Latest drug developments in the field of cardiovascular disease

Craig S Stern RPh PharmD MBA FICA, Jason Lebowitz BS

CS Stern, J Lebowitz. Latest drug developments in the field of cardiovascular disease. Int J Angiol 2010;19(3):e100-e105.

Cardiovascular disease has been responsible for more deaths annually than any other disease category since 1900, except for the influenza epidemic in 1916. Yet, the drug pipeline has been largely bereft of new entrants. In 2008, one new cardiovascular medication was marketed in the United States. In 2009, there were two new cardiovascular medications. In comparison, there were seven new drugs for oncology in 2009. The present review explores new agents within the context of models currently in the drug pipeline. Of course, there is no guarantee that any of these agents will be marketed. A discussion of the models is illustrative of the types of approaches being used to develop new cardiovascular agents.

Key Words: *Cardiovascular disease; Clinical trials; Drug development; Drug pipeline; Drugs; Models; New approvals*

Drug therapy is a major treatment modality in cardiovascular disease, but there have been few new medications approved for treatment. However, the number of new agents does not indicate that the field is bereft of new ideas. The present review explores the newer, more promising models for medication treatments in each of the major cardiovascular conditions, indicating the most promising of those agents being investigated. This discussion is not meant to provide an exhaustive list of every drug under investigation because that would be impossible within the confines of a journal article. Certainly, many of these medication models will not lead to the development of important drugs. Nonetheless, we can hope that these models will provoke intellectual discussion, lead to the discovery of new clinical information or provide direction for future research.

CARDIOVASCULAR DRUG PIPELINE, 2009

The cardiovascular drug market is severely impacted by the scarcity of new agents and the loss of patent protection by 2012 for major statins (Lipitor; Pfizer, USA), angiotensin receptor blockers (ARBs) (Diovan; Novartis, Switzerland) and antiplatelet agents (Plavix; Bristol Myers Squibb Sanofi Pharmaceuticals Partnership, USA) (Table 1).

The movement to generics is expected to change the complexion of the market. The anticholesterol pipeline is devoid of new agents due to the success of statins. The hypertension market is expected to slow after the ARBs lose patent protection beginning in 2010. An additional concern is the current United States (US) Food and Drug Administration (FDA) review (1) of studies indicating an association between ARBs and malignancy. The outcome of this review is still uncertain, but may hasten switches to drugs other than ARBs if the findings are determined to be accurate. However, the biggest impact is expected to be in the antiplatelet and antithrombotic market, which is expected to overtake anticholesterol agents as the sales leader.

NEW APPROVALS, 2009

The current pipeline has produced two agents marketed in 2009; namely, prasugrel and dronedarone. Prasugrel is an ADP receptor blocker that competes with clopidogrel for maintenance of open arteries following percutaneous coronary intervention (PCI). The target patient populations have acute coronary syndrome (ACS) and PCI, are younger than 75 years of age, weigh more than 60 kg, and have not had a transient ischemic attack or stroke. Dronedarone is a treatment for atrial fibrillation (AF) similar to amiodarone; each will be discussed separately under their respective therapeutic models.

CURRENT PIPELINE

The current drug pipeline is focused on two main categories: antidyslipidemic agents and antiplatelet/antithrombotic agents. The American Heart Association estimates that there are 34 million Americans with mixed dyslipidemia. Hence, emphasis has been placed on this category.

The most promising antidyslipidemics are the following:

- Certriad (rosuvastatin [Crestor; AstraZeneca, UK] and fenofibric acid [Trilipix; Abbott Laboratories, USA] combination): The new drug application (NDA) was submitted on June 4, 2009, for management of mixed dyslipidemia. The product is a combination of two marketed agents and was submitted in three dosage combinations – 5 mg, 10 mg and 20 mg of rosuvastatin combined with fenofibric acid (2).
- Darapladib (GlaxoSmithKline Inc, UK): Darapladib is a lipoprotein-associated phospholipase A2 inhibitor that promotes plaque stabilization by blocking the phospholipase A2 enzyme. The emphasis on targeting plaques versus treating laboratory cholesterol values is hoped to be a major shift in management. The agent began phase III trials in December 2008; the NDA filing will depend on the rate of cardiovascular events observed in the phase III Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial (3).

The most promising of the antiplatelet/antithrombotic agents are the following:

- Ticagrelor (AZD6140, Brilinta; AstraZeneca) (4): Ticagrelor is a reversible ADP receptor blocker. The PLATelet inhibition and patient Outcomes (PLATO) phase III trial (5) demonstrated superior effectiveness to clopidogrel (Plavix) for ACS. The bleeding risk was greater than clopidogrel

Pro Pharma Pharmaceutical Consultants Inc, Northridge; and University of Southern California School of Pharmacy, Los Angeles, California, USA
Correspondence: Dr Craig S Stern, Pro Pharma Pharmaceutical Consultants Inc, PO Box 280130, Northridge, California 91328-0130, USA.
Telephone 818-701-5438, fax 818-701-0249, e-mail craig.stern@propharmaconsultants.com

(Plavix), but similar to prasugrel (Effient; Daiichi Sankyo, Japan, and Eli Lilly, USA). The NDA for ticagrelor was submitted in November 2009, and is still pending approval by the FDA.

- SCH530348 (Schering-Plough, USA): This agent is a thrombin receptor antagonist that is initially being studied as potential treatment for ACS, but is ultimately expected to target secondary prevention. The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA*CER) phase III trial (6) is currently being investigated with a sample size of approximately 31,000 subjects, with an NDA possible in 2010.
- Rivaroxaban (Xarelto; Bayer Schering Pharma AG, Germany): Rivaroxaban is on the market in Europe, but has not been approved in the US. It is first in the class of factor Xa inhibitors and is being submitted for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery. The Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) studies (7,8) demonstrated superiority of rivaroxaban to enoxaparin (Lovenox; sanofi-aventis, France). A 'complete response' letter was issued by the US FDA in May 2009, but final US approval is not likely until 2010.
- Dabigatran (Pradaxa; Boehringer Ingelheim, USA): Dabigatran is a direct thrombin inhibitor for treatment of venous thromboembolism (VTE) and prevention of stroke associated with AF. The drug is currently in phase III trials (9) investigating the oral, direct thrombin inhibitor dabigatran etexilate twice daily in the long-term prevention of recurrent, symptomatic VTE. Comparisons of dabigatran to warfarin for AF indicated similar to better efficacy and equal to lower bleeding risks.

The dearth of new products is not reflective of the many options that are being pursued. While there are no guarantees of product approvals, there are a number of therapeutic models that are of interest. These models will be discussed under each targeted disease category.

THERAPEUTIC MODELS: ACS AND ANTITHROMBOTICS

ACS is an umbrella term for conditions that cause chest pain due to insufficient blood supply to the heart muscle, ie, acute myocardial ischemia. ACS includes two conditions: unstable angina (chest pain with electrocardiogram changes compatible with ischemia) and heart attack (non-ST segment elevation myocardial infarction [NSTEMI] or ST segment elevation myocardial infarction). Unstable angina and NSTEMI account for approximately 2.5 million hospital admissions worldwide and are a major cause of mortality and morbidity in western countries.

There are two primary therapeutic models being evaluated for ACS: antiplatelet agents (primarily agents producing ADP receptor blockade), and antithrombotics or coagulation inhibitors.

Antiplatelet agents

Among the antiplatelet agents are the ADP receptor blockers, which act by preventing platelet activation and aggregation by blocking ADP receptors on the platelet surface. The pioneer product is ticlopidine, a thienopyridine compound that acts to antagonize ADP, thereby interfering with ADP-induced binding of fibrinogen to platelets.

TABLE 1
Upcoming patent expirations for cardiovascular drugs

Brand name in United States (US)	Patent expiration in US (month, year)	US sales ($US billion) in year patent expires
Cozaar/Hyzaar*	February 2010	0.80
Lipitor†	November 2011	4.50
Avapro‡	March 2012	0.65
Plavix§	May 2012	6.20
Atacand¶	June 2012	0.30
Diovan**	September 2012	2.00

**Merck & Co, USA; †Pfizer, USA; ‡Bristol Myers Squibb, USA; §Bristol Myers Squibb Sanofi Pharmaceuticals Partnership, USA; ¶AstraZeneca, UK; **Novartis, USA*

However, the major market winner in this category is still clopidogrel. Clopidogrel (Plavix) is inactive in vitro, but undergoes hepatic activation to an active metabolite that irreversibly binds to ADP, preventing binding to its platelet receptor. The active metabolite also irreversibly modifies the ADP receptor on the platelet, affecting it for the remainder of its lifespan. ADP activates the glycoprotein IIb/IIIa complex that is the major fibrinogen receptor. Thus, ADP receptor blockade interferes with fibrinogen activation of platelets, leading to inhibition of platelet aggregation.

The pharmacodynamic problem with ADP receptor blockers is the variability in the extent of binding, leading to variable clinical results. As a result, there is an active search for molecules with more predictable binding properties. The latest entrant is prasugrel, which was investigated against clopidogrel in the Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) (10). Prasugrel (TSE4208) was developed by Daiichi Sankyo, produced by Ube Pharmaceuticals, Japan, and clinically developed with Eli Lilly. As an antiplatelet agent designed to prevent platelet activation and aggregation by blocking ADP receptors on the platelet surface, prasugrel is potentially more active than clopidogrel. Prasugrel has a higher rate of bleeding due to a more predictable binding affinity for the ADP receptors and, as a result, it was approved for higher risk patients with ACS who undergo PCI.

An alternative approach to the binding problem is being studied with the investigational agent, ticagrelor (11). Ticagrelor is being studied as the first reversible oral ADP receptor antagonist for ACS. It is proposed to selectively inhibit the P2Y12 receptor, a key target receptor for ADP on platelets. The main evidence for benefit from ticagrelor and the reversible binding approach is the Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 versus clopidogRel in non-ST-segment Elevation myocardial infarction (DISPERSE 2) (12). DISPERSE 2 was a dose confirmation study assessing the antiplatelet effects of ticagrelor versus clopidogrel in NSTEMI. It is a double-blinded, double-dummy, parallel-group, randomized dose confirmation and feasibility study of ticagrelor plus acetylsalicylic acid (ASA) compared with clopidogrel plus ASA in 990 patients with non-ST segment elevation ACS. Subjects received an ASA first dose of up to 325 mg, then a daily dose of 75 mg to 100 mg, and heparin/low molecular weight heparin and/or glycoprotein IIa/IIIb inhibition as specified by the

treating physician. They were randomly assigned to receive one of two doses of ticagrelor (90 mg or 180 mg twice daily) or clopidogrel 75 mg once daily for up to 12 weeks. One-half of the ticagrelor patients were subrandomized to receive a loading dose of 270 mg while the other one-half started therapy with the maintenance dose. Patients randomly assigned to clopidogrel received a 300 mg loading dose unless they had been on previous clopidogrel therapy, with the option to receive an additional double-blinded 300 mg clopidogrel dose before PCI (total dose 600 mg). The primary end point studied was total bleeding events (major plus minor) within the first four treatment weeks. In patients with ACS, there was no difference in major bleeding, but an increase in minor bleeding at the higher doses.

Antithrombotics

Antithrombotics provide a drug therapy model that is currently focused on thrombin receptor antagonism or clot inhibition. The most promising of the thrombin receptor antagonists is SCH530348, which was fast tracked by the US FDA for ACS treatment and is currently in the phase III TRA*CER trial (6).

The antithrombotic model is focused on inhibitors of factor Xa receptors, thrombin receptors and proteinase-activated receptor (PAR)-1. As successors to heparin and low molecular weight heparins, the model that has demonstrated the greatest progress is the factor Xa inhibitors. Rivaroxaban (Xarelto) is marketed in several countries, but is still under review in the US. It was invented by Bayer Schering Pharma AG (which was subsequently purchased by Johnson & Johnson, USA) and will be marketed in the US by Ortho-McNeil, USA, a Johnson & Johnson subsidiary. Rivaroxaban is the first oral direct inhibitor of factor Xa. It has good oral absorption (bioavailability 80% to 100%) and a half-life of 7 h to 11 h. The pharmacological effect is longer, allowing for once-daily dosing because the factor Xa levels do not return to normal for approximately 24 h. Johnson & Johnson is pursuing indications for VTE first, with ACS to follow. Rivaroxaban is also of interest because it inhibits both free factor Xa in the circulation and proteinase complex-bound factor Xa. Thus, it affects both the contact activation pathway (intrinsic) and tissue factor pathway (extrinsic), but does not affect platelets.

Although not as far along, PRT054021, a factor Xa inhibitor from Portola Pharmaceuticals, USA, has demonstrated both efficacy and safety benefits in comparison with enoxaparin for VTE after total knee replacement in the Evaluation of the Factor Xa Inhibitor, PRT054021, Against Enoxaparin in a Randomized Trial for the Prevention of Venous Thromboembolic Events After Unilateral Total Knee Replacement (EXPERT) (13). PRT054021 is in phase II testing for treatment of VTE and it is unclear whether testing for treatment of ACS will be pursued.

Of minor note is a therapeutic model attacking PAR-2 inhibitors. PAR-2 is a cell surface receptor that is known to play a critical role in acute and chronic inflammation. Multiple small molecule PAR-2 antagonists have been synthesized to identify compounds with increased activity. The potential therapeutic applications of PAR-2 in oncology and inflammatory diseases are currently being studied. The hope is that formation of new blood vessels can impact ACS, but this is very preliminary and without current evidence.

THERAPEUTIC MODELS: ANGINA

Drug therapy models to treat angina have not been productive with regard to producing new therapies. Angina is caused by the imbalance of oxygen supply versus demand to the myocardium, leading to myocardial hypoxemia. Supply-side models directed toward treating coronary artery vasospasm, fixed stenotic lesions or thrombus have been addressed over the past decade with anticoagulants and antithrombotics that are now generally mature, with few new options. Similarly, demand-side models are focused on oxygen consumption regulated by heart rate, inotropy, afterload and preload. Increased oxygen demand has been treated with beta-blockers, Ca^{2+} channel blockers and nitrates, which are now mature drug categories with conceptually few novel approaches. The greatest interest has been directed toward the dysfunctional or diseased vascular endothelium that affects both oxygen supply and demand. The healthy vascular endothelium produces a protective mechanism through the production of nitric oxide (NO) and prostacyclin, which dilate coronary arteries and prohibit clot formation. A dysfunctional vascular endothelium cannot produce adequate supplies of NO and prostacyclin, leading to vasoconstriction, platelet aggregation and clot formation.

The models focus on the activity of NO to protect tissues from ischemia in low doses, but sustained levels of NO lead to tissue toxicity and vascular collapse. Therapies being studied include nitrates, an NO synthase transcription enhancer (AVE9488), Ca^{2+} channel blockers (particularly diltiazem) and a cardiac metabolic modifier (ranolazine).

THERAPEUTIC MODELS: CORONARY ARTERY DISEASE

Treatments for coronary artery disease have taken very different approaches that focus on models attacking atherosclerosis and restenosis, and gene therapy. Atherosclerosis models combine extended-release niacin formulations with statins. The emphasis on extended-release niacin is to decrease flushing, while the statin component is usually simvastatin, available as a generic, put into a combination drug to allow for branded patent extension. Examples are MK-0524A (14) (extended-release niacin and statins), MK-0524B (15) (extended-release niacin and simvastatin) and Niaspan (extended-release niacin; Abbott Laboratories) plus simvastatin.

Restenosis models are targeted to the cell damage caused by angioplasty for narrowed blood vessels using drug-eluting stents. The first stage of restenosis after surgery is targeted with the use of antiplatelet IIa/IIIb inhibitors – eg, tirofiban, eptifibatide and abciximab – to prevent thrombosis. The second stage of restenosis is targeted with medications eluted from the stents that inhibit intimal tissue growth from scar tissue and cell proliferation produced by the stent. Examples of medications being studied include biolimus A9, everolimus (Certican; Abbott Laboratories), zotarolimus (Endeavor; Medtronic, USA), Resten-MP and Resten-NG (Cook Medical, USA, and AVI BioPharma, USA), and paclitaxel (Coroxane; Abraxis BioScience [Celgene, USA] and AstraZeneca).

Gene therapy is also being evaluated to prevent coronary artery disease. Current interest is in hypoxia-inducible factor-1-alpha, which is being developed by BioCardia, USA. Hypoxia-inducible factor-1-alpha regulates oxygen homeostasis by expressing genes that code for proteins involved in angiogenesis,

TABLE 2
Targeted channels of investigational agents

Drug	Channel blocker	Developer	Comments
RSD1235	I_{Kur} + I_{Na}	Cardiome, Canada	Blocks I_{Kur}, I_{to} and I_{KACh}; prolongs atrial refractoriness without significant effect on ventricles or QT; no drug-related proarrhythmias or adverse hemodynamic effects; 56% conversion rate in 2 h
C9356	I_{Kur}	Cardiome, Canada	
NIP142	I_{Kur} + I_{KACh}	Nissan Chemical, USA	
AZD7009	I_{Kur} + I_{Na} + I_{Kr}	AstraZeneca, UK	
AVE0118	I_{Kur} + I_{to} + I_{KACh}	Aventis, Germany	K^+ channel blocker that inhibits I_{Kur}
S9947-S20951	I_{Kur}	Aventis, Germany	
S0100176	I_{Kur}	Aventis, Germany	

Data from reference 24. I_{KACh} Acetylcholine-dependent activation of cardiac K^+ current; I_{Kr} Rapid delayed rectifier current; I_{Kur} Ultrarapid delayed rectifier current; I_{Na} Na^+ current; I_{to} Transient outward current

energy metabolism, erythropoiesis, cell proliferation, vascular remodelling and vasomotor responses.

THERAPEUTIC MODELS: ARRHYTHMIA – AF

AF is the most common symptomatic tachyarrhythmia and is expected to grow as the population ages. The expectation is that the AF population will grow from 2.1 million in 1995 to 5.6 million in 2050. Drug treatment models for AF have addressed the problem from several directions including rate control, rhythm control, agents altering the atrial substrate, anticoagulation and ablation. At this time, only rhythm control studies have produced an approvable agent in dronedarone (SR33589), which is similar to amiodarone.

K^+ channels in the heart determine heart rate, resting membrane potential, action potential shape and duration. These channels are classified as either voltage gated (ie, dependent on inflow/outflow of K^+) or ligand gated (ie, ligands expand the channel, allowing ions to flow into the myocardium). Voltage-gated channels are further classified into transient outward current, delayed rectifier current and inward rectifier current. The delayed rectifier current channel is divided into ultrarapid (I_{Kur}), rapid and slow. These distinctions are not just physiological because the atrium has a greater density of repolarizing K^+ currents, particularly I_{Kur}, that are relatively insensitive to class III agents including amiodarone, sotalol and dofetilide. Ligand-gated channels are distinguished by whether they are dependent on ATP or acetylcholine as their transport substrate.

Research has targeted K^+ channels for atrial-specific arrhythmias using either voltage-gated channel blockers or combinations of voltage- and ligand-gated channel blockers. While there are no recently approved agents, there is still promise. The I_{Kur} channel blockage strategies listed in Table 2 are of interest.

In addition, there are early trials of alternative model channel blockers – ATI 2042 (similar to amiodarone); AVE0118, AVE1231 and azimilide (for New York Heart Association class III patients); AZD7009 (mixed Na^+/K^+ blocker); C9356 (hKv1.5 blocker); GSMtx4 (stretch-activated ion channel blocker) and NIP142 (Na^+ current blocker). There are also early developments of receptor antagonists JTV519 (ryanodine receptor-stabilizing protein) and piboserod (5HT4 receptor antagonist), as well as a gap junction modifier (rotigaptide; ZP-123/GAP-486).

TABLE 3
Multichannel blocking effects of dronedarone versus amiodarone

	Dronedarone	Amiodarone
Outward currents, guinea pig, IC_{50}		
I_{Kr} (ventricle)	2–3 µM	10 µM
I_{Ks} (ventricle)	10 µM	30 µM
I_{Ki} (ventricle)	>30 µM	≤30 µM
I_{KACh} (atrium)	0.01 µM	1 µM
Inward currents		
I_{Na}, human, 3 µM	–97%	–41%
$I_{Ca\text{-}L}$, guinea pig, IC_{50}	0.2 µM	10 µM

Data from reference 25. IC_{50} Half maximal inhibitory concentration; $I_{Ca\text{-}L}$ L-type Ca^{2+} current; I_{KACh} Acetylcholine-dependent activation of cardiac K^+ current; I_{Ki} Inward rectifier current; I_{Kr} Rapid delayed rectifier current; I_{Ks} Slow delayed rectifier current; I_{Na} Sodium current

Dronedarone (SR33589) is an example of an agent designed to relieve the toxicity profile of amiodarone, but provide similar multichannel blocking effects. Amiodarone is the most frequently used rhythm control agent, but it has multiple toxicities and dose-limiting side effects. Dronedarone lacks the iodine moiety; therefore, it has no significant effect on T3, T4 or rT3, and, consequently, it has no thyroid or pulmonary toxicity. It has fewer drug-drug interactions than amiodarone, but has a similar blocking profile. Namely, dronedarone blocks rapid delayed rectifier current, slow delayed rectifier current, L-type Ca^{2+} current, transient outward current, and is also an alpha- and beta-antagonist. It has a different pharmacokinetic profile than amiodarone, with a 24 h half-life, twice-daily dosing and first-pass hepatic metabolism leading to approximately 15% availability; food increases blood levels two to three times (Table 3).

Dronedarone safety and efficacy was studied in the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study (16), A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter (ATHENA) (17) and the Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) (18). ERATO (16) was an efficacy and safety trial that analyzed control of ventricular rate (VR) during AF. The result was a decrease in VR during rest and exercise. ANDROMEDA (18) studied the benefit of control of arrhythmias and decreased mortality in patients with moderate to severe congestive heart failure (CHF) (New York Heart Association class III and IV). This trial identified no adverse drug effects, but found that dronedarone was not superior to placebo. The trial was terminated early due to nonsudden death that was increased when angiotensin-converting enzyme inhibitors and ARBs were discontinued due to an increase in serum creatinine levels. Subsequently, ATHENA (17) was designed to

further study dronedarone's impact on morbidity and mortality. ATHENA was a placebo-controlled trial that assessed the efficacy of 400 mg dronedarone twice daily for the prevention of cardiovascular hospitalizations or death for any cause in patients with AF/atrial flutter (AFl).

There are three primary clinical trials of dronedarone – Dronedarone Atrial Fibrillation aFter Electrical Conversion (DAFNE) (19), European trial in atrial fibrillation or flutter in patients receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS) (20) and American-Australian-African trial of Dronedarone in atrial fibrillation/flutter for the maintenance of sinus rhythm (ADONIS) (20). EURIDIS and ADONIS demonstrated a significant and consistent decrease in ventricular rate after the first AF/AFl recurrence and in symptomatology. They also showed a 20% to 30% decrease in overall risk of recurrence and time to recurrence of AF/AFl. In patients with recurrent AF/AFl, the VR was significantly lower. These trials also demonstrated a profile that was the same as placebo for thyroid, hepatic and pulmonary side effects. In summary, dronedarone was better tolerated than amiodarone, with fewer side effects and drug interactions. However, the profile also included increased serum creatinine levels due to secretion and reabsorption – not due to a decrease in glomerular filtration rate.

THERAPEUTIC MODELS: MYOCARDIAL INFARCTION

There are several approaches in current investigations for treatment of myocardial infarction. There is significant interest in studying myocardial infarction as an inflammatory model. These models include enzyme inhibitors, intracellular electrolytes and complement inhibitors, and anticoagulants/antithrombotics. The anticoagulants and antithrombotics are the furthest along in approvals; namely, alternatives to unfractionated heparins – eg, enoxaparin (Lovenox) – and thrombolytics to compete with tissue plasminogen activator, eg, V10153, a thrombolytic that can be used within 9 h after stroke.

Myocardial infarction has been studied as inflammation that produces ischemic reperfusion injury. The inflammatory cascade has been studied for target points at multiple levels to prevent injury, most notably complement inhibition and inhibition of the proinflammatory transcription factor nuclear factor kappa B. One approach to targeting several levels of the inflammatory cascade is to use heparin that has been desulphated to remove its anticoagulant effect. Although heparin reduces ischemic reperfusion injury to the myocardium by complement inhibition, it has multiple nonanticoagulant benefits – namely, reduced neutrophil adherence to ischemic-reperfused coronary artery endothelium, influx of neutrophils into ischemic-reperfused myocardium, prevention of myocardial necrosis and release of creatine kinase into plasma. To capitalize on these effects, an O-desulphated heparin is being studied as PGX-100.

Other approaches to attack the inflammatory cascade are being studied and all are in the early stages of development. Examples include AMR001 (an autologous bone marrow-derived, CD34-enriched cell product for the treatment of damaged heart muscle following acute myocardial infarction), DG051 (a small molecule leukotriene A4 hydrolase inhibitor), poly(ADP ribose) polymerase inhibitor and KAI-9803 (an isozyme-selective delta protein kinase inhibitor). Less far along in development are mesenchymal stem cell therapy (studied by Boston Scientific, USA, and Osiris Therapeutics, USA) and pexelizumab, an anti-C5 antibody fragment being studied in coronary artery bypass graft surgery to block inflammation.

THERAPEUTIC MODELS: CHF

CHF is being studied from several vantage points – diuretics, renin/aldosterone inhibitors to improve kidney function and produce vasodilation, inhibitors of progressive myocardial remodeling, activation of cardiac myosin (CK 1827452, a direct activator of cardiac myosin), myocardial rescue (eg, MyoCell [BioHeart, USA] and BL-1040) and myoblast transplantation. There are also preliminary studies at Washington University (USA) to study the use of nuclear receptor proteins (peroxisome proliferator-activated receptors) to modulate myocardial energy metabolism.

Diuretics and renin-aldosterone inhibitors in development aim to expand on already mature franchises. These are generally targeted toward preserving kidney function through aldosterone inhibition (eg, carperitide). An alternative approach to preserving kidney function is to produce synthetic forms of naturally occurring peptides that regulate fluid balance and Na^+ homeostasis. Of particular interest are urodilatin (ularitide) and Cardeva (CoGenesys, USA [Teva, Israel]), a beta-type naturetic peptide. These approaches are in the early stages of phase II trials and will not be available, if at all, for many years.

Antidiuretic hormone receptor antagonists continue to attract interest, with the latest being lixivaptan, a selective antidiuretic hormone receptor antagonist. Vasopressin continues to be a target of interest with tolvaptan (OPC-41061), a vasopressin V2 receptor antagonist. A totally unique model is opioid receptor like-1 receptor. This human nociception receptor, referred to as ORL-1, OP4 or NOP, has attracted interest in the treatment of CHF because it produces aquaresis, which is the increased excretion of solute-free urine. This effect has been shown in rats and requires extensive testing in humans to validate the model.

For acute decompensated heart failure with renal insufficiency, Adentri (BG9928), an adenosine receptor antagonist, is in phase III trials. Jointly developed by Biogen, Switzerland, and CV Therapeutics, USA, this agent is being studied in the TRIDENT-1 (21) trial. This is a randomized, multicentre, double-blinded, placebo-controlled, parallel group study to assess the efficacy and safety of intravenous Adentri dosed according to body weight for up to five days in acute decompensated heart failure patients with impaired renal function. The trial is evaluating Adentri against placebo and against standard care in 900 patients in 21 countries.

Acute heart failure is being attacked by pharmacological and nonpharmacological means. Immune modulation using Celacade, a nonpharmacological therapy, is being developed by Vasogen, a Canadian-based biotechnology company. Celacade is a device-based outpatient procedure involving ex vivo exposure of 10 mL autologous blood to heat, ultraviolet irradiation, controlled oxidative ozone therapy and subsequent intramuscular administration at monthly intervals. It is being studied in the Advanced Chronic heart failure CLinical Assessment of Immune Modulation therapy (ACCLAIM) trial (22,23), a

phase III, randomized, double-blinded, placebo-controlled clinical study involving 2408 patients in seven countries with a left ventricular ejection fraction of 30% or less. Vasogen has approval to market Celacade in the European Union and in Latin America. The US FDA has required additional studies.

Early development of pharmacological treatments for heart failure involve enzyme inhibitors such as AVE8134, which binds to DNA and regulates gene expression; AVE3085, an endothelial NO synthase transcription enhancer; and daglutril, an endothelin-converting enzyme inhibitor. These treatments are being studied in animal models and require extensive review in humans.

THE FUTURE

A dearth of new products does not equate to a short supply of new ideas in the cardiology pipeline. The models addressed above may or may not lead to viable new products, but they will surely lead to a better understanding of cardiac function and metabolism.

REFERENCES

1. Sipahi I, Debanne SM, Rowland DY, et al. Angiotensin-receptor blockade and risk of cancer: Meta-analysis of randomised controlled trials. Lancet Oncol 2010;11:627-36.
2. Jones PH, Bays HE, Davidson MH, et al. Evaluation of a new formulation of fenofibric acid, ABT-335, co-administered with statins: Study design and rationale of a phase III clinical programme. Clin Drug Investig 2008;28:625-34.
3. Bui QT, Wilensky RL. Darapladib. Expert Opin Investig Drugs 2010;19:161-8.
4. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: Primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007;50:1844-5.
5. James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 2009;157:599-605.
6. TRA*CER Executive and Steering Committees. The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA*CER) trial: Study design and rationale. Am Heart J 2009;58:327-334.e4.
7. Eriksson BI, Borris LC, Friedman RJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008;358:2765-75.
8. Lassen MR, Ageno W, Borris LC, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008;358:2776-86.
9. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52.
10. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
11. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol 2007;50:1852-6.
12. Cannon CP, Husted S, Harrington RA, et al; DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: Primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007;50:1844-51.
13. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009;361:594-604.
14. Kush D, Hu DY, Ye P, et al. Flushing profile of extended-release niacin/laropiprant at initiation of therapy in Asian lipid clinic patients. Cardiology 2009;114:192-8.
15. Shah S, Ceska R, Gil-Extremera B, et al. Efficacy and safety of extended-release niacin/laropiprant plus statin vs. doubling the dose of statin in patients with primary hypercholesterolaemia or mixed dyslipidaemia. Int J Clin Pract 2010;64:727-38.
16. Davy JM, Herold M, Hoglund C, et al; ERATO Study Investigators. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: The Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. Am Heart J 2008;156:527.e1-9.
17. Hohnloser SH, Crijns HJ, van Eickels M, et al; ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668-78.
18. Køber L, Torp-Pedersen C, McMurray JJ, et al; Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678-87.
19. Dale KM, White CM. Dronedarone: An amiodarone analog for the treatment of atrial fibrillation and atrial flutter. Ann Pharmacother 2007;41:599-605.
20. Singh BN, Connolly SJ, Crijns HJ, et al; EURIDIS and ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357:987-99.
21. Kiesman WF, Elzein E, Zablocki J. A1 adenosine receptor antagonists, agonists, and allosteric enhancers. Handb Exp Pharmacol 2009;193:25-58.
22. Torre-Amione G, Bourge RC, Colucci WS, et al. A study to assess the effects of a broad-spectrum immune modulatory therapy on mortality and morbidity in patients with chronic heart failure: The ACCLAIM trial rationale and design. Can J Cardiol 2007;23:369-76.
23. Torre-Amione G, Anker SD, et al. Advanced Chronic Heart Failure CLinical Assessment of Immune Modulation Therapy Investigators. Results of a non-specific immunomodulation therapy in chronic heart failure (ACCLAIM trial): A placebo-controlled randomised trial. Lancet 2008;371:228-36.
24. Vos MA. Atrial-specific drugs: The way to treat atrial fibrillation. J Cardiovasc Electrophysiol 2004;15:1451-2.
25. Wegener FT, Ehrlich JR, Hohnloser SH. Dronedarone: An emerging agent with rhythm- and rate-controlling effects. J Cardiovasc Electrophysiol 2006;17:S17-S20.