INTRODUCTION

Atherothrombosis, defined as atherosclerotic plaque disruption with superimposed thrombosis, is the leading cause of mortality in the Western World **(Corti et al., 2003).**

In general, atherosclerosis describes the hardening of an artery due to loss of elasticity in its intimal and medial layers. Flexibility is lost when yellowish plaques made up of cholesterol, lipids, and cellular debris form in these inner layers **(Fuster et al., 1996)**.

Atherosclerosis, a chronic inflammatory disease, involves both innate and adaptive arms of immunity which modulate lesion initiation, progression, and potentially devastating thrombotic complications **(Weber et al., 2008).**

Thrombosis often complicates physical disruption of the protective collagen-rich fibrous cap overlying the atheroma, exposing circulating clotting factors to procoagulants expressed within lesions as a result of inflammatory activation and initiation of the coagulation cascade **(Libby, and Theroux, 2005).**

Importantly, inflammation also decisively influences the propensity of a given plaque disruption to lead to a sustained and occlusive thrombus that may manifest clinically as an acute coronary syndrome or ischemic stroke by controlling the balance between fibrinolytic enzymes and their endogenous inhibitors (**Naghavi et al ., 2003)**.

The importance of the link between inflammation and atherothrombosis was reiterated by the largest published series so far evaluating histologic features of symptomatic carotid plaques, in which inflammation showed the strongest association with plaque instability **(Redgrave et al., 2006)**.The role and

implications of C-reactive protein (CRP) continued to be a major focus of attention. Data from the Dallas Heart Study showed no association of CRP concentrations with the burden of subclinical atherosclerosis, suggesting that they reflect different aspects of the disease **(Khera et al., 2006).**

The relation between chronic and acute vascular inflammation is unclear, but platelets are a source of inflammatory mediators, and the activation of platelets by inflammatory triggers may be a critical component of atherothrombosis **(Wagner et al., 2003)**.

Therefore, there has been considerable interest in inflammatory biomarkers to identify patients at risk, especially in the absence of traditional risk factors. Among several new markers, high-sensitivity C-reactive protein (hsCRP) appears to be the most promising marker for cardiovascular disease and a new target for therapy. However, a recent systematic review suggested that the CRP measurement only modestly reclassifies individuals **(Shah et al., 2009)**.

Cardiovascular disease (CVD) is a major public health concern. Despite major progress in diagnosis and treatment over the past 25 years, CVD represents the most frequent cause of morbidity and mortality (28% of all deaths annually) in the developed world, according to the World Health Organization In Europe, CVD is responsible for nearly half (49%) of all mortality – over 4 million each year – with coronary heart disease (CHD) and stroke as the predominant causes of death **(Petersen et al., 2005).**

coronary heart disease (CHD) is the single most common cause of mortality in Europe, accounting for 1.95 million deaths each year. The economic burden of CVD in the European Union is substantial, with overall costs due to CVD estimated at 169 billion Euros **(Petersen et al., 2005 & Leal et al., 2006).**

France represents over 10% of these costs, the majority due to healthcare expenditure **(Leal et al., 2006).**

Platelets are essential for primary hemostasis and repair of the endothelium, but they also play a key role in the development of acute coronary syndromes and contribute to cerebrovascular events. In addition, they participate in the process of forming and extending atherosclerotic plaques **(Hansson.2005)**

Atherothrombosis, which involves direct interaction between atherosclerotic plaque and arterial thrombosis, underlies the majority of cardiovascular events, independently of the specific vascular bed in which they occur. Erosion or rupture of vulnerable, lipid-rich atherosclerotic plaque triggers the formation of a platelet-rich thrombus that may partially or completely occlude the artery. The resulting clinical scenarios encompass stable and unstable angina, acute myocardial infarction (MI), ischaemic stroke and peripheral arterial occlusive disease. **(Steinhubl and Moliterno ., 2005).**

The initiation, progression and ultimate rupture of a vulnerable atherosclerotic plaque with an ensuing thrombo-embolic event typically evolves over several decades. The process of atherogenesis mainly occurs in large and medium-sized arteries and involves endothelial dysfunction, inflammation, cholesterol accumulation, apoptosis, extracellular matrix degradation and oxidative stress **(Corti et al., 2004)**

Atherosclerotic plaques are asymmetric focal thickenings of the intimal (or innermost) layer of the arterial wall, and consist of diverse cell types, connective tissue components, lipids and cellular debris **(Stary et al., 1995).**

Inflammatory and immune cells derived from circulating blood are key constituents of the plaque, together with vascular endothelial and smooth muscle cells **(Corti et al., 2004 & Libby and Theroux., 2005)**.

Although the fatty streak constitutes the initial lesion, subsequent plaque formation and growth are heavily influenced by factors that damage and/or disrupt the normal functioning of the endothelial lining of the artery. Such factors include

smoking (which introduces chemical irritants into the artery), diabetes mellitus (advanced glycation end products), hypercholesterolemia (increased circulation of lipids and monocytes), and hypertension (increased shear forces at arterial branches or points of curvature). Damage can also be caused by circulating vasoactive amines, immune complexes, and, possibly, infectious pathogens **(Yusuf et al., 2004).**

The metabolic syndrome has emerged as a potent risk factor for atherothrombosis that affects up to 45% of the unstable angina (US) population over 50 years old **(Dentali et al., 2009)**.

Hormonal contraception and replacement therapy have been linked to VTE and atherothrombotic events **(Vandenbroucke et al., 2001).**

The growing impact of obesity as an independent risk factor received particular attention. Large, prospective studies showed that not only obesity but also excess weight is independently associated with increased mortality in both men and women, and across various age and ethnic groups **(Adams et al., 2006).**

Platelets are key players in all phases of atherothrombosis, including the initial steps of atherogenesis, the progression of fatty streaks to atherosclerotic lesions., and the resulting thrombotic complications **(Steinhubl and Moliterno ., 2005).**

Because the platelet is central to these processes, it is a prime therapeutic target for the management and prevention of adverse clinical sequelae related to atherothrombosis, and it is therefore the topic of this review **(Ferguson et al., 2000).**

Oral antiplatelet therapies recommended for the secondary prevention of vascular events in at-risk patients include aspirin, clopidogrel, the combination of aspirin and clopidogrel, and the combination of aspirin and extended-release dipyridamole **(Adams et al ., 2008)**.

It is important to assess the safety and efficacy of antiplatelet therapies under development, which include prasugrel, cangrelor, and ticagrelor (formerly called AZD6140). The agent furthermost in development is the thienopyridine prasugrel, which has been shown to inhibit platelet activation to a greater extent than clopidogrel **(Meadows et al., 2007).**

Terutroban, a thromboxane A_2 receptor antagonist, is being evaluated in phase III trials for secondary stroke prevention. In addition to having an antithrombotic effect, terutroban may have activity against vasoconstriction and atherosclerosis. The Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history oF ischemic strOke or tRansient ischeMic attack (PERFORM) study is randomizing 18,000 patients to receive either aspirin or terutroban, and results are expected in 2011 **(Bousser et al., 2009)**.

Clinical evidence indicates that statin-mediated lowering of circulating concentrations of atherogenic, cholesterol-rich lipoproteins (VLDL, VLDL remnants, IDL) halts progression of atherosclerosis and, under conditions of intensive statin therapy, may potentiate reduction in atheroma plaque volume (**Nissen, 2005 & Nissen et al., 2006).** Equally, statin action on atherogenic lipoproteins is also associated with plaque stabilisation, modification of plaque morphology and attenuation of inflammation **(Takemoto and Liao., 2001).**