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Review

Novel risk factors for acute coronary syndromes and emerging therapies

David C. Tong [a,b], Andrew M. Wilson [a,b,c], Jamie Layland [a,b,d,*]

[a] Department of Cardiology, St. Vincent's Hospital, Fitzroy, Victoria, Australia
[b] Department of Cardiology, Peninsula Health, Frankston, Victoria, Australia
[c] University of Melbourne, Department of Medicine, St. Vincent's Hospital, Fitzroy, Victoria, Australia
[d] Department of Medicine, Monash University, Peninsula Campus, Frankston, Victoria, Australia

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ABSTRACT

Acute coronary syndromes represent not merely disrupted atherosclerotic plaques or luminal stenoses but rather a complex clinical syndrome. The traditional conception of pathogenesis and management of ACS has been challenged by numerous recent landmark ACS trials. Current prognostication models lack clinical precision and can be challenging to the clinicians in tailoring management strategies for individual patients. In this review we summarise the emerging evidence of novel risk factors (plaque phenotype, coronary blood flow, endothelial dysfunction, microvascular dysfunction, and inflammation) in predicting future events and outcomes in ACS population. As the search for miracle cure for ischaemic heart disease continues, one is hopeful that emerging therapeutic approaches targeting these novel risk factors will improve long-term outcomes of ACS.

1. Introduction

Cardiovascular disease remains the leading cause of mortality and morbidity globally, with an estimated 7.4 million deaths due to coronary artery disease in 2012 alone [1]. Recent demographic and epidemiologic data show an alarming 40% increase in global cardiovascular mortality over the last two decades owing to the ageing and growth of populations [2]. Despite recent advances in medical therapy and percutaneous coronary intervention (PCI), long-term mortality and cardiac event rates remain high in patients presenting with acute coronary syndromes (ACS) [3]. Traditional cardiovascular risk factors inaccurately predict risk of in-hospital mortality and future adverse events in ACS patients [4]. In addition, demographic factors and angiographic variables have poor discrimination in detecting high-risk patients with vulnerable plaque phenotype [5]. This review presents the pathophysiology of atherogenesis, recent trials that challenge the current paradigm of ACS management, novel risk factors for ACS, and emerging management strategies and therapeutic considerations.

2. Pathophysiology of atherosclerosis, plaque progression, instability and rupture

Atherosclerosis is considered a chronic inflammatory process that predates its clinical manifestations by several decades. It begins with disruption of endothelial integrity and function, which stimulates accumulation and oxidation of low-density lipoproteins (LDL) in the arterial wall [6] (Fig. 1). Circulating monocytes then migrate and reside in the subendothelial intima and undergo maturation into macrophages [6]. Macrophages express scavenger receptors which facilitate accumulation of intracellular lipids and the conversion to foam cells that are rich in cholesteryl ester and free fatty acids [7]. The inflammatory milieu in atherosclerosis is further exaggerated and sustained by the innate immune system involving T-cell activation [8]. Subsequent macrophage apoptosis and lipid pooling lead to formation of acellular necrotic core that is encapsulated by fibrous cap. For much of the lifespan of an atherosclerotic plaque, the artery accommodates the plaque growth by expanding outward to minimise luminal encroachment, a process known as expansive remodelling [9]. Matrix metalloproteinases (MMPs) released from the macrophages are capable of degrading the extracellular matrix and interstitial collagen, resulting in thinning of fibrous cap over time [10]. The integrity of the fibrous cap is further disrupted by inflammation-mediated collagen synthesis inhibition and degradation [11,12]. When the fibrous cap ruptures, the necrotic core contents are exposed to the circulating blood, resulting in activation of the coagulation cascade, platelet activation and aggregation and formation of thrombi, and potentially fatal thrombotic complications of ACS [13].

Although atherosclerotic plaque rupture with luminal thrombosis accounts for the majority of acute coronary syndromes and sudden cardiac death [14,15], little is known about the underlying mechanisms resulting in abrupt transition from chronic stable asymptomatic disease to acute plaque vulnerability.

* Corresponding author at: Department of Cardiology, Peninsula Health, 2 Hastings Road, Frankston 3199, Victoria, Australia.
E-mail address: Jlayland@phcn.vic.gov.au (J. Layland).

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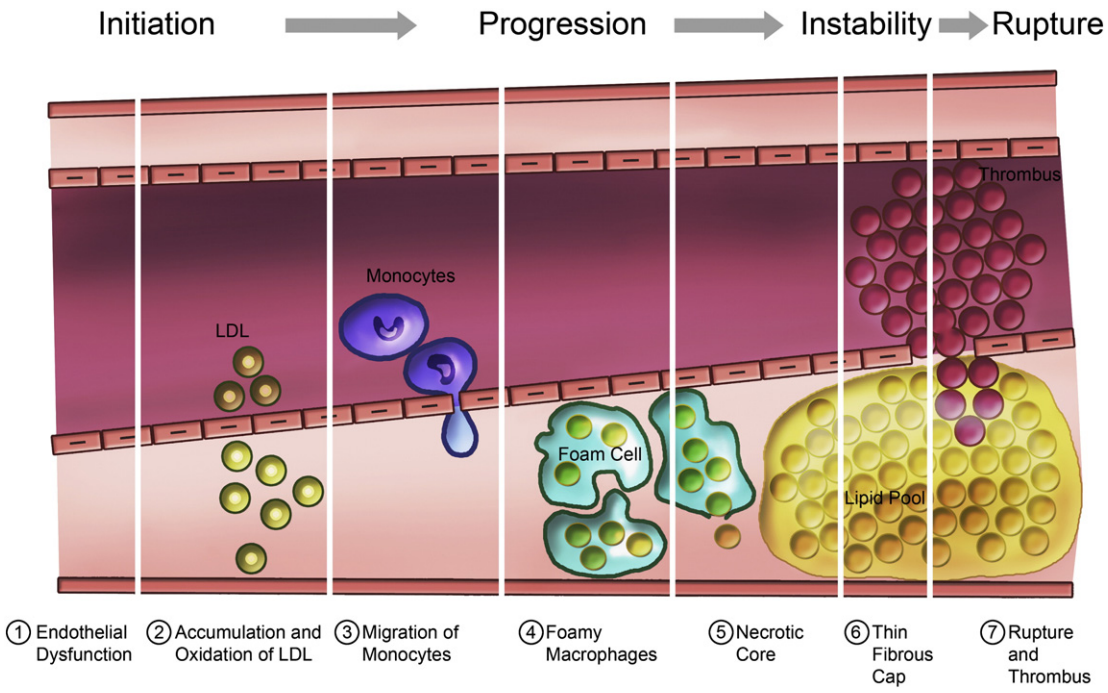

Fig. 1. Pathogenesis of atherosclerosis, plaque progression and rupture. (1) Disruption of endothelial integrity and function secondary to risk factors such as hyperlipoproteinemia stimulates (2) the accumulation and oxidation of LDL in the arterial intima. The disrupted endothelium also expresses adhesion and chemoattractant molecules that (3) recruit inflammatory leukocytes to the arterial wall. The monocytes undergo maturation and become macrophages. Scavenger receptors expressed by the macrophages facilitate accumulation of intracellular lipoproteins, resulting in lipid-laden (4) foam cells. The inflammatory milieu is sustained and amplified through secretion of inflammatory cytokines and growth factors by the leukocytes, causing further leukocyte recruitment and smooth muscle cell migration and proliferation. Subsequent macrophage apoptosis and pooling of lipids lead to the formation of (5) acellular necrotic core, which is encapsulated by fibrous cap consisting of proteoglycan-collagen matrix to protect it from rupturing. MMPs released from the foamy macrophages and other inflammatory mediators result in degradation of extracellular matrix and interstitial collagen, and (6) thinning of fibrous cap over time. When the (7) fibrous cap ruptures, the necrotic core contents are exposed to the coagulation factors in the circulating blood, which promotes thrombus formation. The sequel is clinical presentation of ACS and its thrombotic complications. LDL: low-density lipoprotein; MMP: matrix metalloproteinase; ACS: acute coronary syndromes.

3. Paradigm shift in understanding and managing ACS

The diagnosis and treatment of ACS have been momentous with numerous randomised clinical trials conducted over the last few decades targeting at restoring epicardial coronary blood flow and reperfusing the ischaemic myocardium to reduce acute mortality and morbidity. Despite the proven success of pharmacologic and mechanical interventions, a considerable proportion of ACS patients have adverse long-term clinical outcomes. This is demonstrated in a recent Swedish national registry study which showed that 18.3% of ACS patients had recurrent cardiovascular events within the first 12 months after the index event, and of those who remained event-free for the first 12 months one in five experienced an event during the following 36 months [3]. Indeed, a number of landmark ACS trials in the recent years have challenged our understanding and management of the condition.

3.1. Lesion stenosis does not predict future outcome

Contrary to the traditional paradigm of ACS, recent studies revealed that atherosclerotic plaques at the sites of the culprit lesion responsible for unanticipated future events often have non-significant stenosis on the antecedent angiogram [16]. The PROSPECT study, a prospective longitudinal study examining the relationship of atherosclerotic plaque characteristics with future cardiovascular events using intravascular ultrasound, showed that there was an equal event rate at the sites of culprit and non-culprit lesions (12.9% vs. 11.6%), irrespective of the degree of angiographic stenosis, at a median follow-up of 3.4 years after culprit lesion PCI for ACS [17]. The discrepancy between the degree of stenosis and the propensity to develop an ACS is poorly understood but certainly explains why myocardial infarction (MI) often occurs without any warning symptoms of angina.

3.2. Complete versus target-vessel revascularisation based on angiography

Patients presenting with ACS frequently (30–40%) harbour multiple complex coronary lesions, which are a major risk factor for adverse clinical outcomes [18]. Controversy exists as to whether achieving complete revascularisation is clinically beneficial in ACS patients. Current ACCF/AHA and ESC guidelines on the management of STEMI recommend infarct-related-artery (IRA)-only PCI in patients with multivessel disease (MVD) [19,20]. However, this paradigm is challenged by two recent randomised trials of preventive angioplasty in STEMI patients with MVD. The PRAMI trial demonstrated long-term benefit in the primary endpoint (composite of cardiac death, non-fatal MI or refractory angina) in 465 STEMI patients who underwent immediate preventive revascularisation of non-culprit arteries with ≥50% stenosis at the time of primary PCI [21]. However, the study was not powered to demonstrate differences in cardiovascular mortality. In addition, CvLPRIT demonstrated significantly lower major adverse cardiovascular event (MACE) rates at 12 months in STEMI patients who underwent preventive PCI during index admission compared to IRA-only PCI (HR 0.45) [22]. A large-scale randomized study - the COMPLETE trial with an estimated 3900 participants, is currently underway to assess the impact of complete revascularisation on hard clinical endpoints in STEMI patients with MVD.

The benefit of preventive PCI in NSTEMI population has not been well characterised owing to a lack of randomised clinical trial data. The subset analysis of the ACUITY trial, which included 2954 NSTEACS patients treated with PCI, demonstrated that incomplete revascularisation was strongly associated with 1-year MACE compared with complete