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Editorial

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The Challenge of Dysglycemia and Coronary Heart Disease

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The prevalence of type 2 diabetes mellitus (T2DM) is increasing globally, and although there is a small increase in the incidence of type 1 diabetes mellitus, T2DM accounts for 95% of all individuals with diabetes.[1] A high prevalence of undiagnosed glucose abnormalities has been demonstrated in patients with acute coronary syndrome (ACS) including acute myocardial infarction (AMI),[2] and several studies have shown that newly detected glucose metabolism abnormalities in the form of impaired glucose tolerance and diabetes represent an independent risk for cardiovascular mortality and morbidity.[3,4] There seems to be a curvilinear relation between post-oral glucose tolerance test, glucose levels and the risk for cardiovascular disease, and the risk increases already in the non-diabetic range of glucose levels.

There are several mechanisms linking diabetes to an increased risk of cardiovascular disease. Patients with T2DM are prone to atherothrombosis, which increases the risk of cardiovascular events and mortality. Apart from classical risk factors for atherosclerosis such as hypertension and dyslipidemia, which co-exist in many patients with T2DM, the increased atherothrombotic risk is also explained by a pro-inflammatory state, which is partly due to endothelial and smooth muscle cell dysfunction.[5] Another important factor contributing to the increased risk of coronary events in patients with T2DM is dysregulation of factors involved in coagulation and platelet activation.[6]

Acute ST-elevation myocardial infarction (STEMI) accounts for approximately 30-40% of patients with ACS. In patients with STEMI, peak glycaemia has been found to be an independent predictor of in-hospital mortality.[7,8] Presence of diabetes is also an independent predictor of incomplete ST-segment recovery, which is used to quantify myocardial microvascular dysfunction and is a powerful predictor of long-term mortality in patients undergoing primary percutaneous coronary intervention (PPCI).[9] There is a strong association between T2DM and impaired myocardial perfusion after PPCI.[9-11] It has been demonstrated that despite a successful PPCI and adequate epicardial flow (TIMI 3 flow), suboptimal myocardial perfusion frequently occurs among diabetic patients.[12-14] Interestingly, diabetes is independently associated with 30-day reinfarction after successful PPCI for STEMI.[15-17] Of note, diabetes mellitus seems to abolish the beneficial effect of PPCI on the long-term risk of reinfarction compared with fibrinolysis.[18] Several mechanisms have been proposed to explain the independent association between hyperglycaemia and impaired myocardial microvascular function observed in patients undergoing PPCI. It has been suggested that hyperglycaemia may augment plugging of leukocytes in the capillaries as well as platelet activation and thrombus formation in the capillaries, increasing the risk of no-reflow after PPCI for STEMI. Vascular endothelial dysfunction, which is closely linked to impaired insulin sensitivity, has also been mentioned as a contributing factor to the no-reflow phenomenon. We have shown that microvascular reactivity is severely impaired in patients with diabetes and ACS, and that diabetes has a major influence on microvascular function in patients with coronary artery disease.[19] Strategies which help to restore microvascular endothelial function may thus improve diabetic control, as well as reduce microvascular complications such as myocardial microvascular dysfunction in ACS setting.

CONCLUSIONS

The prevalence of dysglycemia is high in patients with coronary heart disease, and it contrib-

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utes to increased risk for poor clinical outcome. In order to identify targets, modulation of which may improve cardiovascular prognosis in patients with dysglycaemia and ACS, the mechanisms of no-reflow after PPCI and their relationship with hyperglycaemia should be further investigated. Furthermore, new treatment strategies targeting myocardial perfusion after percutaneous coronary intervention and microvascular endothelial function are urgently needed.

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Research

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Beneficial Effects of Pre-Operative Intra Aortic Balloon Pump Support in High Risk Patients Undergoing Coronary Artery Bypass Graft Surgery

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ABSTRACT

Objective: The purpose of this study was to evaluate the efficacy and the cost-benefit of pre-operative Intra-aortic Balloon Pump (IABP) treatment on peri- and post-operative cardiac performance, improved hemodynamic stability, reduced mortality and morbidity and the optimal timing in high-risk patients undergoing Coronary Artery Bypass Grafting (CABG), when compared to patients who did not receive IABP therapy.
Methods: Between January 2011 and June 2012, a total of 1149 patients underwent CABG at our institution of which IABP was inserted in 90 patients, out of which 30 patients satisfied the inclusion criteria. Out of 30 patients 10 had IABP insertion pre-operative, 10 had intra-operative, and 10 had post-operative period. Euro score additive and logistic were comparable in all the three groups to determine the benefit of using IABP prior to operation.
Results: Inotropic support in pre-IABP group is less as compared to intra- and post-IABP group (p<0.02). The mean duration of ICU stay was more in intra-operative and post-operative IABP group (p<0.28). No hospital mortality in pre-operative IABP group (0/10), 2 patient died in intra-operative IABP group (2/10), 3 died in post-operative IABP group (3/10).
Conclusions: This study demonstrated pre-operative IABP therapy is an efficient and safe supportive modality which significantly decreases the risk for hemodynamic instability in high-risk patients undergoing CABG, improved cardiac performance, reduced inotropic requirements, lower rate of hospital mortality and less post-operative morbidity, improve survival and shortens both ICU and hospital length of stay significantly and is therefore cost effective. Further studies with inclusion of more cases are required to verify our findings.

KEYWORDS: Intra-aortic balloon pump; Coronary artery bypass grafting; Coronary artery disease.

ABBREVIATIONS: CABG: Coronary Artery Bypass Grafting; IABP: Intra-aortic Balloon Pump; ICU: Intensive Care Unit; CAD: Coronary Artery Disease; LVEF: Left Ventricular Ejection Fraction.

INTRODUCTION

Pre-operative intra-aortic balloon pump (IABP) therapy is an effective modality in protecting high-risk patients undergoing coronary artery bypass grafting (CABG) surgery.[1-5] Pre-operative IABP therapy improves cardiac performance and facilitates access to the target vessels while maintaining hemodynamic stability, even in high-risk patients.[6,7] In our institution, pre-operative IABP is used selectively as a modality to support CABG surgery in high-risk patients since provides better hemodynamic stability and coronary perfusion and minimizes low output syndrome and organ dysfunction.[8]

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CABG, in low to moderate risk coronary patients, has demonstrated excellent immediate and long-term results,[9] allowing shorter stay in intensive care unit (ICU) and shortening of the total length of hospital stay, which has kept the total procedural cost on a steady level. In contrast to this stands, the CABG procedure performed in high-risk patients, which still is associated with high post-operative mortality and morbidity.[10] This results in a prolonged stay in the intensive unit as well as in the hospital. The purpose of this study was to evaluate the efficacy and the cost-benefit of pre-operative IABP treatment on peri- and post-operative cardiac performance, improved hemodynamic stability, reduced mortality and morbidity and the optimal timing in high-risk patients undergoing CABG, when compared to patients who did not receive IABP therapy.

MATERIAL AND METHODS

Patient Population and Study Design

Institution Ethical Committee (IEC) clearance was obtained for the study. This study was a prospective, cross-sectional study. Between January 2011 and June 2012, a total of 1149 patients underwent CABG at our academic institution of which IABP was inserted in 90 patients, out of which 30 patients met the inclusion criteria. Out of 30 patients 10 had IABP insertion pre-operative, 10 had intra-operative, and 10 had post-operatively.

The treatment was defined as insertion of IABP before surgery and control was represented by patients who did not receive IABP pre-operatively and those who received IABP intra-operatively, or post-operatively.

The definition of high-risk patients was based on the logistic European Risk Score System in Cardiac Operations (EuroSCORE)[11] and the cutoff of 5 points or higher was chosen on the basis of the available literature.[11] The logistic EuroSCORE was calculated using the current online version (www.euroscore.org/calc.html).

Definition of High Risks

Any coronary artery disease (CAD) patient presenting with a minimum of two of the following pre-operative criteria and planned for revascularization was enrolled in this study:

- Left ventricular dysfunction;
- Left ventricular ejection fraction (LVEF) equal or less than 0.40;
- Pre-operative unstable angina despite optimal medical treatment (including nitroglycerin and heparin therapy);
- Left coronary main stem stenosis greater than 70%;
- Chronic occlusion of the three main coronary trunks (left anterior descending, right, and circumflex coronary arteries);
- Tight stenosis (_99%) of the proximal left anterior descending coronary artery (before the first septal or diagonal branch), proximal tight stenosis (_99%) of a dominant right coronary artery with remote branches for the posterior wall of the left ventricle;
- Acute ongoing angina;
- Recent myocardial infarction less than 4 weeks prior to surgery.

Inclusion Criteria

Adult patients with CAD were admitted for elective or urgent myocardial revascularization and classified as high-risk patients according to the definition given above.

Exclusion Criteria

- Post-infarction ventricular septal repair;
- Pre-operative cardiogenic shock;
- Patient planned for additional cardiac surgical procedures.

Patients fulfilling the inclusion criteria were randomly allocated to either of two treatments paths: Group A-therapy Group-pre-operative IABP therapy, started prior to induction of anesthesia, followed by continuous IABP during the entire procedure as well as post-operatively.

Group B-control Group-no pre-operative IABP therapy. CABG was performed on beating heart with or without the use of CPB. Post-operative IABP treatment was initiated if fulfilling definitions stated above.

The amount of pharmacological inotropic support pre-operative and post-operatively (during the first 12 h) required to maintain an acceptable cardiac index (<2.0 L/min/m^2) was monitored. Post-operative mortality and morbidity as well as required stay in the intensive care unit was registered for each of the groups.

Indications for Post-operative IABP

When cardiac index cannot be maintained at a level greater than 2.0 L/min/m^2, despite pharmacological support with adrenaline equal or more then 0.05 µg/kg/min, dobutamine equal or more than 10 µg/kg/min and dopamine equal or more than 10 µg/kg/min, an IABP treatment is indicated.

IABP Support and Timing of Insertion

The Intra aortic balloon (Datascope Sensation 7F, 40 mL; Datascope Corp., Fairfield, NJ, USA) was inserted percutaneously with sheathless technique and was connected to a Datascope CS300 console (Datascope Corp.). Insertion through the best femoral artery was possible in all cases, pre-operatively, in the intensive care unit, on average 24 h prior to the start of surgery and the correct placement was assessed by chest roentgenography. Peri- or post-operative IABP catheter insertion and start was initiated when criteria described above were met. Exact time of insertion and start of IABC as well as termination of IABP was registered, as well as any complications (minor or major) related to the IABP therapy.

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Intraaortic balloon pump assistance was set at a 1:1 ratio in all patients. Patients undergoing pre-operative insertion were therapeutically anticoagulated with heparin after IABP placement. Patients returning from the operating room with an IABP in place where anticoagulated with 1 mg/Kg of heparin once mediastinal drainage subsided (usually within 24 h).

We inserted IABP intra-operatively if the patient experienced hemodynamic instability during OPCAB. We inserted IABP intra-operatively when hemodynamic instability occurred such as a significant decrease of systemic systolic pressure to less than 80 mmHg, elevation of pulmonary diastolic pressure to more than 25 mmHg, or intractable ventricular arrhythmia, in spite of adequate anesthesia management.

Termination of IABC Therapy/Treatment

The IABP support was terminated when hemodynamic stability was restored (maintaining a cardiac index >2.0 L/min/m^2 with minimal pharmacologic support).The same definition was used for termination of post-operative IABP.

Measurements

All patients were equipped with Swan-Ganz catheter, arterial catheter, and multi lead ECG.

Repeated blood gas analysis was performed to evaluate oxygen uptake and oxygen debt. Repeated cardiac output measurements were performed and CI calculated (cardiac performance).

Systemic arterial blood pressure (BP), heart rate (HR), means pulmonary artery pressure (MPAP), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) was registered. Repeated pre-operative and post-operative blood samples for analysis of hematocrit (Hct), platelet count (Plt), CK-MB (creatinine kinase MD fractions), CK (creatinine kinase phosphate).

Surgical Procedure

Surgery was performed in all cases through a median sternotomy. All conduits were harvested as for traditional CABG. Extensive arterial grafting and complete myocardial revascularization were preferred whenever possible. The most critical vessel in almost all the patients, the left anterior descending coronary artery, was revascularized first to provide a backup to the less critical area. The distal anastomosis was constructed using a continuous technique with 8-0 polypropylene sutures for arterial grafts or 7-0 polypropylene suture for a saphenous vein graft. All proximal anastomoses on the ascending aorta were constructed after distal anastomoses, using a single partial clamping of the aorta and 6-0 polypropylene continuous sutures.

The left internal mammary artery was used to the left anterior descending coronary artery in all patients. Saphenous veins were usually preferred for diagonal artery, obtuse marginal coronary artery and right coronary artery revascularization as an aortocoronary graft. The initial heparin dose for OPCAB was 1.5 mg/Kg, with a target ACT greater than 300 seconds. If conversion to CPB was required the heparin dose was 3 mg/Kg to achieve a target activated clotting time of greater than 480 seconds. Temperature was maintained at normothermia using adequate room temperature, warm circulating water blankets, and warm infusion solutions.

For patients undergoing off-pump CABG exposure We used the suction-type (Octopus® 3; Medtronic Inc., Minneapolis, USA) mechanical stabilizers, to immobilize the target coronary artery and Starfish (Medtronic Inc., Minneapolis, USA) was used to expose the posterior and inferior surfaces of the heart. A shunt (Medtronic Inc., Minneapolis, USA) was inserted in the coronary artery during all anastomoses to avoid ischemic damage and peri-operative rhythm disturbances. A blower/mister was systematically used to obtain a bloodless operative field and perfect the visualization of the coronary artery.

Definitions of Perioperative Events

Hospital mortality was defined as death occurring during hospitalization. Conversion to cardiopulmonary bypass was recorded as an unfavorable event. Peri-operative myocardial infarction was defined as new Q waves of greater than 0.04 milliseconds, reduction in R waves of greater than 25% in at least two leads, or both; new akinetic or dyskinetic segment on echocardiography; and a peak troponin I level of at least 3.1 g/L at 12 hours.[12] Post-operative renal failure was defined as an increase in serum creatinine value of greater than 2.5 mg/dL.

Low-output syndrome (LOS) was diagnosed when CI decreased to less than 2.0 L/min/m^2, pulmonary capillary wedge pressure exceeded 15 mmHg, left ventricular stroke work index (LVSWI) decreased to less than 22 g/m/m^2 and results of mixed systemic venous oximetry were less than 60% for at least 30 minutes after correction of all electrolyte or blood gas abnormalities and after pre-load optimization. High dose inotropic support was defined when greater than 7 µg/Kg/min of dopamine or dobutamine was given or any dose of adrenaline was added.

Hospital morbidity was defined as any complication requiring specific therapy or causing a delay in hospital or intensive care unit discharge. Intensive care unit stay was defined as the time (hours) required for intensive care; hospital stay, as the time (days) required for hospitalization starting from the day of the surgery.

Clinical Outcomes

- Hospital mortality;
- Neurological complications (any new transient or permanent deficit appearing after surgery) ;

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- Duration of intubation;
- Required stay in ICU;
- Length of total hospital stay;
- Incidence of renal insufficiency (serum-urea greater than 9 mM and serum creatinine greater than 125 µmin patients with normal pre-operative values);
- Gastro-intestinal complications (any diagnosed gastro-intestinal complication not present prior to surgery) and;
- Pulmonary complications (X-ray verified pneumonia or atelectasis).

Statistical Analysis

Statistical analysis was performed with the Statistical Analysis System Software Package (SASSP) (version 6.12; SAS Institute, Cary, NC, USA). The significance of differences between the group of patients with IABP and without IABP was assessed by unpaired Student's *t*-test, X-square test, or likelihood ratio test. All results are expressed as mean 6 standard deviations, and a value of $p<0.05$ is considered statistically significant.

RESULTS

EuroSCORE additive and logistic were compared in all of the three groups with significant difference noted in the group with use of pre-IABP ($p<0.05$). Inotropic support in pre-IABP group is less as compared to intra- and post-IABP group as the ($p<0.02$).

The mean duration of ICU stay was longer in the post-operative IABP group than that in the intra-operative ($p=0.28$), although this did not reach statistical significance. The post-operative acute kidney injury on day 1 and day 2 was compared in all the three groups with no statistical significant, conversion of off pump to on pump rate was high in intra-operative IABP group, and ventricular fibrillation was more in both intra-operative (2/10) and post-operative IABP (3/10) groups.

No hospital mortality occurred in the pre-operative IABP group (0/10), however, mortality was seen in the two groups with 2 patient died in the intra-operative IABP group (2/10), 3 died in the post-operative IABP group (3/10). Table 1 shows key findings among these three groups.

DISCUSSION

The IABP method has long been established as a valuable mechanical support for temporary ventricular assistance in the treatment of the failing heart.[13] Several clinical studies have reported worse outcome and high rates of complications in patients who required placement of emergency IABP support during intra-operative or post-operative critical hemodynamic decompensation.[14]

The purpose of this study was to evaluate if the use of pre-operative intra-aortic balloon pump treatment could improve the outcome after surgical myocardial revascularization, the optimal timing of IABP insertion and if efficient, to evaluate whether this additional treatment is cost beneficial or not.

Pre-operative prophylactic IABP support has recently been suggested to have proven efficacy in significantly lowering hospital mortality and morbidity in high-risk coronary patients undergoing CABG.[15]

The positive effect of pre-operative insertion of IABP in high-risk patients is thought to be due to an improved myocardial oxygen supply/demand ratio and reduced ventricular wall stress before the operation in addition to diastolic augmentation and decreased afterload resulting in the redistribution of coro-

Table 1: Comparison of Results among the Three Comparable Groups.

Variable	Pre-op IABP	Intra-op IABP	Post-op IABP	*p*-Value
EuroSCORE additive (mean±SD)	7.8±1.54	7.9±1.37	7.1±1.96	<0.05
EuroSCORE logistic (mean±SD)	8.9±3.6	9.2±3.6	7.6±4.9	<0.05
Aki post-operative day 1 (n)	1/10	2/10	2/10	ns
Aki post-operative day 2 (n)	0/10	1/10	2/10	ns
Inotrope hours post-operative (hrs)	40.3±13.7	59.9±24	78±44.8	<0.02
Off-pump to on pump conversion intraoperative (N)	1/10	2/10	2/10	ns
Ventricular fibrillation (n)	0/10	2/10	3/10	ns
LVEF at discharge (%)	43±3	52±5	42±8	<0.05
ICU stay (hrs)	65±20	64±28	91±45	0.28
30 day mortality (n)	0/10	2/10	3/10	ns

IABP = Intraaortic Balloon Pump; LVEF=Left Ventricular Ejection Fraction; ns=not significant.

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nary blood flow toward the ischemic areas of the myocardium enhancement of sub-endocardial perfusion, and in the recovered energy depletion of myocardial cells.[16]

Pre-operative IABP therapy could lead to pre-operative reduction of myocardial ischemia, avoidance of progressive cardiac dysfunction, and minimization of low-flow episodes with subsequent end organ dysfunction, and may thereby permit safer induction of general anesthesia and improve surgical outcome in high-risk coronary patients.[1,17]

Crucial times for higher oxygen demand include when anesthesia is induced and conduits are harvested; thus, any transitory hypotension during these phases may induce critical ischemia leading to acute myocardial damage or even infarction.[18,19]

Intra-operative and post-operative IABP insertion has been disappointing because of the associated high mortality rate, as well as complication rate.[4,5] In patients who had an IABP inserted post-operatively, the treatment was required for a substantially longer time, which not only increases the total procedural cost (by prolonged stay in the intensive care unit and massive pharmacologic support) but also could increase the risk of IABP-related complications.

The Benchmark Registry showed that prophylactic IABP use was associated with reduced mortality in high-risk patients.[20] These data are confirmed by The Society of Thoracic Surgeons National Database, which also clearly showed a survival benefit with pre-operative IABP assistance.[21]

Intraaortic balloon pump insertion can occasionally be cumbersome or risky because of severe and diffuse atherosclerosis of the descending aorta and peripheral arteries, or even contraindicated because of abdominal aortic aneurysms. The major disadvantages related to IABP use thus far were complications associated with its placement, aortic dissection, balloon rupture, balloon entrapment, bleeding, vascular injury, and limb ischemia.[22]

STUDY LIMITATIONS

Firstly, small sample size is one of the main limitations. Further research is needed to include more cases. Preferably in a multi-centre study. Secondly, no follow-up was performed as this study only assessed the hospital mortality and hospital study including duration at ICU.

CONCLUSION

In conclusion, this study demonstrated pre-operative IABP therapy is an efficient and safe supportive modality which significantly decreases the risk for hemodynamic instability in high-risk patients undergoing CABG, improved cardiac performance, reduced inotropic requirements, lower rate of hospital mortality and less post-operative morbidity, improve survival and shortens both ICU and hospital length of stay significantly and is therefore cost-effective.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

Informed consent were obtained from the study patients along with the ethical clearance from the Institutional Ethics Committee (IEC).

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Case Report

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Left Atrial Appendage Thrombus in a Patient with Atrial Fibrillation on Apixiban Successfully Treated with Warfarin and Pulmonary Vein Isolation Ablation

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ABSTRACT

Atrial fibrillation (AF) is a common cardiac arrhythmia that can be seen in hospitalized patients. It has been shown to be a major risk factor for cardioembolic stroke, and therefore patients are frequently started on lifelong anticoagulation. The majority of patients benefit from either cardioverison or pulmonary vein isolation ablation. We herein describe the case of a 58-year-old male with a past medical history of atrial fibrillation surgery who presented to hospital for elective atrial fibrillation ablation after failed medical therapy and persistent symptoms. A transesphageal echocardiogram (TEE) prior to the procedure demonstrated a left atrial appendage clot despite patient's compliance with apixiban. Subsequently, the patient is started on warfarin therapy with a heparin bridge. A TEE performed 6 weeks after discharge showed resolution of the left atrial appendage clot allowing the ablation procedure to be successfully performed.

KEY WORDS: Atrial fibrillation; Left atrial appendage thrombus; Novel anticoagulation; Apixiban; Warfarin.

ABBREVIATIONS: TEE: Transesphageal Echocardiogram; AF: Atrial Fibrillation; FXa: Factor Xa; EF: Ejection Fraction; LV: Left Ventricular; ECG: Electrocardiogram; ICE: Intracardiac echocardiogram.

INTRODUCTION

Atrial fibrillation (AF) is the leading cardiac arrhythmia in the United States (US). More than 2.7 million people in the US are known to have AF and this number is expected to rise to 12 million by 2030.[1-3] AF accounts for $16-26 billion of annual US expenses.[4,5] Stroke is the third most frequent cause of death in US and the leading cause of serious disability; for which AF is a major independent risk factor. It is responsible for 15% of 700,000 strokes occurring in the US each year.[6]

In AF, the uncoordinated atrial pulse causes pooling of blood in the atrium and more specifically in the left atrial appendage.[7] The force of the coordinated atrial contraction can dislodge a thrombus from the left atrial appendage, which then can migrate to the brain causing an ischemic stroke secondary to cardio-embolism.[7] The Copenhagen Stroke Study (a prospective, community-based study of 1197 patients with acute stroke) demonstrated that patients with AF had a higher mortality rate (OR, 1.7; 95% CI, 1.2 to 2.5), longer hospital stays (50 days *vs.* 40 days, $p<.001$), and a lower discharge rate to their own homes (OR, 0.60; 95% CI, 0.44 to 0.85).[8] This study also demonstrated that neurological and functional outcomes were markedly poorer

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in patients with atrial fibrillation due to more severe strokes.[8] Vitamin K antagonists such as warfarin are highly effective in preventing stroke in patients with atrial fibrillation. Warfarin reduces the risk of stroke by two-thirds and mortality by one-quarter compared with control.[9] Warfarin is highly effective in preventing stroke in patients with atrial fibrillation, but has several limitations such as narrow therapeutic window, and drug/food interactions. The limiting factors of warfarin have increased the use of the targeted oral anticoagulants such as Apixiban. Apixiban is direct factor Xa (FXa) inhibitors that prevents FXa from cleaving prothrombin to thrombin.

CASE REPORT

A 58-year-old male with a past medical history of atrial fibrillation (AF), ischemic cardiomyopathy (left ventricular (LV) ejection fraction (EF) of less than 25%), coronary artery disease status post coronary artery bypass graft, aortic stenosis status post bioprosthetic aortic valve replacement, hypertension, hyperlipidemia and obstructive sleep apnea presented pulmonary vein isolation ablation for atrial fibrillation after failed medical therapy and persistent symptoms. The patient initially presented to Pennsylvania Hospital Emergency Department 4 weeks prior with shortness of breath and dyspnea on exertion. He stated that his symptoms had progressively worsened and his electrocardiogram (ECG) revealed that he was in rapid atrial fibrillation. He was subsequently admitted and underwent a transesphageal echocardiogram (TEE) with no visualization of a left atrial appendage thrombus (Figure 1). A direct current cardioversion was performed with restoration of normal sinus rhythm. The patient was started on Apixiban 5 mg twice daily for a CHA_2DS_2-VASc score of 3 (congestive heart failure, coronary artery disease, and hypertension).

He was seen in follow-up as an outpatient on 2 weeks prior to presentation, where he endorsed symptoms of exertional dyspnea. His ECG showed AF. Although, he reported feeling "much better", he still had exertional dyspnea, palpitations, and light headedness. He denied chest pain and syncope. After consultation with an electrophysiologist, he was scheduled for an elective AF ablation procedure. At presentation to the hospital, his vital signs were heart rate of 110 beats per minute, blood pressure of 127/78, oxygen saturation of 97% on room air, temperature of 97.9 °F, and respiratory rate of 18 breaths per minute. On physical exam, he was a morbidly obese male in no acute distress, cardiac exam revealed an irregularly irregular rhythm. His lungs were clear to auscultation bilaterally. A TEE was performed prior to atrial fibrillation ablation procedure which demonstrated an EF of 25% with a new left atrial appendage thrombus (Figure 2). Intracardiac echocardiogram (ICE) also confirmed presence of the thrombus, therefore resulting in cancellation of the procedure. The patient was started on a heparin drip and was subsequently bridged to warfarin, with a goal Indian rupee (INR) of 2-3. He was continued on metoprolol 100 mg every 12 hours orally for rate control.

Outcome

Patient was discharged to home on coumadin therapy once his INR was therapeutic. A repeat TEE 4 weeks later showed resolution of the thrombus in left atrium (Figure 3). The patient underwent a successful pulmonary vein isolation ablation on the same day. There were no complications to the procedure and patient was continued on warfarin indefinitely.

DISCUSSION

Our case describes a patient that has failed apixiban therapy for his AF. The Aristotle trial compared apixiban to warfarin and demonstrated that apixiban 5 mg twice daily was superior to warfarin in preventing stroke or systemic embolism. It also caused less bleeding and resulted in lower mortality.[10] On the other hand, some studies have suggested that Apixiban is known to make thrombi mobile and/or fragile, which causes detachment or partial fragmentation of left atrial appendage thrombus that can result in thromboembolism.[11-13] This is thought to be

Figure 1: TEE of Left Atrial Appendage Prior to Electrical Cardioversion with No Thrombus Present. Red Line Outlines the Border of the Left Atrial Appendage.

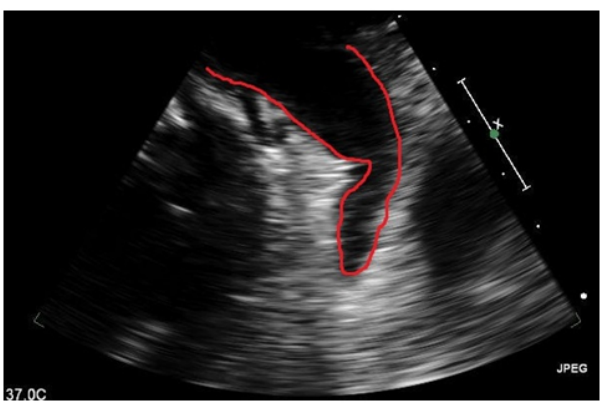

Figure 2: TEE of Left Atrial Appendage Prior to Atrial Fibrillation Ablation. Thrombus is Present. Red Line Outlines the Border of the Left Atrial Appendage.

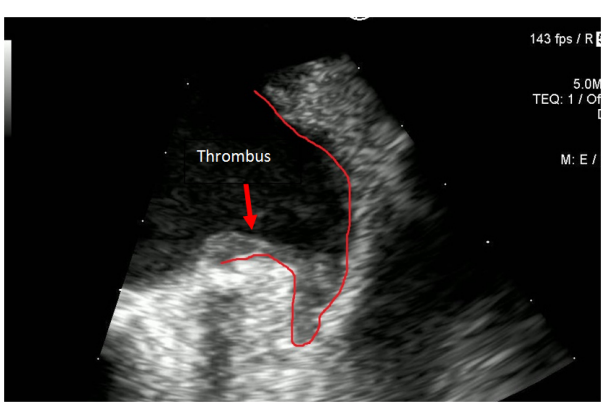

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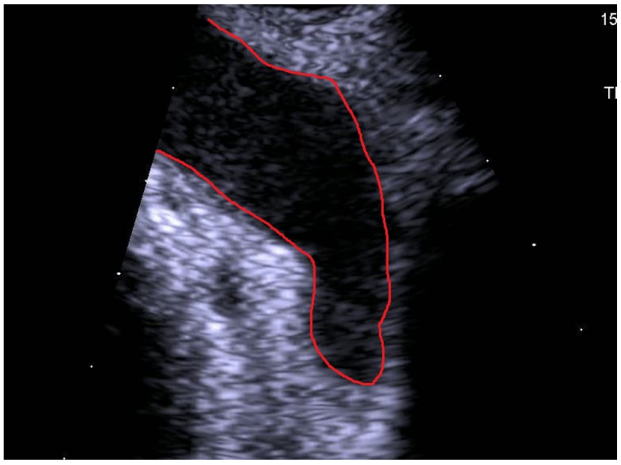
Figure 3: TEE of Left Atrial Appendage Prior to Repeat Atrial ablation after 6 Weeks of Warfarin Therapy. No Thrombus is Present. Red Line Outlines the Border of the Left Atrial Appendage.



secondary to apixiban shifting the coagulation/fibrinolysis balance to a relative predominance of fibrinolytic activity.[13-16]

Current practice is to have a TEE performed if a patient has been in AF for more than 48 hours to rule out a left atrial thrombus. If a patient has an atrial clot, they are anticoagulated for a duration of 4 weeks. A TEE is performed and if there is resolution of the thrombus, then a cardioversion is performed.[17] Current evidence concludes that there does not appear to be a role for routine TEE prior to cardioversion in patients who has been adequately anticoagulated with warfarin or targeted anticoagulant for at least four weeks prior to cardioversion.[18] The 2014 AF guidelines classify this recommendation as level C evidence. Seidl et al[19] demonstrated that, in patients with AF and effective anticoagulation, TEE-guided electrical cardioversion does not reduce the embolic risk. However, TEE before direct-current cardioversion revealed left atrial thrombus in 7.7% of patients with AF and effective anticoagulation. As this case demonstrates, even four weeks of compliance with anticoagulation with direct acting agents such as apixiban does not completely protect against left atrial thrombus formation, and a pre-cardioversion TEE should be considered in all patients.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Mini Review

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Double-Low Dose Protocol of Computed Tomography Pulmonary Angiography (CTPA) in the Diagnosis of Pulmonary Embolism: A Feasible Approach for Reduction of Both Contrast Medium and Radiation Doses

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ABSTRACT

This article discusses a hot topic on double low-dose protocol of computed tomography pulmonary angiography (CTPA) in the diagnosis of pulmonary embolism, with a special focus on a recent paper published in the British Journal of Radiology about the feasibility of this technique. Three aspects will be discussed in this review: First, both kVp and contrast medium can be reduced without affecting image quality when compared to the standard CTPA protocol; second, a low-pitch protocol is comparable to the high-pitch spiral image acquisition with similar image quality achieved, but at lower radiation dose; and finally, the double low-dose CTPA protocol can achieve diagnostic images in patients with body mass index up to 35 kg/m^2.

KEYWORDS: Computed tomography pulmonary angiography; Contrast medium; Optimization; Image quality; Pulmonary embolism; Radiation dose.

ABBREVIATIONS: CTPA: Computed Tomography Pulmonary Angiography; PE: Pulmonary Embolism; VIE: Virtual Intravascular Endoscopy; CIN: Contrast-Induced Nephropathy; BMI: Body Mass Index; CNR: Contrast-to-noise ratio.

Computed tomography pulmonary angiography (CTPA) has become the method of choice for the diagnostic assessment of patients with suspected pulmonary embolism due to technological advancements in CT imaging.[1-8] Modern CT scanners with superior spatial and temporal resolution enable detection of segmental and subsegmental thrombus in the pulmonary arteries with high accuracy.[9,10] In addition to 2D axial images, CTPA allows for generation of different image reconstructions including unique intraluminal views of the thrombus in the pulmonary arteries (Figures 1 and 2).[9] Increased detection of pulmonary embolism seems to be associated with increased use of CTPA, in particular in the emergency department.[11-17]

Although there are no guidelines available about the minimum acceptable yield of CTPA, it is generally agreed that a diagnostic yield of CTPA less than 10% indicates overuse of CTPA as a diagnostic tool.[18,19] Sharma and Lucas recently reported their single center experience of CTPA in the diagnosis of pulmonary embolism over a period of 8 years. Authors found a direct correlation between increased number of CTPA scans and percentage of positive pulmonary embolism (the positive diagnostic yield ranges from 12% to 28.1%), suggesting that the use of CTPA is clinically appropriate.[11] Mountain and colleagues in their multi-center study showed similar findings with association of increasing use of CTPA with increased rates of

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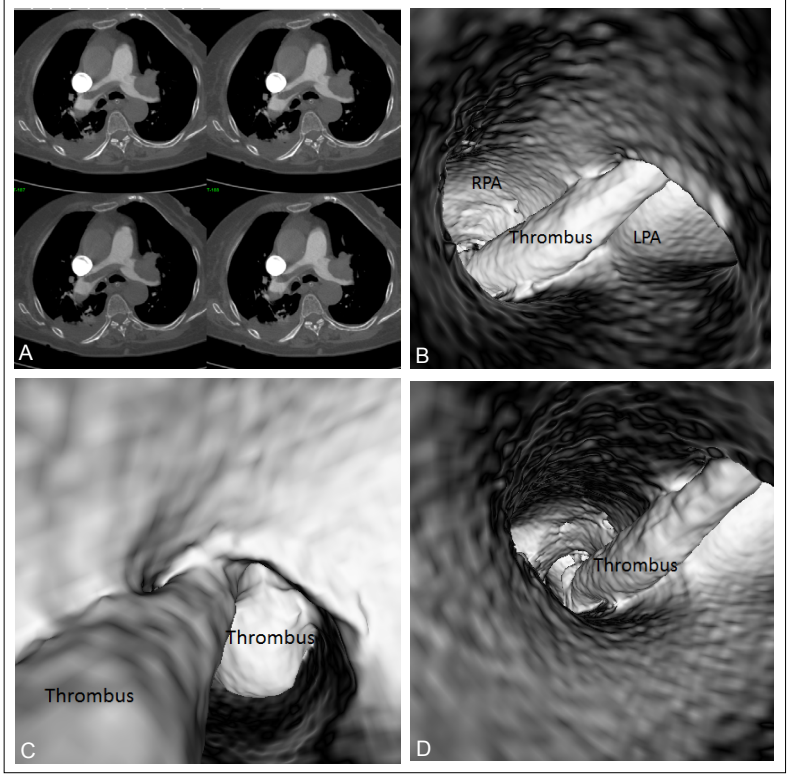

Figure 1: CT Pulmonary Angiography Shows Multiple Pulmonary Emboli in an 85-Year-Old man. A: 2D Axial Images Show Large Thrombus Formation in the Right and Left Main Pulmonary Arteries with Filling Defect Observed. B: 3D Virtual Intravascular Endoscopy (VIE) Shows Large Thrombus Involving Left Pulmonary Artery (LPA) and Right Pulmonary Artery (RPA). C: Close VIE Visualization of the Thrombus in the LPA. D: Close VIE View of the Thrombus Extends to the RPA.

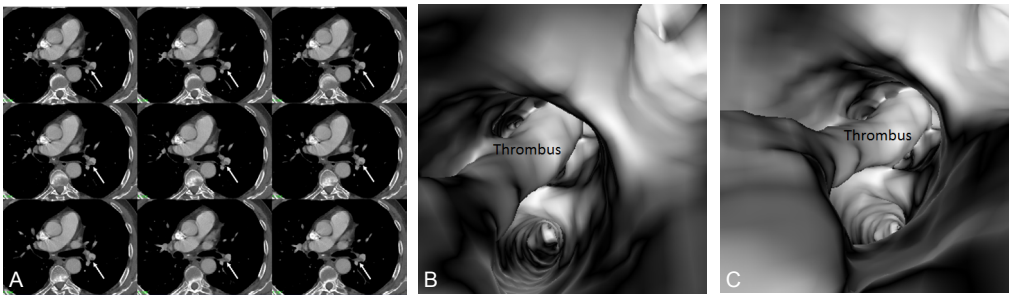

Figure 2: CT Pulmonary Angiography Shows Pulmonary Embolism in a 65-Year-Old Man. A: 2D Axial Images Demonstrate Thrombus in the Left Lower Lobar Artery (arrows). B and C: 3D Virtual Intravascular Endoscopy Offers Intraluminal Views of the Thrombus in the Left Lower Lobar Artery in Relation to the Surrounding Branch Artery.

pulmonary embolism diagnosis. Their study involved 14 clinical sites (15 emergency departments) across Australia and New Zealand consisting of more than 7000 CTPA scans with >94% performed on ≥64-slice CT. The overall diagnostic yield of CTPA at these 14 clinical sites was 14.5% (range: 9.3 to 25.3%) with significant variations in the diagnostic yield among the clinical sites. Of these clinical centers, four sites were found to have significantly lower yield which is less than the acceptable rate of 15.3%. Despite the yield variation in this multi-center study, increased use of CTPA is significantly correlated with pulmonary embolism (PE) diagnosis, thus, justifying its clinical value.[17]

The increased use of CTPA raises concerns about subjecting patients to excessive radiation exposure and contrast-induced nephropathy (CIN).[7,13,20] CT is a well-recognized modality with high radiation dose, although significant dose reduction has been achieved in recent years with implementation of many dose-reduction strategies. This has been widely reported in cardiovascular CT imaging, such as coronary CT angiography,[21-24] abdominal aortic imaging,[25,26] and CTPA.[27-30] Similarly, CIN has been drawing more attention in the recent literature due to routine use of contrast medium injection during CT scans including CTPA. Thus, reduction of contrast medium volume is equally

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important as reduction of radiation dose, which is shown in some studies.[24,31] This leads to the currently recommended protocol of double low-dose CTPA protocol, which has been addressed in a recent study supported by other relevant reports.

Boos et al[31] in their study investigated the feasibility of using double low-dose CTPA protocol in 70 patients with suspected pulmonary embolism. They implemented a new developed scanning protocol defined as a 70-kVp simultaneous acquisition dual-source CTPA in Group A comprising 35 patients with body mass index (BMI) less than 35 kg/m^2. With this protocol, the two X-ray tubes were operated at 70-kVp with a low-pitch of 0.9. Automatic tube current modulation was used with administration of 40 ml of contrast medium followed by a saline flush of 40 ml at a flow rate of 3 ml/sec. The new protocol group was compared to a control group, Group B consisting of another 35 patients with similar demographics in age, gender and BMI. In Group B, CTPA was performed with a high-pitch spiral acquisition mode with use of automatic tube current and automatic tube potential selection. Of 35 patients in Group B, 100 kVp and 120 kVp was used in 6 and 29 patients, respectively, with administration of 70 ml of contrast medium followed by the saline flush protocol as used in Group A. Images were reconstructed with a medium level of iterative reconstruction (Level 3, SAFIRE: sinogram affirmed iterative reconstruction). Quantitative assessment of image quality was based on signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR), while qualitative analysis of image quality was assessed by two independent observers using a four-point scoring scale with score of 1 indicating non-diagnostic, and score of 4 excellent image quality. No significant differences were found in both qualitative and quantitative assessment of image quality between the two groups; however, both radiation dose and contrast medium dose were significantly lower in Group A than in Group B, with corresponding reduction of 50% and 40% achieved. Details of comparative results between the two groups are shown in the Table 1.

There are three observations from Boos study that bear discussions. First, the double low-dose CTPA is feasible in acquiring images for diagnostic assessment of pulmonary embolism with use of low kVp and low contrast medium. Of various dose-reduction strategies, low kVp is highly recommended and it is widely used in many CT angiographic applications, in particular, in cardiovascular CT imaging area.[32,33] According to the society of cardiovascular computed tomography guidelines, selection of kVp is correlated with patient's BMI, with low kVp (100 or 80 kVp) used in patients with smaller BMI.[34] Reduction of kVp shows particular value in CT angiography because of the association between vessel visualization and iodine enhancement. This is confirmed in Boos' study by showing an increase in vascular CT attenuation when kVp is reduced. The CT attenuation measured in main pulmonary trunk and left lower segmental pulmonary artery was found to be significantly higher in Group A than that in Group B (414.3±149.4 HU and 416.4±139.3 *vs.* 259.6±69.7 and 256.0±75.0 HU, $p<0.0001$) with no significant difference in signal-to-noise ratio (SNR) and contrast-to-noise-ratio (CNR) between the two groups ($p>0.05$). Most of the studies tested lowering kVp value with 80 or 100 kVp on CTPA examinations while achieving diagnostic images with low radiation dose,[35-40] while Boos and colleagues in their study further lowered the kVp to 70 without affecting image quality. It is well known that lowering tube voltage is associated with increased image noise, but this can be compensated by iterative reconstruction, which is confirmed by Boos study.

Contrast medium has detrimental effects on renal function, thus, reduction of contrast medium during CT angiography has attracted increasing attention in the literature. Previous protocols using 80-100 ml contrast medium followed by 30-60 ml saline flush are being replaced by low volume of contrast medium, as shown in Boos and others' studies. Further lowering contrast volume to even 40 or 20 ml has also been reported in some studies Saade et al[40] compared two groups of patients

Table 1: Summary of Scanning Protocols and Results in Boos' Study.[31]

Parameters	Group A 35 patients	Group B 35 patients
Data acquisition mode	Simultaneous dual-source protocol	Dual-source, high-pitch helical protocol
Pitch value	0.9	2.2
kVp	70	120 kVp in 29 patients, 100 kVp in 6 patients
mAs	269±91 (range: 100-397)	144±35 (range: 82-211)
Volume of contrast medium (ml)	40	70
Body mass index (kg/m^2)	26.8±3.9	26.8±4.2
Effective radiation dose (mSv)	2.0±0.6	3.9±1.1
Subjective image quality assessment	3.7±0.6	3.7±0.6
SNR_{Trunk}	14.6±6.0	13.9±3.7
SNR_{LLSA}	15.1±8.9	12.0±4.5
CNR_{Trunk}	12.4±5.7	11.6±3.3
CNR_{LLSA}	12.9±8.5	10.0±4.1

SNR: Signal-to-noise ratio, CNR: Contrast-to-noise ratio, LLSA: Left lower segmental pulmonary artery, Trunk: Pulmonary trunk.

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undergoing CTPA with mean contrast volume being 33 ml and 29 ml, respectively. Their results showed significant improvement in the visualization of pulmonary vessels with use of low contrast medium. Another study by Lu et al[30] reported their experience of further lowering the contrast medium to 20 ml with tube voltage of 80 kVp and high-pitch protocol. Of 100 patients with suspected pulmonary embolism, 50 patients were scanned with the CTPA protocol of 100 kVp, pitch of 1.2 and 60 ml of contrast medium, while another 50 patients with the protocol of 80 kVp, pitch of 2.2 and 20 ml of contrast. Comparable image quality and diagnostic accuracy was found between two groups with no significant differences, while the double low-dose protocol using 20 ml contrast medium resulted in 50% radiation dose reduction.

Second, use of a low-pitch CTPA protocol is not associated with higher radiation dose when compared to the high-pitch mode. Pitch value has a direct impact on radiation dose as it is traditionally believed that higher the pitch, lower the radiation dose. However, increasing pitch to a higher level is not recommended due to increase in image noise resulting from suboptimal spatial resolution. With latest CT scanners the potentially high radiation dose associated with a low-pitch protocol could be countered by reducing the tube current time product (mAs), thus improving image quality by decreasing the image noise. This is observed in Boos' study. The mean mAs in Group A was significantly higher than that in Group B (268±91 mAs *vs.* 144±35 mAs, $p<0.0001$). Despite higher mAs being used in Group A, the 70 kVp protocol led to lower radiation dose with improved image quality of pulmonary arteries. High-pitch and low kVp (80 kVp) protocol has been reported in a number of studies demonstrating the further dose reduction to less than 1 mSv without compromising diagnostic image quality.[30,37,38,41] However, lowering kVp and increasing pitch level will increase image noise, thus may impair diagnostic performance of CTPA, hence, it is not widely implemented in clinical practice. It has been reported that better image quality was achieved with a pitch of 2.0 when compared to the CTPA protocol using a pitch of 3.0.[42] The mean effective dose was 2.0 mSv and 3.9 mSv for double low-dose and high-pitch CTPA protocols in Boos study, and this is higher than that reported in Lu's study which used high-pitch CTPA protocol in normal weight patients. Given the improved image quality of pulmonary vasculature, even in large patients with BMI up to 35 kg/m^2, the radiation dose of 2.0 mSv is acceptable from a clinical perspective.

Finally, the double low-dose protocol of CTPA allows for acquisition of images in patients with large BMI, according to this study. BMI is one of the main factors that should be considered during CTPA as in most of the situations, kVp and mAs are adjusted based on patient's BMI because of its impact on the radiation dose and image quality. Of these reported double low-dose CTPA studies, most of them were performed in patients with normal BMI (mean value <25 kg/m^2).[30,35] In contrast, Boos and colleagues presented diagnostic quality images in large patients as well, although they did not include extremely obese patients. The limitations of previous studies including only normal sized patients or with missing data on BMI[43] have been overcome by Boos' study, with findings offering additional value to the current literature.

In summary, Boos and colleagues in their study have demonstrated the feasibility of using double low-dose protocol comprising 70 kVp and 40 ml of contrast medium during CT pulmonary angiography. This protocol leads to significant reduction of radiation dose and contrast medium dose when compared to the high-pitch spiral dual-source CT pulmonary angiography. In addition, this study also confirms that low-dose CT pulmonary angiography is able to produce diagnostic images in patients with body mass index up to 35 kg/m^2. Due to limited small sample size in this study, further research based on a large cohort of patients with assessment of both image quality and diagnostic accuracy is warranted.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Review

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Antibody Based Therapy in Coronary Artery Disease and Heart Failure

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ABSTRACT

The function of the immune system is to protect the host against disease. Antibodies are a key part of the adaptive response, recognising specific antigens and invading pathogens and marking them for destruction or blocking their activities. A mechanistic and molecular understanding of this process has allowed researchers to harness their natural function. They are now routinely used as a diagnostic tool in the clinic and in research to investigate pathological signalling. More recently, antibodies have been utilised for another application – therapy. Antibody based therapy is one of the newest and fastest growing with nearly 70 approved drugs to date and over 1000 in clinical trials. Investment from the pharmaceutical sector shows no signs of abating and this technology is now widely accepted for treating cancer, autoimmune and infectious diseases. In the context of the cardiovascular system however, antibody therapies are relatively limited. This review summarises the monoclonal antibodies approved for clinical use or currently in clinical trials for treating cardiovascular disorders. Presently, coronary artery disease, heart failure and transplant are the main indications, and monoclonal antibody therapies are discussed in the context of their specific applications.

KEY WORDS: Monoclonal antibodies; Coronary artery disease; Atherosclerosis; Hypercholesterolaemia; Heart failure; Heart transplant.

ABBREVIATIONS: ANGPTL3: Angiopoietin-like 3; APC: Antigen Presenting Cell; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; CVD: Cardiovascular disease; CRP: C-reactive Protein; DSA: Donor Specific Antibodies; HAMA: Human Anti-Mouse Antibodies; IL: Interleukin; LPL: Lipoprotein Lipase; LDL: Low-density Lipoprotein; mAb: monoclonal antibody; MHC: Major Histocompatibility Complex; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; PCSK9: Proprotein convertase subtilisin/kexin type 9.

INTRODUCTION

Endogenous Antibody Function and Disease

Antibody-antigen recognition forms a key part of eliciting immunological responses and clearance. Antibodies are generated endogenously by B cell lymphocytes and can be secreted or presented on the cell surface. Interaction of antigen with cell-bound antibodies triggers internalisation of the complex. This is processed into peptides displayed on the surface with major histocompatibility complex (MHC) class II molecules. i.e., the B cell acts as an antigen presenting cell (APC). Binding of T helper cells to the peptide-MHC II complex releases cytokines which fully activate the B cell s along with T killer cells and macrophages (another class of APCs). Activated B lymphocytes proliferate to generate plasma cells that secrete their respective antibodies into the circulation where they coat pathogens or damaged cells. This triggers destruction and removal of the threat by complement activation and/or phagocyte engulfment. Additionally, antibodies can directly neutralize toxins or block interaction with cell surface receptors to prevent host cell infection.

While designed to protect the host, the immune system can also elicit damage to the

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body's own tissues. For example, autoimmune disease occurs when the body erroneously recognises 'self' as being 'non-self' i.e., the host is recognised as being foreign and the immune system attacks to clear the perceived threat. Hypersensitivity allergic responses can also result in host damage. These responses can be very rapid (anaphylactic) and range from mild to fatal reactions. Otherless rapid responses are generally antibody dependent, relating to the recognition of 'self' and destruction of host cells. A more delayed reaction can also occur known as cell-mediated, dependent on immune cells i.e., T cells, monocytes and macrophages.

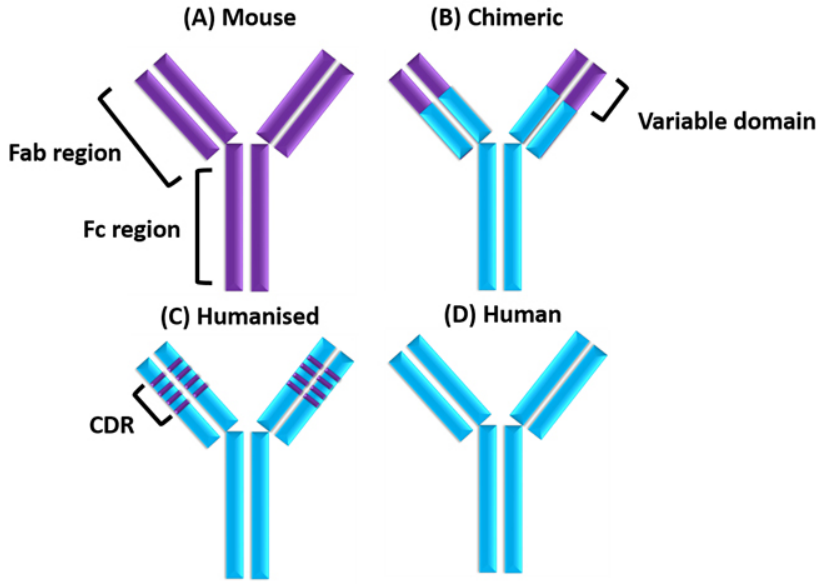
Antibodies as Therapy

Definitions: Monoclonal antibodies (mAbs), that are antibodies that recognise one epitope (the specific antibody binding site) on a particular antigen, are established therapies for conditions including cancers, autoimmune conditions and infectious diseases. The first generation of mAbs were of mouse origin but this elicited hypersensitivity due to recognition of mouse sequences as non-self. Clearance due to host development of anti-mouse antibodies – Human Anti-Mouse Antibodies (HAMA) also reduced efficacy. The next generation(s) of antibodies were humanised or chimeric, designed to reduce the risk of immunogenicity and HAMA production there by improving efficiency. These methods also have the advantage of reducing production costs.[1,2] To further reduce immunogenicity, mAbs can also be generated with fully human sequences. Mouse, chimeric, humanised and human antibody structures and domains are shown in Figure 1.

Nomenclature of antibodies is set by the World Health Organisation (WHO) and the most recent document of International Non-proprietary Names (INN) was published in 2016.[3] This states that:

- ***mab***: monoclonal antibody
- ***omab***: mouse monoclonal antibody
- ***ximab***: denotes a chimeric antibody, genetically engineered to consist of a foreign, non-human (usually mouse) antigen-binding variable domain (Fab) fused onto the human Fc constant domain. The variable domain has a sequence which is composed of more foreign than human sequence.
- ***zumab***: denotes a humanised antibody, defined as one which is composed of human sequence with the exception of the Fab region of the variable domain. Overall, the sequence is more than 85 % human.
- ***umab***: fully human monoclonal antibody
- ***c(i)***: monoclonal antibodies designed for cardiovascular indications

Figure 1: A schematic of mouse, chimeric, humanised and human antibodies for therapeutic application. All contain a Fab (fragment, antigen binding) and an Fc (fragment, crystallizable) region (A). Within the Fab region is the variable domain that binds to antigens, noted on (B). The variable domain contains the complementarity determining or hyper variable regions that are responsible for antigen binding (CDR), noted on (C). The remainder of the structure (non-variable Fab and the whole Fc region) is termed constant, i.e. conserved. By binding to specific proteins the Fc region regulates antibody activity and localisation through binding to cell surface Fc receptors and complement proteins. (A) Mouse antibodies are fully mouse. (B) Chimeric antibodies are genetically engineered so that the variable domain of the Fab region is foreign, non-human (usually mouse) fused onto the human constant domains. The variable domain has a sequence which comprises more foreign than human sequence. Human domains are noted in blue and mouse in purple. (C) Humanised antibodies are comprised of human sequence with the exception of the CDR region of the variable domain which is usually mouse. Overall, the sequence is more than 85% human. (D) Human antibodies are fully human.



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Monoclonal Antibodies to Date for Cardiovascular Indications: By January of 2017, overall 68 mAbs were licenced for clinical use.[4] This is set to expand significantly since over 1300 trials are open to date (https://clinicaltrials.gov/) classed as ongoing, actively recruiting or in preparation. However, only 48 of these have cardiovascular applications and mainly represent different studies for the same few drugs – a total of 10 mAbs. A further 5 mAbs have been withdrawn or discontinued. Three of the current ten are now approved for cardiovascular indications (Alirocumab, Evolocumab and Abciximab) and 3 are repurposed therapies. These were all previously approved for treating infectious and autoimmune diseases (Eculizimab, Canakinumab, Tocilizumab) and are currently being trialled in heart failure or heart transplant patients. Targets, indication and status of all current and withdrawn mAbs are summarised in Table 1. Information was compiled from the FDA Approved Drug Products List, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm the most recent world health organisation (WHO) International Nonproprietary Names (INN) document,[3] https://clinicaltrials.gov/ and from specific references where available (as indicated in the table under mAb name). The 10 mAbs currently in trials or clinical use are highlighted below in the context of their relevant indications.

CARDIOVASCULAR INDICATIONS CURRENTLY TARGETED BY mAb THERAPY

Coronary Artery Disease

Coronary artery disease (CAD) can manifest as angina, myocardial infarction or heart failure. It is generally caused by atherosclerosis (narrowing of the blood vessels due to build-up of fatty deposits and chronic inflammation) and is associated with high levels of low-density lipoprotein (LDL) cholesterol. High LDL cholesterol in turn correlates with cardiovascular events. Therefore, lowering LDL levels is a long-standing clinical goal. Statins are a key therapy for this however they are not always well tolerated and efficacy varies. In patients with hypercholesterolaemia (high cholesterol in the blood, related to genetic causes) statin responses are particularly limited.[2] There is therefore an unmet need for new lipid lowering therapies in these patients. Indeed, this is a common aim of a number of mAbs generated to date for cardiovascular use. Surgical treatments for CAD, percutaneous coronary intervention (PCI) and coronary artery bypass graft-

Table 1: Summary of Targets, Indication and Status of mAbs to Treat Cardiovascular Disease to Date.

mAb Type	Name	Target	Trade Name, Company	Indications	Status
Mouse Cardiovascular	biciromab	Indium-111 radiolabelled Fab fragment to fibrin II	FibriScint, Centocor	Thromboembolism diagnosis	Withdrawn
	imiciromab[28]	Indium-111 radiolabelled Fab fragment to cardiac myosin	MyoScint, Centocor	Myocardial infarction, cardiotoxicity diagnostics	Withdrawn
Human Cardiovascular	alirocumab[10]	Blocks Proprotein convertase subtilisin/ kexin type 9 (PCSK9), lowers LDL	Praluent, Regeneron/Sanofi	Hypercholesterolemia, atherosclerosis, myocardial infarction, unstable angina	Phase III to IV
	canakinumab[14]	Neutralises Interleukin-1beta	Ilaris, Novartis	Atrial fibrillation (terminated) systolic heart failure, atherosclerosis	Phase I to III
	evinacumab	Blocks Angptl3, lowers LDL and TAG	Regeneron	Hypercholesterolemia	Phase I
	evolocumab[9]	Blocks PCSK9 and lowers LDL	Repatha, AMG 145, Amgen	Hypercholesterolemia	Phase I to III
	inclacumab	P-selectin on endothelial cells, blocking inflammatory cell extravasation	RO4905417, Genentech/ Roche	Coronary artery bypass graft, atherosclerosis	Phase II
	orticumab[29]	anti-oxidant forms of LDL cholesterol	Bioinvent/Genentech	Aartherosclerosis	Study Terminated
Chimeric Cardiovascular	abciximab[12]	glycoprotein IIb/IIIa receptor antagonist, inhibits platelet aggregation	Reopro, Janssen Biologicals/Eli Lilly	Percutaneous coronary interventions, unstable angina, atherosclerosis	Phase II to IV
Humanised Cardiovascular	bococizumab	Blocks PCSK9 and lowers LDL	Pfizer	Hypercholesterolemia	Discontinued
	eculizumab[24]	C5 complement inhibitor	Soliris, Alexion Pharmaceuticals	Cardiac transplant	Phase IV
	ralpancizumab	PCSK9	Pfizer	Hypercholesterolemia	Discontinued
	tadocizumab	αIIbβ3 integrin on platelets, blocking interaction with fibrinogen and fibronectin	Yamanōchi Pharma America	Percutaneous coronary interventions	Phase II
	tocilizumab[18]	blocks IL-6 receptor	Actemra, Hoffman-La Roche	Myocardial infarction	Phase II
	TS23	inhibits alpha-2 antiplasmin	Daiichi Sankyo	Ischemia, myocardial infarction, thrombosis	Phase I

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ing (CABG) also carry their own risks, eliciting inflammatory responses and complications due to thrombosis. Drugs that can be used in conjunction with PCI or CABG are therefore also a target area of mAb treatment in CAD.

LDL cholesterol lowering agents: In the context of LDL cholesterol lowering agents, 2 mAbs (Evolocumab and Alirocumab); have the same target, proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 regulates circulating LDL cholesterol, with loss of function mutations being associated with reduced LDL cholesterol and gain of function with higher. Moreover, this correlates negatively and positively respectively with cardiovascular events.[2] PCSK9 increases LDL receptor degradation, reducing bioavailability for binding to and removal of LDL cholesterol from the blood.[2] Therefore, blocking PCSK9-LDL receptor interaction with PCSK9 mAbs increases receptor bioavailability and removal of circulating LDL cholesterol.

PCSK9 has therefore received a lot of interest from pharmaceutical companies. Evolocumab and alirocumab were both shown to reduced levels of LDL cholesterol[5,6] and approved for clinical use in 2015 to treat hypercholesterolaemia and atherosclerosisas an adjunct to other LDL lowering therapies e.g. statin and dietary modifications.[7,8] Importantly, trials have shown that esvolocumab (Repatha/AMG 145 from Amgen)[9] reduces atherosclerosis volume, i.e., it promotes plaque regression,[5] while Alirocumab (Praluent, from Regeneron/Sanofi)[10] treatment was associated with lower incidence of major adverse cardiac events.[6]

A third lipid lowering agent, Evinacumab, is also designed to reduce LDL cholesterol but through a different mechanism. It blocks the activity of Angiopoietin-like 3 (ANGPTL3), an inhibitor of lipoprotein lipase (LPL). Increasing LPL activity in this manner increases breakdown of triglycerides in addition to LDL cholesterol.[11] Like PCSK9, genetic investigations indicate LPL to be another promising target. In this case, loss of function variants increases risk of coronary artery disease and gain of function variants lower it.[11] Further, loss of function variants of ANGPTL3 are associated with decreased triglyceride, LDL and HDL cholesterol and lower incidence of cardiovascular events. At present, Evinacumab has been tested in Phase I with promising results; it was well tolerated and lipid levels were reduced in participants with mild to moderate (otherwise healthy) circulating triglyceride or LDL levels.[11] A phase II trial is planned to assess the benefits in disease cohorts.

Anti-thrombotics in PCI: PCI is a surgical invention/treatment for CAD that directly opens the blood vessels to improve blood flow through balloon angioplasty or stent placement. To date, Abciximab (marketed as ReoPro, Janssen Biologics and Eli Lilly) is the only mAb licensed for use in PCI.[12] Abciximab is a chimeric antibody that acts as an anti-thrombotic by binding to glycoprotein IIb/IIIa receptor antagonist to prevent platelet aggregation. It blocks interaction of ligands including fibrinogen and von Willebrand factor and binds to the vitronectin receptor αvβ3 found on platelets, endothelial and vessel smooth muscle cells, inhibiting their pro-coagulant properties. Adverse indications can arise due to off-target or on-target effects however, and in the case of Abciximab, an on-target adverse effect is increased risk of bleeding.[12] Tadocizumab is also designed to act as an anti-thrombotic in PCI, by blocking platelet αIIbβ3 integrin interaction with fibrinogen and fibronectin. However, it does not appear to have progressed past phase II trials, making Abciximab the only mAb therapy currently available for this use.

It should be noted that another anti-thrombolytic agent suggested to be useful in this context, TS23, has provided promising results from asmall phase I trial. TS23 is an anti-thrombolytic that dissolves clots by targeting and inactivating α2-antiplasmin – a major inhibitor of plasmin, which dissolves blood clots. No adverse effects have been reported (including bleeding) and a2-antiplasmin activity was reduced as expected.[13]

Anti-inflammatories: Atherosclerotic disease has a core inflammatory component, and 2 immunosuppressant mAbs are currently being trialled to mitigate this aspect. Canakinumab (Ilaris, Novartis)[14] acts by neutralising Interleukin (IL)-1β, a key pro-inflammatory cytokine in many disease processes, that was previously approved for treating arthritis. Trials are underway in atherosclerotic patients as well as those with systolic heart failure (secondary to myocardial infarction; MI), to test whether adverse clinical events and plaque burden can be reduced.[15,16] The second is Inclacumab (Genentech, Roche, South San Francisco, CA, USA), which reduces inflammation by blocking P-selectin on endothelial cells to limit inflammatory cell extravasation. It is being currently tested in CABG, with the aim of reducing complications due to destructive inflammatory processes.[17]

Myocardial Infarction

Acute and ongoing damage following MI and subsequent reperfusion injury has significant impact on long-term patient survival and quality of life. Another anti-inflammatory therapy, Tocilizumab (Actemra)[18] is currently in Phase II trials in acute MI (non-ST and ST elevation patients) to test whether adverse cardiac events are reduced short-term (within 30 days) and in ST elevation patients to assess whether long-term myocardial damage is reduced (6 months). Tocilizumab blocks IL-6 receptor activity, which is a secondary response to primary cytokines like IL-1. IL-6 itself, has also been shown to contribute to atherosclerotic plaque formation in addition to mediating ischemic reperfusion injury. It also induces expression of C-reaction protein (CRP), which is an inflammatory biomarker associated with poor outcome.[19] Results from these trials showed a decrease in early CRP and troponin T release (a measure of myocardial damage), although coronary flow reserve (a measure of coronary microvascular function) was unaffected when assessed 6 months later.[19,20]

The LDL cholesterol lowering drug Alirocumab (Praluent),[10] is also being tested in phase IV trials for use in non-ST

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segment elevation MI patients (NSTEMI) that have previously responded poorly to statins. Alirocumab will be administered as a single dose in acute MI, and LDL cholesterol and inflammatory markers measured up to 14 days after infarct. Presumably if this yields promising results, further trials will be performed to assess whether this positively impacts on long-term patient outcome. A phase III trial is underway to also test whether long-term Alirocumab treatment reduces plaque volume in patients who have undergone PCI following MI.

Heart Failure and Transplant

Mechanisms of cardiac rejection: Heart transplant is the last line treatment for heart failure however rejection is the most common cause of death following transplant. Rejection of transplanted hearts is an inflammatory process that starts with induction of proinflammatory cells and recruitment of recipient inflammatory cells to the site of injury or 'non-self' tissue. T cell activation triggers a full immune response leading to rejection, which can be hyperacute, cellular or vascular in nature. All are thought to be either antibody dependent or at least involve antibody mediated responses.[21] Hyperacute rejection is stimulated by pre-existing antibodies to the donor heart (donor specific antibodies (DSA)) in the recipient and is a powerful and rapid response occurring *via* activation of the complement system. The risk of this can be lowered to some extent by avoiding transplantation of donor tissues into a patient who is already sensitised to the donor. However, DSA can also arise *de novo* and these contribute to cellular and vascular rejection. Acute cellular rejection is the most common type and is less rapid (more likely months). This is mediated by T cell lymphocytes and inflammation in the transplanted heart and surrounding vasculature. Vascular/vasculopathy rejection generally occurs later than other subtypes (over years) and is characterised by otherwise unexplained cardiac dysfunction and hemodynamic compromise i.e. concentric arterial narrowing.[21]

First-line treatments include anti-inflammatories such as methylprednisolone, removal of immunogenic antibodies by plasmapheresis and intravenous immunoglobulin transfusion for desensitisation with or without anti-thymocyte globulin to reduce T lymphocyte levels. Anti-lymphocyte antibodies to the cell surface marker CD52 to deplete B and T cell levels can also be used.[22]

mAbs for treating heart failure and cardiac rejection: Current guidelines from the American Heart Association (AHA) in management of antibody-mediated rejection in heart transplant suggest mAbs could be used as a secondary therapy.[22] mAbs are suggested as a treatment to suppress formation of *de novo* donor-specific antibodies following transplantation and for general immunosuppression.[21,22] Rituximab, a B cell suppression agent currently approved for cancer and arthritis has been suggested for this use though has not been trialled in this context, and it should be noted it is not recommended for patients with arrhythmia.[21-23]

As mentioned above in the context of atherosclerosis, the IL-1β neutralising mAb canakinumab is also being trialled in heart failure patients secondary to MI.[16] The main study, CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) is designed to assess whether recurrent cardiovascular events can be reduced in high risk patients, defined as those with persistent high sensitivity CRP elevation. Patients will be followed for up to 4 years, with quarterly treatment. In another arm of the same study, exercise capacity will be assessed for 12 months.[16]

Only one mAb is currently being tested in heart transplantation specifically; Eculizumab.[21] Eculizumab (Soliris)[24] is an agent that blocks complement protein C5. C5 plays a role both in chemotaxis and formation of the membrane attack complex that results in cell destruction. By blocking cleavage of C5, required for both activities, Eculizumab can suppress inflammation by two different mechanisms. It is currently in Phase IV for patients pre-sensitised to antibody mediated rejection, to be given at the time of transplant.

FUTURE PERSPECTIVES

To date, all mAbs being used or trialled in cardiovascular disease act to reduce inflammation, lower lipid levels or prevent thrombosis. These properties are applicable therefore, mainly to coronary artery disease; its complications, manifestations and treatments. Anti-inflammatory therapies are also being tested for efficacy in lowering the likelihood of rejection following heart transplantation.

To date, only 3 antibodies have been approved for standard use in the clinic however, thus this therapeutic avenue is in its infancy. Abciximab is an anti-thrombotic used in PCI while Evolocumab and Alirocumab target PCSK9 to reduce lipid (LDL cholesterol) levels and reduce long-term risk of adverse events. This method of reducing LDL cholesterol levels is particularly important for patients that do not respond well to statins. Another lipid lowering agent that works through a different mechanism, Evinacumab, has passed initial safety testing and a phase II trial is planned to assess effects in hypercholesterolemia patients. Further trials will show whether targeting ANGPTL3 is as effective as PCSK9 (or better) in reducing plaque burden and lowering long-term risk of adverse cardiac events.

Given the high levels of mortality following myocardial infarction and in transplant rejection for heart failure, there is a clinical need for more effective therapies. Antibody-mediated cardiac rejection is the most common cause of death within the first 5 years after transplant.[21] In the case of MI, survivors are at high risk for death, or recurrent MI and other cardiovascular events.[25,26] Although, patient outcome is improving, there is considerable burden on healthcare systems and incidence is increasing in an aging and obese population.[25,26] mAbs being tested in this context are mainly anti-inflammatories that have been repurposed from existing autoimmune and infectious disease

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treatments; Eculizimab, Canakinumab and Tocilizumab. Anti-inflammatory mAbs might therefore represent the next generation of treatment for cardiac transplant rejection in particular. A major concern here however, is that by suppressing the immune system, risk of infection might be substantially increased. As a 'non-sterile' inflammatory setting (as opposed to 'sterile' in the case of arthritis for example), this might be a very relevant issue in transplant. Indeed, for all three of these mAbs, an increased risk of infection has been noted.[5-7] The results of these trials however, if positive, may well encourage development or repurposing of further anti-inflammatory mAbs. Indeed, two others that target IL-6 pathways (as does Tocilizumab) are currently in phase III trials for rheumatoid arthritis[27] and might provide alternative mechanisms of inhibiting this pathways if needed. Currently, IL-1β, IL-6 and complement protein C5 are the only targets, and it might be useful to continue testing antibodies that target alternative inflammatory pathways to assess which carries the lowest risk of infection.

Anti-thrombolytic mAbs, although limited in their use (currently only one, Abciximab is usedin PCI), provide another therapeutic avenue to be explored. A common side effect of anti-thrombotics in general is increased risk of bleeding, as has been noted for Abciximab. Another in early testing, TS23, if equally effective but with lower risk of bleeding, may prove a better therapy. The current data for TS23 is very limited however, but exploring alternative anti-thrombotic mAbs might prove prudent to maintain the desired effects while further limiting adverse events.

The use of mAbs in treating cardiovascular disease is a newly emerging field that represents a small proportion of this therapeutic avenue overall. Perhaps to properly assess the efficacy in this setting requires rather more long-term end points (patient survival or adverse cardiac events over years for example). Trials are increasing in numbers however, and repurposing mAbs approved for other (cardiovascular and non-cardiovascular) uses will fast track these therapies into the clinic. It remains to be seen whether antibody based therapy will become more widely utilised in the future, but at this point, mAbs hold great promise for areas of unmet need. The results of a number of ongoing clinical trials will become available in the next few years, and the outcomes of these will be key in determining the future of mAbs for treating cardiovascular disease.

CONFLICTS OF INTEREST

Dr. Fiedler has nothing to declare.

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