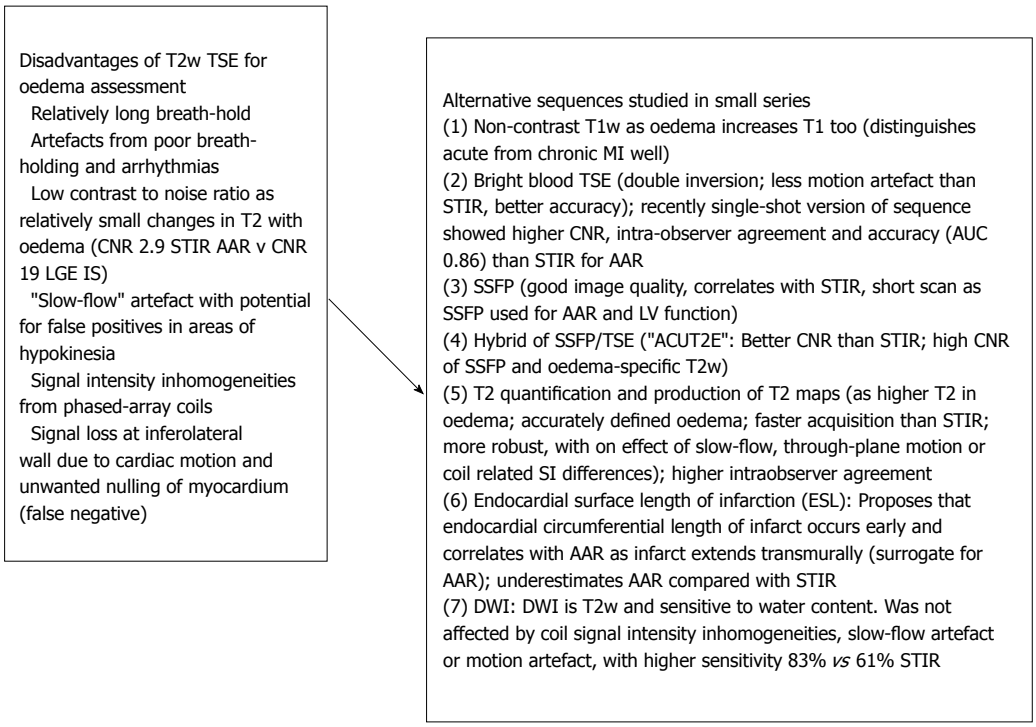

Figure 7 Alternative sequences to dark-blood T2-weighted turbo spin-echo for visualising oedema. Left: Inherent disadvantages of T2w-TSE[134,144-147]; Right: Sequences compared with T2w-TSE: (1)[145], (2)[141,142,144,148], (3)[149,150], (4)[144], (5)[151,152], (6)[153,154], (7)[155]. T2w-TSE: T2-weighted turbo spin-echo; DWI: Diffusion-weighted imaging; AAR: Area at risk.

STEMI)][157].

Equation 1: Myocardial salvage index (MSI, %) = 100 × [(AAR-IS)/(AAR)].

Desch showed excellent intraobserver and inter-observer agreement for MSI assessment using T2w-STIR and LGE (coefficients of variation approximately 5.0%) and excellent test-retest reproducibility in a study of 20 acute STEMI patients[158].

Other determinants of AAR include TTR[91,130,159-162], extent of collateralised IRA territory flow[5,80,159,163], TIMI-flow pre PPCI, LAD IRA and diabetes[91].

Studies of the chronology of oedema suggest that it occurs very early in the ischaemic cascade. Abdel-Aty confirmed the presence of transmural oedema in canines on *in-vivo* T2w imaging at 28 min post LAD occlusion at which point LGE and troponin release were absent, indicating reversible injury[164]. Fernández-Jiménez *et al*[165] however recently demonstrated a bimodal pattern of AAR extent in pigs with T2-mapping CMR and histological water quantification. They showed peak values at 2 h thought to be a direct result of reperfusion, followed by a return to baseline at 2 d and then progressive increase towards peak values at 7 d, with the latter peak felt due to water replacement of cleared cellular debris. Studies of temporal changes in AAR and MSI in humans are summarised in Table 12. Correct timing of oedema imaging is crucial in accurate calculation of AAR and MSI.

The near-resolution of oedema by 6 mo[5,18,21,91,138] allows distinction between acute and chronic infarcts when combined with LGE imaging.

CMR MSI as a predictor of LV function and remodelling in AMI

Myocardial salvage is a strong univariate predictor of medium-term LV function[14,166,167] and adverse LV re-modelling post STEMI[14,27,91,161]. Multivariate analysis demonstrates mixed results. MSI independently predicted LV remodelling in the work of Mather[131] (Table 13). However MSI was not a predictor once IS was added into multivariate models in studies by Monmeneu[91] and Masci[14]. This, in conjunction with the correlation between MSI and IS, and AAR and IS[26] questions whether MSI and IS are truly independent of each other in predicting LV remodelling and prognosis post STEMI. It could be argued that since MSI adjusts IS for the extent of AAR, it may have less inherent variability than IS. Since up to 30% of AAR datasets have been deemed non-diagnostic in previous studies[24,143,144], this may impact on the robustness of MSI quantification whereas IS datasets are exceptionally rarely excluded based on image quality. It is not clear currently whether IS or MSI is the better measure of revascularisation success post PPCI.

Prognostic importance of CMR MSI in AMI

Historically, the prognostic value of MSI was demonstrated using SPECT. Ndrepapa first showed that MSI was the strongest independent predictor of 6-mo mortality[168]. MSI was an independent prognostic indicator in the medium term post STEMI in two studies. Although both studies were from the same patient cohort, they have both been

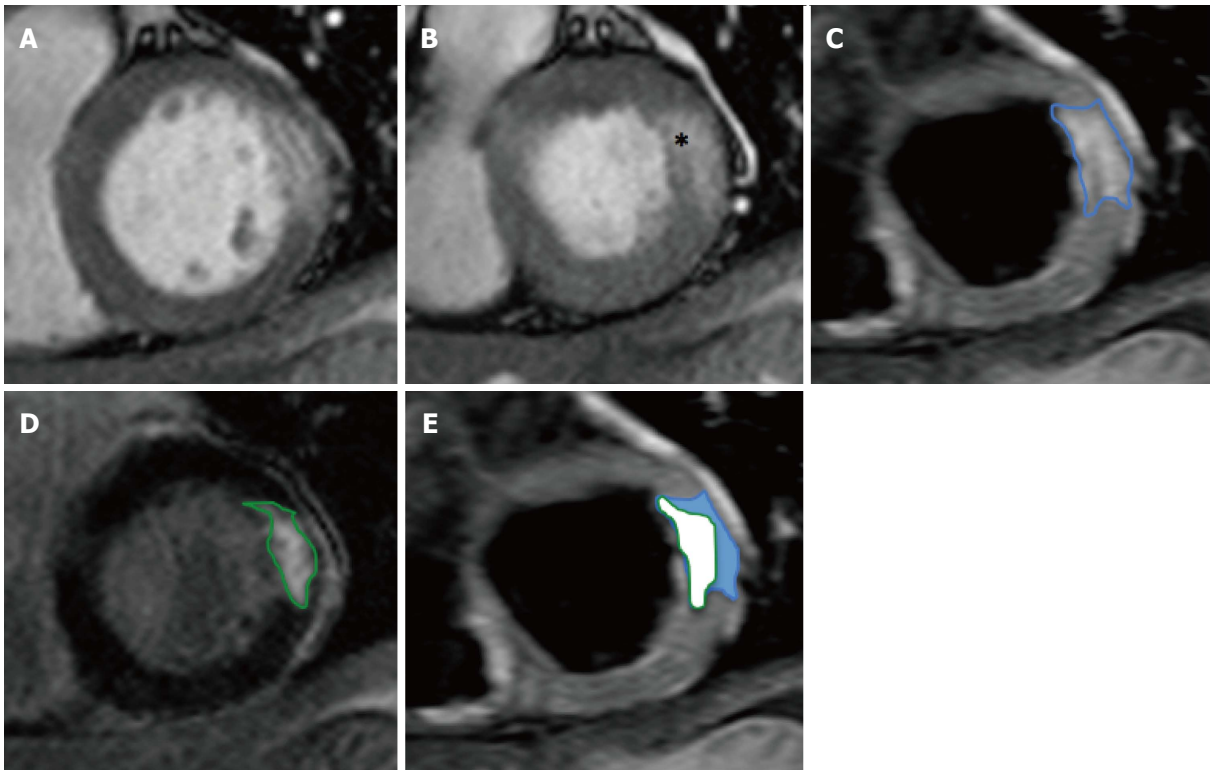

Figure 8 Calculation of salvaged myocardium. A: SSFP end-diastolic cine image; B: SSFP end-systolic cine image showing hypokinetic basal anterolateral segment (*); C: T2w-STIR image showing oedema (AAR) in anterolateral wall consistent with circumflex artery occlusion; D: Corresponding LGE image with near-transmural infarction; E: Calculation of salvaged myocardium in blue. SSFP: Steady-state free precession; T2w-STIR: T2-weighted short-tau inversion-recovery sequence; LGE: Late gadolinium enhancement.

Table 12 Temporal changes in cardiovascular magnetic resonance-derived area at risk and myocardial salvage index in acute myocardial infarction

Ref.	Year	*n*	CMR timepoints post STEMI	AAR, IS method	Main findings
Mather *et al*[18]	2011	48	2 d → 1 wk → 30 d → 3 mo	> 2SD STIR, > 2SD LGE	AAR reduction at successive timepoints, 1-3 mo (-75%). No change MSI at d2 or 1 wk as IS and AAR decreased proportionally
Dall'Armelina *et al*[21]	2011	30	2 d → 1 wk → 2 wk → 6 mo	> 2SD T2p-BB, > 2SD LGE	100% had oedema at d2. AAR stable over 1st week (37% *vs* 39% LVM). Decreased by 2 wk and nearly resolved at 6 mo
Carlsson *et al*[138]	2009	16	1 d → 1 wk → 6 wk → 6 mo	Manual STIR, and LGE	AAR at all timepoints. AAR stable in 1st week, correlated with 1 wk SPECT. Decrease by 1 mo (10% LVM), nearly gone by 6 mo
Ripa *et al*[5]	2007	58	2 d → 1 mo → 6 mo	Manual STIR and LGE	All had oedema at d2. AAR decreased at all time points. No data on MSI in this study

AAR: Area at risk; MSI: Myocardial salvage index; AAR, LGE method: SD: Standard deviations; STIR: T2-weighted short-tau inversion recovery imaging; T2p-SS-BB: T2-prepared single-shot bright-blood; 3T: 3.0 tesla field strength; IS: Infarct size.

included in Table 14 due to their differing primary findings.

T1, T2 AND T2* QUANTIFICATION AND MAPPING IN AMI

The current mainstay of LGE and T2w techniques for the detection of infarct and oedema rely on semi-quantitative threshold-based quantification methods using arbitrary SI cut-offs compared to user-defined regions of interest, automated algorithms or are based on manual planimetry. There is currently no consensus on the optimal quantification method for IS or AAR using these sequences. This can lead to subjectivity and dependence upon optimal nulling of normal myocardium and thus potential for error. In addition, commonly used T2w-TSE sequences suffer from non-diagnostic image quality in upto 30% of patients[24,143,144].

T1, T2 and T2* quantification present an exciting and complementary approach to LGE and T2w imaging. Developed by Messroghli *et al*[169] in 2003, their use in MI research has accelerated over the last 5 years. They allow not only the location and extent of infarction, oedema, MVO and IMH to be determined from subsequent parametric myocardial maps, but also the severity of these pathologies to be assessed through the magnitude

Table 13 Cardiovascular magnetic resonance studies showing the importance of myocardial salvage index on left ventricular function and remodelling in acute myocardial infarction

Ref.	Year	*n*	AAR, IS method	Main findings	CMR timepoint post STEMI	Follow-up
Mather *et al*[131]	2011	48	> 2SD STIR, > 2SD LGE	MSI was IP for LVR (OR 0.95) in model including LV volumes, LVEF, IS, IMH, MVO	2 d	3 mo
Monmeneu *et al*[91]	2012	118	> 2SD STIR, > 2SD LGE	MSI univariate predictor of LVR and final LVEF. However not IP of LVR in model with LVESVI, IS, no. transmural segs	6 d	6 mo
Masci *et al*[14]	2011	260	> 2SD STIR, > 5SD LGE	MSI strong univariate predictor of LVR and final LVEF. However not IP in model including IS, MVO	1 wk	4 mo
Masci *et al*[26]	2010	137	> 2SD STIR, > 5SD LGE	MSI strongest IP for LVR However IS and MSI (r = -0.72) and IS and AAR (r = 0.85) correlated	1 wk	4 mo

IS: Infarct size; IP: Independent predictor; LVR: Left ventricular remodelling; MVO: Microvascular obstruction; LVEF: Left ventricular ejection fraction; LVESVI: Left-ventricular end systolic volume index; STIR: T2-weighted short-tau inversion-recovery; LGE: Late gadolinium enhancement.

Table 14 Cardiovascular magnetic resonance studies illustrating the prognostic importance of myocardial salvage index in acute myocardial infarction

Ref.	Year	*n*	AAR, IS method	Main findings	CMR timepoint post STEMI	Follow-up
Eitel *et al*[34]	2011	208	> 2SD -STIR, > 5SD LGE	MSI was only CMR-based IP of mortality in model with age, IS, MVO, LVEF, TIMI- post PPCI, diabetes, age (IS not IP). MSI not IP of MACE (only IS, LVEF, age were)	3 d	19 mo
Eitel *et al*[161]	2010	208	> 2SD STIR, > 5SD LGE	MSI was only IP for MACE and mortality in model including LVEF, MVO, IS, ST-resolution and TIMI-grade post PCI	3 d	6 mo

IS: Infarct size; PCI: Percutaneous coronary intervention; MACE: Major adverse cardiovascular events; IP: Independent predictor; MVO: Microvascular obstruction; LVEF: Left ventricular ejection fraction.

of values obtained[170,171]. These methods are not reliant on reference regions of interest and do not suffer from T2w-TSE artefacts.

T1 mapping (longitudinal relaxation)

T1 relaxation curves allow calculation of the T1 time (time taken for recovery of 63% of longitudinal magnetization). The currently used curve-fitting sequences used include MOLLI (Modified Look-Locker Inversion Recovery), ShMOLLI (Shortened MOLLI), SASHA (SAturation recovery single-SHot Acquisition) and SAPPHIRE (SAturation Pulse Prepared Heart rate independent Inversion REcovery)[172]. Infarcted and oedematous myocardium demonstrate prolonged pre-contrast T1 values and reduced post-contrast T1 values compared with normal myocardium, allowing infarct visualisation and quantification[169,170,173,174]. Messroghli showed that this technique had high test-retest reproducibility[175], was stable within the range of heart rates commonly seen in clinical practice and showed comparable sensitivity for IS quantification compared with LGE[169,173,176]. T1 values within in the infarct core were recently shown to demonstrate a strong inverse correlation with L-MVO extent, incidence of LV remodelling and all-cause mortality at 2.5 years[177].

T2 mapping (transverse relaxation)

T2w images are generated using a T2-SSFP sequence with log-transformed curve-fitting T2 quantification, with different T2 preparation (TE) times. T2 mapping has shown excellent reproducibility and no effect of slow-flow, through-plane movement, SI loss, or effects of coil SI inhomogeneities[151,178]. T2 mapping accurately assessed oedema in 96% of patients (good image quality in 100%), whereas T2w-STIR detected oedema in only 67% of patients (15% non-diagnostic 15%)[151]. High observer agreement and close agreement between T1 (r^2 = 0.94) and T2 maps (r^2 = 0.96), and fluorescent microspheres for AAR detection was seen in canine myocardium[179].

T2 mapping (transverse relaxation in presence of field inhomogeneities)*

T2* mapping allows visualisation and quantification of IMH due to the presence of paramagnetic haemoglobin breakdown products. A cut-off value of < 20 ms has been used to define the presence of IMH[180]. Although the evidence base for T2* mapping in assessing IMH is currently limited, O'Regan demonstrated that it has greater sensitivity than T2w-STIR imaging (100% *vs* 90%) for IMH. Kali showed good correlation between *in-vivo* T2* and histological assessment of IMH and iron levels in canine myocardium[127,128]. T2* mapping may improve the specificity of IMH detected on CMR[131].

T1, T2 and T2* surrogate markers hold promise for improving the accuracy of detection of infarct, oedema and IMH respectively, and further improving statistical power of STEMI studies. However, due to the importance

Table 15 Cardiovascular magnetic resonance studies illustrating the prognostic importance of right ventricular infarction in acute myocardial infarction

Ref.	Year	*n*	RV LGE analysis method	Main findings	CMR timepoint post STEMI	Follow-up
Jensen *et al*[184]	2010	50	Manual	RVI only IP of MACE in model with age, sex, LVEF, LV IS	3 d	32 mo
Miszalski-Jamka *et al*[98]	2010	99	Manual	RVEF (HR 1.46) and RVI extent (HR 1.50) IP for MACE	"3-5 d"	1150 d
Grothoff *et al*[187]	2012	450	Manual	RVI was IP of MACE (HR 6.70)	"1-4 d"	20 mo

MACE: Major adverse cardiovascular events; IP: Independent predictor; HR: Hazard ratio; RV: Right ventricle; LVEF: Left ventricular ejection fraction; LGE: Late gadolinium enhancement; IS: Infarct size; RVI: Right ventricular infarction.

Table 16 Key studies illustrating the independent predictive value of cardiovascular magnetic resonance markers for left ventricular remodelling

CMR marker	Ref.	Year	*n*	CMR quantification	Main findings	Acute CMR time	Follow-up CMR time
IS	Husser *et al*[33]	2012	304	2SD	IS extent IP for LVR in model with LVEF, IS, LV volumes, MVO	6 d	189 d
IS	Monmeneu *et al*[91]	2012	118	2SD	Number of segments > 50% transmurality IP for LVR	6 d	6 mo
IS	Wu *et al*[94]	2008	122	Manual	IS extent at 2 d only IP for LVEF and LVR	2 d	4 mo
IS	Hombach *et al*[6]	2005	110	Manual	IS extent at 6 d was an IP for LVR in model with MVO, % transmurality	6 d	225 d
L-MVO	Weir *et al*[112]	2010	100	Manual	L-MVO extent was only IP of LVR in model with TIMI post PCI, E-MVO, IS	4 d	6 mo
L-MVO	Hombach *et al*[6]	2005	110	Manual	L-MVO extent IP of LVR in model with baseline IS, infarct transmurality	6 d	225 d
IMH	Carrick *et al*[74]	2016	245	T2*	IMH strongest IP of LVR in model with patient/angio characteristics, LVEDVI	3 d	7 mo
IMH	Husser *et al*[33]	2012	304	T2w-TSE	IMH strongest IP for LVR in model with LVEF, IS, LV volumes, L-MVO	6 d	189 d
MSI	Monmeneu *et al*[91]	2012	118	2SD LGR/ STIR	MSI univariate but not IP of LVR in model with IS, LVESVI, segments > 50%	6 d	6 mo
MSI	Masci *et al*[14]	2011	260	2SD STIR, 5SD LGE	MSI univariate predictor of LVR and final LVEF. However not IP of either	1 wk	4 mo
MSI	Masci *et al*[26]	2010	137	> SD STIR, 5SD LGE	MSI strongest IP for LVR. However IS and MSI and IS and AAR correlated	1 wk	4 mo
T1	Carrick *et al*[177]	2016	300	T1 map, 2SD STIR, 5SD LGE	Infarct core native T1 inverse relationship with LVR (OR 0.91 per -10 ms T1)	2 d	6 mo

Criteria: Individual studies with $n \geqslant 100$ and follow-up CMR $\geqslant$ 3 mo post-PPCI. IS: Infarct size; L-MVO: Late microvascular obstruction; IMH: Intramyocardial haemorrhage; MSI: Myocardial salvage index; SD: Standard deviations; STIR: T2-weighted short-tau inversion recovery; LGE: Late gadolinium enhancement; IP: Independent predictor; LV: Left ventricular; LVEF: Left ventricular ejection fraction; AAR: Area at risk; LVEDVI: Left ventricular end-diastolic volume; CMR: Cardiovascular magnetic resonance.

of protocol standardisation, these techniques are rarely used in multicentre studies at present.

RIGHT VENTRICULAR INVOLVEMENT IN AMI

CMR assessment of right ventricular infarction in AMI

CMR is the gold standard imaging modality for the assessment of right ventricular (RV) volumes, function, oedema[181] and infarction (RVI)[182]. CMR identifies RVI with greater sensitivity than echocardiography, ECG ($V4_R$ ST-segment elevation) and clinical examination[183,184] and demonstrates RV L-MVO[185,186]. There is good interobserver and intraobserver agreement for the identification of RV oedema ($\kappa = 0.62$, $\kappa = 0.62$, respectively) and very good agreement for RVI ($\kappa = 0.70$, $\kappa = 0.70$, respectively)[181]. The high MSI in RVI often > 90%[187,188] is thought to be due the relatively low RV nutrient needs, direct endocardial oxygen diffusion and good collateral blood supply[188,189].

Prognostic importance of CMR-derived right ventricular infarction in AMI

RVI confers adverse short-term prognosis, with a large meta-analysis (n = 7136) demonstrating that RVI on ECG, echocardiography or radionucleotide imaging predicted 30-d mortality and in-hospital MACE[190]. Shah demonstrated the prognostic importance of right ventricular infarction on imaging, where RVEF < 38% on radionucleotide ventriculography post STEMI was a strong independent predictor of 1-year mortality[191]. Right ventricular infarction is a strong independent predictor of medium to long-term prognosis in a small number of CMR

Table 17 Key studies illustrating the independent predictive value of cardiovascular magnetic resonance markers for prognosis

CMR marker	Ref.	Year	*n*	CMR quantification	Main findings	Acute CMR time	Follow-up
IS	Husser *et al*[96]	2013	250	> 2SD	Extent of transmural infarction was only IP for MACE	7 d	163 wk
IS	Izquierdo *et al*[97]	2013	440	> 2SD	IS was IP for arrhythmic cardiac events in model including LVEF, hypertension	7 d	123 wk
IS	Eitel *et al*[34]	2011	208	> 5SD	IS was IP of MACE in model with MVO, LVEF, MSI, Killip, TIMI flow post-PPCI	3 d	18.5 mo
IS	Larose *et al*[67]	2010	103	FWHM	IS strongest IP for MACE in model with LVEF, CK. LGE > 23% for MACE	4.5 h	2 yr
IS	Bodi *et al*[38]	2009	214	> 2SD	Extent of transmural infarction (no. of segments > 50% transmurality) IP for MACE	7 d	553 d
IS	Wu *et al*[99]	2008	122	Manual	IS only IP of 2 yr MACE in model containing LVEF, LVESVI (HR 1.06)	2 d	538 d
L-MVO	Regenfus *et al*[117]	2015	249	Manual	MVO extent strongest IP for MACE in model with IS, LVEF, TIMI and no. vessels	3.7 d	72 mo
L-MVO	Eitel *et al*[119]	2014	738	> 5SD	L-MVO > 1.4% LVM IP of MACE in model with LVEDVI, LVEF, clinical markers	7 d	6 mo
L-MVO	de Waha *et al*[120]	2012	438	Manual	L-MVO extent IP for MACE in model with IS, LV volumes. L-MVO/IS strongest IP	3 d	19 mo
L-MVO	de Waha *et al*[36]	2010	438	Manual	L-MVO strongest IP of MACE/mortality in model with IS, LVEF, STR, TIMI post	3 d	19 mo
L-MVO	Cochet *et al*[37]	2009	184	Manual	L-MVO strongest IP for MACE in model with GRACE, IS, LVEF. E-MVO weaker IP	"3-7 d"	12 mo
L-MVO	Bruder *et al*[116]	2008	143	Manual	L-MVO extent > 0.5% LV mass IP for MACE in model with IS, LVEF, age, DM, sex	4.5 d	12 mo
L-MVO	Hombach *et al*[6]	2005	110	Manual	L-MVO IP for MACE (P = 0.04) in model with LV end-diastolic volume and LVEF	6 d	268 d
IMH	Carrick *et al*[74]	2016	245	T2*	IMH strongest IP of CV death and HF. Multivariate model, L-MVO not predictor	3 d	830 d
IMH	Amabile *et al*[133]	2012	114	T2w-TSE	IMH presence was strongest predictor of MACE in model with MVO, LVEF, STR	4 d	12 mo
IMH	Husser *et al*[33]	2012	304	T2w-TSE	IMH IP for MACE in model with AAR, IS, L-MVO. T2w. No inc. value with LGE	6 d	140 wk
IMH	Eitel *et al*[125]	2011	346	T2w-TSE	IMH IP of MACE in model with L-MVO. T2w inc. value with LGE and cine	3 d	6 mo
MSI	Eitel *et al*[34]	2011	208	> 2SD/> 5SD	MSI only CMR IP of mortality in model with age, IS, MVO, LVEF, TIMI post, IS	3 d	19 mo
MSI	Eitel *et al*[161]	2010	208	> 2SD/> 5SD	MSI only IP for MACE/mortality in model with LVEF, MVO, IS, STR, TIMI post	3 d	6 mo
T1	Carrick *et al*[177]	2016	300	T1 map, > 2SD STIR, > 5SD	Infarct core T1 inverse association with risk of mortality and heart failure hospitalisation, in model with LVEF, infarct T2, IMH. Similar prognostic as L-MVO	2 d	2.5 yr

Criteria: Individual studies with $n \geqslant 100$ and follow-up CMR $\geqslant$ 6 mo follow-up. IS: Infarct size; L-MVO: Late microvascular obstruction; IMH: Intramyocardial haemorrhage; MSI: Myocardial salvage index; SD: Standard deviations; STIR: T2-weighted short-tau inversion recovery; LGE: Late gadolinium enhancement; IP: Independent predictor; LV: Left ventricular; LVEF: Left ventricular ejection fraction; AAR: Area at risk; LVEDVI: Left ventricular end-diastolic volume; CK: Creatine kinase; T2w-TSE: T2-weighted turbo spin echo; MACE: Major adverse cardiovascular events; CV: Cardiovascular.

studies (Table 15).

WHEN IS THE OPTIMAL TIME TO PERFORM CMR ASSESSMENT IN MI?

In acute STEMI, IS, AAR and MSI are best imaged at 7 d post PPCI due to overestimation of necrosis on LGE, and IS at 7 d best predicts final IS, LV remodelling and function and prognosis[5-7,9,18,20,21]. Human studies suggest that AAR is stable during the first week[21,138]. Although Fernández-Jiménez *et al*[165] demonstrated a bimodal AAR peak in pigs, their drop in AAR extent on T2w CMR at 2 d post-reperfusion may be due to a high incidence of IMH in pigs and peak IMH extent at 2 d[74]. Indeed the drop in AAR extent on the gold standard of histological water analysis in their study at 2 d was much less pronounced, and at 7 d AAR extent had returned to stable peak levels. In addition, studies demonstrating close agreement between T2w-derived AAR and the reference non-invasive modality of SPECT[138,139] were undertaken at 7 d post STEMI. MVO and IMH extent peak at 48 h then decrease[18] but are present at 7 d[9,18]. Although undertaking CMR at 7-d may potentially underestimate MVO and IMH extent[9,18,74], this may be minimised by expressing MVO and IMH extent as a proportion of IS rather than LV mass, to correct for the corresponding reduction in IS. Thus, acutely post STEMI for the assessment of IS, MSI, MVO and IMH, imaging at 7 d may provide the best compromise in relation to their

temporal changes[5-7,9,18,20,21] for accurate quantification and prediction of LV function, remodelling and prognosis. This needs to be balanced with contemporary clinical practice where patients are typically discharged at 3-4 d post-PPCI, and the risk of early attrition. Using final IS at follow-up as a primary outcome risks underestimating potential differences in treatment strategies due to greater infarct resorption with the larger infarcts.

Data on the chronology of IS suggests that infarct resorption is essentially complete by 3 mo post MI[9,18,20,74]. However a key objective of follow-up CMR is to assess LV geometry and remodelling and hence must allow the relatively slower adaptations of ventricular volumes (approximately 12 mo), compared with changes in IS and LVEF to complete. LVEF shows no significant change after 1-mo post STEMI. Follow-up CMR at 3 and 6-mo may fail to provide an accurate assessment of LV volumes and remodelling. The evidence base suggests that in order to allow completion of the trio of IS, LVEF *and* LV volumetric changes, follow-up CMR should be performed at 12-mo post STEMI[5,7,18,20,21]. When correlating CMR and clinical outcomes, the longer timepoint of 12-mo also permits more reliable clinical follow-up.

Standardisation of LGE, AAR and IMH sequences and quantification methods is equally important in light of newer T1, T2 and T2*-mapping sequences and inherent image quality issues associated with T2w-TSE.

CONCLUSION

Contrast-enhanced CMR offers robust, validated and reproducible surrogate markers, providing an accurate representation of pathophysiology, assessment of myocardial function and injury, and predictive value for medium to long-term LV function, remodelling and prognosis following PPCI for STEMI. Tables 16 and 17 summarise the key prospective studies illustrating the independent predictive value of CMR markers for LV remodelling (studies where $n > 100$, follow-up CMR $\geqslant$ 3 mo post PPCI) and prognosis (studies where $n > 100$, $\geqslant$ 6 mo follow-up) respectively.

In the acute phase, CMR can be performed accurately for up to 7 d post PPCI. CMR delivers no radiation to the patient and this makes it ideal for serial studies. The multimodal nature of CMR allows a multiparametric study of cardiac function, structure and volumes within a single study, which can be undertaken within approximately 45 min in the majority of patients. It is likely that CMR will become the mainstay of cardiac imaging, providing an important role in risk stratification and treatment post STEMI. Focus needs to be continued in translating findings on the prognostic importance of surrogate markers to development of therapeutic targets post STEMI.

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MINIREVIEWS

Aerobic *vs* anaerobic exercise training effects on the cardiovascular system

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Abstract

Physical exercise is one of the most effective methods to help prevent cardiovascular (CV) disease and to promote CV health. Aerobic and anaerobic exercises are two types of exercise that differ based on the intensity, interval and types of muscle fibers incorporated. In this article, we aim to further elaborate on these two categories of physical exercise and to help decipher which provides the most effective means of promoting CV health.

Key words: Cardiovascular; Exercise; Training; Aerobic; Anaerobic

Core tip: As the association between physical inactivity and the increased risk of cardiovascular morbidity solidified, further data and studies supported the advantages of exercise on physical well-being. Anaerobic and aerobic exercise have a favorable effect on lipid metabolism, anaerobic exercises have been shown to have a positive influence on the lipid profile.

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INTRODUCTION

More than 250000 yearly deaths in the United States are

attributed to cardiovascular (CV) disease resulting from a lack of physical activity. On the other hand, physical inactivity is estimated to cause 30% of ischemic heart disease[1]. The association between physical inactivity and CV disease gained a foothold in the medical community in 1996, when the American Heart Association (AHA) published information advocating the benefit of physical exercise in regards to improvements in hemodynamic, hormonal, metabolic, neurological and respiratory function[2]. As the association between physical inactivity and the increased risk of CV morbidity solidified, further data and studies supported the advantages of exercise on physical well-being. The 2010 recommendations by the World Health Organization (WHO) provided activity recommendations based on three different age groups: Ages 5-17, 18-64, and > 64 years of age. In the age group of 5-17 years, individuals should accrue at least 60 min of moderate activity daily. Those in the group of 18-64 years should perform at least 150 min of moderate activity or at least 75 min of vigorous activity throughout the week. Finally, individuals above the age of 65 years are recommended similar length and intensity exercise programs as the prior group, but with a focus on activities to help enhance balance and to prevent falls[3].

The inherent advantages of physical exercise stem from an increase in the cardiac output and an enhancement of the innate ability of muscles to extract and to utilize oxygen from the blood. This benefit is further compounded by the benefit physical exercise has on high-density lipoprotein cholesterol (HDL-C)[4], adipose tissue distribution[5], increased insulin sensitivity[6], improved cognitive function[7], enhanced response to psychosocial stressors[8], as well as determent of depression[9]. With the benefit of physical exercise well established, the question remains which type of exercise provides the most effective and efficient means to help deter CV disease.

A recent meta-analysis published showed a decrease in the risk of all CV outcomes and diabetes mellitus incidence with increasing levels of physical activities[10]. Another meta-analysis suggested that high level of leisure time physical activity had a beneficial effect on CV health by reducing the overall risk of incident CHD and stroke among men and women by 20% to 30%, while moderate level of occupational physical activity might reduce 10% to 20% risk of CVD[11].

Furthermore, cardiac rehabilitation, which is physical exercise based, is a promising field which showed a favorable outcome among patients with heart failure and post-CVD events[12,13].

AEROBIC EXERCISE

The American College of Sports Medicine (ACSM) defines aerobic exercise as any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature[10]. As the name implies, muscle groups activated by this type of exercise rely on aerobic metabolism to extract energy in the form of adenosine triphosphate (ATP) from amino acids, carbohydrates and fatty acids. Examples of aerobic exercise include cycling, dancing, hiking, jogging/long distance running, swimming and walking. These activities can best be accessed *via* the aerobic capacity, which is defined by the ACSM as the product of the capacity of the cardiorespiratory system to supply oxygen and the capacity of the skeletal muscles to utilize oxygen[14]. The criterion measure for aerobic capacity is the peak oxygen consumption (VO_2), which can be measured either through graded exercise ergometry or treadmill protocols with an oxygen consumption analyzer or *via* mathematical formulas. The value of peak VO_2 can be appreciated by a study performed by Vaitkevicius *et al*[15], in which the VO_{2max} was calculated along with other dimensions, to conclude that higher physical conditioning status was directly correlated with reduced arterial stiffness.

Various studies have been published that prove the advantages of aerobic exercise in reversing and preventing CV disease. In 2002, Wisløff *et al*[16] were the first to show the benefit of aerobic training in the myocardium after an ischemic event. Their study was performed on adult female Sprague-Dawley rats, which were placed into groups categorized based on induced myocardial infarctions (MI) with and without exercise and controls with and without exercise. Their results showed a 15% reduction in the left ventricle (LV) hypertrophy post-infarction, as well as 12% and 20% decreases in myocyte length and width, respectively, with aerobic exercise. Furthermore, a 60% improvement was noted in myocardial contractility in subjects with a MI who were assigned to the training group, suggesting enhanced myocardial Ca^{2+} sensitivity. They were able to conclude the beneficial effects of aerobic training on cardiac remodeling and myocardial contractility[16].

The effect of aerobic exercise were confirmed in human subjects when Wisløff *et al*[17] published another study five years later, which incorporated human subjects with post-MI heart failure. Subjects were enrolled in aerobic interval training (AIT), moderate continuous training (MCT) or a control group. The AIT group showed a 46% increase in peak VO_2, which correlated with a 60% increase in the maximal rate of Ca^{2+} reuptake in the sarcoplasmic reticulum in the skeletal muscles. Additionally, cardiac remodeling was evident in humans, much like the rat subjects in the previous study, as LV diameters declined and LV volumes increased in both the diastolic and systolic phases. Moreover, systolic function was noted to increase by 35% in the AIT group[17], thereby further strengthening the advantages of aerobic exercise.

Furthermore, aerobic exercise has been shown to have a positive impact on other dimensions of CV health. Several studies have shown that aerobic exercise improves the lipid profile, particularly increasing the HDL-C[18]. In an Australian study, aerobic exercise led to a small but statistically significant reduction in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) ranging in a span of 0.08 mmol/L to 0.10 mmol/L. They also showed an increase in HDL-C with their aerobic exercise program of about 0.05 mmol/

L[19]. Similar results have been documented in children and adolescents, as well[20]. In a meta-analysis conducted by Kelley *et al*[21], it was concluded that aerobic exercises contributed to a statistically significant 9% increase in HDL-C and an 11% decline in TG, but no statistically significant changes in TC and LDL-C.

A positive correlation between biochemical signal markers, such as endothelin-I (ET-1) and aerobic exercise was recently speculated by several studies. Vascular endothelial cells produce ET-1, which functions as a vasoconstrictor[22] and promoter of atherosclerosis[23]. Maeda *et al*[24] were able to demonstrate a statistically significant positive linear correlation of increasing age with rising levels of ET-1. They were also able to exhibit a visible reduction in ET-1 levels after a 3 mo aerobic exercise regimen[24].

While aerobic exercise appears to have some beneficial effects, its contribution is limited on frequency and quantity. A very recent publication by a Danish group was able to represent what they called a "U shaped association" between aerobic exercise and mortality. Their research quantified 1 to 2.4 h of exercise over 2 to 3 times per week as the optimal quantity and frequency standard of aerobic exercise to promote improved health. Interestingly, they quantified any amount above that standard as being indifferent to the mortality risk, as that of sedentary individuals[25].

ANAEROBIC EXERCISE

Anaerobic exercise has been defined by the ACSM as intense physical activity of very short duration, fueled by the energy sources within the contracting muscles and independent of the use of inhaled oxygen as an energy source[14]. Without the use of oxygen, our cells revert to the formation of ATP *via* glycolysis and fermentation. This process produces significantly less ATP than its aerobic counterpart and leads to the build-up of lactic acid. Exercises typically thought of as anaerobic consist of fast twitch muscles and include sprinting, high-intensity interval training (HIIT), power-lifting, *etc*. Sustained anaerobic metabolism, in other words, anaerobic exercise, causes a sustained increase in lactate and metabolic acidosis and this transition point is referred to anaerobic threshold (AT)[26]. AT can be directly measured *via* frequent blood samples measuring the blood lactate level during a graded-exercise regimen. Once the blood lactate values are plotted, the point at which the curve makes a sudden sharp incline represents the AT. Other methods include portal lactate analyzers and mathematical formulas involving heart rate (HR).

Similar to aerobic exercise, anaerobic exercise may exert a potentially beneficial influence on the CV system. In a Turkish study completed by Akseki Temür *et al*[27], the effects of anaerobic exercise were evaluated with a member of the natriuretic peptide family, known as C-type natriuretic peptide (CNP). CNP is synthesized by the endothelium and offers a protective effect through its effects on the vascular tone of blood vessels, as well as exerting antifibrotic and antiproliferative properties. It produces a hyperpolarization effect on the smooth muscle layer of blood vessels, which causes vasodilatation[28]. CNP has also been reported to exert its nonproliferative effects on cardiac fibroblasts to help prevent cardiac aging through LV fibrosis *via* the cyclic guanosine monophosphate (cGMP) pathway[29]. In this study, twelve healthy young male subjects were divided into two groups based on their previous history of exercise. Once categorized into groups, the subjects were asked to participate in a thirty second high intensity exercise program, which encompassed the anaerobic exercise factor. Blood samples were obtained from the subjects before exercise and then one minute, five minutes and thirty minutes after exercise and were tested for the levels of aminoterminal proCNP (NT-proCNP), a biologically inactive peptide of CNP. The results showed a statistically significant increase of NT-proCNP level in the five minute mark post-exercise in the physically active group after anaerobic exercise.

Similar to aerobic exercise and their favorable effect on lipid metabolism, anaerobic exercises have been shown to have a positive influence on the lipid profile. A small European study composed of 16 obese subjects was able to show the increased benefits of an aerobic workout followed by anaerobic training, as compared to aerobic training alone. Subjects who underwent core training with both aerobic and anaerobic exercises showed a larger reduction in non-esterified fatty acids. The same group was also found to have the greatest reduction in their body mass index (BMI)[30].

There are speculations about disadvantages of such an exercise program. One such shortcoming was brought to light by an Iranian study published by Manshouri *et al*[31], which concluded that anaerobic training led to a significant reduction in human growth hormone (HGH). It has long been theorized that long-standing HGH deficiencies can attribute to CV morbidity and mortality through the development of premature arthrosclerosis. HGH deficiency has been shown to result in higher BMI and TG, lower concentrations of HDL-C, as well as the development of hypertension (HTN)[32]. Furthermore, cardiac structure is affected in HGH deficient subjects, as manifested by reduced LV posterior wall thickness, smaller LV mass index and compromised LV ejection fraction (LVEF)[33]. The exact mechanism of action for such changes remains to be determined.

CONCLUSION

With the high incidence of CV disease worldwide, it is an irrefutable notion that exercise helps deter CV morbidity and mortality. Both aerobic and anaerobic exercises have unique and collective positive correlations towards improved CV health. Despite all the research, further studies are still warranted to delve further into the impact that both aerobic and anaerobic exercise may have on human physiology to unequivocally determine if there is superiority of one type of exercise over

another.

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MINIREVIEWS

Left atrial appendage occlusion: A better alternative to anticoagulation?

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Abstract

Non-valvular atrial fibrillation is associated with a significantly increased risk of embolic stroke due to blood clot forming predominantly in the left atrial appendage (LAA). Preventive measures to avoid embolic events are permanent administration of anticoagulants or surgical closure of the LAA. Various clinical trials provide evidence about safety, effectiveness and therapeutic success of LAA occlusion using various cardiac occluder devices. The use of such implants for interventional closure of the LAA is likely to become a valuable alternative for stroke prevention, especially in patients with contraindication for oral anticoagulation as safety, clinical benefit and cost-effectiveness of LAA occlusion has recently been demonstrated.

Key words: Left atrial appendage; Thrombus; Occlude; Stroke

Core tip: Non-valvular atrial fibrillation is associated with increased risk of embolic stroke. To date, risk-based anticoagulation is the cornerstore to avoid this. However, several patients have got absolute or relative contraindication to this and thus are undertreated. For these patient population the implantation of a local left atrial appendage occluder might be an alternative.

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INTRODUCTION

The left atrial appendage (LAA) is an external protrusion of the left atrium located next to the pulmonary trunk[1,2]. Compelling evidence points to the LAA as the primary origin of thrombus formation particular in the presence of non-valvular atrial fibrillation (AF); since the major risk of non-valvular AF to suffer from ischemic stroke,

the LAA has drawn much attention in the context of stroke prevention[3-5] considering missing awareness and unrecognized AF prior to strokes[6]. Thus, the current approach for stroke prevention in patients with non-valvular AF of risk-adjusted prevention *via* oral anticoagulants (OAC) or antiplatelet agents[7,8] may be challenged by elective LAA occlusion in selective patients[3,4,9-12]. In the past, physical LAA closure required either surgical excision or exclusion by suture or stapler[10,13]. With the introduction of cardiac occluder devices open surgery is not required any more and redundant for this purpose[14-16]. This review summarizes current knowledge of LAA occlusion as an emerging alternative to chronic OAC therapy for non-valvular AF patients at risk for embolic strokes.

ANATOMY OF THE LAA

The function of the LAA is not fully understood but it has been linked to secretion of the hormone "atrial natriuretic factor" (ANF) and, hence, could be involved in the regulation and homoeostatic control of water, salt and fat[17,18]. Regardless, the anatomy of the LAA is highly diverse and was classified into four different morphological types; "chicken wing" was the most frequently identified type (48%) followed by "cactus" (30%), "windsock" (19%), and "cauliflower" (3%)[19]. The "chicken wing" type has a dominant lobe, which may have secondary lobes or twigs, and is bent in the proximal or middle part or even folds back on itself at some distance from the orifice. The "cactus" type has a dominant central lobe with secondary lobes extending in both superior and inferior directions, whereas the primary structure of the "windsock" type is a dominant lobe with variation in the location and number of secondary or even tertiary lobes. Lastly, the "cauliflower" type has a short overall length with more complex internal characteristics, lacks a dominant lobe but has variable number of lobes and a more irregular shape of the LAA orifice. Previous studies indicate that the "chicken wing" type poses the lowest risk for embolism in contrast to the "cauliflower" type, which, notably, exhibits the highest degree of structural complexity[20]. However, due to the complex anatomy of the LAA, it is difficult to correctly assess length, branches and courses, as well as thrombus formation by transesophageal echocardiography (TEE) and it was demonstrated that the outcome of this visualization is dependent on the selection of the imaging plane[21].

LIMITATIONS OF ORAL ANTICOAGULANT THERAPY

The current gold standard for stroke prevention in patients with non-valvular AF is the oral administration of anticoagulants to reduce the risk of thrombus formation and prevent any embolic events[7,8]. Chronic anticoagulation is carried out by traditional and novel oral anticoagulants (NOACs) also called directly acting oral anticoagulants (DOACs). Traditional anticoagulants include heparins and coumarins (vitamin K antagonists) of which warfarin is the most common. NOACs are inhibitors of coagulation factors such as factors Ⅱa (*e.g.*, dabigatran) or factor Ⅹa (*e.g.*, rivaroxaban, apixaban and edoxaban)[22-25]. However, chronic OAC therapy is not recommended if contraindications are present or potential interference with other therapies. Moreover, difficulties to adjust treatment, dietary restriction, low compliance or even refusal of the patient to follow treatment protocol are considered contraindication for OAC[10,22-26]. Therefore, alternative strategies for stroke prevention in patients with AF are required.

APPROACHES FOR CLOSURE OF THE LAA

There are two fundamental approaches beyond anticoagulation to avoid emboli in patients with non-valvular AF, *e.g.*, surgical excision of the LAA or exclusion by suture line, stapler or cardiac plug[10,13]. Before introduction of cardiac occluder for LAA closure, surgical excision was the superior method while LAA closure requires either suture line[10,13]. However, a surgical excision is not risk free and may cause bleeding[27]. Nonetheless, surgical excision is still an option mostly in conjunction with other cardiac surgery[10,27]. In recent years, an alternative approach for LAA closure was established by sealing the orifice of the LAA with an occluder. Such a LAA occlusion was performed 2001 for the very first time using the PLAATO system which has been taken off market[28,29]. The current generation of occluders are the Amplatzer™ Cardiac Plug (ACP), Amplatzer Amulet™ from St. Jude Medical and the Watchman™ device from Boston Scientific[29,30]. In addition, a small number of novel devices have been mentioned and applied in the last few years such as the WaveCrest™ device and the Lariat™ device[31,32] (Table 1). The ACP-originally used for closure of atrial septal defects[33] - consists of a self-expanding flexible nitinol mesh with a distal lobe filled with polyester and is equipped with fixation barbs to adhere of the LAA. The distal lobe is connected *via* a small waist to a proximal disc sealing the orifice of the LAA[34]. Similar to the ACP, the Watchman™ device consists of a self-expanding nitinol mesh with fixation barbs and a polyester coating covering the surface facing the left atrium[35].

Implantation of both Watchman™ device and ACP can be performed under local anesthesia and is introduced *via* catheter through the femoral vein by transseptal passage[33,36-39]. TEE guiding or intracardiac echocardiography (ICE) during implantation procedure is used to rule out intracardiac thrombus and to facilitate transseptal puncture. After transseptal puncture heparin is administered to achieve an active clotting time of > 250 s. The LAA is fluoroscopically illustrated in at least 2 standard angulations (RAO 30°, RAO 30°/10° caudal) and sized by

Table 1 Different endocardial left atrial appendage occlusion devices[31]

Device name	Company	Design
PLAATO	Appriva Medical Inc.	Single-lobe occluder; nitinol cage; ePTFE membrane hooks
WATCHMAN	Boston Scientific	Single-lobe occluder;nitinol frame; PET membrane; hooks
ACP	St. Jude Medical	Lobe and disc (polyester mesh); nitinol mesh structure; stabilizing wires
Amulet	St. Jude Medical	Lobe and disk (polyester mesh in both); nitinol mesh structure; stabilizing wires
WaveCrest	Coherex Medical	Single-lobe occluder; nitinol frame, polyurethane foam and ePTFE membrane; retractable anchors
Occlutech LAA	Occlutech	Single-lobe occluder; nitinol wire mesh; stabilizing loops; nanomaterial covering
Sideris Patch	Custom Medical Devices	Frameless detachable latex balloon covered with polyurethane
Lambre	Lifetech	Lobe and disk; nitinol; PET membrane; distal barbs anchors
Pfm	PFM Medical	Dual disk (distal anchor, variable middle connector, proximal disk); nitinol frame
Ultrasept	Cardia	Lobe and disk; nitinol frame; Ivalon covering; distal anchors

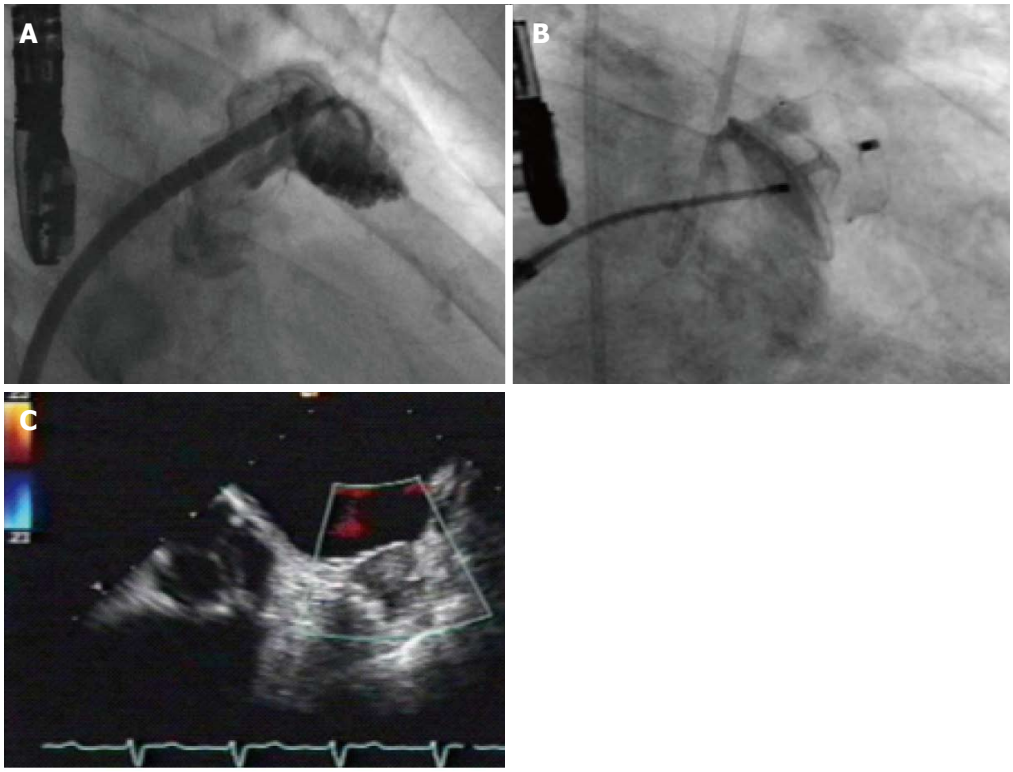

Figure 1 Measurement of left atrial appendage (A), implantation of an Amulet device (B) and postinterventional transesophageal echocardiogram revealing good sealing without any leak (C).

TEE measurements and cine angiography. Device size will be chosen according to manufacturer's recommendations 20% larger than the landing zone (measured from left circumflex coronary artery to the ridge delineating the LAA from the left upper pulmonary vein). Optimally, the device should not protrude more than 5 mm beyond the LAA ostium and should cover the entire ostium with no or minimal (less than 5 mm by colour Doppler) residual flow and a compression grade of 8%-30%. After device releasing and sheath removal the puncture site is dealed with a Z-suture or with a pressure band. Periprocedural anticoagulation is managed by heparine or bivalirudine[14,28,33] (Figure 1). The implanted device becomes initially coated by fibrin and subsequently covered by endothelial cells forming an endocardial lining, which consequently excludes the LAA from circulating blood[40]. In order to allow the process of endothelialization patients have to take warfarin after the intervention for at least 45 d. Warfarin is then replaced by clopidogrel and aspirin for half a year, while aspirin administration is continued life-long[15]. According to newer data a dual antiplatelet therapy is more efficacious than the use of anticoagulants[37,41,42]. In addition to the general risks of catheter-based interventions including air or blood embolism, an incomplete closure of the orifice, pericardial perforation, dislodgement of the implant or the formation of blood clots on the surface of the device leading to prolonged OAC treatment may occur[14,28,33,43]. Finally, since ANF is secreted in the LAA, the LAA closure could interfere with thirst regulation and water retention in the patient, but this theoretical concept has been scarcely investigated so far[17,18].

STATUS QUO OF LAA OCCLUSION

For several years great effort has been devoted to the use of cardiac plugs in the prevention of AF-related

strokes. A number of studies have been published about the PLAATO system including a five-year follow-up study[28,44]. In addition to the PLAATO system, the ACP system which has been used for closure of atrial septal defects for more than 20 years and its features, design and applicability are very well studied and has been reported to be successful for LAA closure[33,34]. It is worth mentioning that a large randomized clinical trial to study the ACP for LAA occlusion was recently halted, probably due to the approval of a competitive product (*i.e.*, Watchman device) by the United States Food and Drug Administration (FDA)[45]. The successful use of the Watchman device for LAA occlusion has been shown in two large, prospective randomized clinical trials-the PROTECT-AF and the PREVAIL study-in which this implant was compared to chronic OAC therapy using warfarin[14,15]. Over five years, the PROTECT-AF study examined about 800 patients, of which 463 had received a Watchman™ device and 244 were left on warfarin[14] and demonstrated that the implant is non-inferior to OAC therapy in patients with non-valvular AF being eligible for OAC. In comparison to the OAC treatment group, the incidence of an embolic event was reduced by approximately 30% in the implant group; the overall mortality showed a reduction of the same magnitude. While the per-protocol analysis was in favor of LAA occlusion, the intention-to-treat results were neutral. Furthermore, the safety data also favored warfarin over LAA occlusion, but this was explained by the learning curve phenomenon. The highest risk from LAA occlusion arises from complications associated with the one-time interventional treatment, while the risks from chronic OAC therapy accumulates during time especially with increasing age of the patient. Recently, a 45-mo follow-up of the PROTECT-AF study demonstrated that LAA occlusion is not only as efficient as warfarin treatment but even superior in term of stroke and cardiovascular mortality[46]. Further, the safety data showed a considerable reduction in the risk for complications during intervention, likely due to increasing experience of the surgeons. However, the FDA criticized the patient selection and raised questions about the safety of LAA occlusion[47]. To address these limitations, a confirmatory randomized trial (PRE-VAIL) comparing LAA occlusion with the Watchman device to warfarin, which mandated inclusion of new operators, slight modifications in inclusion criteria, and elimination of clopidogrel 7 d before implant. In PREVAIL more than 400 patients were randomized to either warfarin (n = 138) or occluder device (n = 269)[15]. This study showed that LAA occlusion achieved non-inferiority in stroke prevention compared to warfarin; the difference between both groups was low and not significant. Most importantly, the number of early safety events (*e.g.*, pericardial effusions) was significantly reduced compared to the PROTECT-AF study and, hence, satisfied the predefined goal. Therefore, the PREVAIL study addressed the concerns rose by the FDA and demonstrated the safety of this intervention for LAA occlusion[15]. As a result of this study the Watchman ™ device was approved by the FDA in 2015[48]. Results from the real-world EWOLUTION registry consisting of 1021 patients being implanted with the Watchman device revealed a procedural success rate of 98.5%[49]. During 30-d follow-up 28 subjects experienced serious adverse events with an overall 30-d mortality rate of 0.7%. Serious procedure related complication rates, defined as stroke, pericardial effusion, device embolism and death, were present in 8.7% in PROTECT-AF, 4.1% in CAP registry, 4.2% in PREVAIL and 2.7% in EWOLUTION. However, the average CHADS2 score of 2.8 and CHA2DS2-VASc score of 4.5 in EWOLUTION indicate a relatively higher risk of stroke than either the PROTECT AF (average CHADS2 of 2.2 and CHA2DS2-VASc of 3.4) or PREVAIL (CHADS2 score of 2. 6 and CHA2DS2-VASc of 4.0) studies. In addition, 40% of EWOLUTION subjects had a HAS-BLED score of $\geqslant$ 3, compared with only 20% of PROTECT AF subjects and 30% of PREVAIL subjects (Table 2). Similar results were obtained in a registry with the ACP device[50] and a large meta-analysis[51] including 2406 patients from the PROTECT AF, PREVAIL, CAP I and CAP II registries with a mean follow-up of 2.69 years. Patients receiving LAA occlusion with the Watchman device had significantly fewer hemorrhagic strokes [0.15 *vs* 0.96 events/100 patient-years (PY); hazard ratio (HR): 0.22; $P < 0.004$], cardiovascular/unexplained death (1.1 *vs* 2.3 events/100 PY; HR: 0.48; $P < 0.006$), and nonprocedural bleeding (6.0% *vs* 11.3%; HR: 0.51; $P < 0.006$) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 *vs* 1.87 events/100 PY; HR: 1.02; 95%CI: 0.62 to 1.7; $P = 0.94$). There were more ischemic strokes in the device group (1.6 *vs* 0.9 and 0.2 *vs* 1.0 events/100 PY; HR: 1.95 and 0.22, respectively; $P = 0.05$ and 0.004, respectively)[51].

COST-EFFECTIVENESS

An analysis of Panikker *et al*[16] on 110 patients being suitable and unsuitable for long-term OAC and outcome analysis from the PROTECT-AF trial and registry study compared warfarin, dabigatran, rivaroxaban, apıxaban, aspirin and no treatment using a network meta-analysis. They revealed that stroke and bleeding rates were significantly lower than PROTECT-AF results. Additionally, LAA occlusion achieved cost parity between 4.9 years *vs* dabigatran 110 mg and 8.4 years *vs* warfarin and at 10 years, occlusion was cost-saving against all therapies. Similarly, another analysis evaluated the cost effectiveness in patients suffering from AF and absolute contraindication for OAC[52]. For this purpose the ASAP study evaluating the Watchman device, the ACTIVE-A trial evaluating aspirin and clopidogrel and the AVERROES trial evaluating apixaban were compared in a cost-effectiveness analysis. At 5 years, LAA occlusion was cost effective compared with aspirin with an incremental cost-effectiveness ratio of 16971 Euro. As compared with apixaban, it was also cost-effective at 7 years with an incremental cost-effectiveness ratio of 9040 Euro. Apart

Table 2 Summary of data for left atrial appendage occlusion

	PROTECT-AF[46]	CAP[43]	ASAP[42]	EWOLUTION[49]	ACP[50]
Patients (*n*)	463	460	150	1021	1047
Follow-up	4 yr	16 mo	14 mo	30 d	13 mo
CHADS-score	2.2	2.4	2.8	2.8	n.a.
CHA2DS2-Vasc score	n.a.	n.a.	4.4	4.5	4.5
Procedural success	88.00%	95.00%	94.70%	98.50%	97.30%
Procedural stroke	1.30%	0	0.70%	n.a.	0.90%
Pericardial effusion	4.80%	2.20%	1.30%	0.50%	1.20%
Device embolization	0.60%	0	1.30%	0.20%	n.a.
Major bleeding	3.50%	n.a.	n.a.	1.60%	1.50%
Long-term stroke	2.30%	1.50%	0.70%	0.30%	2.30%

AF: Atrial fibrillation; n.a.: Not applicable.

Table 3 Different aspects of left atrial appendage occlusio

Pro	Contra
Non-inferiority to oral anticoagulation	Evaluation of other atherothrombotic sources
Alternative in patients with contraindication for anticoagulation	Unknown hemodynamic impact
Cost-effective	Postprocedural medical treatment not well defined
Reduced cumulative bleeding events during follow-up	No comparison between different devices
Good results in real-world registries	Undefined impact of residual leaks

from the population having an absolute contraindication for OAC similar analysis were performed for patient being eligible for OAC, where LAA occlusion was cost-effective at 7 years and novel oral anticoagulation was cost-effective at 16 years. However, LAA occlusion was superior to novel oral anticoagulation by year 5 and to warfarin by year 10 with respect to cost-effectiveness and cost saving for stroke prevention[53].

FUTURE CONSIDERATIONS

In 2012, the European Society of Cardiology (ESC) released a focused update of the guidelines for the management of AF[8]. Interestingly, the ESC also commented on LAA occlusion for prevention of stroke (class Ⅱb recommendation, level of evidence B). Due to insufficient amount of data demonstrating efficacy and safety, the ESC did not recommend an LAA occlusion at this point as a routinely alternative therapy to replace chronic OAC therapy in order to reduce AF-related stroke risk, but recommended to consider this approach for patients with an increased for stroke and contraindications for OAC treatment[8]. However, the references cited as evidence for the recommendation are the PROTECT AF study and the CAP registry. Importantly, neither of these studies included patients who had contraindications to long-term anticoagulation, and both enrolled a majority of patients with relatively low estimated stroke risk. A growing body of evidence suggests that LAA occlusion with the Watchman™ device is an important alternative for OAC therapy using warfarin, yet, a perspective randomized study comparing LAA occlusion to the NOAC is still missing and therefore a final conclusion about the general applicability of LAA occlusion using the Watchman implant cannot be drawn at this point[49,50,54]. Additionally, there are not enough data analyzing different patient cohorts (*e.g.*, sex, age, race, renal insufficiency) as there are data revealing a direct correlation between elevated adiponectin levels and the degree of left atrial blood stasis in men but not in women, and there are more extensive left atrial remodeling and deterioration in LAA function in women than in men[55-57]. There are some subanalyses revealing higher bleeding events in patients older than 75 years after LAA Occluder implantations compared to younger ones (4.4% *vs* 1.4%), as well as in males as compared to females (3.0% *vs* 1.8%)[58]. In accordance with the latest recommendations from the ESC, LAA occlusion should definitely be considered if complications with OAC therapy arise or a high bleeding risk exist, regardless if the patient is treated with traditional or novel anticoagulants. This therapeutic approach is even more justified if the patient undergoing chronic OAC therapy suffers a stroke. Under this circumstance and under the light of recent studies about the safety and efficacy of LAA occlusion, this interventional treatment could be a better choice and advisable for this with a CHA2DS2Vasc Score ⩾ 2 (Table 3). Summing up the current data, LAA occlusion is a very promising treatment to prevent AF-related strokes due to its safety, cost-effectiveness and therapeutic success.

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MINIREVIEWS

Clinical cardiac regenerative studies in children

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Abstract

Although the incidence of pediatric heart failure is low, the mortality is relatively high, with severe clinical symptoms requiring repeated hospitalization or intensive care treatment in the surviving patients. Cardiac biopsy specimens have revealed a higher number of resident human cardiac progenitor cells, with greater proliferation and differentiation capacity, in the neonatal period as compared with adults, demonstrating the regeneration potential of the young heart, with rising interest in cardiac regeneration therapy in critically ill pediatric patients. We review here the available literature data, searching the MEDLINE, Google Scholar and EMBASE database for completed, and www.clinicaltrials.gov homepage for ongoing studies involving pediatric cardiac regeneration reports. Because of difficulties conducting randomized blinded clinical trials in pediatric patients, mostly case reports or cohort studies with a limited number of individuals have been published in the field of pediatric regenerative cardiology. The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in critically ill children with severe or terminal heart failure. Congenital heart disease, myocarditis, and idiopathic hypertrophic or dilated cardiomyopathy leading to congestive heart failure are some possible areas of interest for pediatric cardiac regeneration therapy. Autologous bone marrow mononuclear cells, progenitor cells, or cardiospheres have been applied either intracoronary or percutaneously intramyocardially in severely ill children, leading to a reported clinical benefit of cell-based cardiac therapies. In conclusion, compassionate use of autologous stem cell administration has led to at least short-term improvement in heart function and clinical stability in the majority of the critically ill pediatric patients.

Key words: Congenital heart disease; Heart failure; Cardiac regeneration; Cell-based therapy; Hospitalization; Children

Core tip: This review summarizes the available literature data involving pediatric cardiac regeneration reports.

Due to lack of randomized blinded clinical trials in pediatric cardiology patients, mostly case reports with limited number of individuals have been published in the pediatric regenerative cardiology. The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in children with severe or terminal heart failure, and led to the conclusion, that compassionate use of autologous stem cell administration may lead to at least short-term improvement in heart function and clinical stability in the majority of the critically ill pediatric patients.

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INTRODUCTION

Epidemiology of heart failure in children

The overall prevalence of pediatric heart failure is largely unknown because of the non-unique definition and classification of this disease. According to statistical estimations and pediatric registries, 2.5 million children annually are born with congenital heart disease (CHD) worldwide, and among these children, 15%-25% eventually develop heart failure[1-4].

The incidence of pediatric dilated cardiomyopathy with consequent heart failure is low, calculated as 0.57-2.6 per 100000 children under age 18 years[5,6]. In this group, approximately two thirds of cases are idiopathic, and the remaining involve postmyocarditis syndrome or musculoskeletal diseases[7]. Dilated cardiomyopathy dominates myocardial disease-related heart failure, followed by hypertrophic cardiomyopathy, with restrictive cardiomyopathy identified least frequently[8]. The median age of the patients with dilated cardiomyopathy is approximately 1.8 years when the initial diagnosis is made[8].

The mortality of pediatric heart failure is high, and approximately one third of patients die in the first year following diagnosis[9,10]. The surviving children develop progressive heart failure requiring intensive medical care and heart transplantation[7]. For those surviving at least 2 years after the diagnosis, mortality and the need for heart transplantation are somewhat lower (13.6%)[6]. Approximately 18 of every 100000 children are hospitalized annually because of heart failure, with 0.87 new cases per 100000 children per year[11]. The hospital mortality of these pediatric patients is 7%, and numbers are much higher compared to the adult population (4%)[11,12]. After the first hospitalization, only 21% of pediatric patients remain free from serious adverse events (rehospitalization, death, or heart transplantation)[13]. The lack of sufficient numbers of young donor organs and the relatively high post-transplantation mortality limit the incidence and success of pediatric heart transplantation.

In addition, the cost of hospital treatment for pediatric heart failure is usually extremely high, exceeding 135000 USD per patient. Underlying CHD involving a single ventricle, for example, expands the costs of in-hospital treatment for heart failure to over 200000 USD[14].

The medical therapy for pediatric heart failure includes the whole armamentarium used in adults; however, the benefit cannot be clearly demonstrated for all interventions in children[15]. Some established methods for adult cardiology, such as diverse regenerative therapies or left ventricular assist devices, are rarely available for young patients because of incompatibilities of implant size in growing children. Medical treatment might be insufficient because, as noted, many children end up requiring heart transplantation[16].

Spontaneous cardiac regeneration capacity in children

Newborn mice can regenerate the cardiac apex after resection but only if the resection occurs within the first 7 d after birth[17]. Lineage tracing investigations have revealed that cell cycle entry of pre-existing cardiomyocytes in mice is responsible for this regeneration. Gene expression analysis indicates that neonatal cardiomyocytes maintain proliferation capacity only up to 7 d post-birth, this regeneration property is then lost[17]. Mishra *et al*[18] investigated the prevalence and proliferation capacity of different stem cell-like cells acquired from cardiac biopsy specimens of children undergoing open heart surgery. They showed that plenty of resident human cardiac progenitor cells (hCPCs, a subpopulation of cardiospheres, CDCs) can be found in the neonatal period but that the number of these cells decreases rapidly with advancing age, from 8.9% to 3.2% in the right atrium and from 0.4% to 0.1% in the right ventricle. In addition, c-kit$^+$ hCPCs were three times more frequently found in neonates than in children over age 2 years. The proliferation and differentiation potential of the hCPCs was also greater in neonates, as shown by the higher expression levels of c-kit and Ki67, as well as the expression of NKX2, NOTCH1, and NUMB, the genes responsible for proliferation and differentiation. Furthermore, heart tissue samples of children with CHD contained an increased number of c-kit$^+$ hCPCs and CD133$^+$ cells, and these cells expressed cardiac lineage and endothelial transcription factors during differentiation under *in vitro* conditions[19]. CDCs are a rich source of secreted regenerative substances, such as cytokines and growth factors, *e.g.,* vascular endothelial growth factor, hepatocyte growth factor, or insulin-like growth factor, and exert anti-apoptotic and proangiogenic effects in the myocardium[20,21]. CDCs found in infant hearts have higher telomerase activity compared with those of adults.

Together, these data suggest that the regenerative capacity of the heart in children is much greater than that of adults. Additional evidence comes from clinical observations that the younger heart can exhibit morphological changes after volume unloading by surgical correction of CHD[22]. Additionally, pressure overload from

Table 1 Pediatric cardiac diseases treated with cells

Cell-based cardiac regenerative treatment	Ongoing studies
Dilated cardiomyopathy (Dil. CMP)	Dilated cardiomyopathy (Dil. CMP)
Idiopathic dilated CMP	
Cytostatics-induced dilated CMP	
Postmyocarditis dilated CMP	
Ischemic heart failure (myocardial infarction)	
Anomalous origin of the left coronary arteries	
Takayasu arteritis	
Congenital heart disease	
DORV after surgical correction	
Pulmonary atresia with ventricular septal defect	
HLHS	Hypoplastic left heart syndrome (HLHS)

CMP: Cardiomyopathy; DORV: Double outlet right ventricle; HLHS: Hypoplastic left heart syndrome.

a single right ventricle leads to an increase in the number of cardiac stem cells (0.41% ± 0.24%) compared to dilated cardiomyopathy (0.15% ± 0.09%)[23].

Clinical pediatric cardiac regeneration studies

To establish standardized therapy and guidelines for treatment of diseases, randomized double-blinded clinical studies delivering evidence-based medicine are necessary. In contrast with the huge number of adult clinical trials, in pediatric cardiology, especially for cardiac regenerative therapy, large randomized trials are lacking. In addition to the understandable ethical reasons, other factors also preclude such trials: The relative rarity of heart failure with a limited number of pediatric patients in the stable clinical condition necessary for randomization, a divergence in terminology, proprietary and often incompatible informatics platforms, and variability in data standards in growing children[24]. In 2012, the United States Food and Drug Administration Safety and Innovation Act intensified pediatric product development, also enhancing the number of pediatric clinical trials. In Europe, the Pediatric Regulation and Pediatric Therapeutics programs have strengthened the applications of new medicines in evidence-based pediatric clinical studies. In contrast with the very spare pediatric regenerative cardiology studies, pediatric cancer and HIV/AIDS treatment networks have already been successfully established and developed with standardized data validity and consistency[24]. We review here the available literature data, searching the Medline, Google Scholar and Embase database for completed, and www.clinicaltrials.gov homepage for ongoing studies involving pediatric cardiac regeneration reports.

DISCUSSION

Cardiac diseases for pediatric cardiac regeneration

In most cases, cardiac cell-based therapy has been applied in children with severe heart failure caused by diverse diseases, predominantly idiopathic dilated cardiomyopathy, post-myocarditis, or chemotherapy-induced dilated cardiomyopathy (Table 1 and Figure 1). Severe heart failure has been described also with post-myocardial infarction in cases of an anomalous origin of the left coronary artery from the pulmonary artery or Takayasu's arteritis, treated with different kinds of reparative cells. Other congenital diseases such as double outlet right ventricle, pulmonary atresia with ventricular septal defect, or hypoplastic left heart syndrome (HLHS) causing severely depressed heart function, have been considered for treatment with non-committed cells. Table 2 lists the pediatric diseases for which cardiac cell-based regenerative studies might be considered.

For the reasons described, to date, only two randomized clinical cardiac regenerative trials with a low number of included children have been conducted. Both have revealed benefits of cardiac cell-based therapy[25-29]. In addition to these currently finished trials, case reports or pilot trial results have been published, mainly based on an indication of compassionate use in severely ill pediatric patients. The majority of children receiving cardiac cell-based therapy were in a critical or terminal status of cardiac decompensation, as evidenced by the fact that some of the children had to undergo heart transplants afterwards[22].

Cell types and delivery modes

Different types of cells have been used for cardiac regenerative cell therapy in children, such as bone marrow-derived mononuclear cells, cells from leukocyte apheresis, and mesenchymal stem cells. In all cases, autologous cells were used.

Most of the children received the reparative cells *via* intracoronary injections. To ensure retention of the injected cells, echocardiography-guided transcutaneous intramyocardial delivery was also used, or a transapical delivery mode was applied[30].

Clinical studies

The evidence for pediatric cardiac regeneration is mostly anecdotal, deriving from case reports or cohort studies including very limited number of patients (max. nine treated children in Rupp *et al*[31]). In addition, the only comparative study, published by Ishigami *et al*[32] allocated

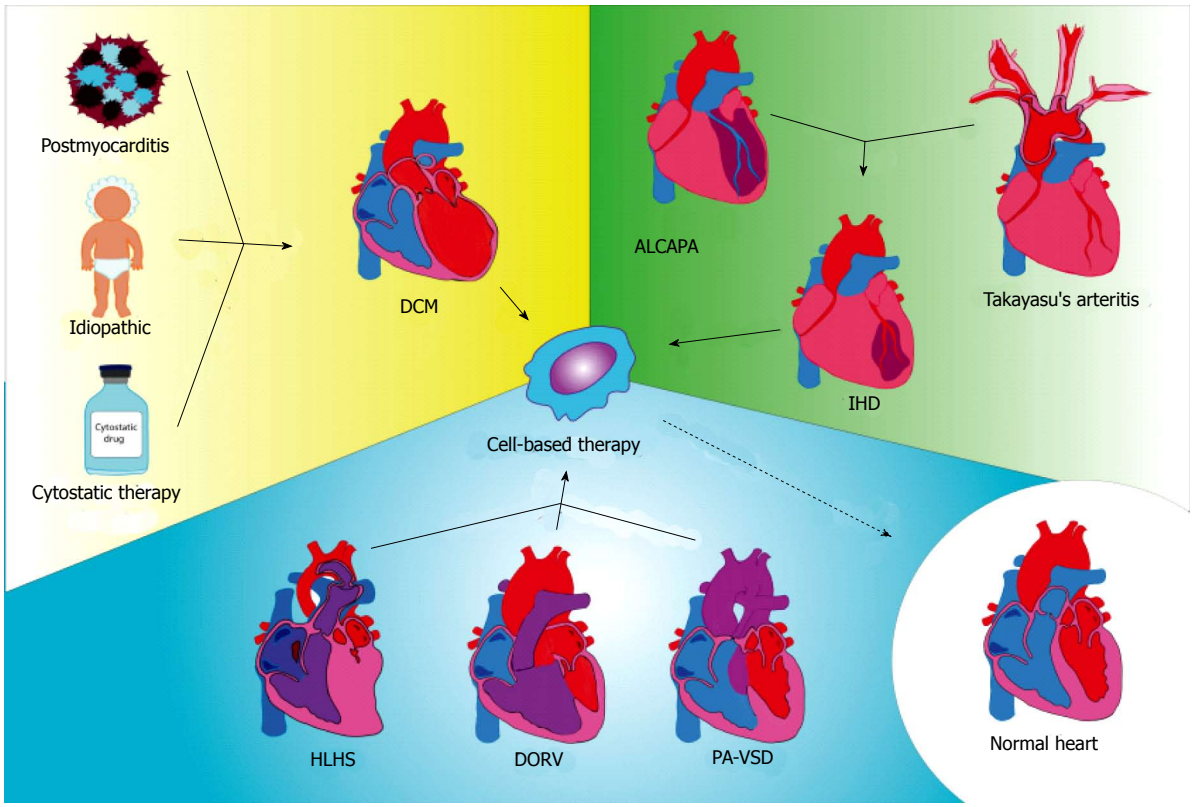

Figure 1 Schematic display of cardiac cell-based regeneration therapies in pediatric population. DCM: Dilated cardiomyopathy; ALCAPA: Anomalous left coronary artery from the pulmonary artery; IHD: Ischemic heart disease; HLHS: Hypoplastic left heart syndrome; DORV: Double outlet right ventricle; PA-VSD: Pulmonary atresia with ventricular septal defect.

14 children with HLHS to receive either autologous CDCs (n = 7) or standard therapy (n = 7) without randomization. Because of these significant limitations of the available literature, a usual review or meta-analysis of cardiac regenerative studies in children is not reasonable. Thus, this review summarizes the published cases and their conclusions.

Autologous stem cell administration has led to at least short-term improvement in heart function and clinical stability in the majority of patients. Because of the lack of randomization and control groups, an unambiguous interpretation of the results is not possible. At the least, the outcomes indicate a compassionate use of cell-based cardiac regeneration in critically ill patients.

Rupp *et al*[33,34] reported two cases of bone marrow-origin progenitor cell intracoronary injection, one involving a 2-year-old boy with dilated cardiomyopathy and the other an 11-mo-old infant with HLHS; both of them were in a critical clinical condition of heart failure. The bone marrow progenitor cells were injected into the left anterior descending and left circumflex coronary arteries in the first case and into the dominant right coronary artery in the second case, using a stop-flow technique. The cardiac cell therapy led to an increase in the left ventricular ejection fraction from 24% to 45% at 6 mo of follow-up in the first case, and to reverse remodeling and marked improvement in clinical status in the second case.

In further work, Rupp *et al*[34] published a somewhat larger cohort study of nine pediatric patients receiving intracoronary injections of autologous bone marrow mononuclear cells (BM-MNCs). The reasons for terminal heart failure in these children were anthracycline-induced dilated cardiomyopathy; post-myocarditis, idiopathic, or congenital cardiomyopathy; CHD with poor ventricular function, such as hypoplastic left heart or double outlet right ventricle; and pulmonary atresia with ventricular septal defect after surgical corrections. Three of the nine patients received a heart transplant and one patient died after cell treatment. The surviving children showed an improvement in clinical status during the 24 to 52 mo of follow-up.

De Lezo *et al*[35] presented a case of a 5-mo-old infant with severe heart failure due to extensive myocardial infarction because of an anomalous origin of the left coronary artery. After surgical re-implantation of the left coronary artery to the aorta, the artery was occluded, then stented, then dilated after stent occlusion. Because of the critical clinical situation, during the second percutaneous procedure, autologous bone marrow-origin mononuclear cells were injected into the left main branch, which led to a gradual improvement in clinical status and allowed the discharge of the patient.

After mobilizing stem cells from the bone marrow with granulocyte colony-stimulating factor (G-CSF), Olguntürk *et al*[36] selected peripheral blood-origin stem cells and performed intracoronary injections of these cells into both the left and right coronary arteries in two patients both with dilated cardiomyopathy and severe

Table 2 Published clinical studies with pediatric cell-based cardiac regeneration

Ref.	Study type	Diagnosis	No. of children	Mean age of children (m)	Sex	Type of stem cell	Cell application	FUP	Main results
Lacis *et al*[30]	Case report	Dil. CMP	1	3.5 mo	F	BM-MNC	IM	4 mo	LV EF from 20% to 41%
Rupp *et al*[31]	Case report	Dil. CMP	9	4 mo-16 yr	NA	BM-MNCs	IC	1-52 mo	3 patients HTX, 1 patient died, others improved
Ishigami *et al*[32] (TICAP study)	Controlled study	HLHS	7 treated and 7 controls	< 6 yr	NA	CDCs	IC	18 mo	Increase in RV EF from 46.9% to 52.1% in treated patients
Rupp *et al*[33]	Case report	HLHS	1	11 mo	M	BMC	IC	14 mo	RV EF from 22% to 44%
Rupp *et al*[34]	Case report	Dil. CMP	1	2 year	M	BMC	IC	6 mo	EF from 24% to 45%, BNP and NYHA decreased
De Lezo *et al*[35]	Case Report	Post-AMI	1	7 mo	NA	BM-MNCs	IC	14 mo	LV EF from 20% to 43%
Olguntürk *et al*[36]	Case report	Dil. CMP	2	6 and 9 yr	M, F	PBSC after GCSF treatment	IC	8 wk, and 6 mo	1st patient LV EF from: 16% to 39%; 2nd patient LV EF from 34% to 54%
Limsuwan *et al*[37]	Case report	HF post-AMI	1	9 yr	F	BMC after GCSF treatment	IC	3 mo	LV EF form 30% to 47%
Zeinaloo *et al*[38]	Case report	Dil. CMP	1	11 yr	M	BM-MSC	IC	1 yr	LV EF from 20% to 42%
Rivas *et al*[39]	Case report	Dil. CMP	2	3 and 4 mo	M	PBSC after G-CSF treatment	IC	4 mo	EF from < 30% to > 40%
Bergmane *et al*[40]	Case report	Dil. CMP	7	4 mo-17 yr	NA	BMC	IM	1 yr	6 patients controlled, LV EF from 33.5% to 54%
Burkhart *et al*[41]	Case report	HLHS	1	3 m	NA	Umbilical cord blood derived cells	IM	3 mo	EF increased to 45%

BMC: Bone marrow cells; CDC: Cardiosphere-derived cells; BNP: Brain natriuretic peptide; HTX: Heart transplantation; NYHA: New York Heart Association Classification; GCSF: Granulocyte-colony stimulating factor; CMP: Cardiomyopathy; LV: Left ventricle; EF: Ejection fraction; BM-MNC: Bone marrow mononuclear cell; PBSC: Peripheral blood stem cell; RV: Right ventricle; IC: Intracoronary; IM: Intramyocardial; FUP: Follow-up; NA: Data not available; HLHS: Hypoplastic left heart syndrome; F: Female; M: Male.

congestive heart failure. At the 4-mo follow-up, both children showed impressive improvement, and one of them could be removed from the heart transplantation list.

Similarly, Limsuwan *et al*[37] applied the first daily injections of G-CSF, followed by bone marrow aspiration and selection of $CD133^+/CD34^+$ cells in an 8.5-year-old girl who had had an acute extensive anterior myocardial infarction related to Takayasu arteritis one year earlier. The selected stem cells were injected into the left anterior descending artery with the stop-flow technique. The 3-mo follow-up showed an increase in ejection fraction from 30% to 47.8% by cardiac magnetic resonance imaging.

Zeinaloo *et al*[38] selected autologous bone marrow mesenchymal stem cells in an 11-year-old boy with a diagnosis of dilated cardiomyopathy and injected them into the left and right coronary arteries. The one-year clinical check-up revealed an improvement of the left ventricular ejection fraction from 20% to 42%.

Lacis *et al*[30] treated a 3-mo-old child, who was in critical clinical condition with dilated cardiomyopathy, with autologous BM-MNCs *via* echocardiography-guided transcutaneous transapical intramyocardial injections. The ejection fraction increased from 20% to 41% at the 4-mo follow-up, and the child's clinical well-being was obvious.

Rivas *et al*[39] treated two children who both had dilated cardiomyopathy and were ages 3 and 4 mo, respectively, by administering peripheral blood progenitor cells, mobilized by G-CSF treatment. One month later, both children presented improvement, but one child developed progression later. This article described a temporary effect of the cell-based cardiac regenerative therapy.

Ishigami *et al*[32] published a nonrandomized prospective cohort study comparing data for seven patients treated with intracoronary injection of cardiosphere-derived cells and seven controls treated with standard therapy. All children had HLHS with planned stage 2 or 3 surgical palliation, which allowed the collection of autologous tissue for selection of CDCs in the treated group. The intracoronary injection of CDCs proved to be safe, and the right ventricle ejection fraction increased and remained constant at the 18 mo follow-up.

Bergmane *et al*[40] treated seven children with dilated cardiomyopathy with autologous bone marrow cells administered transcutaneously and intramyocardially by subxyphoid needle puncture under echocardiographic guidance. Six of the seven patients showed dramatically

Table 3 On-going registered clinical studies

Clinicaltrials.gov ID	Diagnosis	Intervention	Study design	No. of patients to enroll	Age eligible	Status
NCT01504594	Dilated CMP	Intracoronary autologous stem cell infusion	Single Group Assignment	10	1 to 16	Suspended
NCT02256501	CMP	Intracoronary	Randomized	32	1 to 16	Recruiting
NCT02398604	HLHS	intramyocardial injection of allogeneic mesenchymal cells during the Bi-Directional Cavopulmonary Anastomosis	Randomized	30	to 28 d	Study is not yet open
NCT01883076	HLHS	injections of autologous umbilical cord blood cells into the right ventricle of HLHS children undergoing a scheduled Glenn surgical procedure.	Safety Study	10	< 18 mo	Recruiting
NCT01829750	HLHS	efficacy of intracoronary infusion of cardiac progenitor cells in patients with univentricular heart disease	Randomized	34	< 20 yr	Recruiting

HLHS: Hypoplastic left heart syndrome; CMP: Cardiomyopathy.

increased left ventricular ejection fraction at one year after the treatment, paralleled by a decrease in N-terminal proBNP and improved clinical status.

Burkhart *et al*[41] injected autologous umbilical cord blood-derived cells directly into the right ventricle during a second palliative operation of a child with HLHS. Three months later, the ejection fraction had increased to 45% with a marked decrease in plasma pro-BNP. Ongoing registered clinical studies are listed in Table 3.

CONCLUSION

Cell-based cardiac regeneration therapy in pediatric patients has led to at least transient improvement of heart function and improvement of heart failure symptoms in a limited number of pediatric patients included in mostly non-randomized studies or case reports.

The majority of pediatric autologous cell transplantations into the cardiac tissue have been performed in critically ill children with severe or terminal heart failure, indicating that at the moment, this treatment strategy is a supplement after standard therapies have been exhausted. Whether specific age groups or those with structural heart diseases may benefit more than others has to be elucidated.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Optimal timing of same-admission orthotopic heart transplantation after left ventricular assist device implantation

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Abstract

AIM

To investigate the impact of timing of same-admission orthotopic heart transplant (OHT) after left ventricular assist device (LVAD) implantation on in-hospital mortality and post-transplant length of stay.

METHODS

Using data from the Nationwide Inpatient Sample from 1998 to 2011, we identified patients 18 years of age or older who underwent implantation of a LVAD and for whom the procedure date was available. We calculated in-hospital mortality for those patients who underwent OHT during the same admission as a function of time from LVAD to OHT, adjusting for age, sex, race, household income, and number of comorbid diagnoses. Finally, we analyzed the effect of time to OHT after LVAD implantation on the length of hospital stay post-transplant.

RESULTS

Two thousand and two hundred patients underwent implantation of a LVAD in this cohort. One hundred and sixty-four (7.5%) patients also underwent OHT during

the same admission, which occurred on average 32 d (IQR 7.75-66 d) after LVAD implantation. Of patients who underwent OHT, patients who underwent transplantation within 7 d of LVAD implantation ("early") experienced increased in-hospital mortality (26.8% *vs* 12.2%, P = 0.0483) compared to patients who underwent transplant after 8 d ("late"). There was no statistically significant difference in age, sex, race, household income, or number of comorbid diagnoses between the early and late groups. Post-transplant length of stay after LVAD implantation was also not significantly different between patients who underwent early *vs* late OHT.

CONCLUSION

In this cohort of patients who received LVADs, the rate of in-hospital mortality after OHT was lower for patients who underwent late OHT (at least 8 d after LVAD implantation) compared to patients who underwent early OHT. Delayed timing of OHT after LVAD implantation did not correlate with longer hospital stays post-transplant.

Key words: Mechanical circulatory support; Orthotopic heart transplant; Bridge to transplant; Left ventricular assist device outcomes

Core tip: The optimal timing of same-admission orthotopic heart transplantation (OHT) after the implantation of a left ventricular assist device (LVAD) is unknown. The need for clinical stability and time to recover from surgery is counterbalanced by the risk of LVAD complications and formation of adhesions and scarring, particularly when OHT is considered early after LVAD implantation. We reviewed adult patients in the Nationwide Inpatient Sample who underwent same-admission OHT after LVAD between 1998 and 2011. Compared to early transplantation after LVAD, OHT after 8 d of LVAD implantation was associated with decreased mortality risk without increased post-transplant length of stay.

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INTRODUCTION

Heart failure (HF) affects an estimated 5.8 million people in the United States and contributes to over 300000 deaths every year[1,2]. It is the most common cause of hospital admission and readmission in people greater than 65 years of age, annually accounting for over 2.4 million hospitalizations[2,3] and $39 billion in healthcare costs[1,4]. Although most patients respond favorably to standard medical treatment, a considerable number of patients progress to end-stage HF refractory to medical therapy[5]. Currently, orthotopic heart transplant (OHT) is the gold standard therapy for these patients[6-8], but the number of donor hearts available for transplantation is far fewer than the number of patients on the transplant list. For this reason, left ventricular assist devices (LVADs), a class of electromechanical devices used for cardiac circulatory support, are increasingly being used to bridge patients to cardiac transplantation[5].

The REMATCH trial in 2001 showed significant mortality reductions in patients placed on a pulsatile-flow LVAD compared to standard medical treatment[9]. Several subsequent studies since have confirmed the survival benefit of both the older pulsatile and newer continuous-flow LVADs[10-13]. Although LVADs have substantially reduced mortality in end-stage HF patients, the absolute mortality rates still remain high. A large portion of this mortality is attributable to complications and other occurrences during the patient's stay in the hospital[14]. In-hospital mortality rates as high as 27% have been reported in patients after LVAD surgery[15-18].

As the rate of LVAD implantation in the United States continues to increase[19-22], effective recommendations for the in-hospital management of LVAD implantation are needed. Although the majority of cardiac transplants performed after LVAD implantation occur after a patient has been discharged from hospital, there is an important cohort of patients who cannot be discharged from hospital post-LVAD implant due to severe right ventricular failure, arrhythmias refractory to oral therapy, and infectious complications. Patients bridged to OHT with a LVAD achieve similar survival rates as patients who undergo direct heart transplant[14], but there is little data to guide clinicians on the optimal timing of same-admission OHT after LVAD implantation. Though patients receiving LVADs may be considered for OHT while still inpatients, some have argued that performing OHT early after LVAD placement poses an increased risk of morbidity and mortality to patients.

Past studies on the appropriate use and outcomes of LVADs have been mostly limited to institutional experience and case series of select populations. While such descriptive investigations are useful, they are often limited by small sample size and variation between institutions and comparison groups. We used the Nationwide Inpatient Sample (NIS), the largest national database of hospitalizations in the United States with data from over 36 million hospitalizations, to assess the optimal timing of OHT after LVAD implantation. The NIS dataset complements the UNOS database and INTERMACS dataset with additional information on patient comorbidities, additional same-hospitalization procedures, hospital and center characteristics, and markers of patient's socioeconomic status including insurance provider and regional income quartiles. In addition, the NIS dataset contains data on both LVAD and inpatient OHT, which are not simultaneously available in the UNOS or INTERMACS databases.

We analyzed a patient cohort who had OHT performed

during the same admission after LVAD implantation. We hypothesized that early OHT after LVAD implantation would be associated with higher mortality than late OHT, and that the hospital length of stay (LOS) after early OHT would be less than LOS after late OHT.

MATERIALS AND METHODS

Data source

The NIS, from the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality is the largest database of all-payer inpatient discharge information, sampling approximately 20% of all non-federal United States hospitals and including approximately 9 million hospital admissions each year. It contains discharge data from over 5000 hospitals located across 45 states, of which approximately 1200 hospitals are sampled each year to create a stratified sample of United States hospitals. Each NIS entry includes all diagnosis and procedure codes of activity during the patient's hospitalization at the time of discharge, as well as patient demographics, hospital characteristics, and short-term complications of the hospitalization.

Study design and cohorts

This was a retrospective cross-sectional study using the NIS between 1998 and 2011. We identified all hospitalizations from 1998 to 2011 of patients 18 years of age or older who underwent LVAD implantation and for whom the hospital day of each procedure was available. Procedures during the hospitalization in addition to LVAD placement, including OHT, extracorporeal membrane oxygenation, intubation, hemodialysis, invasive hemodynamic monitoring, and surgical revision were identified by associated ICD9 codes (Supplementary Table 1). Additionally, hospital mortality and perioperative morbidity such as post-operative infections, cardiopulmonary complications, and hemorrhagic complications requiring endoscopy were identified.

Statistical analysis

The statistical methods of this study were reviewed by Dr. David Ouyang from the Stanford University Department of Medicine. Python 2.7 (Python Software Foundation, www.python.org) and R 2.13 (R Foundation, www.r-project.org) were used for statistical analysis. *P*-values for numerical and count data were calculated by two-sided *t*-tests and χ^2 tests, respectively, with significance thresholds of 0.05. The multivariate linear model evaluating post-LVAD OHT mortality was performed using a generalized linear model with input variable selection by Bayesian Information Criteria (BIC). The dependent variable was in-hospital mortality. Independent variables of age, gender, median income, race, number of comorbidities, LVAD era, and timing of OHT were evaluated in the model.

RESULTS

Baseline patient characteristics

We identified 2200 patients greater than 18 years of age between 1998 and 2011 who underwent LVAD implantation and for whom hospital day of procedure was listed (66.4% of all LVAD patients in the NIS database 1998-2011). Comparison of baseline characteristics between this study sample and all LVAD patients in the NIS 1998-2011 database confirmed that our study sample is representative of the entire patient population. The two groups were well matched based on age, sex, household income, prevalence of comorbidities, length of stay, and number of comorbidities, however there were more patients without documented race in the overall group (Supplementary Table 2). The mean age of all patients was 53.4 years (SD = 13.7, range = 18-92 years). Baseline patient demographics, patient comorbidities, and hospital characteristics were well matched between LVAD patients with and without same-admission OHT (Table 1). Most LVAD implantations were performed in large (87.8%), urban (99.1%), teaching hospitals (92.4%). The most common comorbidities were diabetes (17.8%), disorders of lipid metabolism (14.1%), hypertension (13.7%), history of or current use of tobacco (6.5%), and BMI $\geqslant$ 30 kg/m^2 (4.4%). The mean day of LVAD implantation was 9.4 d (SD = 12.5 d) into the hospitalization. The overall in-hospital mortality rate was 26.8%, with respiratory failure, cardiac dysrhythmias, right HF, and renal failure among the most frequent in-hospital complications immediately following LVAD implantation (Table 2).

Our dataset includes patients from both the pulsatile-flow era (1998-2005) and the continuous-flow era (2006-2011) of mechanical support (Table 3). Comparing the two eras, there was significantly less mortality in the continuous-flow era compared to the pulsatile-flow era (20.4% *vs* 43.0%; $P < 0.001$) even as patients were older (55.4 years *vs* 53.2 years; $P < 0.001$) and suffering more comorbid diagnoses (13.5 *vs* 10.6; $P < 0.001$). During the continuous-flow era, fewer patients received OHT during the same admission as LVAD implantation (3.8% *vs* 17.3%; $P < 0.001$), and mechanical support was more frequently initiated in large (88.8% *vs* 85.1%; $P = 0.002$), teaching (94.4% *vs* 87.1%; $P < 0.001$) institutions. Median household income quartile and race distribution also were different between the two eras, although there was no difference in gender ratio of patients.

Timing of post-LVAD OHT

Of the patients who underwent LVAD implantation, 164 (7.5%) also underwent OHT during the same admission. OHT occurred a median of 32 d (IQR 7.75-66 d) after LVAD implantation. Patients who underwent OHT at least 8 d after LVAD implantation experienced significantly lower mortality compared to patients who underwent OHT earlier (26.8% *vs* 12.2%; $P = 0.048$; Table 1 and Figure 1). Baseline patient demographics, patient comorbidities, and hospital characteristics were similar between the early and late OHT groups. LVAD patients who underwent late OHT also had lower mortality compared to LVAD patients who were not transplanted (12.2% *vs* 27.0%; $P < 0.001$). However, LVAD patients who underwent early

Table 1 Baseline demographics for patients who waited 0-7 d, 8-31 d, 32-65 d, and ⩾ 66 d for an orthotopic heart transplant after left ventricular assist device implantation

	0-7 d (*n* = 41)	8-31 d (*n* = 38)	32-65 d (*n* = 42)	⩾ 66 d (*n* = 43)	No OHT (*n* = 2036)
Length of stay, mean ± SD	39.3 ± 33.2	48.9 ± 25.6	85.8 ± 40.1	151.2 ± 52.6	37.1 ± 34.6
Length of stay after OHT, mean ± SD	23.8 ± 21.4	21.7 ± 15.8	27.6 ± 37.1	27.1 ± 22.8	NA
Mortality, *n* (%)	11 (26.8)	5 (13.2)	5 (11.9)	5 (11.6)	564 (27.3)
Age, mean ± SD	50.6 ± 12.6	48.6 ± 12.7	47.4 ± 15.3	46.3 ± 13.1	55.4 ± 13.2
Sex, *n* (%)					
Male	33 (80.5)	32 (84.2)	35 (83.3)	34 (79.1)	1525 (74.9)
Female	8 (19.5)	6 (15.8)	7 (16.7)	9 (20.9)	511 (25.1)
Race, *n* (%)					
White	25 (61.0)	19 (50.0)	23 (54.8)	22 (51.2)	1185 (58.2)
Black	3 (7.3)	5 (13.2)	8 (19.0)	6 (14.0)	330 (16.2)
Hispanic	3 (7.3)	7 (18.4)	2 (4.8)	5 (11.6)	125 (6.1)
Asian/Pacific Islander	2 (4.9)	0 (0.0)	1 (2.4)	4 (9.3)	44 (2.2)
Native American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Other or unknown	8 (19.5)	7 (18.4)	8 (19.0)	6 (14.0)	347 (17.0)
Median household income, *n* (%)					
$1-24999	4 (9.8)	8 (21.1)	8 (19.0)	8 (18.6)	447 (22.0)
$25000-34999	10 (24.4)	10 (26.3)	10 (23.8)	7 (16.3)	454 (22.3)
$35000-44999	12 (29.3)	8 (21.1)	10 (23.8)	13 (30.2)	509 (25.0)
$45000 or more	129 (29.3)	12 (31.6)	14 (33.3)	14 (32.6)	579 (28.4)
Unknown	3 (7.3)	0 (0.0)	0 (0.0)	1 (2.3)	47 (2.3)
Comorbidities					
Diabetes	8 (19.5)	5 (13.2)	4 (9.5)	2 (4.7)	373 (18.3)
Hyperlipidemia	5 (12.2)	2 (5.3)	3 (7.1)	3 (7.0)	297 (14.6)
Hypertension	5 (12.2)	1 (2.6)	2 (4.8)	2 (4.7)	291 (14.3)
History of smoking	5 (12.2)	2 (5.3)	0 (0.0)	0 (0.0)	137 (6.7)
BMI ⩾ 30 kg/m^2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	96 (4.7)
No. of comorbid diagnoses, mean ± SD	11.9 ± 3.1	12.3 ± 3.0	12.5 ± 3.2	12.5 ± 3.2	12.8 ± 2.9
Location of hospital, *n* (%)					
Rural	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (0.8)
Urban	41 (100.0)	38 (100.0)	42 (100.0)	43 (100.0)	2017 (99.1)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Size of hospital, *n* (%)					
Small	4 (9.8)	0 (0.0)	0 (0.0)	2 (4.7)	32 (1.6)
Medium	7 (17.0)	6 (15.8)	5 (11.9)	0 (0.0)	211 (10.4)
Large	30 (73.2)	32 (84.2)	37 (88.1)	41 (95.3)	1791 (88.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Teaching status of hospital, *n* (%)					
Nonteaching	1 (2.4)	1 (2.6)	2 (4.8)	1 (2.3)	160 (7.9)
Teaching	40 (97.6)	37 (97.4)	40 (95.2)	42 (97.7)	1874 (92.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)

SD: Standard deviation; BMI: Body mass index; LVAD: Left ventricular assist device; OHT: Orthotopic heart transplant.

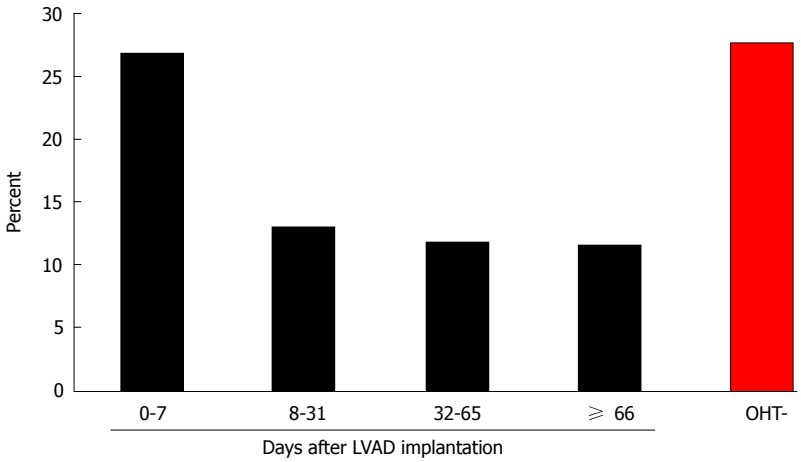

Figure 1 Percent in-hospital mortality by quartiles of wait time for orthotopic heart transplant after left ventricular assist device implantation and no orthotopic heart transplant after left ventricular assist device implantation. Percent mortality for each quartile was calculated as number of deaths per quartile by total number of patients per quartile. LVAD: Left ventricular assist device; OHT: Orthotopic heart transplant.

transplant did not experience a similar mortality benefit (26.8% *vs* 27.0%; *P* = 0.946). The reduced mortality trend with delayed OHT post-LVAD was observed in both the pulsatile-flow (13.8% *vs* 36.4%; *P* = 0.081)

Table 2 Complications in hospitalized patients with or without same admission orthotopic heart transplant after left ventricular assist device

	Early OHT (n = 41)	Late OHT (n = 123)	OHT- (n = 2036)	Total (n = 2200)
Acute renal failure	24 (58.5)	64 (52.0)	963 (47.3)	1051 (47.8)
Reoperation	28 (68.3)	87 (70.7)	803 (39.4)	918 (41.7)
Bleeding requiring transfusion	7 (17.1)	30 (24.4)	780 (38.3)	817 (37.1)
Acute respiratory failure	8 (19.5)	37 (30.1)	518 (25.4)	563 (25.6)
Sepsis	2 (4.9)	17 (13.8)	233 (11.4)	252 (11.5)
Postoperative cardiac complication	7 (17.1)	15 (12.2)	234 (11.5)	256 (11.6)
Acute liver failure	3 (7.3)	9 (7.3)	224 (11.0)	236 (10.7)
Device failure	0 (0.0)	4 (3.3)	62 (3.0)	66 (3.0)
Stroke	1 (2.4)	1 (0.8)	53 (2.6)	55 (2.5)

All pairwise comparisons of early *vs* late OHT were not statistically significant ($P > 0.05$). OHT: Orthotopic heart transplant.

Table 3 Baseline demographics of all left ventricular assist device patients, left ventricular assist device patients from 1998-2005 (pulsatile-flow era), and left ventricular assist device patients from 2006-2011 (continuous-flow era)

	All LVADs (n = 2200)	1998-2005 (n = 589)	2006-2011 (n = 1611)	P-value[a]
Mortality, n (%)	590 (26.5)	253 (43.0)	329 (20.4)	< 0.001
Same admission OHT, n (%)	164 (7.5)	102 (17.3)	62 (3.8)	< 0.001
Early same admission OHT, n (%)	41 (25.0)	22 (21.6)	19 (30.6)	0.373
Early same admission OHT mortality, n (%)	11 (26.8)	8 (36.4)	3 (15.8)	0.319
Length of stay after early OHT, mean ± SD	23.8 ± 21.4	30.9 ± 26.0	17.6 ± 14.3	0.054
Late same admission OHT, n (%)	123 (75.0)	80 (78.4)	43 (69.4)	0.849
Late same admission OHT mortality, n (%)	15 (12.2)	11 (13.8)	4 (9.3)	0.774
Length of stay after late OHT, mean ± SD	25.6 ± 26.9	26.1 ± 22.9	25.4 ± 29.0	0.883
Length of stay, mean ± SD	40.5 ± 38.9	44.7 ± 48.6	39.0 ± 34.6	0.008
Age, mean ± SD	53.4 ± 13.7	53.2 ± 13.4	55.4 ± 13.4	< 0.001
Sex, n (%)				
Male	1659 (75.4)	433 (73.5)	1226 (76.1)	0.23
Female	541 (24.6)	156 (26.5)	385 (23.9)	
Race, n (%)				< 0.001
White	1274 (57.9)	327 (55.5)	947 (58.8)	
Black	352 (16.0)	62 (10.5)	290 (18.0)	
Hispanic	142 (6.5)	28 (4.8)	114 (7.1)	
Asian/Pacific Islander	51 (2.3)	13 (2.2)	38 (2.4)	
Native American	5 (0.2)	1 (0.2)	4 (0.2)	
Other or unknown	376 (17.1)	143 (24.3)	148 (9.2)	
Median household income, n (%)				< 0.001
$1-24999	475 (21.6)	88 (14.9)	387 (24.0)	
$25000-34999	491 (22.3)	126 (21.4)	365 (22.7)	
$35000-44999	552 (25.1)	141 (23.9)	411 (25.5)	
$45000 or more	631 (28.7)	214 (36.3)	417 (25.9)	
Unknown	51 (2.3)	20 (3.4)	31 (2.4)	
Comorbidities				
Diabetes	391 (17.8)	91 (15.4)	300 (18.6)	0.097
Hyperlipidemia	310 (14.1)	61 (10.4)	249 (15.5)	0.003
Hypertension	309 (14.0)	88 (14.9)	221 (13.7)	0.508
History of smoking	131 (6.0)	29 (4.9)	102 (6.3)	0.257
BMI ≥ 30 kg/m^2	96 (4.4)	12 (2.0)	84 (5.2)	0.002
No. of comorbid diagnosis, mean ± SD	12.7 ± 2.9	10.6 ± 2.9	13.5 ± 2.5	< 0.001
Location of hospital, n (%)				0.73
Rural	17 (0.8)	5 (0.8)	12 (0.7)	
Urban	2181 (99.1)	583 (99.0)	1598 (99.2)	
Unknown	2 (0.1)	1 (0.2)	1 (0.1)	
Size of hospital, n (%)				0.002
Small	38 (1.7)	20 (3.4)	18 (1.1)	
Medium	229 (10.4)	67 (11.4)	162 (10.1)	
Large	1931 (87.8)	501 (85.1)	1430 (88.8)	
Unknown	2 (0.1)	1 (0.2)	1 (0.1)	
Teaching status of hospital, n (%)				< 0.001
Nonteaching	165 (7.5)	75 (12.7)	90 (5.6)	
Teaching	2033 (92.4)	513 (87.1)	1520 (94.4)	
Unknown	2 (0.1)	1 (0.2)	1 (0.1)	

[a]Pairwise t-test or χ^2 test for patients before 2006 and patients 2006 and afterwards. SD: Standard deviation; BMI: Body mass index; LVAD: Left ventricular assist device; OHT: Orthotopic heart transplant.

Table 4 A generalized multivariate linear model to evaluate post-left ventricular assist device orthotopic heart transplant mortality (positive estimates reflect positive association with increased mortality)

	Regression coefficient	Standard error	*P*-value
Age	0.003	0.002	0.158
Female sex	0.071	0.075	0.342
Caucasian race	-0.01	0.027	0.695
Median household income	0.013	0.027	0.638
Number of comorbidities	0.006	0.010	0.518
Years 1998-2005	0.096	0.060	0.113
Early OHT	0.2	0.067	0.004[a]

[a]*P*-value < 0.05. OHT: Orthotopic heart transplant.

and continuous-flow eras (9.3% *vs* 15.8%; *P* = 0.672), although due to small sample numbers in each subgroup, the differences were not statistically significant (Table 2). Multivariate linear model also confirmed the strong association between early OHT after LVAD and in-hospital mortality, independent of patient age, LVAD era, comorbidities, and demographics (Table 4).

Comparing the quartiles of post-LVAD OHT transplant times, there was no statistically significant difference in post-transplant length of stay (23.8 ± 21.4 d for the first quartile, 21.7 ± 15.8 d for the second quartile, 27.6 ± 37.1 d for the third quartile, 27.1 ± 22.8 d for the fourth quartile; *P* = 0.6571 comparing first quartile to other quartiles; Table 1). However, as expected, patients who waited longer after LVAD implantation for OHT had longer overall hospital stays (39.3 ± 33.2 d for the first quartile, 48.87 ± 25.6 d for the second quartile, 85.8 ± 40.1 d for the third quartile, 151.2 ± 52.6 d for the fourth quartile; *P* < 0.001 comparing first quartile to other quartiles; Table 1).

DISCUSSION

Our study addresses the difficult question of timing of same-admission OHT after LVAD implantation. Using the inpatient data on procedure timing from the NIS 1998-2011, we show that mortality risk significantly decreases in patients who undergo OHT at least 8 d after LVAD implantation. We also report that post-transplant length of stay is independent of the timing of OHT after LVAD.

For patients who receive an LVAD for bridge to transplant therapy (BTT), the optimal timing of post-LVAD OHT is controversial. The need for clinical stability and time to recover from major surgery is counter-balanced by the risk of LVAD complications and the formation of adhesions and scarring, particularly when OHT is considered early after LVAD implantation.

The high failure rate of the early, pulsatile-flow LVADs had in part led to the initial 1999 UNOS allocation algorithm giving LVAD patients 30 d of IA status on the transplant list. The elective nature of the 30-d IA status allows for optimization of management prior to transplant and suggests the time period immediately post-mechanical support is often not the optimal time for transplant. Our data showing that delaying post-LVAD transplant can lead to superior outcomes is consistent with the excellent long term outcomes of BTT mechanical support, pushing some groups to question the justification of elective IA status[23].

Our study, using a large national database, solidifies and extends previous findings that early transplantation after initiation of BTT mechanical support is associated with worse outcomes. In the pulsatile-flow era of LVAD, John *et al*[24] (2010) had shown that cardiac transplants done less than 6 wk after LVAD confer higher mortality risk in patients, and Gammie *et al*[25] (2003) and Ashton *et al*[26] (1996) have similarly reported optimal timing to be 2 wk after LVAD implantation. With the advantage of procedural timing data of patients who underwent same admission LVAD implantation and transplant, we add to those findings by showing there is an increased mortality associated with early same-admission transplant after LVAD in the continuous flow era.

During the study period between 1998 and 2011, there was a significant increase in the number of LVAD implantations, but patient characteristics of this population - including timing of LVAD, usage of invasive hemodynamic monitoring, and timing of post-LVAD OHT - has remained relatively unchanged. Our sample patient population is representative of LVAD patients studied in other databases with regards to age, gender, race, and other demographic characteristics and also mortality trends between the pulsatile and continuous-flow eras. Without randomized control trials to better characterize the optimal management and timing of transplant after LVAD, our study describes representative clinical practice and trends in outcomes associated with changing practice patterns.

Our study has a few limitations. First, the NIS is a deidentified administrative database dependent on the appropriate coding of individual ICD-9-CM codes. Studies using such databases are susceptible to errors related to coding such as undercoding complications or variation in the application of diagnostic codes. This database also lacks many details available in registries, and unmeasured confounders cannot be excluded. Additionally, the NIS only captures events during the hospitalization, so complications and adverse events after discharge are not recorded. This limitation is counterbalanced by the larger sample size relative to other studies and the absence of reporting bias as compared to studies relying upon the

institutional experiences from a few specialized centers. Additionally, patients who undergo LVAD implantation have long hospital stays that capture most, if not all, of the acute complications causing morbidity and mortality. Finally, the ability of the NIS to capture detailed LVAD implantation and OHT data provided advantages in answering our central question over either the INTERMACS or UNOS databases, which capture largely LVAD or transplant data, respectively.

It is important to note that our cohort only assessed outcomes of OHT after LVAD placement in hospitalized patients. This represents a minority of patients (7.5%) in practice, as most institutions prefer to wait 2-3 mo after LVAD implantation to list patients for cardiac transplantation. Nevertheless, there will continue to be patients in the future who receive same-admission OHT after LVAD implantation, and our study provides meaningful guidelines on the timing of such OHT.

In conclusion, our analysis suggests that delayed same-admission OHT after LVAD implantation decreases mortality risk without increasing post-transplant length of stay, and, therefore, may be the preferred option in such a clinical setting. This new understanding of the optimal timing of same-admission OHT after LVAD implantation can greatly improve patient outcomes, although prospective data will be needed to enhance the validity of our findings.

COMMENTS

Background

Heart failure (HF) affects an estimated 5.8 million people in the United States and contributes to over 300000 deaths every year. Although most patients respond favorably to standard medical treatment, a considerable number of patients progress to end-stage HF refractory to medical therapy. Orthotopic heart transplant (OHT) is currently the gold standard therapy for these patients, but the number of donor hearts available for transplantation is far fewer than the number of patients on the transplant list. For this reason, left ventricular assist devices (LVADs), a class of electromechanical devices used for cardiac circulatory support, are increasingly being used to bridge patients to OHT. The optimal timing of when patients with LVADs should be bridged to OHT is an important consideration for patient care and has yet to be characterized.

Research frontiers

As the rate of LVAD implantation in the United States continues to increase, effective recommendations on the in-hospital management of LVAD implantation are needed. The optimal timing of when to bridge patients with LVADs to OHT remains controversial and is an active area of research.

Innovations and breakthroughs

Few groups have studied the impact of timing of same-admission OHT after LVAD on patient outcomes. Past studies on the appropriate use and outcomes of LVADs have been mostly limited to institutional experience and case series of select populations. The authors used the Nationwide Inpatient Sample (NIS), the largest national database of hospitalizations in the United States with data from over 36 million hospitalizations, to assess the optimal timing of OHT after LVAD implantation. It has been suggested that performing OHT early after LVAD placement confers an increased risk to patient. The study corroborates these claims and concludes that early OHT after LVAD placement (less than 8 d) is associated with increased in-hospital mortality. Therefore, depending on the clinical scenario, it might be reasonable for physicians to defer OHT immediately after LVAD placement.

Applications

This study offers recommendations for cardiologists and cardiac surgeons on the optimal timing of same-admission OHT after LVAD implantation. It also summarizes the demographics and characteristics of LVAD and post-LVAD OHT patients in the United States.

Terminology

Left ventricular assist device (LVAD): A class of electromechanical devices that help the left ventricle pump blood to the rest of the body; Orthotopic heart transplant (OHT): A procedure in which the patient's heart is removed and replaced with a donor heart.

Peer-review

Very interesting and clinically relevant question with novel use of the NIS database. Overall well written with interesting findings.

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ORIGINAL ARTICLE

Clinical Trials Study

Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation

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Abstract

AIM

To investigate whether consumption of an energy drink will acutely impair endothelial function in young healthy adults.

METHODS

Energy drinks are being consumed more and more worldwide, and have been associated with some deaths in adolescents and young adults, especially when consumed while exercising. After fasting and not smoking for at least 8 h prior, eleven medical students (9 males) received an electrocardiogram, blood pressure and pulse check, and underwent baseline testing (BL) of endothelial function using the technique of endothelium-dependent flow mediated dilatation (FMD) with high-resolution ultrasound

(according to recommended guidelines of the University of Wisconsin Atherosclerosis Imaging Research Program Core Laboratory). The subjects then drank an energy beverage (EB), a 24-oz can of Monster Energy, and the above was repeated at 90 min after consumption. The relative FMD (%) was calculated as the ratio between the average post-cuff release and the baseline diameter. Each image was checked for quality control, and each artery diameter was measured from the media to media points by two experts, 3 measurements at the QRS complex, repeated on 3 separate beats, and then all were averaged.

RESULTS

Subjects characteristics averages (given with standard deviations) include: Age 24.5 ± 1.5 years, sex 9 male and 2 female, weight 71.0 ± 9.1 kg, height 176.4 ± 6.0 cm, BMI 22.8 ± 2.7 kg/m^2. The hemodynamics were as follows, BL *vs* EB group respectively (mean ± SD): Heart rate 65.2 ± 11.3 *vs* 68.2 ± 11.8 beats per minute, systolic blood pressure 114.0 ± 10.4 mmHg *vs* 114.1 ± 10.4 mmHg, diastolic blood pressure 68.8 ± 9.3 mmHg *vs* 70.6 ± 7.1 mmHg; all were not significantly different. However after drinking the EB, a significantly attenuated peak FMD response was measured (mean ± SD): BL group 5.9% ± 4.6% *vs* EB group 1.9% ± 2.1%; P = 0.03). Given the increased consumption of energy beverages associated with exercise in young adults, more research is needed.

CONCLUSION

Energy beverage consumption has a negative impact on arterial endothelial function in young healthy adults.

Key words: Energy drinks; Endothelial function; Exercise; Flow mediated dilatation; Blood pressure

Core tip: Energy drinks are being consumed worldwide, and are gaining in popularity, especially amongst youth. We studied the acute effects that one energy drink has on endothelial function, a measure of vascular health. We found that consumption of a single 24-oz can of Monster Energy resulted in attenuation of brachial artery endothelium-dependent flow mediated dilatation in 11 healthy volunteers.

Higgins JP, Yang B, Herrin NE, Yarlagadda S, Le GT, Ortiz BL, Ali A, Infanger SC. Consumption of energy beverage is associated with attenuation of arterial endothelial flow-mediated dilatation. *World J Cardiol* 2017; 9(2): 162-166 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i2/162.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i2.162

INTRODUCTION

Energy beverages are being consumed increasingly worldwide, and have been associated with deaths in adolescents and young adults, especially when consumed while exercising[1].

What effect these energy drinks have on endothelial cells could help explain its effect on the cardiovascular system. These cells are part of the inner lining of blood vessels and have metabolic and also synthetic functions[2]. When endothelial cells are functioning abnormally or "endothelial dysfunction", it is associated with poor vascular reactivity, pro-thrombosis, pro-adhesion, pro-inflammation, and growth promotion[1,3].

Several recent reviews on cardiovascular complications associated with energy drink consumption suggest that the impact on endothelial function could be a factor in subsequent cardiac events[1,4]. Some of their ingredients individually or in combination may be associated with reduced endothelial function[5-7].

Mechanistically, endothelial dysfunction, where the endothelium's ability in regulating vascular resistance is impaired, may be related to reduced coronary blood flow[6,8]. Following exposure to stress such as exposure to cold, mental arithmetic, anger, exercise, cigarette smoking, cocaine, excess food or alcohol, the impaired ability to dilate the coronary arteries could result in supply-demand imbalance or coronary spasm, potentially leading to myocardial ischemia, coronary vasospasm, thrombosis and/or cardiac arrhythmia[6,9]. Importantly, this acute endothelial dysfunction could lead to ischemia, which in turn could lead to serious arrhythmia, coronary vasospasm, and myocardial infarction[1,6,10].

This study describes the acute changes of normal endothelial function after consumption of a single can of a popular energy drink[11].

MATERIALS AND METHODS

After fasting from caffeine for at least 24 h and food for at least 8 h prior, eleven healthy non-smoker medical students (9 males), average age 24.5 years (range 23-27 years), average BMI 22.8, received an electrocardiogram (ECG), blood pressure and pulse check, and underwent baseline testing (BL) of endothelial function using the technique of endothelium-dependent flow-mediated dilatation (FMD) with high-resolution ultrasound according to recommended guidelines of the University of Wisconsin Atherosclerosis Imaging Research Program Core Laboratory by a single registered vascular ultrasonographer who was certified by the University of Wisconsin Atherosclerosis Imaging Research Program Core Laboratory[12].

After resting supine for 10-min in a temperature-controlled room, a blood pressure cuff was placed on the widest part of proximal right forearm approximately 1 cm distal to the antecubital fossa. Using a 10 MHz resolution linear array vascular ultrasound transducer with a Philips iE33 ultrasound machine, the brachial artery was located above the elbow and scanned in longitudinal sections. After recording baseline B-mode digital images of the brachial artery and spectral Doppler images of

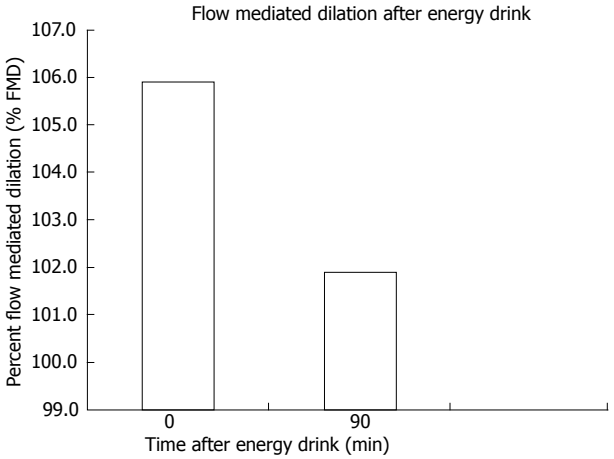

Figure 1 Flow mediated dilation at baseline (0 min) and after energy drink (90 min). Consumption of the EB resulted in a significantly attenuated peak FMD response (mean ± SD): BL group 5.9% ± 4.6% *vs* EB group 1.9% ± 2.1%; *P* = 0.03. FMD: Flow mediated dilatation; BL: Baseline testing; EB: Energy beverage.

flow, the forearm cuff was inflated to 250 mmHg for 5 min to induce reactive hyperemia. Immediately after deflation, spectral Doppler images are obtained to verify hyperemia. FMD of the brachial artery was measured 60 and 90 s after cuff deflation. The relative FMD (%) was calculated as the ratio between the largest post-cuff release and the baseline diameter. Each image was checked for quality control, and each artery diameter was measured from the media to media points by two experts, 3 measurements at the QRS complex, repeated on 3 separate beats, and then averaged.

The subjects then drank an energy beverage (EB), a 24-oz can of Monster Energy Drink® in approximately 1 min. The contents of this can include 54 g Sucrose, glucose, sucralose, maltodextrin, Sodium 360 mg Sodium Citrate Sodium Chloride, Caffeine 240 mg, Taurine 2000 mg, Niacin 40 mg 200% RDA Niacinamide, Pyridoxine 4 mg 200% RDA, Cyanocobalamin (B12) 12 mcg 200% RDA, Riboflavin (B2) 3.4 mg 200% RDA, Ginseng Extract 400 mg, Glucuronolactone, Inositol (B8), Guarana Extract, and L-Carnitine all listed as a part of a 5000 mg "Energy Blend", and Sodium Benzoate.

The subjects had FMD repeated at 90 min after consumption of the EB. The subjects were in the supine position for all ECGs and FMD measurements.

Statistical analysis

Statistical analyses were performed by John P Higgins and the statistical methods of this study were reviewed by Benjamin Yang using Microsoft Excel 2010 and the Data Analysis ToolPak. We used the *t*-test: Paired Two Sample for Means, and significance was defined as a *P*-value of 0.05 or less.

RESULTS

Subjects characteristics averages (given with standard deviations) include: Age 24.5 ± 1.5 years, sex 9 male and 2 female, weight 71.0 ± 9.1 kg, height 176.4 ± 6.0 cm, BMI 22.8 ± 2.7 kg/m^2.

The hemodynamics were as follows, BL *vs* EB group respectively (mean ± SD): Heart rate 65.2 ± 11.3 *vs* 68.2 ± 11.8 beats per minute, systolic blood pressure 114.0 ± 10.4 mmHg *vs* 114.1 ± 10.4 mmHg, Diastolic blood pressure 68.8 ± 9.3 mmHg *vs* 70.6 ± 7.1 mmHg; all were not significantly different.

With drinking the energy beverage, a significantly attenuated peak FMD response was found (mean ± SD): BL group 5.9% ± 4.6% *vs* EB group 1.9% ± 2.1%; *P* = 0.03 (Figure 1).

DISCUSSION

There are few studies exploring the effects on endothelial function following consumption of energy drinks.

In one study, fifty healthy volunteers (34 male, aged 22 ± 2 years) consumed either a 250-mL sugar-free energy drink or 250 mL carbonated water (control)[13]. They found that an hour after consumption of an energy drink, there was an acute decreased in endothelial function and increased platelet aggregation[7,13].

Another study involving 25 healthy young adults (13 male, aged 22.5 ± 0.6 years) who consumed either 355-mL Red Bull or 355-ml tap water noted that 2 h later, while blood pressure, heart rate and cardiac output were significantly increased, there was no reduction in endothelial function *via* finger skin microcirculation[14].

A 47-year-old healthy Caucasian male was noted to have a progressive attenuation of peak flow-mediated dilatation at 45 and 90 min following consumption of a 24-oz can of Monster Energy Drink®[7].

Energy drinks likely increase myocardial oxygen demand, and this may be increased under stress. For example, one study has noted that the combination of Red Bull and mental stress results in greater increases in heart rate and blood pressure, *i.e.*, a greater cardiovascular load[15].

While our study has noted a change in endothelial function after consumption of energy drinks, which is consistent with some of the previous studies, it still however conflicts with other studies. A possible explanation for these contrasting results on endothelial function, blood pressure, and heart rate in response to energy drinks include difference in methods of assessing endothelial function, difference in methods of monitoring blood pressure, difference in types of energy drinks consumed, difference in study participant profiles, and varying environmental stimuli[15,16]. Further investigations should take in account these differences, and also investigate how energy drink consumption in stress conditions affect endothelial function, as it would help simulate conditions in which energy drinks are used in real-life.

Weaknesses of our study include the fact that human measurement was performed on the arterial segments, which may be less accurate than automated detection methods. However one study analyzing variability and

reproducibility of FMD found that the mean absolute difference in %FMD from baseline FMD assessment was 1.04% and 0.99% for short-term (48 h) and medium-term (3 mo) repeat measurements, respectively[17]. Potential improvements in the future include a water load as a control, and having FMD baseline measurements performed on one day, followed by the FMD measurements with energy beverage consumption on the next day. In addition, this was a small sample, and such medical student volunteers may be healthier than the normal population.

Consumption of energy drinks may lead to an acute attenuation of endothelial function. Given the popularity of energy drinks, especially among youth, the combination of their consumption and exercise/extreme sports, and the rise in emergency room visits associated with their consumption, it is important that the specific physiological effects they are having be elucidated. Due to the potential endothelial dysfunction that may occur with energy drinks and the potential morbidity when consumed with exercise, further research is needed to explore these mechanisms and significance of their effects.

COMMENTS

Background

Energy drinks are being consumed more and more worldwide, and have been associated with deaths in adolescents and young adults, especially when consumed while exercising. Adverse cardiovascular events can be caused by abnormal endothelial cell function or "endothelial dysfunction". Endothelial cells form the inner lining of blood vessels and have metabolic as well as synthetic functions, which allow them to carry out multiple important tasks such as regulating vascular resistance. Mechanistically, reduced coronary blood flow may be a symptom of endothelial dysfunction, and is associated with poor vascular reactivity, pro-thrombosis, pro-adhesion, pro-inflammation, and growth promotion.

Research frontiers

There is a paucity of studies describing the effects on endothelial function following consumption of energy drinks. Several recent reviews on cardiovascular complications associated with energy drink consumption suggest that effects on endothelial function may play a role in subsequent cardiac events. Some of their ingredients individually or in combination may be associated with reduced endothelial function.

Innovations and breakthroughs

The current study describes the acute changes of normal endothelial function following consumption of a single can of a popular energy drink. While the study has noted a change in endothelial function after consumption of energy drinks, which is consistent with some of the previous studies, it still however conflicts with other studies. A possible explanation into these contrasting results on endothelial function, blood pressure, and heart rate in response to energy drinks include a difference in study methods and energy drink types. Further investigations should take in account these differences, and also investigate how energy drink consumption in stress conditions affect endothelial function, as it would help simulate conditions in which energy drinks are used in real-life.

Applications

Consumption of energy drinks may lead to an acute attenuation of endothelial function. Given the popularity of energy drinks, especially among youth, the combination of their consumption and exercise/extreme sports, and the rise in emergency room visits associated with their consumption, it is important that the specific physiological effects they are having be elucidated. Further, due to the possibility that endothelial dysfunction may play a role in morbidity with concomitant energy drink intake and exercise, more research is recommended to clarify the mechanisms of and significance of these effects.

Terminology

Energy drinks are also known as energy beverages. Popular brand names include Monster Energy Drink® and Red Bull Energy Drink® that contain high caffeine content, along with other ingredients. Flow-mediated dilatation is a non-invasive technique using high-resolution ultrasound to assess a vessel's endothelium-dependent (nitric oxide release) vasomotor function.

Peer-review

In this study, Dr. Higgins and his colleagues have done a very interesting investigation even though the report is very brief. They show a significant result that one kind of the "energy beverage" is associated with endothelial disfunction. The study is well designed and outcome is enough to warn the lovers of those drinks.

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ORIGINAL ARTICLE

Observational Study

Critical analysis of ineffective post implantation implantable cardioverter-defibrillator-testing

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Abstract

AIM

To test of the implantable-cardioverter-defibrillator is done at the time of implantation. We investigate if any testing should be performed.

METHODS

All consecutive patients between January 2006 and December 2008 undergoing implantable cardioverter-defibrillator (ICD) implantation/replacement (a total of 634 patients) were included in the retrospective study.

RESULTS

Sixteen patients (2.5%) were not tested (9 with LA/LV-thrombus, 7 due to operator's decision). Analyzed were 618 patients [76% men, 66.4 + 11 years, 24% secondary prevention (SP), 46% with left ventricular ejection fraction (LVEF) < 20%, 56% had coronary artery disease (CAD)] undergoing defibrillation safety testing (SMT) with an energy of 21 + 2.3 J. In 22/618 patients (3.6%) induced ventricular fibrillation (VF) could not be terminated with maximum energy of the ICD. Six of those (27%) had successful SMT after system modification or shock lead repositioning, 14 patients (64%) received a subcutaneous electrode array. Younger age (P = 0.0003), non-CAD (P = 0.007) and VF as index event for SP (P = 0.05) were associated with a higher incidence of ineffective SMT. LVEF < 20% and incomplete revascularisation in patients with CAD had no impact on SMT.

CONCLUSION

Defibrillation testing is well-tolerated. An ineffective SMT occurred in 4% and two third of those needed implantation of a subcutaneous electrode array to pass

a SMT > 10 J.

Key words: Implantable cardioverter defibrillator; Implantable cardioverter-defibrillator; Sudden cardiac death; Defibrillation test; Safety margin test; Ventricular fibrillation; Subcutaneous electrode array

Core tip: The implantable cardioverter defibrillator is crucial for primary and secondary prevention of severe life-threatening ventricular tachyarrhythmia. However the importance concerning intra-operative defibrillation testing and clinical relevance of inadequate testing of implantable cardioverter-defibrillator (ICD) devices remains still under debate. In this study, we analyzed our singe-center data of patients undergoing ICD implantation or replacement to determine the number of failed internal defibrillation testing at the time of ICD implantation and the consequences for management. We critically reflect the progressive trend to omit defibrillation testing at the time of ICD placement.

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INTRODUCTION

The implantable cardioverter defibrillator (ICD) is widely accepted for primary[1,2] and secondary prevention[3,4] of severe life-threatening ventricular tachyarrhythmia. The Heart Rhythm Society updated appropriate use criteria for ICD therapy[5], however the importance concerning intra-operative defibrillation testing and clinical relevance of inadequate testing of ICD devices remains still under debate[6-10].

One limitation of recent observational studies is a bias against testing in patients with more severe illness who are felt to be at increased risk for complications during intra-operative defibrillation testing[11-14]. Although severely impaired left ventricular function predicts higher intra-operative defibrillation threshold[8,15,16], patient with lower left ventricular ejection fraction (LVEF) are less likely[11-14] or even excluded[17] to undergo intra-operative defibrillation testing. Furthermore, severe, non revascularized coronary artery disease (CAD) is described as an absolute or relative contraindication for intra-operative defibrillation testing[15,18,19] and were less likely to undergo such testing in recent studies[12,14,16,19] although these patients would probably benefit most from an adequate defibrillation threshold.

We analyzed all consecutive patients between January 2006 and December 2008 undergoing ICD implantation or replacement to determine the number of failed internal defibrillation testing at the time of ICD implantation and the consequences for management. Our study extends the existing literature by also including patients excluded in previous studies. We critically reflect the progressive trend to omit defibrillation testing at the time of ICD placement[9,10,14].

MATERIALS AND METHODS

All consecutive patients undergoing initial ICD implantation or generator replacement from January 2006 to December 2008 were analyzed in this retrospective, single-center analysis.

Devices of all 4 important international companies were implanted. They were implanted in the catheter laboratory by 5 experienced cardiologists. In all patients, adequate ventricular sensing (> 9 mV) and pacing threshold (< 1 V) was confirmed. In the absence of absolute contraindications [*e.g.,* left atrial appendage (LAA) or left ventricular (LV) thrombus], intra-operative ICD testing was routinely performed to confirm correct sensing, processing, shock delivery and termination of T-wave shock-induced VF. Our protocol for intra-operative ICD testing required at least one induction of VF with successful first shock terminating VF at a safety margin of at least 10 Joule (J) below the maximum output of the implanted device. If the first shock was not successful, a second shock at the maximum output of the device was delivered. In case this shock was still not successful, external defibrillation with a 360 J biphasic shock was performed. Patients with the need of a second shock at the maximum output or external defibrillation in order to terminate VF were considered as ineffective safety margin testing (SMT) and were included in our study. Further management of these patients included intra-operative right ventricular lead reposition or ICD-system modification such as addition or subtraction of the superior vena cava (SVC) shock coil and polarity reversal, respectively. In case the SMT was still ineffective, the implantation of a subcutaneous electrode array, considered to be the most effective method for reducing defibrillation threshold[20], was planned.

Clinical characteristics, the consecutive management of pts with ineffective SMT and follow up data were explored by reviewing the medical records. Biplane left ventricular ejection fraction (LVEF) was derived by echocardiography and all measurements were done or supervised independently by an experienced cardiologist specialized in echocardiography. According to our center's standard practice, all patients underwent coronary angiography prior to ICD placement, ascertaining a definite coronary status. The implanted subcutaneous electrode array was solely a Medtronic 6996SQ.

Statistical analysis

Descriptive data were reported as frequencies, means and standard deviations or median and interquartile

range, respectively. Two-sided *t*-tests for independent samples were used for continuous variables. χ^2 analysis was used to compare categorical variables and one-way analysis of variance (ANOVA) was used to compare continuous variables. All statistics were computed with SPSS software (SPSS Inc, Chicago, Illinois). All probability values are 2-sided, with values of < 0.05 considered significant.

RESULTS

Patient characteristics

From 634 analyzed patients, 16 (2.5%) had no intra-operative defibrillation testing (9 patients (1.4%) due to LV- or LAA-thrombus and 7 (1.1%) due to decision of the operator (mainly atrial fibrillation with ineffective oral anticoagulation). Included in this retrospective analysis were 618 consecutive patients who received defibrillation testing after transvenous ICD implantation or ICD replacement. The population is described in Table 1. LVEF was $\leqslant$ 20% in 284 patients (46%). The indications for ICD placement included primary (76%) as well as secondary prevention (24%). The index arrhythmia for secondary prevention was sustained ventricular tachycardia (VT) in 72% and ventricular fibrillation (VF) in 28%, respectively. Patients with coronary artery disease (CAD) were further divided in those complete revascularized (56%) and those with residual significant stenoses > 70% or a central occluded main vessel, respectively (29% and 15%, respectively). Further on we distinguished whether one (36%) or more than one main vessel (8%) was not completely revascularized. Patients with the diagnosis of a non-ischemic cardiomyopathy were subdivided whether they suffered from post myocarditis dilated cardiomyopathy (DCM) or from other types of cardiomyopathy (*e.g.,* ARVD, LV non-compaction, HOCM, primary channelopathy).

Results of intra-operative defibrillation testing

Effective defibrillation SMT was performed in 596 patients (96.4%) with a mean energy of 20.8 + 2.3 J. In 22 patients (3.6%) induced VF could only be terminated with the maximum energy of the implanted device or with an external defibrillation (Table 1). There were no severe complications (death, major or minor strokes or cardiogenic shock) in any of the 618 SMT performed.

In 22 patients (3.6%) a > 10 J SMT could not be achieved intra-operatively with the initial ICD configuration. The patients with ineffective SMT were younger ($P = 0.003$), and in univariate analysis they were less likely to have CAD as underlying diagnosis ($P = 0.007$) or VT as the index arrhythmia ($P = 0.05$) for secondary ICD indication (Table 1).

Variables without impact on the efficiency of SMT in univariate analysis included whether or not patients had a LVEF < 20%, had a secondary preventive indication for ICD, were incompletely revascularized, had more than one main coronary vessel significantly diseased and were taking amiodarone, respectively (Table 1).

Management of patients with ineffective initial SMT

The characteristics of the patients with ineffective SMT are depicted in Table 2. One or more of the following system modifications were initiated: Reprogramming the defibrillation polarity in 21 and deactivation of the SVC shock coil in 19 patients as well as repositioning the right ventricular lead in 12 patients. Six patients (27%) passed subsequent SMT, 16 patients had still ineffective SMT and were planned for a subcutaneous electrode array. Two patients refused further procedures and in the remaining 14 patients an adequate SMT > 10 J was documented post implantation of a subcutaneous electrode array.

Tachyarrhythmia events during follow up

The mean follow up was 23.6 (+21) mo for patients with initially effective SMT and 15.8 (+21) mo for those with initially ineffective SMT. Antiarrhythmic medication was equally balanced between both groups (Table 3). In general, there were significantly more events in patients with CAD (19.6%) compared to patients with non CAD (12.1%) $P = 0.02$. There was a trend towards more events in patients with secondary prophylactic ICD indication ($P = 0.08$). No death or resuscitation occurred during the follow-up period, and 124/530 patients (23.4%) with initial effective SMT and 2/22 patients (9.1%) with initially ineffective SMT ($P = 0.02$) experienced tachyarrhythmia events (Table 3).

DISCUSSION

We analyzed a very large population undergoing intra-operative ICD defibrillation testing[6], including a significant group of patients (284 patients, 46% of total) with an LVEF < 20%, a patient group that was unlikely undergoing intra-operative ICD testing[11-14,16] or was even excluded from former studies[17].

Our data show several important findings: (1) Ineffective SMT occurred in roughly 4% of ICD implantations. Despite ICD-System reprogramming as well as RV shock lead repositioning, two thirds of those required implantation of a subcutaneous electrode array to pass a SMT > 10 J; (2) SMT can be performed safely and without major complications, even in patients with an LVEF < 20%. There was no impact on the efficacy of SMT compared to patients with an LVEF > 20%; (3) Severe coronary 2 or 3 vessel disease with residual significantly stenosed/occluded main vessels showed no impact on safety and efficacy of SMT; and (4) The percentage of patients who are unsuitable for intra-operative defibrillation testing is small (2.5% of our study population).

Ineffective intra-operative safety margin testing

Despite advancements during the last years in ICD systems and lead technology resulting in enhanced defibrillation efficacy, 4% in our patient population failed to

Table 1 Baseline characteristics

	All	Effective SMT	Ineffective SMT	*P*-value
Number, *n* (%)	618	596 (96.3)	22 (3.7)	
Sex				
Male, *n*	470	452	18	
Female, *n*	148	144	4	
Age (years)				
Mean (± SD)	66.4 (± 11)	66.7 (± 10.6)	54.6 (± 16.5)	*P* = 0.0003
Median (IQR)	69 (60-74)	69 (62-74)	54 (41-69)	
LVEF (%)				
Mean (± SD)	31 (± 12.4)	31 (± 12.5)	26.9 (± 9.0)	*P* = n.s.
Median (IQR)	30 (22-35)	30 (23-35)	30 (20-35)	
LVEF > 30%, *n* (%)	248 (40.1)	240 (36.9)	8 (3.2)	
LVEF < 30%, *n* (%)	370 (59.9)	356 (56.1)	14 (3.8)	*P* = n.s. (> 30% *vs* < 30%)
LVEF > 20%, *n* (%)	334 (54.0)	320 (49.8)	14 (4.2)	
LVEF < 20%, *n* (%)	284 (46)	276 (43.2)	8 (2.8)	*P* = n.s. (> 20% *vs* < 20%)
BMI (kg/m^2)				
Mean (± SD)	28.4 (± 4.7)	28 (± 4.7)	29 (± 4.0)	*P* = n.s.
Median (IQR)	28 (17-28)	28 (25-31)	29 (25.5-33)	
Indikation				
Primary prevention, *n* (%)	468 (76)	452 (72.6)	16 (3.4)	
Secundary prevention, *n* (%)	150 (24)	144 (20)	6 (4.0)	*P* = n.s. (pp *vs* sp)
Type of arrhythmia for secondary prevention, *n* (%)				
Sustained VT	108 (72)	106 (70.1)	2 (1.9)	
VF	42 (28)	38 (18.1)	4 (9.5)	*P* = 0.05 (VT *vs* VF)
SMT-Energy (J)				
Mean (± SD)	21 (± 2.3)	20.8 (± 2.3)	30.9 (± 2.0)	
Median (IQR)	20 (20-22)	20 (20-20)	30 (30-30)	
Diagnosis				
Non CAD, *n* (%)	270	254 (94.1)	16 (5.9)	
DCM (myocarditis), *n* (%)	232 (85)	218 (79)	14 (6.0)	
Other CM (non myocarditis), *n* (%)	38 (15)	36 (9.8)	2 (5.2)	
CAD, *n* (%)	348	342 (98.3)	6 (1.7)	*P* = 0.007 (nonCAD *vs* CAD)
Complete revascularized, *n* (%)	196 (56)	192 (54)	4 (2.0)	
Not complete revascularized, *n* (%)	152 (44)	150 (42.7)	2 (1.3)	*P* = n.s. (complete *vs* in-complete revascularized)
One vessel disease	124 (81.6)	122 (80.0)	2 (1.6)	
> One vessel disease	28 (18.4)	28 (18.4)	0 (0)	*P* = n.s. (one vesel *vs* > one)
Stenosed	100 (65.8)	100 (65.8)	0 (0)	
Occluded	52 (34.2)	50 (30.4)	2 (3.8)	*P* = n.s. (stenosed *vs* occluded)
Medication				
Amiodaron medication, *n* (%)	124 (20)	118 (15.2)	6 (4.8)	
No amiodaron, *n* (%)	494 (80)	478 (76.8)	16 (3.2)	*P* = n.s. (amio *vs* no amio)

SMT: Safety margin test; *n*: Number; SD: Standard deviation; IQR: Interquartile range; LVEF: Left ventricular ejection fraction; BMI: Body mass index; pp: Primary prevention; sp: Secondary prevention; VT: Ventricular tachycardia; VF: Ventricular fibrillation; CAD: Coronary artery disease; DCM: Dilated cardiomyopathy; CM: Cardiomyopathy; amio: Amiodarone; n.s.: Not significant; n/a: Not applicable.

achieve the conventional SMT > 10 J. This in line with similar findings of 6%-7% insufficient SMT in older retrospective studies[11,16] using less sophisticated ICD-systems, suggesting that an adequate defibrillation threshold is not only dependent on the implanted ICD-system. Russo *et al*[16] found that simply changing to a high output ICD-system to pass an initially insufficient SMT was not enough in 48% of patients. This further highlights the fact that an SMT < 10 J exhibits a more complex problem than just deliver higher shock energy[9] and that individual measures have to be taken to reach an acceptable SMT > 10 J. According to our data and in line with previous findings, VF as the index arrhythmia for ICD implantation, the diagnose of a non-ischemic cardiomyopathy and younger age were associated with a higher incidence of ineffective SMT. However, none of these predictors helped to identify the 22 patients of our study who failed to pass a SMT > 10 J (Table 2). In line with previous findings[12,16], our study revealed that still two third of patients after ICD system modification and RV lead replacement required further measures to reach a subsequent SMT > 10 J. In our study, we implanted a subcutaneous electrode array, a measure that is considered to be the most effective for reducing defibrillation threshold[15]. Inconsistent evidence exists regarding long term outcome of patients who do not meet an intra-operative SMT > 10 J[6,7,18] or where not tested at all[9,10].

On the other side, the HRS/EHRA/APHRS/SOLACE expert consensus statement on ICD programming and testing[21] states with a Class IIa recommendation, "that it is reasonable to omit defibrillation testing in patients undergoing initial left pectoral transvenous ICD implantation procedures where appropriate sensing, pacing and impedance values with fluoroscopically

Table 2 Characteristics of patients with failed intra-operative safety margin test

n	Age at time of implantation (years)	Sex (m/f)	Indication for ICD implantation	LVEF (%)	Primary *vs* secondary ICD indication	Further management after failed initial SMT
1	46	m	LAD stenosed	30	pp	Subcutaneous array
2	45	w	oCM	15	pp	PDT OK
3	74	w	oCM	36	pp	Subcutaneous array
4	41	m	cmpl revasc	39	pp	Subcutaneous array
5	54	w	DCM	10	pp	Subcutaneous array
6	25	m	oCM	20	sp	Subcutaneous array
7	68	m	DCM	35	sp	Subcutaneous array
8	69	m	RCA occluded	31	sp	PDT OK
9	73	m	oCM	30	pp	PDT OK
10	37	m	TGV surgery	30	pp	Subcutaneous array
11	69	m	DCM	20	pp	none
12	46	m	LAD stenosed	30	pp	Subcutaneous array
13	45	w	DCM	15	pp	PDT OK
14	74	w	DCM	36	pp	Subcutaneous array
15	41	m	cmpl revasc	39	pp	Subcutaneous array
16	54	w	DCM	10	pp	Subcutaneous array
17	25	m	DCM	20	sp	Subcutaneous array
18	68	m	DCM	35	sp	Subcutaneous array
19	69	m	RCA occluded	31	sp	PDT OK
20	73	m	DCM	30	pp	PDT OK
21	37	m	*vs* D surgery	30	pp	Subcutaneous array
22	69	m	DCM	20	pp	None

m: Male; w: Women; ICD: Internal cardioverter defibrillator; LAD: Left anterior descendent coronary artery; oCM: Other cardiomyopathy; cplm revasc: Complete revascularized; RCA: Right coronary artery; TGV: Transposition of the great vessels; VSD: Ventricular septum defect.

Table 3 Follow up

		All	Effective SMT	Ineffective SMT	*P*-value
FU, *n* (%)		552 (89.3)	530 (96)	22 (100)	
FU duration (mo)	Mean (± SD)	21.1 (± 21)	21.5 (± 21)	15.8 (± 21)	*P* = n.s.
Antiarrhythmica, *n* (%)					
	Amiodarone		122 (23.0)	6 (27)	*P* = n.s.
	Sotalex		2 (0.4)	0 (0)	*P* = n.s.
	β-blocker		485 (91.5)	20 (91)	*P* = n.s.
Events during FU, *n* (%)			124 (23.4)	2 (9.1)	*P* = 0.02
	Inadequate therapy		4 (0.8)	2 (9.1)	*P* = n.s.
	ATP		58 (10.9)	0 (0)	
	Shock delivery		36 (6.8)	0 (0)	
	ATP and shock delivery		20 (3.8)	0 (0)	
	VT ablation		6 (1.1)	0 (0)	

FU: Follow up; ATP: Anti tachycardia pacing; n.s.: Not significant.

well-positioned RV leads". Furthermore, with a class IIa recommendation the expert consensus state "that defibrillation testing is reasonable in patients undergoing a right pectoral transvenous ICD implantation or ICD pulse generator changes".

For the arguments mentioned above we recommend that a decision to perform intraoperative testing during ICD placement without absolute contraindication should be taken case-by-case. Our data suggest that the intraoperative testing should be considered for patients who are younger, patients with non-CAD as underlying disease and VF as the index arrhythmia for secondary ICD indication. Furthermore patients with HCM, special conditions such as severe obesity, amiodarone use and right pectoral implants as well as pre-existing RIATA (SJM) leads should be considered to be tested intraoperatively.

Rationale for intra-operative defibrillation testing

Up to 65% of implantation procedures are performed without any induction test[6,14]. Patients less likely to be tested were sicker and therefore more likely to have adverse outcomes, including death[6,11,13,16]. The strength of our study is that intra-operative testing was done in 97.5% of all consecutive patients. In contrast to former studies[11-13,16] we could show that testing the ICD at the time of placement is safe and effective, even if sicker patients (*e.g.*, LVEF < 20% and severe, non revascularized coronary 2 or 3 vessel disease) were included. Newer ICD systems with advancements in

defibrillator and lead technology and resulting enhanced defibrillation efficacy may be one reason for this finding. Nevertheless, 22 patients (4%) of our study population had an ineffective intra-operative SMT and would have been missed without consequently passing all patients without a clear contraindication through an intra-operative defibrillation test. Even if only a small fraction of patients could potentially benefit from a SMT at ICD-implantation, it poses a forensic issue to prove at least once device efficacy in adequate sensing, computing and termination of VF. In our study, 14/22 patients needed the implantation of a subcutaneous electrode array to achieve adequate DFTs. Although several reasons imply that long term survival may not necessarily be affected whether or not defibrillation testing is done[6,9,10,18], one study suggested that not having a defibrillation test was an independent risk factor of SCD even if sicker patients were the ones not tested[11]. However, no study so far was sufficiently powered to establish equivalence or superiority of a strategy of no testing *vs* SMT at the time of ICD placement as Strickberger *et al*[22] calculated a sample size of approximately 29000 patients that would need to be randomized in a mortality study to achieve definite conclusions on this question with an adequate statistical power.

Two recently published randomised studies showed that defibrillation testing at the time of ICD implantation does not appear to predict total mortality[9,10]. But still it remain legal and regulatory considerations: The labelling on all ICD's recommend an assessment of defibrillation efficacy at implant not least to document the defibrillation behaviour with new drugs and the integrity of new ICD systems coming to the market.

For the reasons mentioned above and underlined with the finding of our study, we conclude that defibrillation testing remains an important part of ICD placement and the decision to perform or omit testing should be taken case-by-case.

In conclusion, in the absence of sufficiently powered studies evaluating long term outcome of patients with an ineffective intra-operative defibrillation testing, our findings underline that routine SMT still remains an important part of ICD placement. An ineffective SMT occurs in about 4% of patients, and even after ICD system modification and RV shock lead repositioning three quarter of those need implantation of a subcutaneous electrode array to pass a SMT > 10 J.

COMMENTS

Background

The implantable cardioverter defibrillator (ICD) is widely accepted for primary and secondary prevention of severe life-threatening ventricular tachyarrhythmia. However the importance concerning defibrillation testing at the time of implantation and clinical relevance of inadequate testing of ICD devices still remains under debate.

Research frontiers

Defibrillation testing was done at the time of implantation in randomized trial investigating the efficacy of ICD therapy. They critically reflect the progressive trend to omit defibrillation testing at the time of ICD placement.

Innovations and breakthroughs

Two recently published randomised studies showed that ICD implantation without defibrillation testing is non-inferior to implantation with testing. Although one of these studies included 2500 patients, it is still underpowered to address the question of future shock efficacy or reduction of arrhythmogenic death. The authors' study present a large cohort of patients undergoing ICD-implantation and showed that in 4% of the patients the ICD did not terminate induced VT during intraoperative testing. Furthermore their data suggested that intraoperative testing of the ICD is a well-tolerated procedure.

Applications

The data of their study showed that intraoperative ICD-testing lead in a not negligible percentage of patients to a system modification or even a subcutaneous array implantation to prove correct detection and termination of induced ventricular fibrillation at the time of ICD-implantation.

Terminology

ICD are routinely implanted since 30 years to prevent sudden cardiac death. The detection of a life-threatening ventricular arrhythmia leads to a biphasic high energy 30-40 J impulse between the RV-coil and the subscapular located aggregate to terminate the arrhythmia. Testing the correct detection and termination of induced ventricular fibrillation at the time of ICD implantation is included as a recommendation in product labels.

Peer-review

This is a well-written paper.

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ORIGINAL ARTICLE

Observational Study

Association between high cystatin C levels and carotid atherosclerosis

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Institutional review board statement: This study was reviewed and approved by the Human Ethics Committee of Juntendo University.

Informed consent statement: The participants' clinical data were retrospectively retrieved from an institutional database. All of the examinations included in this study were performed as a routine part of the program, and none were aimed at specifically collecting data for the current study. The study protocol was approved by the institutional ethics committee. So, we did not obtain informed consent from every participant.

Conflict-of-interest statement: None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriate influence or bias the content of the paper.

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at tykobaya@juntendo.ac.jp. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM

To investigate the association between carotid atherosclerosis and cystatin C (CysC) and to determine the optimal CysC cut-off value.

METHODS

One hundred twenty-eight subjects were included in this study. Atherosclerosis was defined as a maximum carotid plaque thickness (MCPT) of greater than 2 mm. A receiver operating characteristic curve analysis was used to determine the diagnostic value of serum CysC for atherosclerosis. The subjects were divided into two groups according to the CysC cut-off value. We screened

for diabetes, hypertension, dyslipidemia, smoking status, alcohol consumption, and exercise behavior. The association between atherosclerosis and CysC levels was assessed using multivariate analysis.

RESULTS

The subjects were then divided into two groups according to the CysC cut-off value (0.73 mg/L). The median age of the high CysC group was 72 years (85% males), whereas that of the low CysC group was 61 years (63% males). The CysC levels were significantly correlated with Cr and estimated glomerular filtration rate (eGFR) values. Body-mass index, visceral fat area, hypertension, diabetes mellitus, and MCPT were significantly higher in the high CysC group than in the low CysC group. Furthermore, the eGFR was significantly lower in the high CysC group. Regarding lifestyle habits, only the exercise level was lower in the high CysC group than in the low CysC group. Multivariate analysis, adjusted for age and sex, revealed that high CysC levels were significantly associated with an MCPT of $\geqslant$ 2 mm (odds ratio: 2.92; 95%CI: 1.13-7.99).

CONCLUSION

Higher CysC levels were associated with an MCPT of $\geqslant$ 2 mm. The CysC cut-off value of 0.73 mg/L appears to aid in the diagnosis of atherosclerosis.

Key words: Cystatin C; Atherosclerosis; Carotid plaque; Maximum carotid plaque thickness; Visceral fat

Core tip: Atherosclerosis is a leading worldwide cause of morbidity and mortality. The association between cystatin C (CysC) and atherosclerotic disorders remains controversial, and the cut-off value of CysC for atherosclerosis is unknown. Our study revealed that the optimal CysC cut-off point was 0.73 mg/L by receiver operating characteristic curve analysis. Higher CysC levels were significantly and independently correlated with an maximum carotid plaque thickness of $\geqslant$ 2 mm in multivariate analysis. Our data indicate that CysC could be a useful laboratory tool for predicting atherosclerosis during health checkups.

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INTRODUCTION

Atherosclerosis is a leading worldwide cause of morbidity and mortality[1,2]. The incidence of cardiovascular diseases (CVDs), including cerebrovascular, peripheral arterial, and coronary artery disease, is increasing and accounts for approximately one-fourth of all deaths in World Health Organization member states[3]. More than 17 million people die annually from CVDs, and, by 2030, more than 23 million CVD-related deaths are expected to occur worldwide. In Japan, the age-standardized fraction of mortality from CVDs is approximately 30%.

The ankle-brachial index, pulse-wave velocity, flow-mediated dilation, and ultrasonic evaluation have been introduced as methods for assessing the structural and functional effects of atherosclerosis[4-6]. Carotid atherosclerosis, estimated by intima-media thickness (IMT), is a sensitive surrogate marker for CVD and can now be non-invasively measured by B-mode ultrasonography[7,8]. IMT is a marker for systemic subclinical atherosclerosis and a strong predictor of incident myocardial infarction and ischemic stroke[9,10]. Carotid plaque may be an even more powerful predictor of vascular outcomes than IMT[11,12]. Maximum carotid plaque thickness (MCPT), widely used for assessing atherosclerotic change, is associated with an increased risk of vascular morbidity[13].

High plasma adiponectin independently predicted death and major adverse cardiovascular events in a large community-based population[14]. High-sensitivity C-reactive protein serum levels were reported to be significantly related to the severity of coronary atherosclerosis[15]. In addition to these markers, serum cystatin C (CysC) has recently been proposed as a more reliable biomarker for atherosclerosis and chronic renal disease. Furthermore, high CysC levels are indicated as a useful marker for identifying an elevated risk of CVD and a higher total mortality among patients assessed as being at low risk by both creatinine (Cr) and estimated glomerular filtration rate (eGFR) values[16,17]. A previous study revealed that atherosclerotic changes associated with inflammation could be one mechanism by which CysC is associated with CVD[16]. However, the association between CysC and atherosclerotic disorders remains controversial, the cut-off values of CysC for atherosclerosis are unknown, and previous reports on this association as well as the association between CysC and MCPT are limited[18-20]. A diagnostic CysC cut-off value has not been determined. In this study, we examined the association between CysC levels and atherosclerotic changes in Japanese subjects.

MATERIALS AND METHODS

Subjects

The present cross-sectional study included 133 Japanese subjects who underwent an inpatient medical health checkup at Juntendo University Hospital, Tokyo from October 2010 to January 2013. Among these subjects, five were excluded because of missing laboratory data. Thus, 128 subjects [98 men and 30 women; median age, 70 years (age range, 39-87 years)] were included.

The subjects were asked to complete a self-administered questionnaire about their sociodemographic characteristics, past medical history (diabetes, hypertension, and dyslipidemia), and lifestyle behaviors (alcohol

consumption, current smoking status, and daily exercise activity).

The body weight, height, and waist circumference of the patients were measured, and the body-mass index [BMI (kg/m^2)] was calculated. Systolic and diastolic blood pressure were measured in a sitting position after a 15-min rest using a standard mercury sphygmomanometer. Venous blood samples were collected following overnight fasting. Plasma glucose concentrations, hemoglobin A1c (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), Cr, and CysC levels were also measured. Low-density lipoprotein cholesterol was estimated using the Friedewald equation [TC-HDL-C-(TG/5)]. For the assessment of visceral fat accumulation, abdominal fat areas were measured from abdominal CT scans taken at the umbilical level while in the supine position and during late expiration, according to the Japanese Guidelines for Obesity Treatment[21].

The following parameters were calculated: eGFR was calculated using the Japanese GFR inference formula, which was developed by the Japanese Society of Nephrology[22]: eGFR (mL/min per 1.73 m^2) = 194 × serum Cr (mg/dL) - 1.094 × age (years) - 0.287 (× 0.739 if female).

HbA1c was calculated as the National Glycohemoglobin Standardization Program (NGSP) value (%), which was developed by the Japan Diabetes Society[23]: HbA1c = NGSP (%) × 1.02 + 0.25.

Lifestyle-related diseases were defined using several criteria: (1) diabetes mellitus was defined as an HbA1c level of ⩾ 6.5%, a fasting plasma glucose level of ⩾ 126 mg/dL, or current antidiabetic therapy[24]; (2) hypertension was defined by a systolic blood pressure of ⩾ 140 mmHg, a diastolic blood pressure of ⩾ 90 mmHg, or current antihypertensive therapy[25]; and (3) dyslipidemia was defined as a fasting TG level of ⩾ 150 mg/dL, a low-density lipoprotein cholesterol level of ⩾ 140 mg/dL, or an HDL-C level of < 40 mg/dL[26]. Three unhealthy lifestyle behaviors were evaluated in this study: Drinking alcohol more than once a week, current smoking, and no regular physical activity.

A detailed protocol for measuring carotid artery atherosclerosis has been published[27]. Carotid plaque and IMT were measured using high-resolution B-mode ultrasonography to estimate atherosclerosis in the carotid artery. Eight technicians who were trained by a supervisor physician and who were certified in the protocol assessed carotid plaque and the mean IMT of the common carotid artery. A plaque was defined as a maximum IMT of > 1.0 mm. MCPT was measured at the peak plaque prominence in any of the carotid artery segments. Atherosclerosis was defined on the basis of the severity of carotid atherosclerosis by MCPT at a cut-off level of 2 mm. As previously reported, an MCPT of ⩾ 2 mm is defined as an atherosclerotic change[13].

Statistical analysis

The results were expressed as medians of the test parameters. The Youden index, a point on the receiver operating characteristic (ROC) curve, was used to determine the diagnostic values of serum CysC levels that were indicative of atherosclerosis.

In a second analysis, the subjects were divided into two groups according to CysC levels above and below the cut-off value. Their demographic characteristics were then compared using the *t* test for continuous variables and the chi-square test for categorical variables. Multiple logistic regression analysis with adjustments for age and sex was conducted to determine the correlations between an MCPT of ⩾ 2 mm and metabolic variables including CysC level. Our study included only 128 subjects, of whom 52 had arteriosclerosis. Because there is a limit to the number of adjusted variables, we combined several metabolic related variables in one item. Variables that were significantly associated with an MCPT of ⩾ 2 mm were then investigated with multiple logistic regression analysis.

Statistical test results were considered significant when the *P* value was < 0.05. All calculations were performed using JMP Pro, version 11 (SAS Institute, Cary, NC, United States). The study protocol was approved by the Human Ethics Committee of Juntendo University. The participants' clinical data were retrospectively retrieved from an institutional database. All of the examinations included in this study were performed as a routine part of the program, and none were aimed at specifically collecting data for the current study. The study protocol was approved by the institutional ethics committee, so it was not necessary to obtain informed consent from the participants. A biostatistician reviewed the study.

RESULTS

The subject characteristics are shown in Table 1. The median age was 70 years (77% males). Twenty-three (18%) subjects smoked, 78 (61%) were alcohol consumers, and 90 (70%) did not exercise regularly. The median visceral fat area was 125.2 cm^2. Sixty-one (48%) subjects were diagnosed with hypertension, 72 (56%) with dyslipidemia, and 29 (23%) with diabetes mellitus. The ROC analysis conducted to determine the cut-off value of CysC revealed a significantly higher risk of atherosclerosis at 0.73 mg/L (Figure 1) (sensitivity: 82.7%, specificity: 52.6%).

The subjects were then divided into two groups according to the CysC cut-off value (0.73 mg/L). The subjects' characteristics according to the CysC level are shown in Table 2. The median age of the high CysC group was 72 years (85% males), whereas that of the low CysC group was 61 years (63% males). The CysC levels were significantly correlated with Cr and eGFR values. BMI, visceral fat area, hypertension, diabetes mellitus, and MCPT were significantly higher in the high CysC group than in the low CysC group. Furthermore, the eGFR was significantly lower in the high CysC group. Regarding lifestyle habits, only the exercise level was

Table 1 Baseline characteristics of the study population

Variables	Median (min, max) or *n* (%)
Age (yr)	70 (39, 87)
Sex (male)	98 (77)
Body-mass index (kg/m^2)	24.2 (15.1, 38)
Lifestyle-related items	
Current smokers	23 (18)
Alcohol consumers	78 (61)
No exercise habits	90 (70)
Visceral fat area (cm^2)	125.2 (22.9, 281.7)
Clinical history	
Ischemic heart disease, *n* (%)	6 (5)
Blood pressure	
Systolic blood pressure (mmHg)	122 (92, 156)
Diastolic blood pressure (mmHg)	68 (50, 86)
Diagnosed hypertension	61 (48)
Lipid metabolism	
Total cholesterol (mg/dL)	194.5 (115, 727)
High-density lipoprotein cholesterol (mg/dL)	54 (30, 96)
Low-density lipoprotein cholesterol (mg/dL)	111 (41, 205)
Triglycerides (mg/dL)	99.5 (37, 593)
Diagnosed dyslipidemia	72 (56)
Glucose metabolism	
Fasting plasma glucose (mg/dL)	93.5 (74, 226)
Hemoglobin A1c (%)	5.3 (4.5, 8.3)
Diagnosed diabetes mellitus	29 (23)
Kidney function	
Creatinine (mg/dL)	0.75 (0.38, 1.36)
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	78.4 (38.9, 122.6)
Cystatin C (mg/L)	0.78 (0.49, 1.45)
Carotid ultrasonography	
Right common carotid artery plaque thickness (mm)	0 (0, 3.6)
Right carotid bulb-internal carotid artery plaque thickness (mm)	1.5 (0, 5.5)
Left common carotid artery plaque thickness (mm)	0 (0, 2.8)
Left carotid bulb-internal carotid artery plaque thickness (mm)	1.5 (0, 4.2)
Right common carotid artery maximum intima-media thickness (mm)	1.0 (0.6, 1.9)
Left common carotid artery maximum intima-media thickness (mm)	1.0 (0.7, 2.3)

lower in the high CysC group than in the low CysC group. In addition, sensitivity, specificity, positive predictive value, and negative predictive value as calculated from the data in Table 2 were 83%, 53%, 54% and 82%, respectively.

Next, we compared differences in demographics and clinical variables between subjects with MCPTs of ⩾ 2 mm or < 2 mm (Table 3). Age, visceral fat area, hypertension, diabetes mellitus, Cr, eGFR, and CysC were significantly higher in the MCPT of ⩾ 2 mm group than the < 2 mm group. Furthermore, the eGFR was significantly lower in the MCPT of ⩾ 2 mm group. The two groups did not differ with regard to lifestyle habits.

The factors associated with an MCPT of ⩾ 2 mm are shown in Table 4. Multivariate analysis, adjusted for age and sex, revealed that high CysC levels were significantly associated with an MCPT of ⩾ 2 mm (odds ratio: 2.92; 95%CI: 1.13-7.99).

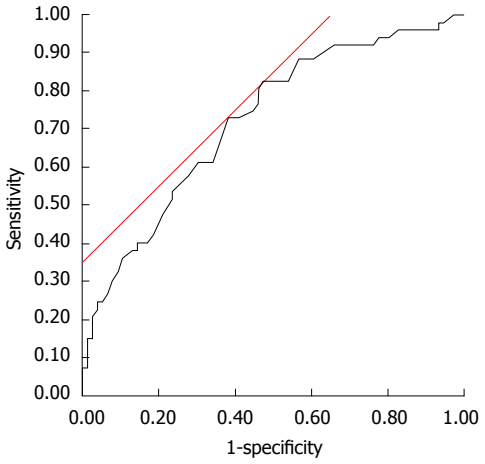

Figure 1 Receiver operating characteristic curve for predictive value of serum cystatin C levels. The receiver operating characteristic curve for the predictive value of serum CysC levels in detecting an MCPT of > 2 mm in 128 subjects had an area under the curve of 0.724. A serum CysC level of ⩾ 0.73 mg/L indicated an MCPT of > 2 mm with 82.7% sensitivity and 52.6% specificity. CysC: Cystatin C; MCPT: Maximum carotid plaque thickness.

DISCUSSION

In this study, multivariate analysis revealed that higher CysC levels were significantly associated with carotid atherosclerosis, as defined by an MCPT of ⩾ 2 mm, in middle-aged and elderly Japanese subjects. The cut-off CysC value (0.73 mg/L) could aid in the diagnosis of atherosclerosis. To our knowledge, this is the first report demonstrating an association between CysC and carotid atherosclerosis as assessed by MCPT. The CysC cut-off level potentially has promising clinical value in the diagnosis of atherosclerosis.

Our results revealed a significant association between high CysC levels and an MCPT of ⩾ 2 mm. A meta-analysis previously revealed that CysC is strongly and independently correlated with the risk of subsequent cardiovascular disease[28]. Although several studies have revealed an association between high CysC levels and atherosclerosis, their results differed from ours because of the different targets and indicators used. A previous study, which analyzed 637 Japanese subjects without chronic kidney disease, revealed that CysC was positively correlated with the cardio-ankle vascular index in women[19]. In a study of 60 Japanese hypertensive patients, serum CysC levels were positively correlated with carotid IMT[29]. In data collected *via* 64-slice CT coronary angiography, a high CysC level was found to be significantly correlated with early-stage coronary atherosclerotic plaques in 405 Japanese patients without established chronic kidney dysfunction[18]. Our results are in agreement with the previous hypothesis that CysC level is a reliable marker for atherosclerosis.

There are several possible explanations for the association between CysC and atherosclerotic change. First, inflammation may be associated with both CysC and atherosclerosis. The Cardiovascular Health Study[30], which

Table 2 Subject characteristics associated with cystatin C levels

Variables	Median (min, max) or *n* (%)		*P* value
	Higher cystatin C (≥ 0.73) (*n* = 79)	Lower cystatin C (< 0.73) (*n* = 49)	
Age (yr)	72 (46, 87)	61 (39, 80)	< 0.01[1]
Sex (male)	67 (85)	31 (63)	< 0.01[2]
Body-mass index (kg/m^2)	24.9 (17.0, 38.0)	23.5 (15.1, 30.2)	< 0.01[1]
Visceral fat area (cm^2)	142.7 (48.3, 281.7)	103.7 (22.9, 249.2)	< 0.01[1]
Lifestyle habits			
Current smokers	14 (23)	9 (19)	0.88[2]
Alcohol consumers	47 (59)	31 (63)	0.67[2]
No exercise habits	28 (35)	10 (20)	0.07[2]
Diagnosed hypertension	48 (61)	13 (27)	< 0.01[2]
Diagnosed dyslipidemia	45 (57)	27 (55)	0.84[2]
Diagnosed diabetes mellitus	24 (30)	5 (10)	< 0.01[2]
Kidney function			
Creatinine (mg/dL)	0.81 (0.45, 1.36)	0.62 (0.38, 0.97)	< 0.01[1]
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	70.6 (38.9, 110.2)	88.7 (59.7, 122.6)	< 0.01[1]
Carotid ultrasonography			
Maximum carotid plaque thickness ≥ 2 mm	43 (54)	9 (18)	< 0.01[2]

[1]Student *t* test was used for estimating the significance; [2]χ^2 test.

Table 3 Subject characteristics associated with maximum carotid plaque thickness

Variables	Median (min, max) or *n* (%)		*P* value
	MCPT ≥ 2 mm (*n* = 52)	MCPT < 2 mm (*n* = 76)	
Age (yr)	72 (51, 87)	66 (39, 83)	< 0.01[1]
Sex (male)	42 (81)	56 (74)	< 0.35[2]
Body-mass index (kg/m^2)	24.1 (17.0, 38.0)	24.3 (15.1, 31.7)	< 0.35[1]
Visceral fat area (cm^2)	138.9 (30.5, 281.7)	115.8 (22.9, 249.2)	< 0.10[1]
Lifestyle habits			
Current smokers	9 (17)	14 (18)	0.85[2]
Alcohol consumers	28 (54)	50 (66)	0.17[2]
No exercise habits	18 (35)	20 (26)	0.31[2]
Diagnosed hypertension	32 (62)	29 (38)	< 0.01[2]
Diagnosed dyslipidemia	29 (56)	43 (57)	0.93[2]
Diagnosed diabetes mellitus	18 (35)	11 (14)	< 0.01[2]
Kidney function			
Creatinine (mg/dL)	0.80 (0.45, 1.36)	0.75 (0.38, 1.17)	< 0.03[1]
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	73.3 (38.9, 111.9)	80.2 (47.9, 122.6)	< 0.02[1]
Cystatin C (mg/L)	0.83 (0.55, 1.45)	0.72 (0.49, 1.22)	< 0.01[1]

[1]Student *t* test was used for estimating the significance; [2]χ^2 test.

analyzed 4637 ambulatory elderly patients, revealed a significant linear association between CysC and C-reactive protein but not Cr or eGFR[31]. It is well known that inflammation plays a role in atherogenesis, atherosclerotic plaque progression, and acute coronary syndrome. Second, CysC plays an important role in maintaining atherosclerotic plaque stability. A previous study[32] analyzed 31 plaques removed by endarterectomy, demonstrating with immunohistochemistry that CysC in human carotid plaques localized with collagen and elastin. An imbalance between cysteine proteases and CysC in arterial wall remodeling occurs in vascular diseases, such as atherosclerosis and abdominal aortic aneurysm[33].

Imaging assessments, such as ultrasound and CT, are often performed for assessing arteriosclerotic vascular disease. However, not all institutions can practice such assessments because of the lack of sonographers or appropriate devices. Therefore, it is potentially important that atherosclerosis can be evaluated using a blood test, such as for CysC levels. A diagnostic CysC cut-off value has not been previously determined. Our study revealed that the CysC cut-off value of 0.73 mg/L could contribute to the diagnosis of atherosclerosis.

Our study had a few limitations. First, the subjects were selected from a single institution, the sample size was small, and > 70% of our subjects were healthy men. Selection bias may have affected the analysis, as the investigated cohort did not accurately represent the Japanese population. Thus, future large-scale cohort studies are required. Second, lifestyle habits were evaluated using a self-administered questionnaire, and the subjects may have stated that they had a healthier lifestyle than they actually did. Further evaluations of lifestyle habits based on a validated questionnaire are

Table 4 Univariate and multivariate logistic regression analysis for variables associated with an maximum carotid plaque thickness of ≥ 2 mm

Variables	Univariate		Multivariate[1]	
	Odds ratio	95%CI	Odds ratio	95%CI
Cystatin C	5.31	2.27-12.39	2.92	1.13-7.99
Diabetes mellitus	3.13	1.33-7.37	1.82	0.70-4.86
Hypertension	2.59	1.26-5.36	1.56	0.69-3.53
Dyslipidemia	0.97	0.48-1.97		
Current smoking	0.91	0.36-2.30		
Alcohol consumers	0.61	0.29-1.25		
Exercise habits	0.67	0.31-1.45		
Visceral fat area ⩾ 100 cm^2	1.31	0.62-2.78		
AICc[2]			158	
$^3R^2$			0.16	

[1]Adjusted for age and sex; [2]Akaike's Information Criterion; [3]Coefficient of determination.

necessary. Third, causal inferences cannot be made because of the cross-sectional nature of the study design. A prospective study is required for determining whether higher CysC levels are associated with the development of atherosclerosis-related diseases or death.

In conclusion, higher CysC levels were correlated with carotid atherosclerosis as defined by an MCPT of ⩾ 2 mm among middle-aged and elderly Japanese subjects. Higher CysC levels have a low specificity but a high sensitivity and can therefore help exclude atherosclerosis. The CysC cut-off value of 0.73 mg/L appears to aid in the diagnosis of atherosclerosis. Our data indicate that CysC could be a useful laboratory tool for predicting atherosclerosis during health checkups.

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COMMENTS

Background

Atherosclerosis is a leading worldwide cause of morbidity and mortality. Carotid plaque may be a powerful predictor of vascular outcomes. Maximum carotid plaque thickness (MCPT), widely used for assessing atherosclerotic change, is associated with an increased risk of vascular morbidity.

Research frontiers

Serum cystatin C (CysC) has recently been proposed as a reliable biomarker for atherosclerosis and chronic renal disease. However, the association between CysC and atherosclerotic disorders remains controversial, the cut-off values of CysC for atherosclerosis are unknown, and previous reports on this association as well as the association between CysC and MCPT are limited. A diagnostic CysC cut-off value has not been determined.

Innovations and breakthroughs

Higher CysC levels were associated with an MCPT of ⩾ 2 mm. The CysC cut-off value of 0.73 mg/L appears to aid in the diagnosis of atherosclerosis.

Applications

It may be difficult for an institution to practice imaging assessment because of the lack of sonographers or appropriate devices. Therefore, it is potentially important that atherosclerosis can be evaluated using a blood test, such as CysC levels. The CysC cut-off value of 0.73 mg/L could contribute to the diagnosis of atherosclerosis.

Terminology

CysC is a 13-kD protease inhibitor which is produced by all nucleated cells. It is mainly used as a biomarker of kidney function. Recently, it has been studied for its role in predicting new-onset or deteriorating cardiovascular disease.

Peer-review

This is a well-written article investigating the association between CysC and carotid atherosclerosis.

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META-ANALYSIS

Ivabradine in the treatment of systolic heart failure - A systematic review and meta-analysis

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Abstract

AIM

To perform a systematic-review and meta-analysis to compare outcomes of ivabradine combined with beta-blocker to beta-blocker alone in heart failure with reduced ejection fraction (HFrEF).

METHODS

We searched PubMed, Cochrane, EMBASE, CINAHL and Web of Science for trials comparing ivabradine + beta-blocker to beta-blocker alone in HFrEF. We performed a systematic-review and meta-analysis of published literature. Primary end-point was combined end point of cardiac death and hospitalization for heart failure.

RESULTS

Six studies with 17671 patients were included. Mean follow-up was 8.7 ± 7.9 mo. Combined end-point of heart failure readmission and cardiovascular death was better in ivabradine + beta-blocker group compared to beta-blocker alone (RR: 0.93, 95%CI: 0.79-1.09, P = 0.354). Mean difference (MD) in heart rate was higher in the ivabradine + beta-blocker group (MD: 6.14, 95%CI: 3.80-8.48, P < 0.001). There was no difference in all cause mortality (RR: 0.98, 95%CI: 0.89-1.07, P = 0.609), cardiovascular mortality (RR: 0.99, 95%CI: 0.86-1.15, P = 0.908) or heart failure hospitalization (RR: 0.87, 95%CI: 0.68-1.11, P = 0.271).

CONCLUSION

From the available clinical trials, ivabradine + beta-blocker resulted in a significantly greater reduction in HR

coupled with improvement in combined end-point of heart failure readmission and cardiovascular death but with no improvement in all cause or cardiovascular mortality. Given the limited evidence, further randomized controlled trials are essential before widespread clinical application of ivabradine + beta-blocker is advocated for HFrEF.

Key words: Ivabradine; Heart failure

Core tip: Ivabradine was recently given a class IIa indication in the 2016 focused update on systolic heart failure in the ACC/AHA/HFSA guidelines. But it is unclear whether ivabradine offers any additional benefit over and above that offered by beta blockers. Our analysis showed lower heart rate and combined end point of cardiac death and heart failure hospitalization at follow-up with ivabradine combined with beta blocker compared to beta blocker alone. Combined therapy did not improve cardiovascular mortality, all cause mortality or heart failure hospitalization. Further studies are essential before widespread use of combination therapy with ivabradine can be recommended.

Anantha Narayanan M, Reddy YNV, Baskaran J, Deshmukh A, Benditt DG, Raveendran G. Ivabradine in the treatment of systolic heart failure - A systematic review and meta-analysis. *World J Cardiol* 2017; 9(2): 182-190 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i2/182.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i2.182

INTRODUCTION

Chronic congestive heart failure affects nearly 2%-3% of population and is associated with a one-year mortality of 6.4% in a recent study[1]. Standard pharmacological treatment for heart failure with reduced ejection fraction (HFrEF) includes beta-blockade which unequivocally decreases cardiovascular and heart failure related morbidity and mortality, in addition to promoting beneficial reverse remodeling[2,3].

Elevated resting heart rates has been shown to be an independent predictor of mortality in heart failure, presumably acting through increased myocardial oxygen demand, and also serves as a marker of severity of underlying neurohormonal activation and cardiovascular disease[4-6]. In regard to the former, in patients with left ventricular dysfunction associated with ischemic cardiomyopathy, heart rates > 70 beats per minute (bpm) are associated with a 34% increase in cardiovascular mortality and 53% increase in hospitalization when compared to heart rates below 70 bpm[7]. Benefits derived from beta-blockers seem to be derived partly from their heart rate lowering properties[8]. However, their negative inotropic properties can have undesirable actions on myocardial contractility[9].

Ivabradine is a novel drug that inhibits the pacemaker current I(*f*) thereby slowing heart rates without exhibiting negative inotropic effect on the myocardium[10] or altering ventricular action potential[11]. In SHIFT[12], ivabradine improved the composite end point of hospitalization and cardiovascular death in patients with HFrEF in sinus rhythm with heart rates $\geqslant$ 70[12,13]. The 2016 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) Focused Update on the Management of Heart Failure[14] and the European Society of Cardiology (ESC) guidelines[15] have given a Class IIa (level of evidence B) recommendation for ivabradine use for patients with chronic HFrEF who are on guideline directed medical therapy [includes a maximum tolerated dose of beta-blocker, ACEi and mineralocorticoid receptor antagonist (MRA)] and who are in sinus rhythm with resting heart rates above 70 bpm (> 75 bpm in the European Society). It should be noted that in the SHIFT trial[12], only 26% of the patient population were on target beta-blocker dosage. Thus the utility of ivabradine in the modern era, particularly with the recent approval of sacubitril with its dramatic improvement in mortality and heart failure outcomes[16] remains uncertain. To consolidate the available evidence regarding ivabradine in HFrEF, we performed a systematic review and meta-analysis including all the available clinical trials to date to evaluate the benefit of ivabradine therapy in combination with beta-blocker compared to beta-blocker alone in chronic HFrEF.

MATERIALS AND METHODS

Data search

An electronic database search was performed with the following search terms "ivabradine", "heart failure with reduced ejection fraction", "resting heart rates" and "systolic heart failure" in PubMed, EMBSASE, Cochrane, CINAHL and Web of Science for studies published between January-1960 and August-2016 comparing the addition of ivabradine to beta-blocker *vs* beta-blocker only therapy. Supplementary appendix-1 shows PubMed search strategy.

The systematic review and meta-analysis was performed per PRISMA guidelines as shown in the Supplementary checklist[17] and Supplementary Figure 1 shows the PRISMA flowchart. We also reviewed relevant editorials, review articles and reference sections of included studies. We excluded conference abstracts with unpublished data as mentioned in the Cochrane guidelines for meta-analysis. An expert biostatistician has reviewed the paper for statistical accuracy.

Inclusion criteria

Studies selected met the following criteria: Randomized controlled trials (RCTs), retrospective or prospective observational cohorts; included HFrEF of < 40%; compared two groups, one with ivabradine and beta-blocker and the other with beta-blocker alone; included adult patients;

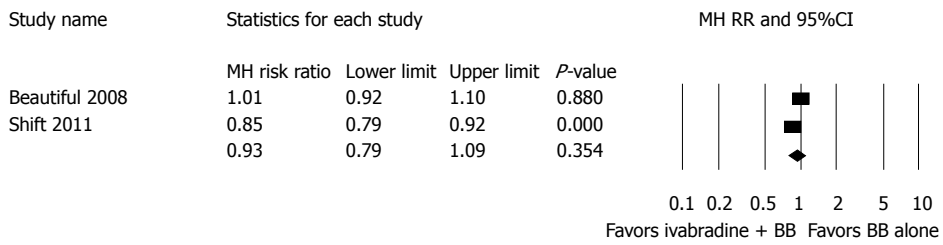

Figure 1 Comparison of Mantel-Haenszel risk ratio for combined end points of cardiovascular death and hospitalization for heart failure between ivabradine + beta-blocker *vs* beta-blocker alone. MH RR: Mantel-Haenszel risk ratio; BB: Beta blockers.

published in English language.

Study definitions

We defined all cause mortality as death from any cause at follow-up. Cardiovascular mortality was defined as death from any cardiac cause including heart failure, myocardial infarction, arrhythmia, sudden cardiac death or stroke.

Data extraction

Table 1 shows extracted patient demographics including mean age, sample size, co-morbidities, mortality data and risk estimates. Authors Mahesh Anantha Narayanan and Yogesh N Reddy reviewed the studies independently. A consensus was achieved by a third reviewer when the first two reviewers could not resolve any disagreement. We sought help from an experienced librarian when articles were not available online.

Outcomes

The primary outcome was combined end-point of heart failure and cardiovascular death. Secondary outcomes included mean reduction in heart rate at follow up compared to baseline, all cause mortality, cardiovascular mortality, six-minute walking distance (6MWD) and ejection fraction (EF) at follow up.

Statistical analysis

We used comprehensive meta-analysis (CMA) version 3.3.07 for statistical analysis. Categorical events were pooled using the random effects model, with pooled effect size represented by Mantel-Haenszel (MH) risk ratio (RR) with a 95% confidence interval (CI) limit. MH RR is a technique that generates an estimate of association between exposure and outcome after adjusting for confounding. Difference in Means (MD) was used for reporting outcomes with continuous variables. The combined ivabradine and beta-blocker group was the experimental group and so any MH RR (with 95%CI) that is less than 1 favors this cohort. Funnel-plots were used for assessing bias visually. Cochrane's Q-statistics were used to determine heterogeneity. I^2 values of > 50%, 25%-50% and 0%-25% were considered to be high, moderate and low heterogeneity, respectively. We used an exclusion sensitivity analysis to analyze heterogeneity when required. P value of < 0.05 was considered statistically significant. A meta-regression was performed when necessary to analyze the impact of moderator variables on outcomes of interest.

RESULTS

Characteristics of the included studies

A total of 696 studies were obtained using the initial search strategy as shown in Supplementary Figure 1. Initially 7 studies[12,18-23] met our inclusion criteria. We excluded the SHIFT sub group study as the sub group was not independent of the main SHIFT study population. Finally, we included 6 studies[12,18-21,23] with a total of 17671 patients. Mean follow-up was 8.7 ± 7.9 mo. A total of 8845 patients received ivabradine with beta-blocker and 8826 patients received only beta-blocker. Table 1 shows characteristics of the included studies and Supplementary Table 1 summarizes the results of analyses comparing ivabradine and beta-blocker *vs* beta-blocker alone in patients with chronic HFrEF.

Combined end point of cardiovascular death and hospitalization for worsening heart failure

A total of two studies reported combined end-point of cardiovascular death and hospitalization at follow up between the combined ivabradine + beta-blocker and the beta-blocker only group (Figure 1). MH RR was lower in the combined therapy group when compared to beta-blocker only group (MH RR: 0.93, 95%CI: 0.79-1.09, P = 0.354). Heterogeneity was high (I^2 = 87%) among the included studies.

Heart rates at follow up

Change in heart rates at follow up from baseline was reported in all included studies. Difference in means (MD) for reduction in heart rate from baseline was greater in the ivabradine + beta-blocker group when compared to beta-blocker alone difference in means (MD): 6.14, 95%CI: 3.80-8.48, P < 0.001 (Figure 2). Funnel-plot showed low risk of bias as shown in Supplementary Figure 2A and heterogeneity was high (I^2 = 95). A sensitivity analysis performed with exclusion of the study[18] with the maximum strength did not alter the results of the analysis (MD: 6.24, 95%CI: 2.71-9.78; P = 0.001). Analysis of only RCTs still showed that mean reduction in heart rates from baseline was greater in the combined ivabradine and beta-blocker group when compared to beta-blocker alone (MD: 6.88, 95%CI:

Table 1 Patient demographics

Ref.	Type of study	Total No. of patients	Age mean or median in years		Ivabradine + beta blocker (*n*)	Beta blocker alone (*n*)	Follow up time (mean/ median) months	Mean baseline HR	NYHA class Ⅲ - Ⅳ %		Coronary artery disease *n* (%)	Mean baseline ejection fraction	Atrial fibrillation	Beta blockers	
			Ivabradine + beta blocker	Beta blocker alone					Ivabradine + beta blocker	Beta blocker alone				Ivabradine + beta blocker	Beta blocker alone
ETHIC-AHF[23] 2016	RCT	71	66 (15)	68 (12)	33	38	4	88	93	97	5 (10)	30%	NA	88	97
Bagriy *et al*[21] 2015	Prospective non-randomized	69	63 (12)	62 (11)	33	36	5	83	59	58	39 (57)	37%	NA	100	100
CARVIVA HF[20] 2011	RCT	80	67 (9)	67 (10)	42	38	3	78	50	42	NA	27%	NA	55	57
Amosova *et al*[19] 2011	Retrospective cohort	29	59 (5)	59 (6)	17	12	2	75	NA	NA	29 (100)	39%	NA	100	100
BEAUTIFUL[18] 2011	RCT	10917	65 (9)	65 (8)	5479	5438	19	72	24	23	9645 (88)	32%	NA	87	87
SHIFT[12] 2010	RCT	6505	61 (11)	60 (12)	3241	3264	23	80	52	52	3666 (56)	29%	8%	89	90

HR: Heart rate; RCT: Randomized controlled trial.

4.17-9.59; $P < 0.001$ for RCTs) (Figure 3).

All cause mortality

Three studies that reported all cause mortality at follow-up were analyzed (Figure 4). There was no difference in all cause mortality between the combined group and the beta-blocker alone group (MH RR: 0.98, 95%CI: 0.89-1.07, $P = 0.609$). Heterogeneity was low ($I^2 = 17\%$). When we excluded the study with maximum weight[12], results remained unaltered (MH RR: 1.04, 95%CI: 0.89-1.07, $P = 0.609$). A meta-regression of follow up time on all cause mortality was insignificant (Supplementary Figure 2B).

Cardiovascular mortality

Two studies reporting adverse events at follow-up were analyzed (Figure 5). There was no difference in cardiovascular mortality between the combined group and the beta-blocker alone group (MH RR: 0.99, 95%CI: 0.86-1.15, $P = 0.908$). Heterogeneity was high ($I^2 = 66\%$).

Hospitalization for heart failure

Two studies reported hospitalization for heart failure (Figure 6). There was no difference in heart failure hospitalization between the combined group and the beta-blocker alone group (MH RR: 0.87, 95%CI: 0.68-1.11, $P = 0.271$). Heterogeneity was high ($I^2 = 89\%$).

6MWD

Two studies reported 6MWD at follow up when compared to baseline between the combined therapy group with ivabradine plus beta-blocker and the beta-blocker alone group (Figure 7). 6MWD improved significantly from baseline in the combined therapy group (MD: 46.47, 95%CI: 14.678.3, $P = 0.004$). Heterogeneity was low ($I^2 = 0\%$).

Ejection fraction

Three studies reported ejection fraction at follow up (Figure 8). Improvement in ejection fraction was better in the combined therapy group with ivabradine plus beta-

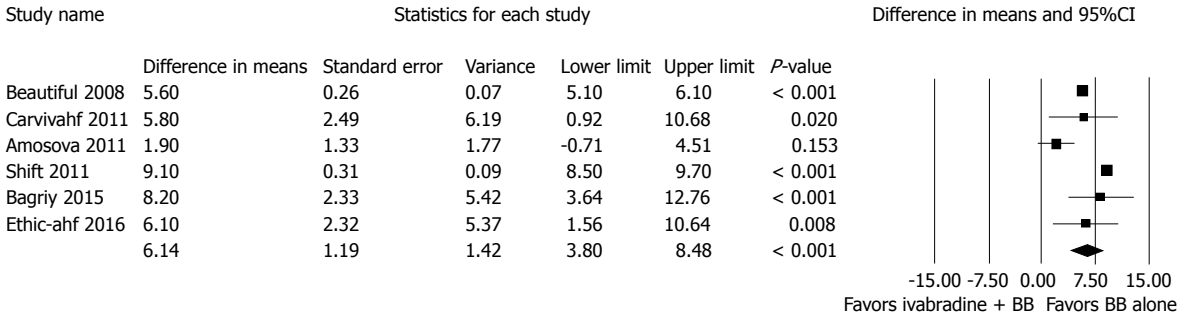

Figure 2 Comparison of mean change in heart rates from baseline between ivabradine + beta-blocker *vs* beta-blocker alone. BB: Beta blockers.

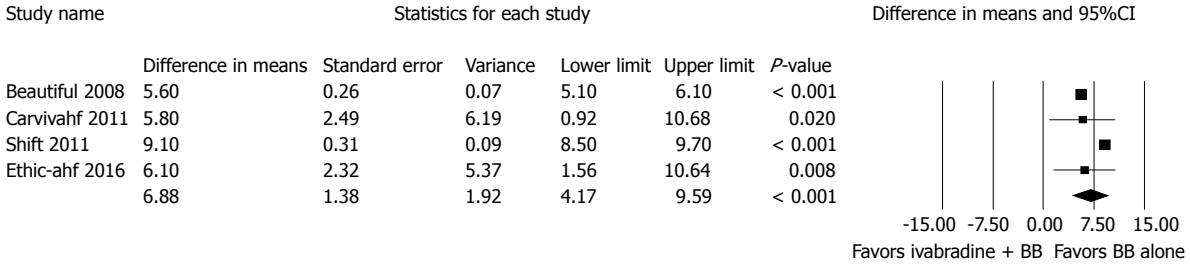

Figure 3 Comparison of mean change in heart rates from baseline between ivabradine + beta-blocker *vs* beta-blocker alone including only randomized controlled trials. BB: Beta blockers.

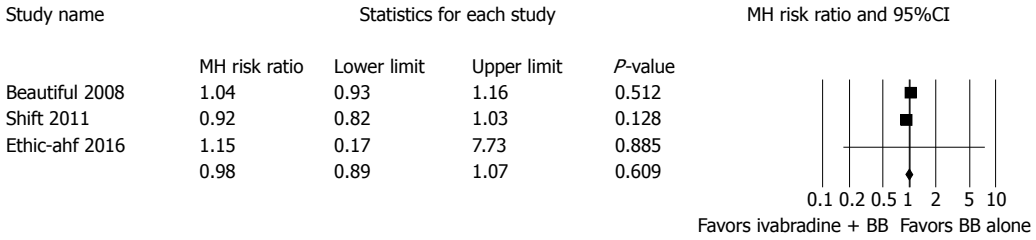

Figure 4 Comparison of Mantel-Haenszel risk ratio for all cause mortality between ivabradine + beta-blocker *vs* beta-blocker alone. BB: Beta blockers.

blocker when compared to the beta-blocker alone group (MD: 3.27, 95%CI: 0.42-6.13, P = 0.025). Heterogeneity was moderate (I^2 = 45%).

DISCUSSION

In this meta-analysis, ivabradine combined with beta-blockers resulted in a greater reduction of heart rates at follow up when compared to beta-blocker only group. Also, combined therapy was associated with significantly lower composite end-point of cardiovascular death or hospitalization for worsening heart failure. On the other hand, in the relatively short follow-up offered by the included studies, there was no improvement in secondary outcomes including isolated cardiovascular or all cause mortality or individual outcome of heart failure hospitalization. However surrogate markers such as 6MWD and ejection fraction appeared to improve in the ivabradine plus beta-blocker group *vs* beta-blocker alone. The importance of an improvement in EF with more bradycardia is difficult to determine since at slower heart rates more complete emptying can occur and may manifest as an improvement in EF without a true increase in LV intrinsic contractility or end systolic elastance.

Ivabradine was approved by the United Sates Food and Drug Administration for treatment of HFrEF in 2015. It is a very specific inhibitor of hyperpolarization activated cyclic nucleotide gated channels, which decreases the diastolic I(*f*) current and reduces sinus rate[24]. Ivabradine has no effect on the atrio ventricular node itself[24]. In addition, it has been shown that I(*f*) channels may increase in chronic heart failure in ventricular myocytes, and this could be arrhythmogenic[25], therefore inhibition of these channels by ivabradine could be beneficial in patients with HFrEF. Ivabradine has use dependency[26] and thus the reduction in heart rate is proportional to the baseline heart rate in individuals. Given all these characteristics and its effect of lowering heart rate without inducing the negative inotropic effect of beta-blockers, ivabradine was expected to not only be better tolerated than beta-blockers in HFrEF, but also to be

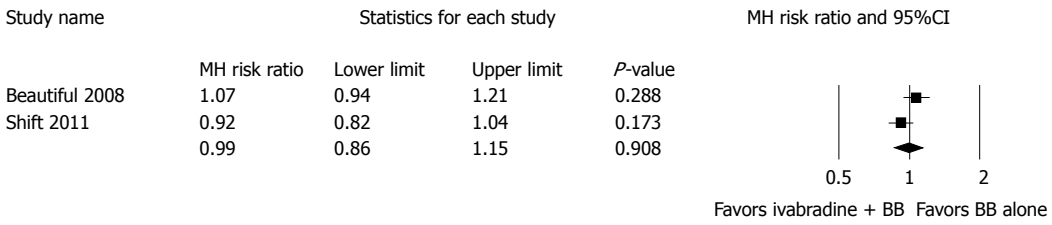

Figure 5 Comparison of Mantel-Haenszel risk ratio for cardiovascular mortality between ivabradine + beta-blocker *vs* beta-blocker alone. BB: Beta blockers.

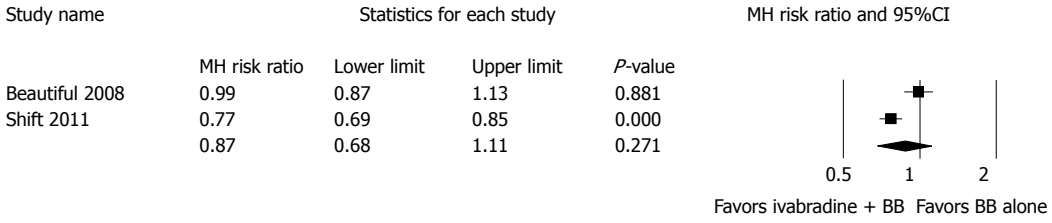

Figure 6 Comparison of Mantel-Haenszel risk ratio for heart failure hospitalization between ivabradine + beta-blocker *vs* beta-blocker alone. BB: Beta blockers.

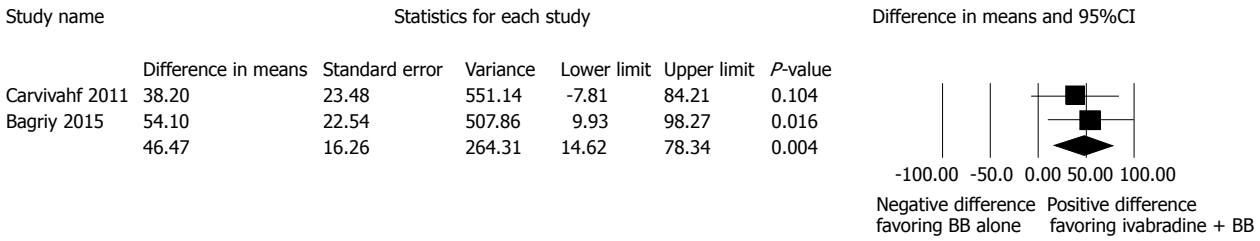

Figure 7 Comparison of difference in means of 6-min walking distance between ivabradine + beta-blocker *vs* beta-blocker alone. BB: Beta blockers.

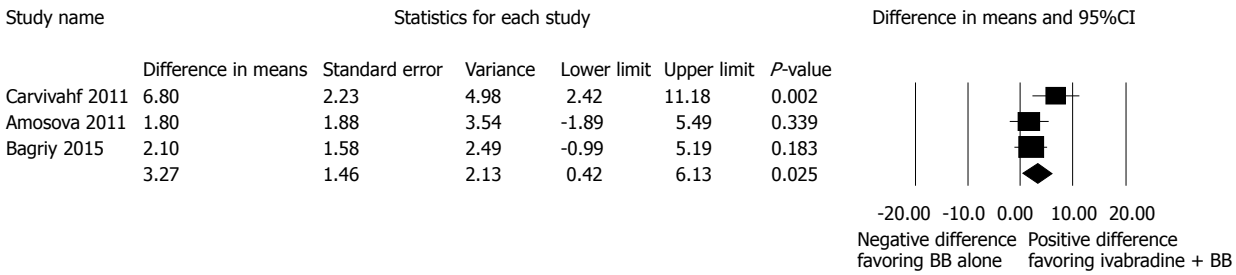

Figure 8 Comparison of difference in means of ejection fraction between ivabradine + beta-blocker *vs* beta-blocker alone. BB: Beta blockers.

beneficial by minimizing the adverse cardiac structural changes associated with tachycardia[12].

Summary of existing trials

In the BEAUTIFUL trial[18], a double blind RCT, 10917 patients with coronary disease and HFrEF and an EF < 40% were randomized to either ivabradine or placebo. Both groups were on optimal conventional heart failure medications with 87% of the patient population in both groups on beta-blockers; though there was no mention of whether the subjects were on maximal tolerated beta-blocker doses. The BEAUTIFUL study[18] reported that 84% of population was in NYHA Class Ⅱ or Ⅲ. Four percent of subjects were lost during follow-up. At 24 mo follow up, ivabradine group had a greater improvement in Heart rate with a MD (difference in means) of 5.6 bpm when compared to the placebo group. However, although mortality benefit with heart rate reduction has been shown in multiple studies, BEAUTIFUL[18] failed to show any benefit in terms of combined cardiovascular end-point of cardiovascular death, hospital admission for myocardial infarction or new onset worsening heart failure. Also there was no improvement in individual secondary outcomes including all cause mortality, cardiac mortality, hospitalization or worsening heart failure in both the groups.

In the sub-group with heart rates of 70 bpm or more[18], the MD in change from baseline was 6.9 bpm at 24 mo in the ivabradine arm. Although there was no difference between the groups in their primary end-points, there was a statistically significant reduction in secondary outcomes including number of follow

up hospital admissions for myocardial infarction and coronary revascularization. A borderline reduction in the composite end-point was noted in the ivabradine group when 14% of patients with activity limiting angina were analyzed separately, both in the overall group and in the sub group of HR > 70 bpm.

The SHIFT trial[12] is the next largest ivabradine RCT, and randomized 6505 patients with stable chronic ischemic and non-ischemic HFrEF of < 35% to receive either ivabraine or placebo in conjunction with optimal medical therapy for heart failure. SHIFT reported that 89% of patient population were being treated with beta-blockers at the beginning of the trial. All patients were in NYHA Class Ⅱ-Ⅳ with almost 99% patient population in class Ⅱ and Ⅲ. The study mentioned that only 26% of the patient population was receiving optimal target dose of beta-blocker, and the most common reason for not being able to achieve the target dose was hypotension (almost 45% population in both groups). The results showed that the ivabradine group had a lower incidence of combined end-point of cardiovascular death or hospitalization for worsening of heart failure though all cause-mortality was not different between the groups. The sub-group carvedilol only study[22] still retained the benefit for combined end-point in the ivabradine plus carvedilol but cardiovascular mortality was not different between ivabradine plus carvedilol and the carvedilol only group.

In a pooled analysis of the SHIFT[12], and the BEAUTIFUL[18] trials[27], ivabradine achieved highest heart rate control in patients with a baseline HR of > 75 bpm when compared to patients with HR < 60 bpm; this finding is consistent with the use-dependence property of the drug. The lower heart rate at follow up in the ivabradine sub-group was associated with the lowest mortality (17.4% in < 60 bpm *vs* 32.4% in > 75 bpm). When the investigators did a statistical adjustment for heart rate and other prognostic factors, the benefit of ivabradine was eliminated. Consequently, it may be that ivabradine improved the combined end-point mainly by heart rate reduction, although other possible mechanisms including I(*f*) blockade in ventricular myocardium in chronic HFrEF cannot be eliminated. In SHIFT[12], the MD in heart rate from baseline in the ivabradine group was greater than in BEAUTIFUL[18]; the relatively lower heart rate reduction achieved in BEAUTIFUL could be a possible explanation for absence of improvement in combined end-point of cardiovascular death or hospitalization for heart failure in the latter.

It should be noted in SHIFT[12] that patients on < 50% of the target beta-blocker dosage achieved more benefit at the combined end-point when combined with ivabradine, as compared to the overall group. One possible explanation could be patients with < 50% of target beta-blocker dosage have a higher HR and these patients tend to achieve higher benefit with ivabradine therapy than patients with a lower HR (secondary to the use-dependence property of ivabradine).

In ETHIC-AHF, a smaller recent RCT published by Hidalgo *et al*[23], 71 patients with acute heart failure and with EF of < 40%, sinus rhythm and HR > 70 bpm were randomized to ivabradine plus beta-blockers and beta-blockers alone. HR at 1-mo and at 4-mo follow-up were lower in the ivabradine group but the difference did not translate into improved clinical outcomes which showed no difference between the two groups in hospitalization rates for heart failure or death at follow-up.

The European Medical Agency set 75 bpm as HR cut-off[15] while the ACC/AHA guidelines[14] recommended 70 bpm as cut off for use of ivabradine in chronic HFrEF. Though the combined end-point of heart failure hospitalization or cardiac mortality was reduced along with improvement in ejection fraction and 6MWD, there was no reduction in all cause mortality, cardiovascular mortality or heart failure hospitalization alone in the current study. Also, in SHIFT[12], the benefit was higher in patients on < 50% target dose of beta-blocker, limiting its generalizability and suggesting, that there may be only a sub group that might benefit from ivabradine therapy. Therefore, before further evidence becomes available, it is essential to follow the current guidelines and up-titrate the dosage of beta-blockers before initiating ivabradine therapy for HFrEF. Further randomized trials with long term follow-up will determine if the short-term benefit in composite end-point translates to long term mortality benefit.

Limitations

The limitations of our meta-analysis are similar to any meta-analysis, including all limitations and biases associated with the original studies. We did not have access to patient level data and so we were not able to include outcomes of interest not reported in some articles. The meta-analysis included four RCTs and two sub-groups from RCTs along with two non-randomized trials and could be a source of bias. To diminish the bias, we analyzed RCTs separately which did not alter the outcomes. We could not adjust for confounding variables that were not adjusted for in the primary studies. The optimal dosage of beta-blockers tolerated was not reported in some trials and thus we could not analyze the correlation between baseline beta-blocker dose and ivabradine dependent outcomes. Thus, it still remains unclear if ivabradine would maintain its efficacy in patients who are on maximal tolerated doses of beta-blockers. Unavoidably, publication bias is a limitation of any meta-analysis.

In summary, the results of our systematic review and meta-analysis of the published literature supports use of ivabradine in patients with chronic HFrEF in sinus rhythm and with HR of > 70 bpm per guidelines, however the strength of evidence supporting this recommendation is weak. This approach is associated with demonstrable benefit in terms of composite end-point of cardiovascular mortality or hospitalization for heart failure. There was an improvement in ejection fraction and 6MWD at follow up but this was not reported in the majority of the published trials. More evidence is needed before ivabradine can be recommended more broadly to patients with HFrEF. The

current evidence supporting its approval is limited.

ACKNOWLEDGMENTS

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COMMENTS

Background

Ivabradine is a novel heart rate reducing agent by selectively inhibiting the cardiac pacemaker current if thereby slowing heart rates without exhibiting negative inotropic effect on the myocardium. It was approved by the United States Food and Drug Administration for treatment of heart failure with reduced ejection fraction (HFrEF) in 2015.

Research frontiers

The 2016 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) Focused Update on the Management of Heart Failure and the European Society of Cardiology (ESC) guidelines have given a Class Ⅱa (level of evidence B) recommendation for ivabradine use for patients with chronic HFrEF who are on guideline directed medical therapy. It is unclear, however, whether ivabradine offers any additional benefit when combined with beta-adrenergic blockade.

Innovations and breakthroughs

Two large RCTs (BEAUTIFUL and SHIFT) and some small RCTs compared the efficacy of ivabradine with beta blockers combined with beta blocker alone in people with chronic systolic heart failure. Both BEAUTIFUL and SHIFT failed to show mortality benefit but target beta blocker dosage achieved in these studies was lower, creating bias and suggesting there may be only a sub group that might benefit from ivabradine therapy.

Applications

The systematic review and meta-analysis supports use of ivabradine in patients with chronic HFrEF in sinus rhythm and with HR of > 70 bpm per the updated guidelines. Further randomized controlled trials are essential before ivabradine can be recommended more broadly to patients with HFrEF and the current evidence supporting its approval is limited.

Peer-review

A useful and interesting paper that should be published after authors make some changes to ensure the article is clearer, easy to read and not too technical statistically.

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CASE REPORT

Dysphagia after arteria lusoria dextra surgery: Anatomical considerations before redo-surgery

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Author contributions: Mayer J drafted the initial and further case report; Kroll J as experienced pediatric cardiovascular surgeon performed both operations and contributed important, detailed information for the surgical and anatomical discussion; Grohmann J was one of the leading cardiologists in charge during the entire duration of treatment and played an important role in developing and reviewing the final manuscript; all authors were involved in the patient management as an interdisciplinary team, critically reviewed the manuscript and approved the final manuscript as submitted.

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Abstract

Aberrant right subclavian artery (arteria lusoria) is the most common congenital root anomaly, remaining asymptomatic in most cases. Nevertheless, some of the 20%-40% of those affected present tracheo-esophageal symptoms. We report on a 6-year-old previously healthy girl presenting with progressive dysphagia over 4 wk. Diagnostics including barium swallow, echocardiography and magnetic resonance angiography (MRA) revealed a retro-esophageal compression by an aberrant right subclavian artery. Despite the successful, uneventful transposition of this arteria lusoria to the right common carotid *via* right-sided thoracotomy, the girl was suffering from persisting dysphagia. Another barium swallow showed the persistent compression of the esophagus on the level where the arteria lusoria had originated. As MRA showed no evidence of a significant re-obstruction by the transected vascular stump, we suspected a persisting ligamentum arteriosum. After a second surgical intervention *via* left-sided thoracotomy consisting of transecting the obviously persisting ligamentum and shortening the remaining arterial stump of the aberrant right subclavian artery, the patient recovered fully. In this case report we discuss the potential relevance of a persisting ligamentum arteriosum for patients with left

aortic arch suffering from dysphagia lusoria and rational means of diagnosing, as well as the surgical options to prevent re-do surgery.

Key words: Arteria lusoria dextra; Persisting ligamentum arteriosum; Dysphagia; Retroesophageal compression; Redo-surgery

Core tip: We present a pediatric case of dysphagia caused by the common congenital root anomaly of an aberrant right subclavian artery. However, persisting symptoms after primary treatment *via* right-sided thoracotomy required redo-surgery *via* left-sided thoracotomy with transection of a persisting ligamentum arteriosum and shortening of the remaining lusorian arteries' stump. Based on this experience, we want to emphasize the potential co-existence of a compressing ligamentum arteriosum even in patients with left aortic arch.

Mayer J, van der Werf-Grohmann N, Kroll J, Spiekerkoetter U, Stiller B, Grohmann J. Dysphagia after arteria lusoria dextra surgery: Anatomical considerations before redo-surgery. *World J Cardiol* 2017; 9(2): 191-195 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i2/191.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i2.191

INTRODUCTION

Aberrant right subclavian artery is the most common congenital root anomaly in general population with a prevalence ranging from 0.5% to 1.8%[1]. The arteria lusoria was first described in 1794 by David Bayford[2]; it results from an atypical obliteration of the 4th aortic arch, whereby the right subclavian artery is formed by the persistent right dorsal aorta in connection with the 7th intersegmental artery. The resulting aberrant right subclavian artery has an atypical origin from the descending aorta and reveals a retro-esophageal course to supply the right arm with blood[1,3].

The aberrant right subclavian artery usually remains asymptomatic[4]. Nevertheless 20%-40% of patients have tracheo-esophageal symptoms, with dysphagia being the most frequent symptom in 90% of patients with clinical symptoms[1,5]. Respiratory symptoms like cough, dyspnea, stridor, increased respiratory infections or thoracic pain are more frequent in children than in adults[6].

Surgical treatment should be restricted to seriously symptomatic patients and is usually performed *via* right-sided thoracotomy. This operative intervention consists of mobilization and transection of the aberrant right subclavian artery from the descending aorta, and re-implantation into the right common carotid artery[7].

CASE REPORT

A 6-year-old girl presented with recurrent and progressive dysphagia over 4 wk. At first contact, she had lost 8 kg over 4 wk, showed severe difficulty swallowing solid foods and also suffered from recurrent thoracic pain. She underwent a barium swallow for differential diagnosis purposes which demonstrated a severe compression of the esophagus in its intermediate third, highly suspicious of vascular compression (Figure 1A). Subsequent echocardiography led to the presumptive diagnosis of an aberrant right subclavian artery with its origin in the descending aorta and a retro-esophageal course to the right side. The authors also diagnosed a truncus bicaroticus. Subsequent MRA confirmed the diagnosis of an isolated arteria lusoria (Figure 1B and C), which was considered as the proven cause for the girl's dysphagia.

Because her dysphagia had worsened so rapidly (she could only swallow liquids), her discomfort and significant weight loss, the decision for an operative intervention was made. *Via* right-sided thoracotomy over the 4th intercostal space (ICS), the aberrant right subclavian artery was mobilized, transected behind the esophagus and transposed to the right common carotid by an end-to-side-anastomosis. There were no perioperative complications. Upon her discharge on day 12 after surgery, the patient was free of symptoms such as dysphagia or thoracic pain.

During follow-up a few weeks later, she returned suffering again from dysphagia, hypersalivation, dry cough and sore throat. Analgesics had not relieved her symptoms.

As the girl kept presenting with recurrent thoracic pain and mild symptoms of dysphagia accompanied by intermittent symptom-free periods and the lack of significant findings in clinical and diagnostic examinations, a somatoformic disorder was suspected as the origin of her symptoms.

Sixteen months after corrective surgery and following a symptom-free 7-mo interval, the patient presented again with severe dysphagia (no solid food) but no thoracic pain as described before. Another barium swallow was performed (Figure 1D) which showed persistent compression of the esophagus on the level where the arteria lusoria had originated. Subsequent MRA displayed the vascular stump with a maximum length of 10 mm and diameter of 4-5 mm (Figure 1E). There were no further changes compared to the images taken 12 mo earlier. The region of the vascular anastomosis showed no abnormalities (Figure 1F). Finally, the suspicion of two factors causing the ongoing compression of the esophagus and the recurrent symptoms arose: First, compression by the persisting stump of the aberrant right subclavian artery and second, an incomplete vascular ring due to a persisting ligamentum arteriosum, which was not transected.

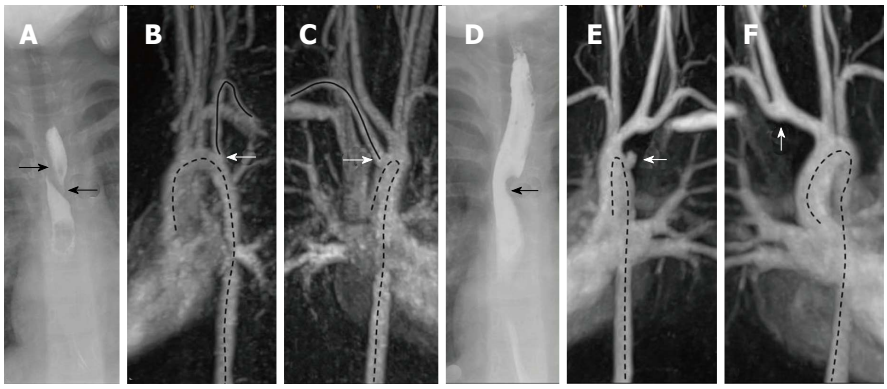

Figure 1 Fluoroscopy and magnetic resonance angiography at initial presentation and at follow-up. A-C: Fluoroscopy and MRA at initial presentation; A: The arrows mark the outer boundary of the esophagus. There is a filling defect in between which runs from right side superior to left side inferior due to compression of the vessel; B and C: The arrow marks the right sided subclavian artery which originates distally to the left supraaortic vessels. The course of the artery is shown by the uninterrupted line. The dotted lines mark the course of the thoracic aorta; D-F: Fluoroscopy and MRA at follow up; D: The arrow marks a filling defect of the esophagus; E: The arrow marks the vascular stump. The dotted lines mark the course of the thoracic aorta; F: The arrow marks the anastomosis. The dotted line represents the course of the aorta. MRA: Magnetic resonance angiography.

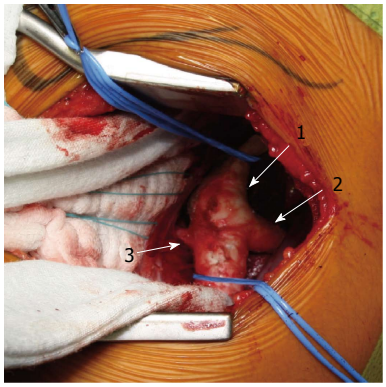

Figure 2 Operative findings in redo-surgery: Surgical approach over the 3th intercostal space *via* left-sided thoracotomy: A structure consistent with the ligamentum arteriosum can be presented leading to the descending aorta distal the left subclavian's origin. 1: Aorta descendens; 2: Left subclavian artery; 3: Ligamentum arteriosum.

Therefore, redo-surgery was performed, this time over the 3th ICS *via* left-sided thoracotomy (Figure 2) and consisted of shortening the remaining lusorians' stump and transecting the ligamentum arteriosum. The patient experienced an uneventful and complete recovery.

The barium swallow she underwent 6 wk after re-operation demonstrated no more signs of esophageal compression. At all subsequent clinical follow-ups over 6 mo after surgery, she had no more dysphagia and had regained weight.

DISCUSSION

We report on a 6-year-old girl presenting with dysphagia attributed to an aberrant right subclavian artery that unexpectedly caused persisting symptoms after corrective surgery *via* right-sided thoracotomy.

As the aberrant right subclavian artery often remains asymptomatic[3], surgical repair is restricted to highly-symptomatic patients, and it is usually very successful. Nevertheless, a small percentage of these patients return complaining of recurrent respiratory or swallowing problems[8].

There is a potential anatomical explanation for ongoing postoperative symptoms like dysphagia: Compared to a left-sided aortic arch, the right-sided aortic arch combined with an aberrant left subclavian artery maintains a persisting ligamentum arteriosum. In contrast, in those with a left-sided aortic arch and an aberrant right subclavian artery, a left-sided ligamentum arteriosum is much rarer but it remains a potential anatomical finding. Such a ligamentum arteriosum - a fibrous relict of the ductus arteriosus - leads from the proximal descending aorta to the left pulmonal artery. In the presence of a coexisting aberrant right subclavian artery, an incomplete vascular ring can form that compresses the esophagus[9].

We thus maintain that, to ensure optimum recovery after a surgical intervention for arteria lusoria, it is essential to be fully aware of the patient's cardiothoracic anatomy beforehand, especially the existence of a persisting ligamentum arteriosum. In selecting the diagnostic tools, we suggest an age-dependent approach. In fetuses, newborns and infants presenting the incidental finding of an arteria lusoria, echocardiography has great potential to validate the cardiovascular system in detail, especially a vascular ring with a fibrous ductus arteriosus. Echocardiography remains highly informative even in symptomatic infants and children. Barium swallow and MRA are additional key diagnostic tools in this age group. In case of older children and adolescents, the first-line modality should be MRA. At that age, echocardiography becomes secondary because it precludes a thorough evaluation of the patient's anatomy.

Another key factor for surgical success is the choice of surgical access. Regarding the preferred approach to the aberrant right subclavian artery in children, van Son *et al*[10] found that this vessel originates from the posteromedial side of the distal aortic arch. Therefore,

a strong argument for currently-mandated right-sided thoracotomy in children is the vessel's optimal mobilization, transection and reconnection.

However, assessing a ligamentum arteriosum is limited in this access path, thus in case of a left aortic arch with left-sided ligamentum arteriosum, the recommended surgical access to reach this usually fibrous strand is *via* left-sided thoracotomy.

In summary, we suggest considering a median thoracotomy to address both contrary structural conditions and to effectively treat a right arteria lusoria in combination with a left ligamentum arteriosum at the same time. *Via* this median access, the course of the aberrant right subclavian artery can be corrected, and the surgeon is able to explore and transect a persisting ligamentum arteriosum.

In conclusion, we suggest that our patient continued to suffer dysphagia after initial surgery of the aberrant right subclavian artery due to the persisting pathology of a ligamentum arteriosum causing further esophageal compression. Since this experience, our recommendation for other patients with a left-sided aortic arch and right arteria lusoria is first to focus on obtaining a detailed preoperative visualization of the individual's anatomy by means of diagnostic imaging, especially to watch out for a ligamentum arteriosum. In case of a potential ligamentum arteriosum, we favor a median thoracotomy because of its optimal provision of intraoperative anatomical overview and accessibility to both the aberrant artery and ligamentum arteriosum.

ACKNOWLEDGMENTS

We are grateful to Carole Cürten for language editing.

COMMENTS

Case characteristics

This is a rare pediatric case about a 6-year-old girl with an aberrant right subclavian artery unexpectedly presenting with persisting severe dysphagia after initial corrective surgery *via* right-sided thoracotomy.

Clinical diagnosis

Apart from mild symptoms such as hypersalivation and a dry cough, there were no other significant anomalies in clinical examination.

Differential diagnosis

Ingested foreign bodies, esophageal infection or neoplasia, disorders in esophageal innervations or secondary to cardiovascular compression or thyroid disease.

Laboratory diagnosis

The authors' laboratory tests revealed no pathology.

Imaging diagnosis

The initial diagnosis of an aberrant right subclavian artery was confirmed *via* barium swallow, subsequent echocardiography and magnetic resonance angiography (MRA), whereas during the persistent dysphagia after her first intervention, only the barium swallow demonstrated a dorsal esophageal compression that led us to suspect an incomplete vascular ring due to a persisting ligamentum arteriosum.

Pathological diagnosis

Persisting esophageal compression after arteria lusoria dextra surgery caused by an incomplete vascular ring due to a persisting ligamentum arteriosum.

Treatment

Redo-surgery *via* left-sided thoracotomy entailing the transection of a persisting ligamentum arteriosum and shortening of the remaining lusorian arteries' stump.

Related reports

Although arteria lusoria is the most common embryologic abnormality of the aortic arch and its potential esophageal compression can result in dysphagia, a case of persisting symptoms after corrective surgery because of a co-existing ligamentum arteriosum in patients with left aortic arch has never been reported in the literature so far.

Term explanation

Magnetic resonance angiography (MRA) is a type of magnetic resonance imaging scan to evaluate blood vessels and helps to identify vascular abnormalities by using a powerful magnetic field and pulses of radio wave energy.

Experiences and lessons

Based on this experience, the authors wish to emphasize the potential co-existence of a compressing ligamentum arteriosum even in patients with left aortic arch; furthermore, the authors would like to inspire discussion about an age-dependent approach regarding which diagnostic tools are employed for pre-operative planning, as well as what constitutes the optimal surgical approach.

Peer-review

This is a rare case report about a pediatric case of dysphagia attributed to an aberrant right subclavian artery that unexpectedly caused persisting symptoms after corrective surgery *via* right-sided thoracotomy. The authors suggest considering a median thoracotomy to address both contrary structural conditions and to effectively treat a right arteria lusoria in combination with a left ligamentum arteriosum at the same time. This manuscript is nicely structured and well written.

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CASE REPORT

Very late transcatheter heart valve thrombosis

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Author contributions: All authors contributed to the acquisition of data, writing, and revision of this manuscript.

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Informed consent statement: The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

Conflict-of-interest statement: Dr. Masson is a proctor/consultant for Edwards Lifesciences Inc. All other authors have no conflicts of interests to declare.

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Abstract

We describe a case of very late transcatheter heart valve (THV) thrombosis of a first-generation SAPIEN prosthesis (Edwards Lifesciences, Irvine, CA) implanted in a 64-year-old woman with severe symptomatic aortic stenosis. More than 54 mo after implantation, she presented with severe symptomatic prosthesis dysfunction (stenosis) which was successfully treated with oral anticoagulation. To our knowledge, this is the tardiest case of THV thrombosis ever reported. This case should increase clinical awareness for THV thrombosis even beyond the first two-year period following implantation.

Key words: Valve thrombosis; Transcathether heart valve; Transcatheter aortic valve replacement

Core tip: We describe the tardiest case of transcatheter aortic valve replacement (TAVR) thrombosis ever reported. A 64-year-old woman with severe symptomatic aortic stenosis underwent TAVR with a first-generation SAPIEN prosthesis. More than four years (> 54 mo) following implantation, she presented with a severe symptomatic prosthesis dysfunction (stenosis) which was successfully treated with oral anticoagulation.

Couture EL, Lepage S, Masson JB, Daneault B. Very late transcatheter heart valve thrombosis. *World J Cardiol* 2017; 9(2): 196-199 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i2/196.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i2.196

INTRODUCTION

We describe a case of very late transcatheter heart valve (THV) thrombosis of a first-generation SAPIEN prosthesis (Edwards Lifesciences, Irvine, CA) implanted in a 64-year-old woman with severe symptomatic

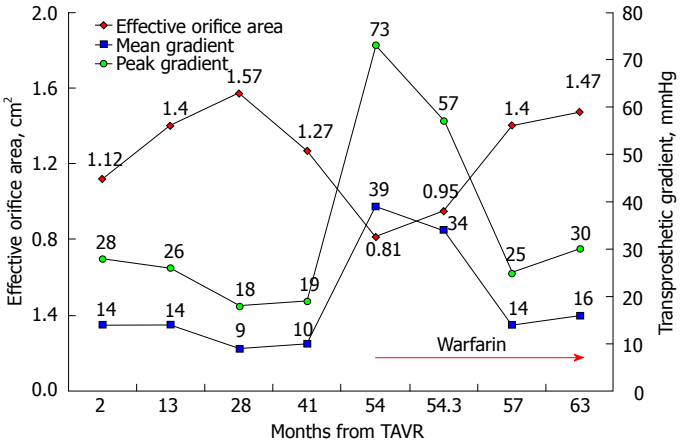

Figure 1 Transprosthetic gradients and effective orifice area following transcatheter aortic valve replacement (2 to 54 mo), at the time transcatheter heart valve thrombosis (54 mo) and following anticoagulation therapy (54 to 63 mo). TAVR: Transcatheter aortic valve replacement; THV: Transcatheter heart valve.

aortic stenosis. More than 54 mo after implantation, she presented with severe symptomatic prosthesis dysfunction (stenosis) which was successfully treated with oral anticoagulation. To our knowledge, this is the tardiest case of THV thrombosis ever reported. This case should increase clinical awareness for THV thrombosis even beyond the first two-year period following implantation.

CASE REPORT

A 64-year-old woman with severe symptomatic aortic stenosis and porcelain aorta underwent transcatheter aortic valve replacement (TAVR) using a first-generation balloon-expandable Edwards SAPIEN (Edwards Lifesciences, Irvine, CA) 23 mm THV in January 2011. The patient was discharged home with aspirin and clopidogrel for three months followed by low dose aspirin.

More than 54 mo following TAVR, she presented with progressive dyspnea, angina and dizziness on moderate exertion. Transthoracic echocardiogram (TTE) revealed a severe THV dysfunction with an aortic valve area (AVA) of 0.81 cm^2, peak and mean trans prosthetic gradients (TPG) of 76 and 39 mmHg respectively and a preserved left ventricular ejection fraction (Figure 1). Transesophageal echocardiogram (TEE) did not demonstrate abnormal leaflet function neither THV thrombosis (Figure 2) but revealed a moderate paravalvular leak (PVL) (Figure 2D) already known from the immediate post-TAVR TEE. THV thrombosis was suspected given the absence of other explanatory findings and the abrupt progression of TPG. Therefore, anticoagulation with warfarin and unfractionated heparin was empirically started. A coronary angiogram and a cardiovascular magnetic resonance (CMR) were also performed. Angiogram revealed a severe, non-thrombotic, left main mid-shaft stenosis and percutaneous coronary intervention (PCI) with a drug-eluting stent was performed. CMR revealed an aortic regurgitation fraction of 23% consistent with the moderate PVL previously seen on the TEE. No evidence of THV thrombosis other than elevated peak velocity was detected on CMR. Nine days after initiation of anticoagulation, a repeat TTE showed mild improvement in TPG (Figure 1). The patient was discharged home with aspirin, clopidogrel and warfarin for three months, followed by clopidogrel and warfarin. Angina was relieved immediately after PCI, but dyspnea on exertion improved over weeks. After three months, symptoms had resolved completely and TPG returned to their baseline values. They remained unchanged after nine months under chronic anticoagulation (Figure 1).

DISCUSSION

In two series, less than 30 cases of THV thrombosis have been reported with a median presentation time of 6 mo (range, 3-735 d) with only two cases occurring beyond one year[1,2]. A case of a Direct Flow Medical THV thrombosis three years following TAVR has also been reported recently[3]. To our knowledge, never a THV thrombosis has been described so late after implant (> 54 mo) as in this case. THV thrombosis is a new entity that needs to be recognized not only by TAVR specialists. Even though estimated incidence is low (0.61%), consequences can be catastrophic if appropriate therapy is not initiated promptly[1]. Only reported cases treated with anticoagulation had favorable outcome. Therefore, a sudden increase in TPG should trigger further investigation or therapies to exclude THV thrombosis. Valve hemodynamic deterioration (VHD), defined by an increase in mean TPG of more than 10 mmHg over time, was observed more frequently in patients with smaller THV (23 mm) and those not receiving oral anticoagulation[4]. Most of these patients did not have a progressive deterioration after the first year. VHD does not seem to be part of a continuum towards THV thrombosis and this later remains unpredictable. However, the pathophysiology of VHD may include some degree of sub-clinical leaflet thrombosis.

In our case, TEE evaluation was not diagnostic. In a series of 3 pathology-proven THV thrombosis, TEE was also negative in each cases[2]. However, Makkar *et al*[5] showed that 4D-CT and TEE had a diagnostic concordance of 100% in 10 patients presenting reduced leaflets motion following TAVR. Whether 4D-CT is the optimal imaging modality remains to be proven. CMR was chosen over CT scan to assess PVL severity but

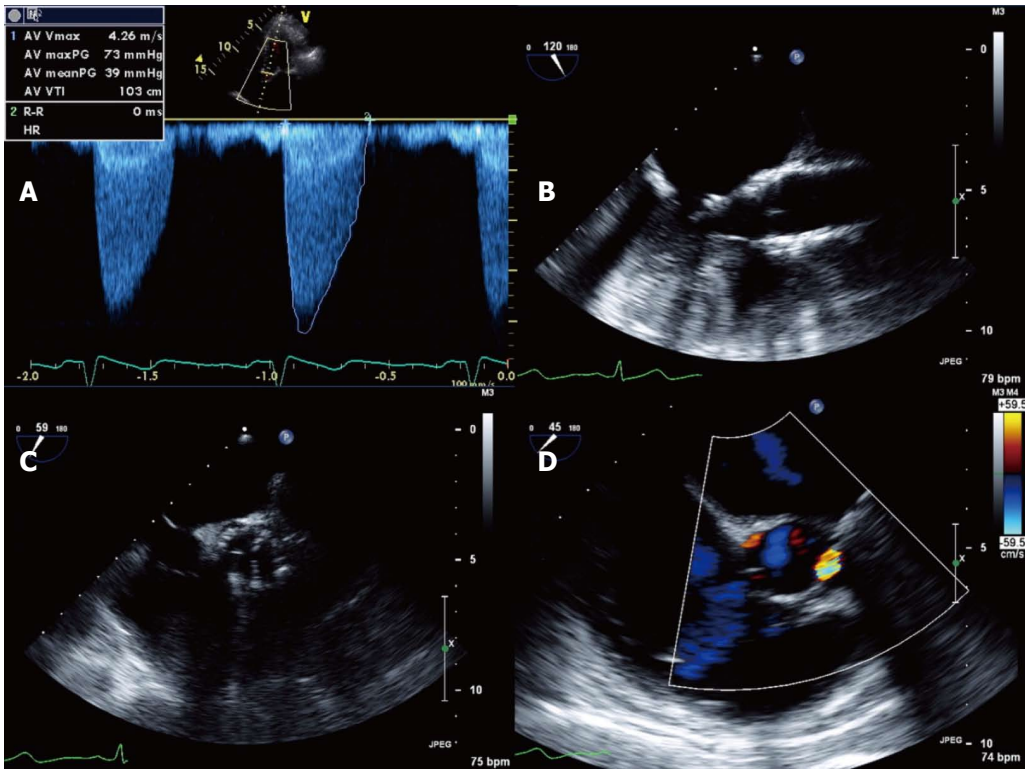

Figure 2 Transesophageal echocardiogram. It shows transprosthetic gradients compatible with severe aortic stenosis (A); Absence of obvious mass or valve thrombosis on Transesophageal echocardiogram (B, C) but moderate paravalvular leak (D).

also failed to identify the THV thrombosis. Therefore, negative imaging should not preclude an anticoagulation trial when the diagnostic is highly suspected.

Reports have revealed subclinical leaflet thrombosis detected by TEE and 4D CT scan early after THV implantation[5]. Most of these cases were seen in patients who did not receive anticoagulation. The clinical significance of these findings remains unknown at this point. Studies are ongoing to evaluate the optimal antiplatelet/anticoagulant therapy after TAVR. The ARTE (clopidogrel; NCT01559298) and REAC-TAVI (ticagrelor *vs* clopidogrel; NCT02224066) trials are evaluating different antiplatelet strategies and the GALILEO (rivaroxaban; NCT02556203) and ATLANTIS (apixaban; NCT02664649) studies are looking at the effect of non-vitamin K oral anticoagulant following TAVR. Similarly, the POPular-TAVI trial (NCT02247128) is evaluating the effect of adding clopidogrel for 3 mo following implantation in patients with and without ongoing vitamin-K oral anticoagulation treatment.

This case is also particular because of the concurrent left main stenosis. Although thrombus migration in the left main could be considered an explanation, the angiographic appearance was more in favor of disease progression of a previous non-significant lesion seen on the pre-TAVR angiogram. Moderate PVL could be associated with a different flow pattern over the leaflets and in the left main that could lead to THV thrombosis as well as accelerated progression of atherosclerosis although this relationship is speculative.

This case should increase clinical awareness for THV thrombosis even beyond the first two-year period following implantation. Risk predictors for THV thrombosis and optimal antiplatelet/anticoagulant therapy post TAVR are still unknown and warrants clinical trials.

COMMENTS

Case characteristics

More than 54 mo following transcatheter aortic valve replacement, a 64-year-old woman presented with progressive dyspnea, angina and dizziness on moderate exertion.

Clinical diagnosis

Prosthesis dysfunction.

Differential diagnosis

Transcatheter heart valve (THV) degeneration; THV thrombosis; THV endocarditis.

Imaging diagnosis

Transesophageal echocardiogram (TEE) revealed a prosthesis dysfunction with a severe stenosis. TEE failed to revealed THV thrombosis as well as vegetations.

Treatment

Empiric treatment with unfractionated intravenous heparin followed by long-term anticoagulation with warfarin.

Related reports

Less than 30 cases of THV thrombosis have been reported with a median presentation time of 6 mo (range, 3-735 d) with only two cases occurring beyond one year.

Experiences and lessons

This case should increase clinical awareness for THV thrombosis even beyond the first two-year period following implantation. Even if TEE does not reveal THV thrombosis.

Peer-review

The paper is well written.

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