Innovative therapies for optimizing outcomes of coronary artery disease

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Chapter 5

Emerging drugs for coronary artery disease. From past achievements and current needs to clinical promises

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ABSTRACT

Introduction Coronary artery disease (CAD) is one of the major causes of morbidity and mortality worldwide, exerting a huge economic burden. Although drug treatment in the past decades has made large advances, significant residual risk remains. However, in the coming years there is still a lot ahead with great advances and major breakthroughs expected.

Areas covered New treatments are expected to provide higher efficacy, with favorable safety profile. In this review article we are providing an almost full coverage of the recent and emerging drug therapies of CAD. This includes: drugs for treatment of atherogenic dyslipidemia, drugs that stabilizes atherosclerotic plaque and halts its progression guided by novel anti-inflammatory concepts in atherosclerosis treatment, anti-anginal treatments, renin-angiotensin-aldosterone system (RAAS) inhibitors, antiplatelet and anticoagulant drugs.

Expert opinion Efforts have been made to improve the clinical effectiveness and safety of established treatment strategies, or to target new frontiers through developing novel treatment strategies that tackle different mechanisms of action. Better understanding of the different molecular and cellular mechanisms underlying CAD resulted in more innovations and achievements in CAD drug therapy, and still a lot is anticipated in the forecoming years.

Keywords CAD, emerging drugs, lipid.

1. BACKGROUND

Coronary artery disease (CAD) is one of the most important causes of morbidity and mortality world-wide, and it is estimated that mortality from cardiovascular diseases will have increased worldwide by 90% by the year 2020 when compared with the situation in 1990[1]. Over the past decade drug development in the field of primary and secondary prevention of CAD has shown broad advances, particularly after getting to know more about the molecular and cellular biology of atherosclerosis, thrombosis and lipid disorders which are the main entities contributing to the occurrence of CAD.

Results from 2 large randomized trials for the management of coronary artery disease; COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation)[2] and BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes)[3] have drawn much attention towards optimizing drug therapy of coronary artery disease before invasive/operative vascular procedures. There are two main treatment goals in patients with coronary artery disease: relief of symptoms and ischemia; and prevention of progression of coronary artery disease leading to myocardial infarction, left ventricular dysfunction, congestive heart failure, and premature cardiovascular death. Currently, coronary artery disease cannot be fully eradicated but with the newly emerging drug treatments and other risk factor modifications, the natural history of the disease can be significantly altered in the right direction.

2. MEDICAL NEED

2.1 Lipid therapy

Elevated low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) are among the major risk factors for the development of cardiovascular disease (CVD). Despite the widespread use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) therapy, the incidence of cardiovascular morbidity and mortality remains elevated in many patients with dyslipidaemia, and particularly in those exhibiting metabolic disease and insulin resistance[4]. In large landmark trials, reduction in low-density lipoprotein cholesterol (LDL-C) levels with statins has been shown to decrease the incidence of major cardiovascular events by 25–45%[5-7]. Nonetheless, considerable residual cardiovascular risk, which includes a high frequency of recurrent events, remains even with an aggressive statin treatment regimen[8-12]. New therapeutic options, targeting additional lipid risk factors, are clearly needed to further improve the treatment of atherogenic dyslipidaemia by reducing residual cardiovascular risk.

The Framingham Heart Study in the 1980s demonstrated that the risk of coronary heart disease (CHD) was significantly lower among persons with higher levels of high-density lipoprotein cholesterol (HDL-C) (normal range 40 to 60 mg/dl)[13]. Significantly, a recent post

hoc analysis of the 'Treating to New Targets' trial demonstrated that low HDL-C is predictive of major cardiovascular events in patients receiving aggressive statin therapy[14].
Clinical studies have shown that therapeutic raising of HDL-C levels was associated with attenuated progression of intima-media thickening in the carotid artery, slowed progression of coronary artery atherosclerosis, and reduced cardiovascular risk[6, 15-18]. The clinical benefits of raising low HDL-C levels observed in lipid intervention trials and the limitations of available therapies have stimulated the search to identify new, more efficacious HDL-raising agents.

2.2 Atherosclerosis anti-Inflammatory therapy

For a long time atherosclerosis was considered as a lipid-driven disease, but now it is evident that it also involves the simultaneous and combined effect of inflammation and immunological pathways[19-21]. The development of new treatments specifically targeted against inflammatory mediators can be seen as a new phase in cardiovascular drug development.

2.3 Anti-anginal medications

2.3.1 Heart rate reduction

In patients with coronary artery disease, epidemiological studies have demonstrated that a low resting heart rate is associated with low total mortality and low cardiovascular mortality[22-25]. A recent study confirmed the impact of resting heart rate on cardiovascular events in a prospective setting[26]. Not all patients could tolerate the classical treatments to achieve HR reduction (B-Blockers and non-dihydropyridine Ca antagonists); which although effective, could present negative effects on regional myocardial blood flow and negative inotropic effects.

2.3.2 Coronary vasodilators

Nitrates are known to be effective coronary vasodilators, although their effect is limited by the side effects of nitrate-induced flushing, hypotension and syncope, as well as the reported nitrate tolerance. Moreover, intact epicardial coronary arteries dilate promptly after the administration of nitrates or other kinds of vasodilators[27], while in contrast, it remains controversial[28-30]as to whether the coronary atherosclerotic site responds to vasodilator agents; this continues to be an important topic in terms of the treatment of stable angina pectoris. Therefore, other vasodilators than nitrates should be used to more accurately assess the vasodilator potential at atherosclerotic lesions.

2.4 RAS Inhibition

Epidemiologic and experimental data suggest that activation of renin-angiotensin system (RAS) has an important role in pathogenesis of atherosclerosis. Although angiotensin converting enzyme (ACE) inhibitors and angiotensin-2 (AT2) receptor blockers have been used for more than a decade, their benefit in terms of absolute risk reduction is modest. Many

patients with established atherosclerosis continue to suffer from recurrent events related to ongoing disease. There is direct experimental animal evidence to support direct renin inhibitor therapy as means to reduce atherosclerotic plaque progression in thoracic aorta[31].

2.5 Antiplatelet therapy

The use of antiplatelet agents, both oral and parenteral, in the treatment of CHD was introduced based on the solid evidence for the major role of platelets both in the early stages of atherosclerosis as well as in thrombus formation during rupture of the vulnerable plaque.
Despite the progress achieved, it is generally accepted that our strategies are far from being considered optimal. The need for new oral antiplatelet agents is mainly driven by two reasons: the increased bleeding risk, particularly in those patients in need for double or triple antiplatelet therapy, and the variable response or "resistance" of patients to treatment clinically expressed as thrombotic complications or "treatment failure". The increased bleeding risk is strongly associated with the irreversible nature of current agents' platelet inhibition and represents a major issue in the setting of urgent cardiac or non-cardiac surgery. This has led to a lot of discussion regarding the appropriate selection of cases suitable for glycoprotein (GP) IIb/IIIa inhibitors administration, timing of their administration (in respect to patients' catheterization) and duration of treatment. On the other hand, "resistance" to antiplatelet treatment is both difficult to be assessed and multi-factorial in its nature involving (commonly neglected) parameters such as poor compliance and inadequate absorption but also drug interactions and pharmacogenetic factors. Moreover, it has been shown that lower response to aspirin and clopidogrel is frequent among acute coronary syndrome (ACS) patients as well as in those with hypertension, diabetes type 2, smoking, obesity (particularly in females), heart failure and hypercholesterolemia with the involved pathophysiological mechanisms to a significant extent unclear[32].

2.2 Antithrombotic therapy

Given the central role of thrombosis in the pathophysiology of ST elevation myocardial infarction and ACS, heparin and other antithrombotic agents have always been considered fundamental elements of our treatment strategies. Despite the availability of wide range of parenteral and oral anticoagulants with different mechanisms of action, yet it still remains with many limitations regarding increased bleeding risk, dosing regimens, therapeutic response, and thrombocytopenia[33]. All this have urged the development of newer classes that are supposed to have better safety and tolerability profiles, especially among oral anticoagulants, with the increasing need of triple antithrombotic therapy (dual antiplatelet plus oral anticoagulant therapy) in treating co-morbidities directly or indirectly related to CAD e.g. vein thromboembolism, prosthetic valves, atrial fibrillation, severe left ventricular (LV) dysfunction, LV aneurysms and thrombi.

3. EXISTING TREATMENT

Given the fact that atherosclerosis is a multifactorial disease, current medical treatment of CHD is diverse and includes a broad spectrum of agents with a variety of pharmacological and physiological effects. To date the conventional drug treatment for coronary artery disease has been:

Nitrates: Mainly relieve symptoms by increasing myocardial oxygen supply (coronary artery vasodilatation and redistribution of blood flow to ischemic areas) and decreasing myocardial oxygen demand (decreased preload and afterload)[34].

ß-Blockers: Reduce death and nonfatal MI in patients who have had a previous MI[35, 36]. Symptomatic improvement of angina[37]by decreasing myocardial oxygen demand (decreased inotropy, chronotropy, and hypertension) and increasing myocardial oxygen supply (increased duration of diastole).

Ca antagonists: Not only relieve symptoms but diminish clinical events as well[38]. It exerts its anti-ischemic effect by reducing myocardial oxygen demand (decreased afterload ± decreased inotropy and chronotropy) and increasing myocardial oxygen supply (coronary artery vasodilatation ± increased duration of diastole). It is the drug of choice for coronary vasospasm[39].

Renin-angiotensin-aldosterone system (RAAS) blockers: ACE inhibitors decrease cardiovascular death, all-cause death, nonfatal MI, stroke, revascularization procedures, and chronic heart failure (CHF)[40, 41]. The effects of ACE inhibitors extend beyond blood pressure reduction to endothelial protective effect and possibly directly influencing the atherosclerosis process[42]. A recent meta-analysis of 3 large clinical trials left no doubt that CAD patient should receive ACE inhibitors unless contraindicated[43]. However, the same cannot be said of ARBs, The major ARB trials in high risk patients demonstrated almost complete lack of reduction in MI and mortality despite significant reduction in blood pressure. In fact, the rates of MI in some trials have actually increased with ARBs[44, 45], raising the issue of "ARB-MI paradox"[46]which has triggered a lot of discussion and debate. So far, there is no consensus on whether ARBs have a tendency to increase MI, but there is also no substantive evidence to indicate that ARBs are able to reduce MI.

A recent meta-analysis has raised further debate suggesting that ARBs, particularly Tilmesartan, may be associated with a modestly increased risk of new cancer diagnosis[47]. This has been refuted by a later meta-analysis and trial sequential analysis of 324,168 participants from randomized trials, nevertheless showing that an increased risk of cancer with the combination of ACE inhibitors and ARBs couldn't be ruled out[48].

Lipid therapy

The reduction of LDL-C with **statins** has a strong positive effect on the occurrence of cardiovascular events[49]. A decrease in LDL-C levels from statin therapy is associated with a decrease

in the progression of atherosclerosis[50]. Increases in HDL-C between 5% and 15% have been reported with statin-mediated therapy, with an average increase of ~ 9%[16].

Fibrates are peroxisome proliferator-activated receptor (PPAR) - α agonists that lower LDL-C by 10% to 20%, lower triglycerides by 25% to 45%, and increase HDL-C modestly by 10% to 15%, and have shown, at least in subgroups, to reduce cardiovascular events[51].

Ezetimibe selectively blocks absorption of dietary and biliary cholesterol from the gut by blocking uptake of cholesterol into jejunal enterocytes[52]. Ezetimibe has an additional LDL cholesterol-lowering effect of around 15–20%, either alone or in the presence of a statin[53]. In a recent meta-analysis of randomized trials, ezetimibe monotherapy was found to induce significant potentially favorable changes in lipid and lipoprotein levels relative to baseline[54]. Nevertheless, ezetimibe monotherapy has never been shown to reduce event rates in a mortality-morbidity trial. In the recently published ARBITER 6-HALTS trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis)[55], comparing the effect of ezetimibe versus extended-release niacin (ER niacin) on atherosclerosis, showed that the regression of carotid intima-media thickness (CIMT) induced by ER niacin is superior to ezetimibe in patients taking statins. This trial was terminated early on the basis of the pre-specified interim analysis showing superiority of niacin over ezetimibe on change in CIMT.

Bile-acid sequestrating agents or resins that are currently available are colestyramine, colestipol and colesevelam. Their mode of action is usually considered to be similar. They are anion exchange resins which bind bile acids in the intestinal lumen. Therapy with bile-acid sequestrants has been shown to lower circulating LDL cholesterol by increasing hepatic catabolism via the LDL receptor-mediated pathway[56]. Colesevelam is a newer bile-acid sequestrant which causes fewer side-effects and, in combination with a statin, has been shown to decrease C-reactive protein levels more markedly than with statin alone[57], which might confer greater protection against CHD.

Antiplatelet therapy

The Antithrombotic trialists' meta-analysis published in 2002 can be considered as the cornerstone for the implementation of guidelines of current oral antiplatelet therapy[58]. Overall, antiplatelet therapy reduces the combined outcome of any serious vascular event by 25%, non-fatal myocardial infarction by 30%, non-fatal stroke by 25% and vascular mortality by 16% with no apparent adverse effect on other cause mortality. Furthermore, for this group of patients studied, clopidogrel and its analogue ticlopidine further reduced serious vascular events by 10% when compared with aspirin.

Aspirin has always been considered the "reference" to which any other compound is compared. It irreversibly inhibits platelet cyclo-oxygenase-1 (COX-1), therefore impairing activated platelets' ability to produce endoperoxides PGG2 and PGH2 and eventually thromboxane A2 (TXA2). TXA2 is a potent prothrombotic agent that stimulates platelet activation

and increases their aggregation by mediating the expression of the glycoprotein complex GPIIb/IIIa in the cell membrane of platelets. An intrinsic limitation of aspirin, bound to its mechanism of action, is that it invariably inhibits endoperoxide PGH2 synthesis in endothelial cells as well, therefore preventing the production of prostacyclin (PGI2) in the endothelium, a potent anti-aggregating and vasodilator agent. Its value in primary prevention has been questioned in recent meta-analysis, considering the increase of major bleeding events[59], while there have been concerns regarding its effectiveness in women[60].

Thienopyridines / P2Y12 antagonists: Ticlopidine was the first agent of a new class of antiplatelet drugs, the thienopyridines, that exert their action through inhibition of adenosine diphosphate (ADP) binding to P2Y12 receptors on the platelet surface. Despite its proven efficacy, particularly in ACS patients undergoing percutaneous coronary intervention (PCI) with stent implantation[61, 62], ticlopidine was also characterized by significant side effects the most common being gastrointestinal (diarrhea 12.4%) and the most severe hematological toxicity (neutropenia 2.4%, rare cases of aplastic anemia and thrombotic thrombocytopenic purpura). Therefore it was replaced in clinical practice by clopidogrel, a thienopyridine with less toxicity but mostly the same pharmacodynamic properties[63-65]. Clopidogrel's main disadvantage is that it's actually a pro-drug that undergoes a two-step metabolism to an active compound by cytochrome (CYP) P450 isoenzymes in the liver, making its bio-availability more sensitive to other drugs' co-administration.

Platelet Glycoprotien (GP) IIb/IIIa receptor anatgonists: Abciximab, eptifibatide and tirofiban are potent parenteral antiplatelet agents, exhibiting their action through inhibition of platelet surface membrane glycoprotein (GP) IIb/IIIa receptors. Following platelet activation, the GP IIb/IIIa receptor undergoes a conformational change rendering it competent to bind protein ligands including fibrinogen, fibronectin, von Willenbrand factor and vitronectin thereby facilitating and stabilizing platelet adhesion and thrombus formation. Abciximab is a Fab fragment of a chimeric human-murine monoclonal antibody irreversibly inhibiting GP IIb/IIIa receptor, while tirofiban and eptifibatide are high affinity non-antibody receptor inhibitors demonstrating a reversible mode of action with platelet activity restored within 4 to 5 hours following discontinuation of intravenous infusion. GP IIb/IIIa receptor antagonists have all proved particularly beneficial in reducing major cardiovascular peri-procedural events for both elective and urgent PCIs[66-69]. The benefit seems to be higher for diabetics and high risk patients[70], while for tirofiban and eptifibatide there is evidence for a possible beneficial effect in ACS patients even if a PCI is not scheduled[68, 71]. The major drawback of GPIIb/IIIa inhibitors has to do with the observed increased risk of bleeding, due mainly to their potent platelet anti-aggregatory properties although a small risk of thrombocytopenia has also been reported (1.5 to 2.8%). The potent inhibition of platelet aggregation represents a significant problem in cases where an urgent coronary artery bypass graft (CABG) operation is warranted or major hemorrhagic complications from the puncture site are observed. This has led to a lot of discussion regarding the appropriate selection of cases suitable for GPIIb/

IIIa inhibitors administration, timing of their administration (in respect to patients' catheterization) and duration of treatment.

Anticoagulant therapy

Unfractionated heparin (UFH) exerts its action by forming a complex with antithrombin (AT, formerly known as ATIII) therefore becoming a potent inhibitor of thrombin, factor Xa and to a lesser extent factors XIIa, XIa, and IXa. Despite its extensive use, heparin's limitations are well recognized. A major limitation, deriving from its mechanism of action, has to do with its dependency on antithrombin to exert its function and its inability to inhibit clot-bound thrombin. Moreover, it is characterized by a marked interpatient variability in its therapeutic response and the need for frequent partial thromboplastin time (PTT) monitoring. Therapeutic window is relatively small and the risk of bleeding increases substantially in patients with low body weight, female gender and advanced age. Moreover, heparin induced thrombocytopenia (HIT) is a well-recognized and potentially fatal complication of UFH therapy, occurring to 2.6% of patients exposed to heparin for more than 4 days while there have been concerns for reactivation of ischemia in ACS patients treated conservatively following heparin discontinuation, most likely due to a rebound thrombin generation[72].

Many of these issues have been addressed with the use of **low molecular weight heparins (LMWH)** the main representatives being enoxaparin, nadroparin, dalteparin and tinzaparin. Compared to UFH they have a better bioavailability when given by subcutaneous injection and a longer duration of anticoagulant effect permitting administration once or twice daily. Despite their potent Xa inactivation, they have a smaller effect on thrombin and they do not prolong PTT. This characteristic, along with their weight-adjusted dosing scheme, makes regular monitoring unnecessary (for non-pregnant patients) and they have proven safe for administration even in the outpatient setting[73]. Finally, they are much less likely to induce HIT compared to UFH[74]. Main limitations of LMWH have to do with the increased bleeding risk, particularly in patients above the age of 75, cumbersome dose calculation in patients with renal insufficiency and lack of an efficient antidote to reverse its action in case of emergency.

Fondaparinux is a synthetic pentasaccharide closely related but not belonging to the class of LMWH. It binds to AT with a higher affinity compared to UFH or LMWH, therefore effectively inhibiting Xa, it lacks however any kind of action against thrombin. The use of fondaparinux as an antithrombotic agent in the setting of unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI) and ST elevation myocardial infarction (STEMI) was tested in the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-5 and 6) trials where it proved as least as effective to enoxaparin and UFH respectively in terms of primary end point reduction, while significantly reducing bleeding rates[75, 76].

Vitamin K antagonists are not any more routinely prescribed for secondary prevention of STEMI/NSTEMI survivor patients, since dual antiplatelet therapy proved more convenient, safer and at least as efficacious[77, 78]. The narrow therapeutic window, the increased bleeding

risk, the need for frequent international normalized ratio (INR) control, the potential teratogenic effects when prescribed during pregnancy, set significant limitations in vitamin K antagonists' use.

4. CURRENT RESEARCH GOALS

Based on a better understanding of the molecular and cellular mechanisms underlying atherosclerosis, thrombosis and lipid disorders, and given the shortcomings and restrictions of the current therapy, the current research goals and new drug developments in CAD are focused on: 1) Lipid therapy; including HDL-raising medications, and novel treatments of dyslipidemia among diabetics, 2) Anti-inflammatory treatment of atherosclerosis and vulnerable plaque stabilization, 3) New anti-anginal medications; including novel heart rate-reducing and vasodilating agents, and 4) New antiplatelet and anticoagulant treatment.
Medical research is simultaneously pointing into two directions, namely evolution of current therapeutic strategies by developing newer agents that will prove either more effective or with less side-effects and research for novel therapeutic targets that have not been explored yet.

5. SCIENTIFIC RATIONALE

5. 1 Novel HDL-C raising therapies

There are different proposed mechanisms for the HDL-C protective role; reverse cholesterol transport, the process of transporting excess cholesterol from the arterial wall's foam macrophages to the liver, bile, and feces is one of HDL's anti-atherogenic properties[79, 80]. Furthermore, HDL's anti-oxidative activity further protects against atherosclerosis[81, 82]. In the endothelium, nitric oxide protects against inflammation, HDL promotes vasoprotection by enhancing nitric oxide synthase and thereby increasing the production of nitric oxide[83, 84]. In addition to protection against platelet activation through endothelial protection, HDL inhibits the coagulation cascade through serine protease protein C, which inactivates factors Va and VIIa[83].
Circulating HDL particles are very heterogeneous with a very complex metabolic profile. There are three subclasses of HDL which vary in quantitative and qualitative content of lipids; discoid HDL particles (lipid-free HDL or apolipoprotein A-1) which mediates reverse cholesterol transport; further esterification of these HDL particles generates the other two subclasses; HDL2 and HDL3 which are spherical HDL particles. These mature HDL particles may induce further cholesterol efflux. Smaller HDL3 particles may more efficiently promote cholesterol efflux[79, 85]. Thus it appears that the subtype of HDL seems to matter. The next few years should provide answers to whether we should target raising specific HDL subclasses rather than HDL-C itself.

Structural and functional changes accompany HDL in the setting of acute or chronic inflammation, CHD or type 2 diabetes mellitus. These changes are induced by leukocyte myeloperoxidase which may alter the function of the normally atheroprotective anti-inflammatory HDL molecules into the so-called dysfunctional HDL with pro-inflammatory properties. This results in reduced efficacy of reverse cholesterol transport, and the ability of HDL to counteract the inhibitory effect of oxidized LDL on vascular relaxation[86, 87].

5.1.1 CETP inhibitors

Cholesteryl ester transfer protein (CETP) is a plasma protein that catalyzes the exchange of cholesteryl esters and triglycerides (TG) between the atheroprotective HDL and the atherogenic apolipoprotein (apo) B– containing lipoproteins, especially very low density lipoprotein (VLDL)[88]. Reduction in CETP activity resulting from genetic mutations or pharmacologic inhibition has been associated with reductions in cholesterol within the apo B-containing particles and cholesterol enrichment of HDL[89, 90].

5.1.2 Extended-release (ER) Niacin and ER Niacin/Laropiprant combination

Niacin was the first lipid-lowering drug developed[91]. Despite clear lipid-lowering effects and some proof of clinical benefit in early prevention studies[92, 93], niacin is not used very often in clinical practice. There are multiple reasons, the most important being the high rate of side effects and the stronger LDL-C reduction and the better documented effects of statins[94, 95]. Currently, with the rising interest in HDL-raising therapies, niacin has been under intense re-evaluation.

The main side effect of niacin is flushing, which is a result of cutaneous vasodilatation mediated via prostaglandin D2 (PGD2)[96], although the rate of flushing was decreased by using the extended-release formulations, it still represents a hurdle for its clinical use. Since the flush induced by niacin is primarily mediated through the interaction of prostaglandin D2 with a specific receptor (prostaglandin-D2-receptor-1) a selective antagonist of this receptor was developed (MK-0524, laropiprant)[97, 98], thus it seems rational to combine ER niacin with laropiprant especially that the addition of laropiprant doesn't change the effect of niacin on lipoproteins[99].

5.1.3 Dual Peroxisome proliferator-activated receptor (PPAR)-α/γ agonists

Peroxisome proliferator-activated receptors (PPARs) are ligand-dependent transcription factors that control gene expression. Dual PPARα/γ agonists have the potential to combine the beneficial PPARα agonist properties of fibrates (decreasing plasma levels of triglycerides and very low-density lipoprotein particles and increasing levels of high-density lipoprotein cholesterol) with the beneficial PPARγ agonist effects of thiazolidinediones (reduction of free fatty acid flux, insulin resistance, and blood glucose levels)[100].

5.1.4 Reconstituted HDL infusion

Short-term infusions of reconstituted HDL have been a target of reverse cholesterol transport therapy. CSL-111 is reconstituted HDL consisting of apolipoprotein A-1 from human plasma combined with soyabean phosphatidylcholine and chemically and biologically resembles native HDL[101].

5.1.5 Apolipoprotien A-1(Apo A-1) Milano infusion

ApoA-I Milano is a variant of apolipoprotein A-I identified in individuals in rural Italy who exhibit very low levels of HDL (10-30 mg/dl), yet despite of that had a reduced atherosclerotic disease burden and longer lives[102, 103]. Infusion of recombinant Apo A-I Milano–phospholipid complexes (ETC-216) produces rapid regression of atherosclerosis in animal models, which can occur in as little as 48 hs[104, 105]. Moreover, it was recently found in animal studies that ApoA-1 Milano administration not only induced plaque size regression but was also associated with a significant reduction in markers of plaque vulnerability, suggesting further plaque stabilization[106].

5.2 Atherosclerosis anti-inflammatory and antioxidant therapy

5.2.1 Selective phospholipase A2 inhibitors

There are two groups of phospholipase A2; secretory phospholipase A2 (sPLA2), and lipoprotein-associated phospholipase A2 (Lp-PLA2). The sPLA2 represent a family of enzymes that hydrolyze fatty acids, in a calcium-dependent process, producing lipoprotein particles that are proatherogenic[107]. Lp-PLA2 represents a calcium-independent phospholipase that is predominantly synthesized by macrophages[108, 109]. Lp-PLA2-modified and sPLA2-modified lipoproteins and the resulting oxidized bioactive by-products activate redox-sensitive inflammatory pathways[110], impair endothelial-dependent vasorelaxation[111] and serve as chemo-attractants for monocytes[110, 112]. The products of Lp-PLA2 activity have been identified in human atherosclerotic vessel wall[113]. Lp-PLA2 and sPLA2 have gained more interest as emerging biomarkers of CV risk that are pharmacologically modifiable.

5.2.2 Heme oxygenase-1 inhibitors (Probucol analogues)

Probucol is a lipid-lowering prototype agent which exhibits vascular protective effect through anti-inflammatory and antioxidant activities. Probucol has demonstrable anti-inflammatory actions in animal models of atherosclerosis[114]. It reduces adhesion of mononuclear cell to the endothelium in vivo[115] and inhibits the expression of vascular cell adhesion molecule-1[116]. This result in reduced macrophage infiltration, associated with a decrease in matrix metalloproteinases and other enzymes that may participate in plaque rupture and proatherogenic activities which likely translates into improved plaque stability[116].

However, Probucol is no longer available in many countries due to concerns of efficacy[117] and safety[118, 119]. In search of other compounds with similar anti-inflammatory and antioxidant properties but without the potentially deleterious effect of probucol, succinobucol, previously known as AGI-1067, was developed[120].

5.3 New Anti-anginal treatments

5.3.1 Ivabradine

Ivabradine (IVA) is a novel, specific, heart rate (HR)-lowering agent that acts in sinoatrial node (SAN) cells by selectively inhibiting the pacemaker I*f* current in a dose-dependent manner by slowing the diastolic depolarization slope of SAN cells, and reducing HR at rest and during exercise with minimal effect on myocardial contractility, blood pressure, and intracardiac conduction[121]. It has been shown to be non-inferior to B-Blockers[122] or calcium antagonists[123] in HR reduction. Whether Ivabradine has a role beyond mere heart rate reduction is still a matter of focused scientific research.

5.3.2 Rho-Kinase (ROCK) Inhibitors

Rho-kinase (ROCK) inhibits myosin phosphatase activity by phosphorylating the myosin-binding subunit of the enzyme, promoting actin-myosin-mediated contractile force generation, thus resulting in the augmented vascular smooth muscle contraction in a calcium-independent manner[124, 125].

The activation of ROCK is involved in the regulation of vascular tone, endothelial dysfunction, inflammation and remodeling .The inhibition of ROCK has a beneficial effect in a variety of cardiovascular disorders. Evidence from animal models and from clinical use of ROCK inhibitors, such asY-27632, fasudil supports the hypothesis that ROCK is a potential therapeutic target[126].

5.3.3 Ranolazine

Ranolazine, a piperazine derivative, acts through the inhibition of the late sodium current (I_{Na} current) in cardiac myocytes. During myocardial ischemia, there is a build-up of intracellular sodium, which leads to an increase in intracellular calcium via the sodium-calcium exchanger[127]. By regulating this imbalance in ion shifts, ranolazine may improve myocardial relaxation and reduce left ventricular diastolic stiffness, which in turn can enhance myocardial contractility and perfusion. Ranolazine has minimal effects on the resting and exercise heart rate and blood pressure in patients with angina, and has shown antiarrythmic activity in experimental models[128].

5.4 RAS inhibition- Direct renin inhibitors

Renin catalyzes the rate-limiting step in RAS activation, i.e. the formation of angiotensin I from angiotensinogen and shows remarkable substrate specificity for angiotensinogen. These characteristics make it an attractive target for a therapeutic RAS blockade. Renin inhibition differs mechanistically from the established strategies of RAS blockade with angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). The increase of plasma rennin concentration caused by renin inhibition is much more pronounced compared to ACE inhibitors and ARBs[129]. This may be of clinical relevance because recent evidence suggests that renin, besides its enzymatic function, might exert direct, angiotensin II-independent, cellular effects via the (pro)renin receptor (PRR). Stimulation of this receptor may increase profibrotic pathways and activate gene programs implicated in vascular end organ damage and atherogenesis[130, 131].

5.5 Novel antiplatelet agents

1.5.1 Cox-1 Inhibitors

As mentioned before, a major limitation of aspirin is that irreversibly inhibits COX-1 of both platelets and endothelium therefore reducing the production of beneficial prostacyclin as well. Aiming the same pathophysiological mechanism, i.e. inhibition of TXA2 pathway, three different alternatives would seem feasible: selective inhibition of platelet only COX-1, thromboxane-synthase direct inhibition (therefore reducing the end-product) and thromboxane-receptors blockade since it has been shown that accumulating peroxides can per se activate them, the same way as TXA2[132].

5.5.2 Novel ADP/P2Y12 receptor anatgonists

Introduction of platelet ADP receptor inhibitors represented a breakthrough in the modern treatment of ACS, especially in the field of interventional cardiology. Newer agents resolving the bioavailability issues of clopidogrel are expected to minimize treatment failures and improve outcomes whereas it seems reasonable that agents with reversible inhibition of the ADP receptor will result in less bleeding complications.

5.5.3 Protease Activator Receptor 1 (PAR-1) inhibitors

Thrombin is arguably the most potent activator of platelets, exerting its action through the protease activator receptor 1 (PAR-1). *In vitro* studies suggest that minimal concentrations of thrombin are sufficient to activate this platelet receptor leading to platelet shape modification and aggregation, making development of PAR-1 inhibitors a challenging therapeutic option.

5.5.4 Selective 5-Hydroxytryptamine,5-HT2A receptor antagonists

Serotonin (5-Hydroxytryptamine, 5-HT) is known to participate in the regulation of cardiovascular system and is therefore linked to cardiovascular events. Serotonin release following a vascular injury induces platelet aggregation, vasoconstriction, increase of vascular permeability and cell proliferation following a vascular injury. These functions are mediated by the $5\text{-}HT_{2A}$ receptor and development of selective inhibitors could be used for the effective treatment of ischemic heart disease.

5.6 Novel antithrombotics

The previously mentioned limitations of current antithrombotic agents have led medical research to the development of new compounds. The major classes of these newer anticoagulants are the factor Xa inhibitors and the direct thrombin inhibitors with some of these agents being orally administered.

5.6.1 Direct thrombin inhibitors

Thrombin is the final enzyme in the clotting cascade, representing a reasonable target of most of the current clinical anticoagulants. The rationale for the clinical use of direct thrombin inhibitors is their ability to inactivate fibrin-bound thrombin, in contrast to both UFH and LMWH – AT complexes. They are also unaffected from other limitations of current therapeutic strategies like acquired or inherited AT deficiency, they demonstrate a better bioavailability profile, and avoid the problem of HIT.

5.6.2 Factor Xa inhibitors

Factor Xa inhibitors demonstrate a high affinity to Xa, without the need of AT, achieving effective inhibition of the thrombotic cascade. As in the case of thrombin inhibitors, these agents seem to have a rapid onset and offset of action making the concomitant use of UFH/LMWH obsolete while at the same time being safer in terms of bleeding complications. They are designed to have a relatively stable pharmacodynamics profile, without need for routine monitoring, making them theoretically superior to vitamin K antagonists for long-term use.

5.6.3 Other agents

Other agents have also been tested, taking advantage of our extensive knowledge regarding the clotting cascade. Factors V, VII, VIII, IX, and XII have all been considered as potential targets of treatment, therefore interfering in the different steps of the cascade. Thrombin is unique among the serine proteases of this cascade that possesses both pro-coagulant and anti-coagulant properties. It induces coagulation by activating platelets through their PAR-1 receptors, activating factors V, VIII, XI and XIII and inhibiting fibrinolysis through the thrombin-activated fibrinolysis inhibitor; on the other hand, when bound to thrombomodulin on the vascular endothelial cell surface it becomes an anticoagulant enzyme by activating

protein C. Since currently developed thrombin inhibitors interfere with both types of thrombin activity, engineering an inhibitor that would selectively inhibit thrombin's pro-coagulant properties, leaving its anti-coagulant functions intact would seem reasonable. In the same context, administration of recombinant activated protein C, therefore promoting natural anti-coagulation mechanisms, could be expected to produce favorable results.

6. COMPETITIVE ENVIRONMENT (TABLE)

6.1 Novel HDL-C raising therapies

6.1.1 CETP inhibitors

Several efficacious CETP inhibitors have been identified; these include torcetrapib (Pfizer, New York, NY, USA), dalcetrapib (previously referred to as RO4607381/JTT-705, Roche/Japan Tobacco, Basel, Switzerland), and anacetrapib (MK-0859, Merck & Co., Whitehouse Station, NJ, USA).

Torcetrapib, a CETP inhibitor, has been shown to produce substantial increases in HDL-C and modest reductions in LDL-C[133-138]. However, in a study conducted on hyperlipidemic mice, it was found that torcetrapib did not reduce atherosclerosis beyond atorvastatin and induced more proinflammatory lesions than atorvastatin[139]. Moreover, treatment with torcetrapib was associated with an increase in blood pressure, an effect that has not been reported with other CETP inhibitors in development[140, 141]. This blood-raising effect of torcetrapib may be merely compound-specific and unrelated to the mechanism of CETP inhibition, and is thought to be related to an increase in plasma aldosterone and corticosterone levels[142]. A clinical outcomes study of torcetrapib in high-risk patients, ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events), was stopped early owing to an excess in cardiovascular events and death in patients treated with the combination of torcetrapib and atorvastatin versus atorvastatin alone[133]. Subsequently, 3 studies have reported that torcetrapib did not reduce the atherosclerotic burden assessed in the coronary arteries (by intravascular ultrasonography) and in the carotid arteries (by ultrasonography of intima-media thickness)[134, 136, 138].

Dalcetrapib has demonstrated a favorable safety profile in a phase II study, and no changes in vital signs including blood pressure have been observed[143-145]. Several phase III clinical trials are ongoing with the objective of evaluating the clinical efficacy and safety of dalcetrapib. One of these, dal- VESSEL, is focused on modulation of vascular function by CETP inhibition and will shed further light on the mechanisms implicated in the improved endothelial function which was recently observed in hypercholesterolaemic subjects with low baseline HDL-C subsequent to dalcetrapib treatment[146]. Another trial, the impact of dalcetrapib on atherosclerotic plaque development (dal-PLAQUE), has been initiated in some 100 patients with CHD

using positron emission tomography/computerized tomography and magnetic resonance imaging[147]. Finally, in order to evaluate the effects of dalcetrapib on mortality and morbidity, >15 600 high-risk CHD patients considered to have stable disease after a recent acute coronary syndrome event have been recruited into the ongoing dal-OUTCOMES trial[148, 149].

Anacetrapib is currently the most potent CETP inhibitor under evaluation, with associated increases in HDL-C levels up to 129% and decreases in LDL-C levels of up to 38%[141]. Two phase I RCTs for anacetrapib have demonstrated the efficacy and safety of the new drug without blood pressure effects or serious side effects[141], and a phase III RCT recruiting a total of 1623 patients with CAD or CAD equivalents is still ongoing in order to obtain sufficient safety and efficacy data[150, 151].

Table: Newly developing drugs in CAD treatment:

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Torcetrapib	Pfizer	CETP inhibitor	CAD	Phase III-terminated	HDL-raising therapy
Dalcetrapib	Hoffmann-La Roche	CETP inhibitor	CAD	Phase II/III- expected results in 2011-2013	HDL-raising therapy
Anacetrapib	Merck	CETP inhibitor	CAD	Phase III-expected results by end of 2012	HDL-raising therapy
ER Niacin	Abbott	Water-soluble vitamin-B complex	CAD	Phase III-expected results in 2012	HDL-raising therapy
ER Niacin/ Laropiprant	Merck	Niacin/selective prostaglandin-D receptor antagonist	CAD	Phase III-expected results by beginning 0f 2013	HDL-raising therapy
Ragaglitazar	Novo-Nordisk	PPAR-α/γ agonist	Atherogenic dyslipidemia in diabetic patients	Phase II-completed	HDL-raising therapy
Tesaglitazar	AstraZeneca	PPAR-α/γ agonist	Atherogenic dyslipidemia in diabetic patients	Phase II-completed	HDL-raising therapy
Muraglitazar	Bristol-Myers Squibb/Merck	PPAR-α/γ agonist	Atherogenic dyslipidemia in diabetic patients	Phase III-completed	HDL-raising therapy
Aleglitazar	Hoffmann-La Roche	PPAR-α/γ agonist	Atherogenic dyslipidemia in diabetic patients	Phase III-expected results by mid-2014	HDL-raising therapy

Table: Continued

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
CSL 111	CSL limited	Reconstituted HDL	CAD	Phase II-completed	HDL-raising therapy
CSL 112	CSL limited	Reconstituted HDL	CAD	Phase I-expected results by 2011	HDL-raising therapy
APL 180	Novartis	Reconstituted HDL	CAD	Phase I/II-completed but no results yet	HDL-raising therapy
CER-001	Cerenis Therapeutics,SA	Apo-A1 based HDL mimetic	CAD	Phase II-expected results by end of 2012	HDL-raising therapy
Varespladib	Anthera	sPLA2 inhibitor	CAD	Phase II/III- expected results 2009/2010-2012	Atherosclerosis anti-inflammatory treatment
Darapladib	GlaxoSmithKline	Lp-PLA2 inhibitor	CAD	Phase III-expected results 2012-2014	Atherosclerosis anti-inflammatory treatment
Succinobucol	AtheroGenics	Heme oxygenase-1 inhibitor	CAD	Phase III-completed	Atherosclerosis anti-inflammatory treatment
Ivabradine	Servier	I_f current blocker	CAD	Phase IV-expected results in 2012	Anti-anginal treatment
Fasudil	Schering AG	Rho-Kinase inhibitor	CAD	Phase II-completed but no results yet	Anti-anginal treatment
Ranolazine	A. Menarini Pharma/ Gilead Sciences	Late sodium current (I_{Na}) blocker	CAD	Phase III completed/ Phase IV-expected results in 2011	Anti-anginal treatment
Aliskiren	Novartis	Direct rennin inhibitor	Hypertension/ CAD	Phase II/III-completed/ expected results	Anti-hypertensive and plaque stabilization
Triflusal	Uriach Laboratories	COX-1 inhibitor	CAD, CVD	Phase IV	Antiplatelet agent
Prasugrel	Eli Lilly / Daiichi Sankyo	P2Y12 receptor inhibitor	CAD, PCI	Phase III and IV	Antiplatelet agent
Ticagrelor	Astra Zeneca	P2Y12 receptor inhibitor	CAD, PCI	Phase III	Antiplatelet agent

Table: Continued

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Cangrelor	Medicines Company	P2Y12 receptor inhibitor	CAD, PCI Bridge to CABG	Phase III	Antiplatelet agent
Elinogrel	Portola Pharmaceuticals / Novartis	P2Y12 receptor inhibitor	CAD, PCI	Phase II	Antiplatelet agent
Vorapaxar	Merck	PAR-1 receptor inhibitor	CAD, PCI, CVD	Phase II and III	Antiplatelet agent
Atopaxar	Eisai Inc.	PAR-1 receptor inhibitor	CAD	Phase II	Antiplatelet agent
Terutroban	Servier	TXA2 receptor inhibitor	CAD, CVD	Phase III	Antiplatelet agent
Picotamide	LGM Pharma	TXA2 receptor and TXA2 synthase inhibitor	PAD	Phase III	Antiplatelet agent
Cilostazol	Otsuka Pharmaceutical	Phosphodiesterase inhibitor	CAD, PAD, CVD, PCI	Phase III and IV	Antiplatelet agent
DZ-697b	Daiichi Sankyo	Ristocetin-mediated platelet activation inhibitor	CAD, CVD	Phase I	Antiplatelet agent
Hirudin	Speedel Pharma Ltd.	Direct thrombin inhibitor	HIT	Established therapy	Anticoagulant
Lepirudin	Schering AG / Pharmion GmbH	Direct thrombin inhibitor	HIT	Established therapy	Anticoagulant
Argatroban	GlaxoSmithKline	Direct thrombin inhibitor	HIT, CVD	Phase IV	Anticoagulant
Bivalirudin	The Medicines Company	Direct thrombin inhibitor	HIT, CAD, PCI	Phase IV	Anticoagulant
Ximelagatran	AstraZeneca	Direct thrombin inhibitor	AF	Phase III, withdrawn due to hepatotoxicity	Anticoagulant
Dabigatran	Boehringer Ingelheim	Direct thrombin inhibitor	VTE, AF	Phase III and IV	Anticoagulant
Idraparinux	Sanofi-Aventis	Factor Xa inhibitor	VTE, PE, AF	Phase III, withdrawn due to bleeding complications	Anticoagulant
Idrabiotaparinux	Sanofi-Aventis	Factor Xa inhibitor	VTE, AF	Phase III	Anticoagulant
Otamixaban	Sanofi-Aventis	Factor Xa inhibitor	CAD, PCI	Phase II and III	Anticoagulant
Ultra low molecular weight heparin	Sanofi-Aventis	Factor Xa inhibitor	VTE	Phase III	Anticoagulant
Rivaroxaban	Johnson & Johnson / Bayer	Factor Xa inhibitor	VTE, PE, AF, CAD	Phase II and III	Anticoagulant

Table: Continued

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Apixaban	Bristol-Myers Squibb / Pfizer	Factor Xa inhibitor	VTE, PE, AF, CAD	Phase III	Anticoagulant
Edoxaban	Daiichi Sankyo	Factor Xa inhibitor	VTE, PE, AF	Phase III	Anticoagulant
SR123781A	Sanofi-Aventis	Factor Xa inhibitor, thrombin inhibitor	VTE, CAD	Phase II and III	Anticoagulant
LY517717	Eli Lilly	Factor Xa inhibitor	VTE	Phase II	Anticoagulant
Betrixaban	Portola Pharmaceuticals	Factor Xa inhibitor	VTE, AF	Phase II	Anticoagulant
YM150	Astellas Pharma	Factor Xa inhibitor	VTE, AF, CAD	Phase II and III	Anticoagulant

PCI: percutaneous coronary intervention, CAD: coronary artery disease, CVD: cerebrovascular disease, PAD: peripheral artery disease, HIT: heparin induced thrombocytopenia, VTE: venous thromboembolism, AF: atrial fibrillation, PE: Pulmonary embolism.

6.1.2 Extended-release (ER) Niacin and ER Niacin/Laropiprant combination

Two recently published Phase III RCT[93, 152], have shown the efficacy of ER Niacin as regards to lipid lowering and retarding atherosclerosis progression. It has been recently documented that endothelial-vasoprotective effects of HDL-C are impaired in patients with type 2 diabetes mellitus compared to healthy subjects, and that ER Niacin not only increases HDL-C plasma levels but markedly improves endothelial-protective functions, which is potentially more important[153].

In studies evaluating the combination of niacin with laropiprant on flushing it was shown that the rate of flushing was significantly decreased compared to patients on niacin without laropiprant[99, 154, 155]. Currently, the AIM-HIGH study (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) is an ongoing RCT which randomly allocates patients (45 years and older) with vascular disease and atherogenic dyslipidemia to therapy with simvastatin alone or simvastatin and ER niacin, and are being evaluated over a 5-year period to better define the additive effect of HDL-raising therapies[156]. Another trial, the HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events)[157], is recruiting 25,000 patients with a history of CHD, stroke, or peripheral arterial disease and randomizing them to placebo or the new ER niacin/laropiprant combination.

6.1.3 Dual Peroxisome proliferator-activated receptor (PPAR)-α/γ agonists

Ragaglitazar increased HDL-C by 31%, decreased triglycerides by 62%, and decreased hemoglobin A1c by 1.3%, but the adverse events of edema, anemia, and leukopenia have drawn concern[158, 159]. *Muraglitazar* increased HDL-C by as much as 16% in type 2 diabetic patients, but, as with ragaglitazar, weight gain and edema were more common with muraglitazar therapy[160, 161]. An analysis of muraglitazar's phase 2 and 3 data revealed an increase in risk of

death, cardiovascular events, and congestive heart failure associated with muraglitazar[162]. *Tesaglitazar*, a third agent in this drug class, can increase HDL-C by 13%[163-165]. Because of the observed side-effects, all these aforementioned compounds were stopped. Recently, a phase 2 trial of *aleglitazar* was shown to increase HDL-C by 20% and also decrease hemoglobin A1c in a dose-dependent manner, with a small increase in edema but not congestive heart failure or myocardial infarction[166]. As a result, a phase 3 study (Alecardio study) of aleglitazar in type 2 diabetic patients with a recent acute coronary syndrome is now ongoing[167].

6.1.4 Reconstituted HDL(rHDL) infusion

In a small study of healthy subjects, these intravenous infusions promoted reverse cholesterol transport[168]. Based on that a randomized placebo-controlled trial was conducted, ERASE[101], which showed that short-term infusions of reconstituted HDL (CSL 111) in patients with recent onset acute coronary syndromes showed no significant reduction in coronary atheroma volume, nonetheless, it induced a possibly favorable change in the quality of coronary atheroma. There was a high incidence of liver function test abnormalities with the high doses of HDL infusions, these were however self-limiting without any clinical consequence or intervention. Recently published results from a first-in-man randomized controlled study evaluating the safety and feasibility of autologous delipidated HDL plasma infusions (Plasma selective delipidation converts αHDL to preβ-like HDL, the most effective form of HDL for lipid removal from arterial plaques) in patients with ACS showed promising results regarding regression in the atheroma volume. Two ongoing phase I/II trials are testing the safety and efficacy of single intravenous infusions of rHDL in healthy volunteers[169, 170].

6.1.5 Apolipoprotien A-1(Apo A-1) Milano infusion

This therapy was piloted in humans when ETC-216, recombinant apolipoprotein A-I Milano complexed with phospholipid, was randomly infused in 57 patients within 2 weeks of an acute coronary syndrome (ACS) over 5 weekly treatments[171]. There was significant reduction in intravascular ultrasound (IVUS)-measured coronary atheroma burden with ETC-216, with 1 patient reported to have a significant rise in transaminases[171]. In a trial of 47 patients after an acute coronary syndrome, recombinant apolipoprotein A-I Milano infusion was associated with reverse coronary remodeling and reduced atheroma burden[172]. A future study will assess the effects of CER-001, an ApoA-I-based HDL mimetic, on indices of atherosclerotic plaque progression and regression as assessed by IVUS measurements in patients with ACS[173].

6.2 Atherosclerosis anti-inflammatory and antioxidant therapy

6.2.1 Selective phospholipase A2 (PLA2) inhibitors

6.2.1.1 Selective secretory phospholipase A2 (sPLA2) inhibitors

Varespladib sodium (A-001; Anthera Pharmaceuticals, San Mateo,CA or previously Eli-Lilly LY 315920), and varespladib methyl (A-002; Anthera Pharmaceuticals, San Mateo,CA or previously Eli-Lilly LY 333013) are both selective sPLA2 inhibitors. Varespladib sodium is intravenous formulation and varespladib methyl is the oral formulation of the selective sPLA2 inhibitors.

A phase II, randomised, double-blind, placebo-controlled, dose-response study (Phospholipase Levels and Serological Markers of Atherosclerosis [PLASMA])[174] conducted in 393 CAD patients showed that varespladib methyl reduced the enzymatic activity of sPLA2, LDL-C and oxidized LDL levels in a dose-dependent manner, and had anti-inflammatory effects as evidenced by a reduction in inflammatory markers, which suggest that A-002 might be an effective anti-atherosclerotic agent. In the 500 mg A-002 treatment group, there was one serious adverse event (exacerbation of underlying chronic obstructive pulmonary disease), but the proportion of patients reporting treatment-emergent adverse events did not differ from placebo. The main side-effects of the drug included headache, nausea, and diarrhea. PLASMA II is an ongoing RCT that examines the effects of once daily dosing of varespladib methyl (250mg, 500mg) on sPLA2 mass, lipids and lipoproteins in 135 patients with stable CAD[174, 175]. Other ongoing studies, FRANCIS-ACS and VISTA-16 trials, will assess the safety and efficacy of A 002 in subjects with ACS[176, 177]. Furthermore, The sPLA 2 Inhibition to Decrease Enzyme Release after PCI (SPIDER-PCI) trial will investigate the effects of treatment with varespladib methyl on peri-percutaneous coronary intervention (PCI) myocardial infarction incidence in patients undergoing elective PCI[178].

6.2.1.2 Selective lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitors

Several selective and highly potent azetidinone inhibitors have been developed as pharmacological tools. Darapladib (SB 480848, GlaxoSmithKline, Philadelphia, PA) represents the azetidinone selected for human clinical trials.

In a phase II multicenter, randomized, double-blind, parallel-groups study involving 959 stable CAD or CAD equivalent patients receiving atorvastatin, it was found that darapladib produced sustained inhibition of plasma Lp-PLA2 activity, and reduction of cardiovascular inflammatory biomarkers with no serious adverse events, only malodor of urine and faeces was reported in the darapladib treated group[179]. In another study, Integrated Biomarker and Imaging Study-2 (IBIS-2)[180], Lp-PLA2 inhibition with darapladib prevented necrotic core expansion, a key determinant of plaque vulnerability. Further ongoing phase III trials are addressing the potential role of darapladib in atherosclerotic plaque stabilization[181, 182]

and improved endothelial function[183]. These findings suggest that Lp-PLA2 inhibition may represent a novel therapeutic approach, whether this was associated with favorable effects on CV events needs to be further emphasized in future studies.

6.2.2 Heme oxygenase-1 inhibitors (Probucol analogues)

Succinobucol (AGI-1067, AtheroGenics Inc., Alpharetta, GA, USA) is a metabolically stable, orally available derivative of probucol. It has greater intracellular antioxidant efficacy in vitro than probucol without its QT prolonging effect[184]. Succinobucol has anti-inflammatory properties[185, 186], and has been found to reduce some circulating biomarkers of inflammation namely myeloperoxidase, but not C-reactive protein (CRP)[187]. Both succinobucol and probucol lower the risk of restenosis after percutaneous coronary intervention[184]. Additionally, succinobucol seemed to reduce progression of atherosclerosis in non-treated coronary reference segments[184], although this was not confirmed in a recently published study[187].

In a phase III, randomized, double-blind, placebo-controlled study among 6144 patients with recent acute coronary syndromes, the Aggressive Reduction of Inflammation Stops Events (ARISE) trial[188], succinobucol had no effect on the composite primary endpoint (of time to first occurrence of cardiovascular death, resuscitated cardiac arrest, MI, stroke, unstable angina, or coronary revascularization), however, the composite secondary endpoint of cardiovascular death, cardiac arrest, MI or stroke occurred in fewer patients in the succinobucol group, and there was 63% relative reduction in the tertiary endpoint of the occurrence of new-onset diabetes. These results were seen despite the unfavorable changes in lipids (increasing LDL-C and decreasing HDL-C), blood pressure, and CRP, suggesting that the antioxidant and anti-inflammatory effects of succinobucol might have favorably affected the clinical outcomes. These hypothesis-generating observations should draw further attention to future trials with succinobucol targeting high risk CAD patients.

In the ARISE trial, it is worth mentioning that there were more cases of hepatic derangement in the succinobucol arm, and one patient had liver failure which resolved after discontinuation of the drug. There was an increase in the occurrence of new onset atrial fibrillation in the succinobucol arm. Whether this observation is related to the small increase in blood pressure noted with succinobucol needs further studies.

6.3 New Anti-anginal treatments

6.3.1 Ivabradine

Ivabradine (Procoralan, Les Laboratories Servier, France; also available under the following names: Coralan, Corlentor, and Coraxan) has been established as an effective treatment to prevent myocardial ischemia in patients with chronic stable angina[122, 189, 190], and recent subgroup analysis raised the hypothesis that ivabradine may be helpful to reduce major cardiovascular events[26, 191]. This constituted the rationale for an ongoing study, Study assess-

InG the morbidity–mortality beNefits of the I_f inhibitor ivabradine in patients with coronarY artery disease (SIGNI_fY), which will assess the effects of ivabradine in terms of CV morbidity and mortality[192]. It has been found as well, that ivabradine therapy on top of commonly used dosage of B-Blocker therapy had an additional efficacy with no untoward effect on safety or tolerability[193].

In the recently published results of the SHIFT randomized placebo-controlled study (Ivabradine and outcomes in chronic heart failure)[194], it was found that in patients allocated to ivabradine , the relative risk of the primary end-point (cardiovascular death or hospital admission for worsening heart failure) dropped by 18% compared to placebo, supporting the importance of heart rate reduction with ivabradine for improvement of clinical outcomes in heart failure patients.

Pre-clinical animal studies have shown that ivabradine effect might extend beyond heart rate reduction. It was associated with decreased vascular oxidative stress, improved endothelial fuction and reduced atherosclerotic plaque formation[195]. This has stimulated further research with a planned phase IV RCT, to assess the effect of ivabradine therapy on reducing inflammatory markers in patients with acute coronary syndromes[195, 196].

6.3.2 Rho-Kinase (ROCK) Inhibitors

Recently, it was shown that inhibition of ROCK's activity by fasudil (Schering AG, Berlin, Germany) exerts anti-ischemic benefits. Fasudil inhibits coronary vasospasm in patients with unstable angina pectoris[197], and significantly increases the ischemic threshold of angina patients during exercise with a trend toward increased exercise duration[198]. The vasodilatory effect of fasudil is more potent than that of nitroglycerin[199] and has been shown to further dilate segments of vasospastic coronary artery that have already been pre-treated with nitroglycerin[200]. These findings support the potential of fasudil as a novel therapeutic agent for coronary vasospasm and ischemia.

Furthermore, Fasudil has been found to improve endothelial function in patients with CAD, through restoration of NO bioavailability in humans with atherosclerosis.[201]. This has fueled further research to determine whether fasudil would be useful in treating atherosclerosis and hypercholesterolemia[202]

6.3.3 Ranolazine

Ranolazine (Ranexa, A. Menarini Pharma UK, High Wycombe, UK) has been shown in several large trials to be an efficacious adjunctive agent in reducing symptoms of CAD[203-206]. It has been shown to increase exercise duration, reduce frequency of angina and reduce need for increased antianginal therapy. Ranolazine was generally well tolerated with the most commonly occurring side effects being dizziness, nausea, asthenia, and constipation[207], and its safety has been emphasized on long term follow-up[208]. Interestingly, the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes (MERLIN)-

TIMI 36 trial has indicated potential antiarrhythmic effects of ranolazine in a large population of NSTEMI-ACS patients, through reducing the percentage of clinically significant ventricular arrhytmias[205]. Currently, a phase IV RCT is ongoing to evaluate the effect of ranolazine 1000 mg administered twice daily compared to placebo on exercise-induced reversible myocardial perfusion defect size (PDS), assessed by gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) in subjects with documented exercise induced myocardial ischemia at baseline[209].

6.4 RAS inhibition-Direct rennin inhibitors

Aliskiren is a direct renin inhibitor, with potent antihypertensive effects. Recently, a group of phase 2 and 3 clinical trials have been launched to assess the influence of aliskiren on plaque progression in established atherosclerosis using high resolution 3-D MRI[210] or using intravascular ultrasound[211], and to examine the influence of aliskiren in improving ventricular hemodynamics in subjects stabilized after ACS[212]. Also another study is planned; hypothesizing that long-term Aliskiren treatment will improve endothelial function and the production and function of endothelial progenitor cells (EPCs) in patients with early atherosclerosis[213]. We are still awaiting the results of the ASPIRE trial evaluating the efficacy and safety of aliskiren on the prevention of left ventricular remodeling in high risk post-acute myocardial infarction patients when added to optimized standard therapy[214].

6.5 New Antiplatelet agents

6.5.1 COX-1 inhibitors

Triflusal is an antiplatelet agent structurally related to aspirin, although it does not belong to salicylates. Its mechanism of action involves inhibition of TXA2 production through selective COX-1 inhibition, while at the same time preserving vascular prostacyclin synthesis. Moreover, triflusal is also a phosphodiesterase inhibitor resulting in cyclic AMP increase and therefore leading to reversible inhibition of platelet aggregation, vasodilation, and inhibition of vascular smooth muscle cell proliferation. Evidence from small clinical studies suggest that it is as effective as aspirin in prevention of vascular events (myocardial infarctions and strokes) while associated with lower risk of bleeding complications[215].

6.5.2 Novel ADP/P2Y12 receptor anatgonists

6.5.2.1 Prasugrel

Prasugrel (CS-747, LY640315) is an orally administered thienopyridine prodrug that, as in the case of clopidogrel, is activated in the liver through CYP. The active metabolite irreversibly binds platelet ADP receptor, to a similar extent as the active metabolite of clopidogrel. However, in the case of plasugrel, in vivo availability of the active metabolite is significantly higher

compared to clopidogrel. As a result, the recommended loading dose of 60 mg followed by a 10 mg daily maintenance regimen induces a more rapid, potent and consistent inhibition of platelet function compared to the currently used doses of clopidogrel (300 to 600 mg loading, followed by 75 mg daily for maintenance)[216]. Prasugrel has already been established as a valuable therapeutic option in clinical practice following the results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction (TRITON-TIMI 38), a phase III 13608-patient randomized trial, including moderate to high risk ACS patients undergoing PCI. In this study where prasugrel (60 mg loading and 10 mg maintenance) in addition to aspirin was immediately compared to clopidogrel (300 mg loading and 75 mg maintentance) plus aspirin, prasugrel was associated with a significant reduction of the primary end point (cardiovascular death, nonfatal MI, or nonfatal stroke) over a 15-month follow up period, in the expense of an increase in major bleeding (including fatal bleeding)[217]. The beneficial results of prasugrel were associated with a significant reduction of definite or probable stent thrombosis (1.1 vs 2.4%) while as predicting determinants of major bleeding were identified the history of stroke or transient ischemic attack, age of more than 75 years and body weight of less than 60 kg. In a pre-specified TRITON-TIMI 38 study of 3524 STEMI patients undergoing primary PCI, prasugrel also proved more effective than clopidogrel in preventing ischemic events, without a significant excess of bleeding complications[218]. Largely based on the TRITON-TIMI 38 trial, prasugrel has now been approved both in Europe and by FDA for the prevention of ischemic events in ACS patients undergoing PCI.

6.5.2.2 Ticagrelor

Ticagrelor (AZD6140) belongs to a new class of antiplatelet agents, the cyclopentyltriazolopyrimidines. Although its mechanism of action is also exerted through P2Y12 platelet receptor inhibition, in contrast to clopidogrel and prasugrel, this inhibition is reversible. It's an active metabolite (no metabolism of a pro-drug is required) with a rapid onset of action and greater degree of platelet inhibition compared to clopidogrel. The efficacy and safety of ticagrelor were evaluated in the Platelet Inhibition and Patient Outcomes (PLATO) trial where 18624 ACS patients (38% of them with STEMI) were randomly assigned to either ticagrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel (300 to 600 mg loading dose followed by 75 mg daily) for one year. All patients were also receiving aspirin. At the end of the follow up period, patients on ticagrelor presented significantly lower rates of the composite primary end point (cardiovascular death, myocardial infarction or stroke) compared to clopidogrel (9.8 vs 11.7%) without any significant difference in the rates of major bleeding among the two groups[219]. Despite the encouraging results, ticagrelor is not clinically available yet, while some have serious concerns regarding the effects of a possible poor compliance to medication; given the reversible nature and the not yet fully explained side-effect of dyspnea. Pending in official registration, ticagrelor is already, like prasugrel,

announced in the new ESC guidelines for myocardial revascularization as class I indication for the treatment of NSTE-ACS and STEMI[220].

6.5.2.3 Cangrelor

Cangrelor is a direct acting reversible platelet P2Y12 inhibitor. Unlike the previously described agents, cangrelor is administered intravenously with its effect rapidly reversed following end of the infusion. Similar to prasugrel and ticagrelor, cangrelor is characterized by a rapid onset of action and more effective platelet inhibition compared to clopidogrel, with a favorable safety profile concluded from the initial phase II trials. Cangrelor underwent two phase III clinical trials, the "Clinical Trial to Demonstrate the Efficacy of Cangrelor (PCI)"[221, 222] and the "Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (Platform)"[223] that were discontinued due to insufficient evidence of cangrelor's clinical effectiveness. Cangrelor is still being studied as a bridge for patients on clopidogrel who are planned for CABG operation (BRIDGE: Maintenance of Platelet inihiBition With cangRelor After dIscontinuation of ThienopyriDines in Patients Undergoing surgery)[224].

6.5.2.4 Elinogrel

Elinogrel (PRT060128) is a novel, direct-acting, reversible P2Y12 antagonist that can be administered both orally and intravenously resulting in a simplified and effective treatment regimen and covering the full spectrum of care from acute onset to chronic care. A recent pilot trial (Early Rapid ReversAl of Platelet ThromboSis with Intravenous Elinogrel before PCI to Optimize REperfusion in Acute Myocardial Infarction, ERASE-MI) provided preliminary data about the feasibility and tolerability of escalating doses of intravenous elinogrel as an adjunctive therapy for primary PCI for STEMI[225]. Another double blind, randomized, phase II trial completed earlier this year (a Novel Antiplatelet Therapy in Patients Undergoing Non-urgent Percutaneous Coronary Interventions, INNOVATE-PCI), evaluated the safety, tolerability and efficacy of elinogrel in patients undergoing non-urgent PCI[226].

6.5.3 PAR-1 receptor inhibitors

Vorapaxar (SCH 530348) is an orally administered agent that reversibly inhibits platelet protease activated receptor-1, through which thrombin induces its effect on platelet aggregation, and thus, thrombus formation. A number of phase II clinical trials have provided promising results and two phase III clinical trials are ongoing; Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Acute Coronary Syndrome (TRA•CER)[227] and Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA 2°P - TIMI 50)[228]) examining the safety and efficacy of vorapaxar in preventing the composite end-point of cardiovascular death, MI, stroke or urgent coronary revascularization in patients with an ACS (UA/NSTEMI) or atherosclerosis. Results of these studies are still pending.

Another agent of this class, Atopaxar (E5555) with potential antithrombotic and anti-inflammatory properties has recently completed two phase II trials (Japanese - Lesson from Antagonizing the Cellular Effect of Thrombin or J-LANCELOT, and Lesson from Antagonizing the Cellular Effect of Thrombin in Acute Coronary Syndromes or LANCELOT ACS)[229, 230] in a Japanese population with either ACS or high risk CAD. Results from these studies have been announced in the ESC 2010 and TCT 2010 congresses with atopaxar demonstrating a satisfactory safety profile in terms of bleeding complications and a potential to reduce major adverse cardiovascular events. There were some concerns regarding the liver function and prolongation of the QTc interval which may be due to the increased atopaxar doses used[231]. Further studies with phase III clinical trials and reduced dosing schemes are expected.

6.5.4 Thromboxane synthase and thromboxane receptor inhibitors

Terutroban (S 18886) is a selective antagonist of thromboxane receptor, inhibiting thromboxane induced platelet aggregation and vasoconstriction. Preliminary studies in humans have shown that terutroban induced regression and stabilization of atherothrombotic plaques in magnetic resonance studies[232] and that it successfully inhibited platelet aggregation in peripheral artery disease patients (an effect comparable to aspirin). A phase III clinical study (Prevention of cerebrovascular and cardiovascular events of ischemic origin with terutroban in patients with a history of ischemic stroke or transient ischemic attack, PERFORM) has recently been completed and the results are expected[233]. Recruiting 18000 patients, this study investigated the efficacy of terutroban in secondary prevention of further cerebrovascular and cardiovascular events following a stroke or a TIA, compared to aspirin.

Picotamide acts as an equally effective TXA2 synthase and TXA2 receptor inhibitor. It inhibits aggregation of human platelets while it also preserves prostacyclin production by re-orienting endoperoxides' metabolism, accumulated as a result of the TXA2 synthase blockade[234]. Picotamide inhibits TXA2 formation both intra and extra-vascular while, apart from platelets, it has an effect on other cells (monocytes etc) and seems to interact *in vivo* with the vascular endothelium[235]. The effects of picotamide in clinical practice have been tested in the double blind, randomized ADEP (Atherosclerotic Disease Evolution by Picotamide) and DAVID (Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics) trials that both involved patients with peripheral artery disease (PAD)[236, 237]. In the DAVID study, 1200 patients with PAD and diabetes were randomized to receive either picotamide (600 mg twice daily) or aspirin (320 mg once daily), with all-cause mortality as a primary end point. Patients on picotamide did significantly better with a total mortality of 3% vs 5.5% for the aspirin group[237]. Moreover this didn't come on the expense of more bleedings, with the agent being well tolerated. The DAVID study was a landmark study, demonstrating the increased efficacy of an agent (compared to aspirin) in the highly problematic group of diabetic patients. However its potential role in the treatment of patients with CAD needs further investigation.

6.5.5 Other agents

We previously discussed the potential role of triflusal in the treatment of CAD. The role of other phosphodiesterase inhibitors is also under investigation; cilostazol has been approved for the treatment of intermittent claudication. It has also been found to reduce smooth muscle proliferation and intimal hyperplasia after endothelial injury, properties that led to trials evaluating its efficacy for the prevention of restenosis after PCI[238, 239]. In the largest of these trials, cilostazol on top of regular aspirin and clopidogrel treatment significantly reduced angiographic in-stent restenosis, although this did not reflect to a difference in the rate of target vessel revascularization[238]. Moreover, these studies were performed before the era of drug eluting stents that largely resolved the issue of in-stent restenosis. Further studies are needed to determine a possible role of cilostazol (or other phosphodiesterase inhibitors) in current treatment strategies.

Better understanding of platelet biology and function has indicated other potential treatment targets; DZ-697b is a new orally active antiplatelet agent that inhibits collagen and ristocetin-mediated platelet activation. It does not require metabolisation to generate its active compound and has a safer profile than clopidogrel in pre-clinical studies. In a recently published study, oral DZ-697b showed potent, dose-dependent, antithrombotic effects comparable to clopidogrel, without prolonging bleeding times[240]. Its clinical efficacy remains yet to be studied.

6.5.6 Reduced dose of GP IIb/IIIa receptor antagonists

Although GPIIb/IIIa inhibitors are routinely used in clinical practice, increased concern of bleeding complications and their potential effect on outcomes, has led to re-evaluation of our strategies and set the pace for studies investigating the safety and efficacy of bolus-only GPIIb/IIIa receptor antagonists schemes[241]. In a study reporting single-center experience with 1001 patients, bolus-only dosing schemes of abciximab, tirofiban and eptifibatide resulted in low rates of in-hospital death (0.1%), myocardial infarction (4.3%), and repeat revascularization (0%) that are comparable to the outcomes observed when mainstream dosing schemes are followed, while achieving lower rates of major or minor bleeding (2.3%)[242]. However, since this was an observational and not a randomized trial, the results must be cautiously evaluated.

6.6 New Antithrombotic agents

6.6.1 Direct thrombin inhibitors

6.6.1.1 Parenteral direct thrombin inhibitors

Hirudin, lepirudin (a recombinant hirudin), argatroban and bivalirudin are all parenterally administered direct thrombin inhibitors. The rationale for their clinical use as well as their benefits over UFH and LMWH has been analyzed before.

Hirudin and (its recombinant analogue) lepirudin are mainly used for the treatment of HIT. Lepirudin has also been evaluated for the treatment of acute coronary syndromes (both unstable angina and non-ST elevation myocardial infarction) but results were disappointing; a benefit was indeed observed in terms of death, re-infarction and revascularization reduction, but this was on the expense of increased moderate or major bleeding, attributed to its narrow therapeutic window[243, 244]. Similarly, in the case of STEMI patients, randomized trials failed to support a substantial benefit from the use of either hirudin or lepirudin, although in this case an increased risk of bleeding was not observed[243, 245].

Argatroban has also been FDA approved for the treatment of HIT. It has a short in vivo half-life and dose adjustments are not required in the presence of renal failure. As in the case of hirudin/lepirudin, a randomized trial failed to prove a benefit from using it in the setting of acute myocardial infarction patients[246].

Bivalirudin has also a short plasma half-life (of about 25 minutes) and undergoes predominantly non-organ elimination (proteolysis), inclining for a rather safe profile in terms of bleeding complications. It is the first agent of this class that has been approved as an effective anticoagulant in the setting of interventional cardiology. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) study (involving 14000 patients with moderate or high risk ACS undergoing PCI) bivalirudin (as the only anticoagulant) proved as effective as the combination of UFH or enoxaparin with GPIIb/IIIa in terms of ischemic complications at 30 days, while significantly reducing the bleeding complications, with the greater benefit observed in those aged more than 75 years[247]. The efficacy of bivalirudin in the setting of STEMI was further studied in the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial, where bivalirudin plus provisional use of GPIIb/IIIa was tested against standard therapy, in a series of 3600 patients. Both at the 30-day and 12-month time points, bivalirudin proved safer in terms of the combined end point of major bleeding or major cardiovascular event[248]; however a slightly higher risk of acute stent thrombosis (i.e within the first 24 hours) was observed in the bivalirudin group, underlying the need for early P2Y12 inhibitors initiation and possibly for a prolonged bivalirudin infusion, in selected patients[249]. Based on the results of HORIZONS AMI and ACUITY, bivalirudin has been included in the guidelines of treatment of ACS patients. Bivalirudin (with provisional use of GPIIb/IIIa inhibitors) can also be used as a substitute of UFH-GPIIb/IIIa

combination for stable angina and low risk ACS patients, as demonstrated in the Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events (REPLACE-2) study[250].

6.6.1.2 Oral direct thrombin inhibitors

Ximelagatran was the first oral direct thrombin inhibitor to get into phase III clinical trials. However, despite the promising results of the Stroke Prevention by ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) trials in terms of thromboembolism prevention, it was withdrawn due to the observed incidence of hepatotoxicity[251, 252].

Dabigatran etexilate is a prodrug of the active compound dabigatran that has been tested for the prevention and treatment of both venous and arterial thromboembolic disease[253, 254]. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial published recently, 18113 patients with atrial fibrillation and at least one risk factor for stroke (mean CHADS2 score 2.1) were randomly assigned to receive either dabigatran (two dosing schemes were tested, 110 or 150 mg twice daily) or warfarin (target INR 2.0-3.0). Dabigatran in the lower dosing scheme proved as effective as dose adjusted warfarin (in terms of ischemic stroke and systemic embolism prevention) while safer in terms of hemorrhagic stroke and major bleeding incidence. On the other hand, the higher dosing scheme of dabigatran proved more effective in terms of thromboembolic events' prevention, being at the same time as safe as warfarin in major bleeding incidence[253]. Dabigatran represents an attractive alternative to contemporary warfarin treatment, since (in addition to the advantages of both dosing schemes mentioned) it does not require monitoring of the INR, it's less susceptible to dietary and drug interactions and it's not limited by warfarin's narrow therapeutic window. On the other hand, besides the increased cost of therapy, adoption of the new agent cannot yet be recommended due to the lack of long term safety data. Other issues that can be mentioned are the inconvenient dosing scheme (twice daily), the lack of data for patients with renal insufficiency and the lack of an effective antidote.

6.6.2 Factor Xa inhibitors

In addition to the thrombin inhibitors previously mentioned, a new class of direct factor Xa inhibitors is under clinical development. This new class of agents (xabans) that has both oral and parenteral representatives is generally characterized by a rapid onset of action and a rather stable pharmacodynamics profile without a need for routine monitoring, making them an attractive option as a substitute of traditional anti-coagulants.

6.6.2.1 Parentral factor Xa inhbitors

Idraparinux sodium (SR34006) is a synthetic pentasaccharide administered subcutaneously with a similar chemical structure and same method of action as fondaparinux but with a much longer elimination half-life, making feasible a once-a-week dosing scheme. The drug

never reached the market due to concerns of excessive bleeding following the use of this agent, documented in the AMADEUS trial which tested its efficacy in preventing thromboembolic events, against adjusted dose vitamin K antagonists, in patients with atrial fibrillation[255]. Instead Idrabiotaparinux (SSR126517), a biotinylated version of idraparinux, was developed. Despite the similar mode and duration of action, Idrabiotaparinux can be safely inactivated, if this becomes necessary, by i.v. infusion of avidin that neutralizes its anti-Xa activity[256]. Results from phase III trials, assessing idrabiotaparinux's efficacy in preventing thromboembolism in the setting of deep vein thrombosis and atrial fibrillation, are expected[257, 258].

Otamixaban (XRP0673) is a short-acting, intravenously administered, selective inhibitor of factor Xa. It has already been tested in two phase II trials in the setting of routine PCI interventions and NSTEMI ACS ((Prevention of Ischemia with Anti-Xa inhibition in acute coronary syndromes 1 - Thrombolysis in Myocardial Infarction 42, SEPIA-ACS1 TIMI 42 and Otamixaban in Comparison to Heparin in Subjects Undergoing Non-Urgent Percutaneous Coronary Intervention, SEPIA-PCI) with promising results[259, 260]. A Phase III trial, comparing it to standard therapy in high risk ACS patients undergoing early invasive strategy, is currently recruiting patients[261].

Ultra low molecular weight heparin (AVE5026) is a hemi-synthetic molecule with an average molecular weight of 2000 to 3000 Da (almost half compared to other LMWH). It has nearly pure anti-Xa activity and is currently being assessed in phase III trials as an alternative to standard therapy for prevention of DVT thromboembolism[262-264].

6.6.2.2 Oral factor Xa inhibitors

Rivaroxaban (BAY 59-7939) is an orally administered direct factor Xa inhibitor with a bioavailability of 80 percent and peak plasma concentrations occurring 2.5 to 4 hours following administration. As in the case of previous agents mentioned in this category, it does not require routine monitoring. It has proved favorable to enoxaparin in the prevention of venous thromboembolism in patients undergoing orthopedic surgery, without increasing the bleeding complications[265]. A phase II clinical trial in ACS patients demonstrated a beneficial effect in terms of ischemic events reduction along with a dose-dependent increased bleeding risk[266]. Phase III clinical trials are currently testing its efficacy in the setting of ACS[267], recurrent thromboembolism prevention[268] and prevention of stroke in the setting of non-valvular atrial fibrillation[269].

Apixaban (BMS-562247-01) has also been tested for the prevention of thromboembolism, mainly in the setting of orthopedic surgery. In a recently published study, apixaban did not meet the pre-specified non-inferiority criteria compared to enoxaparin but its use was associated with lower rates of clinically relevant bleeding[270]. However, in another phase III clinical trial also involving knee-replacement surgery patients, apixaban proved more effective than enoxaparin without increasing bleeding risk[271]. Further studies, assessing its efficacy in the setting of atrial fibrillation[272] and ACS patients[273] are on their way.

Edoxaban (DU-176b) has completed a number of phase II clinical trials testing its efficacy in non-valvular atrial fibrillation[274] and phase II and III trials in thromboembolism prevention following orthopedic surgery[275, 276]. A large phase III trial (Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48, Engage AF-TIMI 48) comparing edoxaban to warfarin in terms of stroke prevention in patients with non-valvular atrial fibrillation is currently recruiting patients[277], with results expected in 2012.

SR123781A is a synthetic hexadecasaccharide with a mixed profile of AT-dependent anti-Xa and anti-thrombin activities. In a dose-ranging study for the prevention of thromboembolism following orthopedic surgery (NCT00338897), it demonstrated a reasonable risk to benefit ratio compared to enoxaparin[278].

LY517717 and Betrixaban (PRT-054021) are two more agents of this category that have been tested in phase II trials against enoxaparin in orthopedic patients[279, 280]. Both were well tolerated and gave promising results, with further phase III trials expected in the near future.

YM150 is another direct factor Xa inhibitor that is currently being tested in a phase II study in subjects with acute coronary syndromes[281] after proving safe and effective for prevention of venous thromboembolism after hip replacement.

7. POTENTIAL DEVELOPMENT ISSUES

7.1 Cell-based therapy

Cell-based revascularization strategies have the potential to become a major therapeutic advance for severe CAD. Intra-myocardial bone marrow stem cell injection is currently being investigated as a new therapeutic option for patients with chronic ischemia who are ineligible for revascularization. Bone marrow mononuclear CD34+ stem cells, harvested from the iliac crest or by leukapheresis after granulocyte colony–stimulating factor, are injected into the ischemic myocardium. In small randomized placebo- controlled studies[282, 283], myocardial injection was found to be safe and to be associated with a modest but statistically significant improvement in myocardial perfusion, left ventricular ejection fraction (LVEF), exercise capacity, and Canadian cardiology society (CCS) class. This technique is still in the experimental stages, and further studies are required to assess long-term results and efficacy for reducing mortality and morbidity.

7.2 New therapeutic targets of cholesterol metabolism

With the increasing burden of CAD, there will be a continuing demand for on-going research into cholesterol metabolism and the development of drugs to modify it favorably:

7.2.1 Squalene Synthase inhibitors

Squalene synthase inhibitors decrease circulating LDL cholesterol by the induction of hepatic LDL receptors in a similar manner to statins without the risk of myotoxicity[284]. Two new potent squalene synthase inhibitors (EP2306 and EP2302) have been described *in vitro*[285], the squalene synthase inhibitor EP2302 inhibited cholesterol synthesis in a dose-dependent manner with a similar potency to that of simvastatin. Further *in vivo* studies are required for further evaluation.

7.2.2 Microsomal triglyceride transfer protein (MTP) inhibitors and Apo-B mRNA antisense oligonucleotides

An alternative approach to lowering LDL-C is to limit hepatic assembly of very low density lipoprotein (VLDL), the precursor of LDL. One strategy is to develop inhibitors of MTP (which is essential for the assembly of VLDL). Whilst this may effectively lower LDL cholesterol, it also causes hepatic triglyceride accumulation[286]. Another approach is to use Apo B mRNA antisense oligonucelotides (Apo B is the principal protein of VLDL and LDL)[287]. These hold the promise of preventing VLDL formation without causing hepatic steatosis[288], and might hold promise for treatment of patients not reaching target LDL cholesterol levels on stable statin therapy[289]

7.3 Anticoagulants in development

Apart from improving the pharmacodynamics and pharmacokinetics of currently available agents, new anticoagulants aiming other factors of the coagulation cascade are also developed and tested. In a relatively recent study, recombinant nematode anticoagulant protein c2 (rNAPc2), a potent inhibitor of the tissue factor/factor VIIa complex, gave promising results without increasing major or minor bleeding[290]. In the same perspective, selective inhibitors of factors IXa and XIIa have also been considered as potential therapeutic agents[291, 292].

An alternative method seems to be manipulating the clotting cascade pathway by either interfering with key-cofactors (like factors Va and VIIIa) or modulating the pro-coagulant/anticoagulant balance of thrombin activities. In this context recombinant activated protein C, that inactivates factors Va and VIIIa, has been shown to ameliorate the coagulopathy associated with severe sepsis and reduce mortality[293]. Whether this agent would prove effective as an anticoagulant in the treatment of CAD is not yet known. Furthermore, recombinant soluble thrombomodulin (ART-123), an agent that binds thrombin and inactivates its procoagulant effects while leaving its anti-coagulant properties intact, has been tested in septic patients with disseminated intravascular coagulation[294] while another phase II trial suggests it's efficacious for venous thromboembolism prophylaxis following total hip replacement surgery[295].

8. EXPERT OPINION

- There is established evidence that high levels of HDL-C in nature are associated with a lower risk of CAD. Unlike LDL-C, the mechanisms controlling HDL-C are more complex. Lifestyle interventions are safe but only modestly increase HDL-C. The best treatments available currently seem the niacin derivatives, although the newer CETP inhibitors, reconstituted HDL infusion and apolipoprotein A-1 Milano infusion hold much promise. The next 5 years should provide information on whether improving vascular protective function of HDL is more important than HDL-C levels and also whether we should target raising specific HDL subclasses rather than HDL-C itself.
- Treatment of dyslipidemia in diabetic patients remains a very challenging issue in CAD prevention, there is an increased interest in treatments that has a dual favorable effect on both glycemic control and lipid control, most important in this issue is the up-growing role of glitazars, especially aleglitazar, which is foreseen to be the upcoming treatment for lipid regulation in diabetic patients.
- Nowadays, with a better understanding of the immunological and inflammatory mechanisms underlying atherosclerosis, treatments that stabilize vulnerable plaques and halts atherosclerosis progression are gaining wide interest and will show promising results within the next few years. Lp-PLA2 is an emerging biomarker of CV risk that is pharmacologically modifiable through specific Lp-PLA2 inhibitors, as darapladib. Moreover, Aliskiren, a direct renin inhibitor is gaining wide interest in terms of plaque stabilization and regression in established atherosclerosis.
- Combination therapy can provide marked lipoprotein changes in patients at risk for atherosclerotic events. Three large clinical trials, involving more than 45,000 patients in aggregate, are currently testing the effect on major clinical endpoints of adding niacin or ezetimibe to statin treatment in patients at high risk[156, 157, 296]. Results of these trials are expected in 2012–2013. Nevertheless, a recent systematic review of 102 studies found no benefit of combination therapy over high-dose statin monotherapy in terms of mortality, MI, stroke, and revascularization procedures in patients requiring intensive lipid-lowering therapy[297]. An effective strategy in patients requiring intensive lipid-lowering therapy is critically needed and still controversial, and is a field for further research.
- Novel anti-anginal treatments, as ivabradine, fasudil and ranolazine have gained wide interest because of the absence of effect on blood pressure, regional myocardial blood flow or myocardial contractility, a benefit that they have over conventional anti-anginal therapies. They have proved to have an additive benefit in terms of anginal pain relief and exercise tolerance. Whether these treatments have a further role beyond anti-anginal effect, as vasoprotective and endothelial function influence, is still a field of intensive research and the ongoing studies will answer this question.

- Antiplatelet agents and anti-thrombotics represent a major advancement in the current treatment of ACS and CAD. Despite the progress achieved, the fraction of non-responders among the population treated, the narrow therapeutic window of many of the agents used and the increased bleeding complications often observed limit their usefulness and sets the pace for the research and introduction of novel therapeutic options.

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