An acute coronary syndrome (ACS) is the most ominous manifestation of coronary artery disease (CAD). The burden of ACS and its impact are striking. Cardiovascular disease is now the most common cause of mortality worldwide, and among cardiovascular deaths, the majority are attributable to CAD. As a result, although CAD in general is a major global public health concern, ACS is particularly worrisome because it is both prevalent but at the same time portends a poor prognosis. Although advanced therapies may alleviate ACS-related morbidity and mortality in well-served communities located in affluent countries, many persons in less-fortunate situations living in low- and middle-income countries remain exposed to the ravages of this disease.

Despite this outlook, rapid progress is being made in understanding the pathology, in prevention, and in treatment of ACS. As readers will find even by perusing the headings of the articles in this ACS Compendium, there is much to be optimistic about. As Editors of this ACS Compendium, we are privileged to have played a small role in helping to provide the framework for the esteemed authorship groups to leverage their collective expertise and provide for us a definitive overall review of ACS. In working with these world-renowned scientists and clinicians on this collection of ACS articles, which also included a cadre of expert reviewers (to who we are especially thankful), we found ourselves in the enviable position of being privy to a deeply insightful, cutting-edge, and forward-looking appraisal of the current state-of-the-science for ACS. Although this fund of knowledge is clearly set out in the articles that follow, several unexpected points arose from these interactions. The most obvious, somewhat surprisingly, was the question of what exactly is an ACS?

**What Constitutes an ACS Event, and Is This Definition Evolving?**

The term ACS appeared relatively recently in the medical lexicon. A simple search in PubMed reveals that the first article to use the term ACS in the title or abstract appeared in 1986. In this article titled Flow Characteristics of Coronary Balloon Catheters, the following sentence appeared in the abstract: “Sudden reocclusion leads frequently to an acute coronary syndrome (acute myocardial infarction, hypotension, arrhythmias) that requires emergency surgery and also leads to permanent myocardial damage of various degrees.” Clearly, this 1986 use of the term ACS (meaning acute myocardial infarction [MI], hypotension, and arrhythmia) differs significantly from its meaning today. When we used the term only a few
Nonstandard Abbreviations and Acronyms

| ACS          | acute coronary syndrome |
| CAD          | coronary artery disease |
| MI           | myocardial infarction   |

years later in 1992 in an article titled The Pathogenesis of Coronary Artery Disease and the Acute Coronary Syndromes, we defined ACS as MI, unstable angina, or ischemic sudden death. As a historical point in the evolution of the use and meaning of the term ACS, it is interesting to note that one of the themes of our 1992 article was the concept that MI, unstable angina, and ischemic sudden death are all part of a spectrum of manifestation of the same atherosclerotic coronary artery substrate. Although this is now an established principle of CAD and atherosclerosis, this understanding paved the way for the contemporary use of the term ACS because it unified these syndromes through their common pathological basis. Further extending this observation, what could be the potential advantages of considering biomarker-negative angina as a non-ACS entity? Although this may be a dubious distinction at the level of the plaque (see article by Drs. Fog Bentzon, Otsuka, Virmani, and Falk in this ACS Compendium, page 1852), a biomarker-negative chest pain syndrome nevertheless implies a lack of acute vessel occlusion or distal embolization, which may therefore at least partially distinguish troponin-negative from troponin-positive events at a pathological level. Furthermore, by excluding biomarker-negative chest pain syndromes from the ACS definition and by relying on troponin to diagnose minor events with small biomarker elevations, there can be little if any uncertainty as to what constitutes an ACS-type event, and its diagnosis is greatly simplified. As a practical advantage, this would remove the current uncertainty in ACS diagnosis of interpreting a patient’s historical account of their angina and determining if this is stable or otherwise. Although unstable angina is often a subjective clinical symptom, a positive troponin is an objective laboratory result. Indeed, troponin assays are now so sensitive that with paired samples drawn sequentially several hours apart after presentation to an emergency department, the sensitivity of this test for diagnosing MI approaches 100%. Therefore, particularly in a busy emergency department setting, there is obvious appeal in relying on a troponin assay to rule in/out what is considered to be an ACS-type event. Moreover, this also has the advantage of eliminating false-positive ACS diagnoses in patients who are thought to have unstable angina but who in reality have stable angina or even noncardiac chest pain.

What might be the disadvantages of relying on a troponin assay to rule in/out ACS-type events? Most concerning is that patients with truly unstable angina may be managed conservatively, when a more proactive ACS treatment algorithm would be more appropriate. Nevertheless, as reflected by both the GRACE (Global Registry of Acute Coronary Events) and TIMI (Thrombolysis In Myocardial Infarction) risk scores and other studies, biomarker-negative patients are generally at lower risk for adverse events. Therefore, the clinical consequences of conservatively managing a low-risk, troponin-negative ACS as stable angina might generally be expected to be minimal. This is supported by current guidelines, with the routine invasive evaluation of patients with low-risk ACS being not recommended by the European Society of Cardiology and of uncertain benefit according to US guidelines. Chest pain observation units make use of this fact and are now increasingly being used in certain centers to rule in/out and initiate management for ACS in the initially low-risk patient.

Collectively, therefore, we think that due to a combination of the widespread use of high-sensitivity troponin assays, changing definitions of MI, the generally favorable prognosis of low-risk troponin-negative patients, and increased overall simplicity, the implied meaning and practical use of the term ACS is slowly evolving to exclude troponin-negative unstable angina. Although support is not universal, a strong...
case has been made that in the high-sensitivity troponin era, troponin-negative unstable angina would be better categorized as a subtype of severe stable CAD rather than together with MI. However, we caution that there remains a specific clinical entity of a high-risk unstable angina patient with negative troponin. These patients are characterized by several features, such as older age, heart failure, and low blood pressure. Therefore, although we think a gradual shift in the implied meaning of ACS may be occurring, great clinical care is required for certain troponin-negative but high-risk patients.

What Is Not an ACS Event?

We have set out above the reasons we perceive that biomarker-negative chest pain syndromes are now less commonly considered an ACS. However, clinicians will likely be more familiar with the opposite issue—that patients with any number of noncardiac problems may have a weakly positive troponin result and are, for practical purposes, labeled as having an ACS. Typically, these are medically unwell patients who present with a broad spectrum of acute illnesses, such as heart failure, renal failure, blood loss, or sepsis. Often, the criteria for MI are not met because ECG changes or chest pain may be absent. Therefore, as they have neither MI nor unstable angina, they also do not meet the usual criteria for an ACS. Despite this, as any practicing cardiologist will attest, medically unwell patients are frequently triaged as if they had an ACS event based solely on a weakly positive troponin. These patients may be wrongly admitted to a coronary care unit or cardiology service, which only serves to misdirect resources and medical efforts. This emerging clinical problem is currently the focus of much attention and was recently dubbed the plague of troponinitis. Although it is clear that nobody in the medical community is advocating for these medically unwell patients to be included in the definition of ACS, we highlight this concern as an issue yet to be resolved in the accurate triage and management of patients with a true ACS event.

In summary, the definition and practical use of the term ACS is in a state of continued evolution. It is not a term which is rigorously defined by a consensus committee such as MI. Rather, it is a term whose meaning is to some extent governed by popular use and which is entwined in our increasing knowledge of this disease and improved diagnostic and therapeutic tools.

ACS Compendium

Readers will find the following articles move in a logical sequence through mechanisms of plaque formation, the role of inflammation and lipids, genetics, ACS imaging, diagnosis, invasive and medical treatments, and finally global perspectives. As a disclaimer, not every detail of ACS is covered in this Compendium. Broadly, we deliberately omitted material that we thought was either too detailed (eg, technical details of stent implantation) or which has evolved little in the last decade (eg, ECG changes of myocardial ischemia). We think the articles which follow are, collectively, a contemporary and unsurpassed cross-disciplinary review of ACS.

Assuming its rightful place as the first review in this ACS Compendium, Drs Fog Bentzon, Otsuka, Virmani, and Falk have, as one reader memorably described it, provided a Magnum Opus covering Mechanisms of Plaque Formation and Rupture (see page 1852). The authors logically describe stages of atherosclerotic plaque formation and mechanisms of rupture. In addition, the authors cover numerous other relevant aspects, including atherosclerotic disease activity, scientific areas of uncertainty (eg, mechanisms of plaque erosion), and opportunities for ACS prevention from a histopathologic perspective. This article elegantly sets the stage for this ACS Compendium and lays a foundation of understanding for the articles that follow.

Moving from general mechanisms of plaque formation and rupture, 2 articles then follow that are dedicated to specific, fundamental aspects of ACS biology: inflammation and lipid metabolism. In the first of these, Drs Libby, Tabas, Fredman, and Fisher review the details of Inflammation and its Resolution as Determinants of Acute Coronary Syndromes (see page 1867). Many important aspects of the inflammatory responses that govern ACS are explored, including defective efferocytosis in advanced plaques that is associated with a large necrotic core—akin to a vascular graveyard of inflammatory, smooth muscle, and other cell types leading to rupture-prone lesions that may culminate in ACS. As an emerging aspect of plaque progression, the concept of failure of resolution of inflammation is also broached with specialized proresolving mediators being novel biological agents to prevent ACS. Although several familiar agents such as aspirin and statins may act as partial specialized proresolving mediators (in addition to their antiplatelet and lipid lowering effects, respectively), the appreciation that enhanced resolution of inflammation may mitigate ACS and CAD has paved the way for novel therapeutic agents targeting highly specific aspects of vascular inflammation without compromising host immune defense.

In an article that transcends biomarkers, mechanisms, and therapy, Drs Rosenson, Brewer, and Rader drill down on a topic at the core of atherosclerosis, CAD, and ACS: lipoproteins in the setting of ACS (see page 1880). Although on one hand it could be argued that the great bulk of data about lipoproteins are in patients with prior MI or those with stable CAD, Rader and colleagues effectively draw from the existing literature and illustrate the pivotal role of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and other lipid moieties in ACS. From a treatment perspective, this is an especially important article because it covers the role of statins and introduces novel agents, such as PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors, which hold hope for the future primary prevention of ACS.

The genetics of CAD and MI has been an area of striking progress in the past decade. Although a strong genetic component was previously suspected, it was only as recently as 2007 that this field exploded with the discovery of the 9p21 CAD risk variant. In his Compendium review, Dr Roberts covers the full spectrum of this field (see page 1890). Interestingly, the genome-wide association data underpinning this research has used the general end points of presence of CAD and occurrence of MI. There are few, if any, data pertaining directly to ACS and certainly to ST-elevation MI versus non–ST-elevation MI or unstable angina. Therefore, as an exception to this ACS Compendium series, Dr Roberts’s article is not entirely specific to ACS but relates more to presence of CAD. These notwithstanding, several fundamental messages are delivered in this article that shape our outlook on CAD, including that the heritable component of common atherosclerosis is driven...
by the cumulative risk inferred by the inheritance of multiple genetic variants, each conferring only a marginal increment in risk. These variants are common, with more than half being present in >50% of the population. As another major and unexpected finding arising from genome-wide association and other data, it is becoming increasingly clear that high-density lipoprotein cholesterol levels may be unrelated to developing CAD. This article will serve as a concise, interpretive summary of this field as it stands in 2014, capturing the excitement of these recent genetic insights yet the profound complexity of the genetic and molecular pathways that remain to be unraveled.

A major area of recent progress has been in imaging of atherosclerosis, CAD, and ACS. This includes noninvasive and invasive (intracoronary) modalities, which have collectively played a key role in helping to elucidate the pathobiology, natural history, and optimal treatment strategies for ACS. Drs Garcia-Garcia, Jang, Serruys, Kovacic, Narula, and Fayad have concisely reviewed this field in their article titled Imaging Plaques to Predict and Better Manage Patients With Acute Coronary Events (see page 1904). Of the many important lessons learned through cardiovascular imaging, perhaps one of the most notable is that CAD does not occur in isolation, but rather it is part of a systemic disease process affecting the entire arterial tree. In addition, although it is possible to identify vulnerable or rupture-prone coronary plaques, each lesion has a low overall likelihood of causing an ACS. This knowledge has driven interest away from potential interventions seeking to individually treat a specific lesion to prevent ACS. Rather, these imaging data have generally reinforced the need to tackle atherosclerosis, CAD, and prevention of ACS at the systemic level by attention to risk factors and optimal medical therapy.

Next, we move to a series of 3 articles that focus on the acute and secondary treatment of ACS. In the first of these treatment-focused articles, Drs Bagai, Dangas, Stone, and Granger review reperfusion strategies in ACS, or in other words, options for reopening the culprit vessel(s) that causes an ACS event (see page 1918). In broad terms, this can be divided into either mechanical reperfusion in a catheterization laboratory with coronary angioplasty and stent implantation (which may be considered for any patient with ACS) or intravenous thrombolytic therapy such as tenecteplase or alteplase (which is only efficacious for ACS with ST-segment elevation). As well as reviewing this field and providing an update on current best practice in angioplasty/stenting and thrombolysis, a significant section of this article is appropriately devoted to the logistic aspects of the timely reopening of the culprit ACS vessel. In the context of an ST-segment elevation MI, it has been well documented that time is muscle, and prompt reperfusion to reduce morbidity and mortality is a critical component of current treatment algorithms.

In their review of Antiplatelet and Anticoagulation Therapy for Acute Coronary Syndromes, Drs Bhatt, Hulot, Moliterno, and Harrington provide a focused expose of what has been a rapidly developing field (see page 1929). Although aspirin and warfarin have been in our armamentarium for many years, readers should be aware that almost all of the other agents discussed in this article have appeared in the past 2 decades. Even clopidogrel, which in addition to aspirin is arguably the cornerstone of antiplatelet therapy in ACS, is a relatively new agent. Many readers will recall that is was only in 1999 to 2000 that clopidogrel replaced ticlopidine (Ticlid) as the preferred second agent after aspirin, and in the brief ensuing period, clopidogrel has gone on to become one of the most important cardiovascular agents on the market. In addition to these therapies, a diverse array of newer agents that inhibit platelet function are now available and appropriate for use in ACS. The recently emerged anticoagulants targeting thrombin or factor Xa are also now under investigation for their possible utility in ACS, potentially in conjunction with antiplatelet agents. Although perhaps not living up to its promise, the study of the pharmacogenomics of clopidogrel has also been an area of intense interest and has concurrently served to propel the genetic investigation of response to cardiovascular therapies to the forefront of investigation. Although there is still clearly a trade-off between bleeding risk and potential for thrombosis in ACS, with their improved pharmacological profiles, we think that it is reasonable to surmise that contemporary agents are slowly shifting this trade-off toward a more favorable balance in risk.

In the current era, optimal medical therapy has become a mandatory cornerstone of the management of not only ACS but almost the full spectrum of conditions encountered in clinical cardiology. In their article Nonantithrombotic Medical Options in Acute Coronary Syndromes: Old Agents and New Lines on the Horizon, Drs Soukoulis, Boden, Smith, and O’Gara deliver a must read for those who treat or are interested in ACS (see page 1944). Woven around salient aspects of cardiac physiology during ACS, the authors first comprehensively review the currently available therapeutic options, such as β-blockers, nitrates, angiotensin-converting enzyme inhibitors, and aldosterone antagonists, with close reference to pivotal trials and current guidelines. This is followed by an exciting look at new and upcoming treatments in late-phase clinical studies and important areas for further investigation. Broadly, newer areas that are now becoming the focus of attention include the prevention of the no-reflow phenomenon, minimizing myocardial reperfusion injury, ischemic pre- and postconditioning (and developing important mediators of this process as therapies for ACS), and modulation of inflammation and cellular metabolic activity. The approaches being studied are diverse and include sophisticated biological agents, older agents such as cyclosporine and β-blockers (the latter of these may reduce ischemia-reperfusion injury via nitric oxide synthase activation), remote conditioning by manual blood pressure cuff inflation/deflation while en-route to the catheterization laboratory, and simple mechanical thrombus aspiration catheters that are used during percutaneous coronary intervention for ACS. Certainly, we perceive these to be important areas for research moving forward.

In an article that could have been positioned first rather than last in this Compendium, Drs Vedanthan, Seligman, and Fuster broaden the frame of reference for ACS with their article Global Perspective on Acute Coronary Syndrome: A Burden on the Young and Poor (see page 1959). Although the earlier articles in this Compendium might read as back-to-back success stories of how high-income countries have systematically gone about understanding ACS and translating this understanding into reduced morbidity and mortality from this disease, low- and middle-income countries are still struggling to define the exact magnitude of the problem at hand. It is a telling point that due to the paucity of data on ACS in low- and middle-income countries, to a certain extent the authors of this article had to extrapolate...
broader information relating to ischemic heart disease and cardiovascular disease to piece together the global picture of ACS in these nations. As an example of these unknowns, the median age of mortality from ischemic heart disease in men is a decade younger in low- and middle-income countries than high-income countries, which may be because of earlier onset of ACS and ischemic heart disease or shorter survival after initial presentation. Differences between countries, regions, and races add to these uncertainties. Of course, these are but some of the major challenges faced, and other key problems to be overcome are carefully detailed in this article. These data sit as a sobering conclusion to this Compendium, highlighting that while much has been achieved, we are only just beginning our global fight against ACS and ischemic heart disease.

As Guest Editors of the ACS Compendium, we were honored and humbled by the enthusiasm and contributions of the distinguished authors of these articles. As readers will identify, each authorship team comprises true thought leaders and cutting-edge scientists at the vanguard of these respective disciplines. More than just their contribution in writing these articles, it is by their hard work and notable contributions over the last several decades, along with those from their many peers, that we have now reached the current point of understanding of ACS described herein and are making an impact on patient outcomes.

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None.

References

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Valentin Fuster and Jason C. Kovacic

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