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Review

*Corresponding author
Lorna R. Fiedler, PhD
MRC Weatherall Institute of Molecular Medicine
Oxford University
John Radcliffe Hosptial
Headley Way, Oxford OX3 9DS, UK
E-mail: lorna.fiedler@gmail.com

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Antibody Based Therapy in Coronary Artery Disease and Heart Failure

Lorna R. Fiedler, PhD*

MRC Weatherall Institute of Molecular Medicine, Oxford University, John Radcliffe Hosptial, Headley Way, Oxford OX3 9DS, UK

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; 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.

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

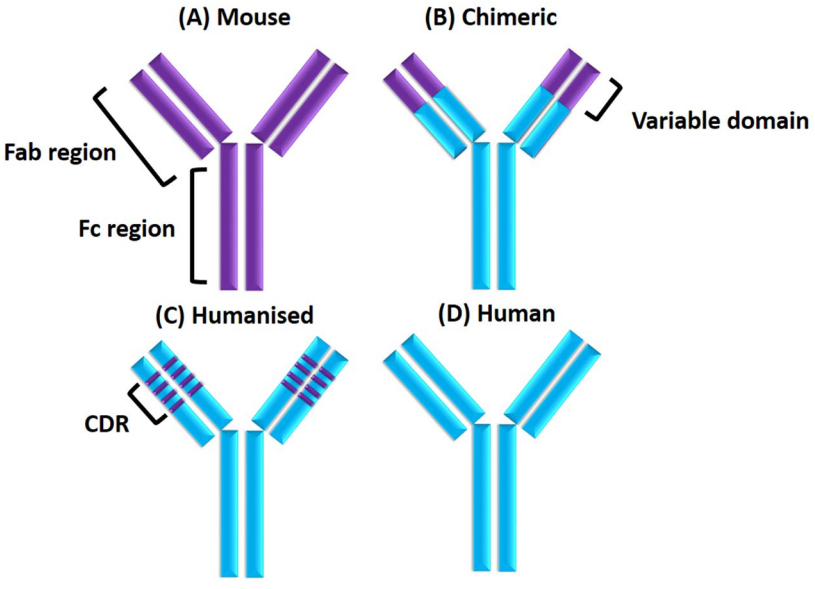
Antibodies as Therapy

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 WHO 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 grafting (CABG) also carry their own risks, eliciting inflammatory

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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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 Evolocumab (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 α2-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 segment elevation MI patients (NSTEMI) that have previously

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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 treatments; Eculizimab, Canakinumab and Tocilizumab. Anti-inflammatory mAbs might therefore represent the next genera-

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tion 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 used in 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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