Heart Metab. (2018) 75:3

Acute coronary syndromes: changing face

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Since the beginning of this century, an overwhelming body of evidence has prompted a deep revision of our understanding of ischemic heart disease, which was traditionally based on the misconception that myocardial ischemia is closely linked with coronary artery atherosclerotic obstructions. The revision was initially focused on chronic ischemic syndromes or "stable angina" and, with it, the acknowledgment of the multifactorial nature of this condition with a number of possible precipitating mechanisms, including severe stenosis, coronary vasospasm, and microvascular dysfunction. It was also acknowledged that multiple mechanisms might be present at the same time or alternate in time. In addition, the diagnostic and therapeutic implications of this new understanding have yet to be fully implemented in clinical practice.

More recently, the traditional concepts on the pathogenesis of acute ischemic syndrome have also been strongly challenged. The classic model was based on the assumption that acute ischemic syndromes are precipitated by plaque rupture, fissure, or erosion. However, recent reports do not support this concept. In summary, most vulnerable plaques identified in patients with acute ischemic syndrome are located in nonculprit vessels, not all patients with acute ischemic syndrome have vulnerable plaques at coronary angiography, and vulnerable plaques are a common observation, also in stable or asymptomatic patients.

Longitudinal studies with repeat intracoronary imaging have shown that plaques are dynamic structures with rapid changes from a vulnerable pattern to a stable pattern and vice versa, and these changes are not associated with clinical events. The most recent reports on the subject have concluded that, of the more than 82 patients with acute ischemic syndrome analyzed, 31 had no evidence of erosion or rupture at optical coherence tomography, and the latest guidelines from the European Society of Cardiology on non–ST-segment elevation myocardial infarction acute coronary syndrome (NSTEMI-ACS) admit that up to 20% of patients have normal coronary angiography.

This issue of *Heart and Metabolism*, with its suggestive title, aims to offer the readers some useful hints on being an active participant in this process. Readers will find cases of acute ischemic syndrome in patients with clean coronary arteries, will learn how to interpret the biochemical markers of cardiac damage, will be helped by experts to manage acute ischemic syndromes in patients with no coronary obstruction, will be informed on the role of cardiac energy metabolism as a possible cause of acute ischemic syndrome and, at the same time, a possible therapeutic target, and will also find a critical appraisal of current therapeutic results.

The invited authors have done a spectacular job and I am personally indebted to them for their outstanding contributions. ■

Heart Metab. (2018) 75:4-8

The changing face of acute coronary syndromes

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Abstract

Acute coronary syndrome is a leading cause of ischemic heart disease mortality and morbidity. Despite the rising prevalence of obesity and diabetes, the epidemiology of acute coronary syndrome appears to be shifting with an observed decreased incidence of ST-segment elevation myocardial infarction (STEMI) and hospital mortality accompanied by an increased incidence of non–STEMI across all age groups and in both women and men. Underlying potential contributors to this change include aging of the population, implementation of primary and secondary prevention strategies, which result in changes in atherosclerotic coronary artery disease, and technological improvements that have increased the sensitivity of cardiac diagnostic tests. Appreciation of sex differences in ischemic heart disease, identification of nonobstructive coronary disease, and the diagnosis of coronary microvascular dysfunction as contributors to ischemia with no obstructive coronary artery disease (INOCA) is increasing. Work is ongoing to fill the gaps in knowledge needed for evidence-based guidelines for the changing face of acute coronary syndrome. ■ *Heart Metab*. 2018;75:4-8

Keywords: acute coronary syndrome; non–ST-segment elevation myocardial infarction; stable ischemic heart disease; sex differences; ST-segment elevation myocardial infarction

Introduction

Despite an aging population and an increasing burden of obesity and diabetes, the epidemiology of acute coronary syndromes (ACS) appears to be shifting with an observed decreased incidence of ST-segment elevation myocardial infarction (STEMI) and mortality that is accompanied by an increased incidence of non–STEMI (NSTEMI) across all age groups and in both women and men *(Figure 1)*.[1,2] In this review, we discuss the evidence and possible contributors to the changing face of ACS.

Evidence

The incidence of acute myocardial infarction (AMI) has been stable with only a modest decline over the past four decades.[1,2] Recent studies on trends suggested sharper declines in the recent millennial years as compared with the 1980s and 1990s *(Figure 2)*.[2-4] A shift in ACS presentation was also reported over this period, where the incidence of NSTEMI doubled,[1,2,5] which was accompanied by a marked decline in the incidence of STEMI (from 133 to 50 cases per 100 000 person-years).[6] The aging of the population

Abbreviations

ACS: acute coronary syndrome; **AMI:** acute myocardial infarction; **CAD:** coronary artery disease; **CCTA:** coronary computed tomography angiography; **CK-MB:** creatine kinase–myocardial isoenzyme; **IHD:** ischemic heart disease; **INOCA:** ischemia with no obstructive coronary artery disease; **IVUS:** intravascular ultrasound; **NSTEMI:** non–ST-segment myocardial infarction; **PCI:** percutaneous coronary intervention; **STEMI:** ST-segment myocardial infarction

likely contributes to the increase in NSTEMI, which is more common in elderly patients. Hospital mortality, on the other hand, has been steadily declining in both groups with a reported decline in overall mortality >50%, mostly for patients with STEMI who are admitted to the intensive or acute coronary care units as shown in multiple studies done in the US and around the world.[4,7-10] Of note, patients with NSTEMI complicated by cardiogenic shock had a higher hospital mortality rate than did patients who presented with STEMI and cardiogenic shock. This observation was attributed, at least in part, to delays in revascularization among the NSTEMI group vs the STEMI group.[11] An improvement in survival and a reduction in the 6-month mortality rate was significantly associated with the use of invasive coronary strategies among NSTEMI patients.[12] Notably, there is an overall significant reduction in the severity of AMI presentation in both groups with decreased complications, specifically that of heart failure.[13,14] The decline in mortality was predominantly attributed to technological improvements in cardiac care and shorter times in delivering reperfusion therapy, primarily with percutaneous coronary intervention (PCI). However, recent studies suggest that the secondary prevention and treatment of heart failure have played a more significant role in mortality reduction than reperfusion alone.[7]

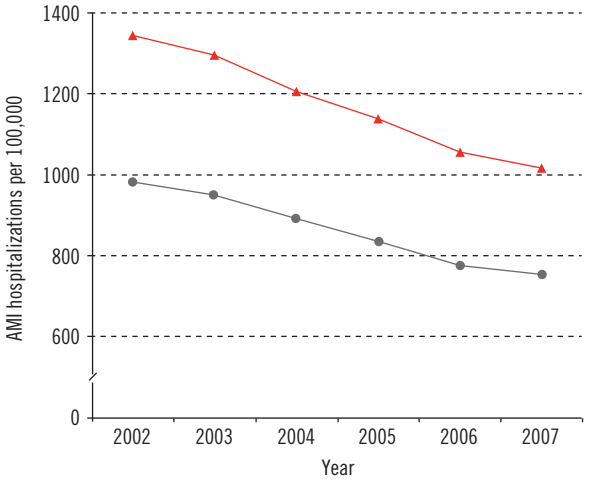

Fig. 1 *Acute myocardial infarction hospitalization rate for men and women from 2002 to 2007; not adjusted for age. Rates for men and women are represented by triangles and circles, respectively.*
Abbreviations: *AMI, acute myocardial infarction.*
From reference 9: *Chen et al.* Circulation. *2010;121(11):1322-1328.*

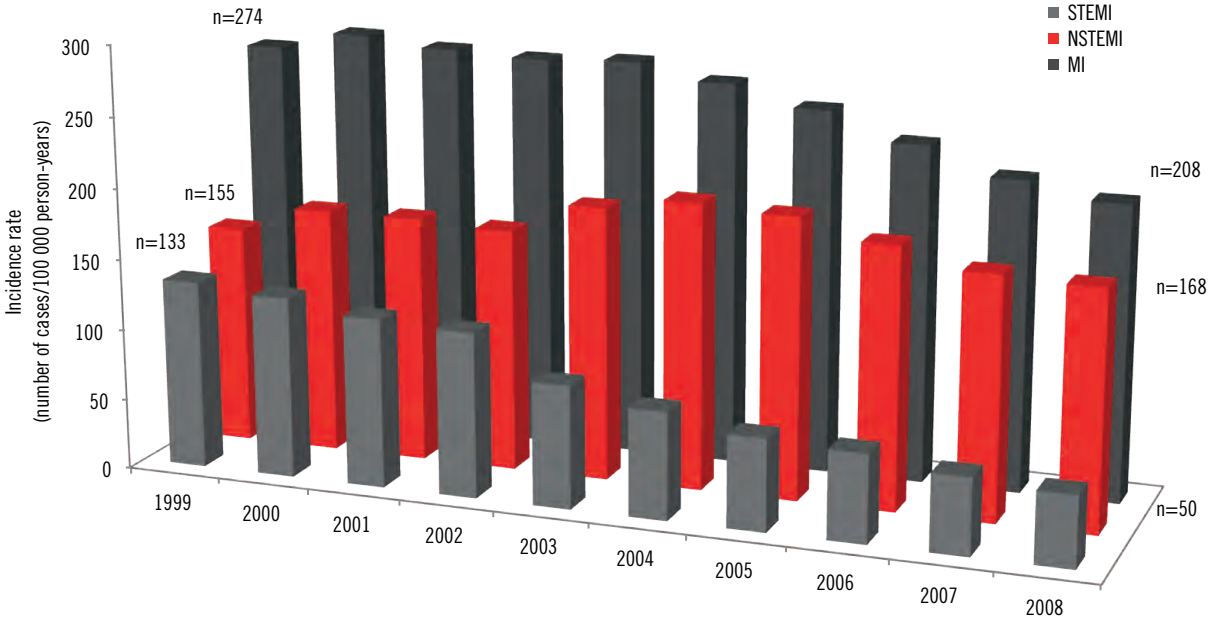

Fig. 2 *Age- and sex-adjusted incidence rates of acute myocardial infarction from 1999 to 2008.*
From reference 2: *Yeh et al.* N Engl J Med. *2010;362(23):2155-2165.*

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Potential contributors to the change

Potential contributors to the changing face of ACS likely include improved diagnostics and changes in atherosclerotic coronary artery disease (CAD) itself.

Improved diagnostics

Improved diagnostics include the use of high sensitivity cardiac biomarkers, improved noninvasive imaging, and the redefinition of ACS.[15] Many patients who previously met the criteria for unstable angina were reclassified as NSTEMI after the introduction of troponin I (TnI) instead of the creatine kinase–myocardial isoenzyme (CK-MB) in the late 1990s, which led to an increased diagnosis of NSTEMI. In a study of the National Registry of Myocardial Infarction between the years of 1990 and 2006, the proportion of NSTEMI had increased from 14.2% to 59.1%, whereas the proportion of STEMI had decreased.[5,16] Further, the increasing use of improved noninvasive imaging techniques (nuclear stress test and stress echocardiogram) has identified patients with evidence of myocardial ischemia after presenting with chest pain, despite not meeting electrical or biochemical criteria for an AMI, and "no obstructive coronary disease" on angiography. This observation is now called ischemia with no obstructive coronary artery disease (INOCA) and it is seen in patients with ACS or stable ischemic heart disease (IHD) populations.[17] The exact mechanism for INOCA is unclear, but it is hypothesized that nonatherosclerotic mechanisms may precipitate myocardial ischemia (eg, coronary vasospasm, microvascular dysfunction, and inflammation).

While invasive coronary angiography is considered the gold standard in diagnosing and estimating the severity of coronary stenosis, it is a two-dimensional luminogram, which is insensitive to nonobstructive plaque. Advanced imaging, including intravascular ultrasound (IVUS) and noninvasive coronary computed tomography angiography (CCTA), are sensitive techniques for the measurement of atherosclerosis, which is a contributor to adverse long-term outcomes, coronary remodeling, and STEMI.[18,19] Further work with these advanced imaging modalities may characterize and identify the pathophysiology of myocardial ischemia and coronary plaque better to improve prophylactic guideline approaches and reduce the incidence of AMI further.

Changes in atherosclerotic coronary artery disease

Changes in atherosclerotic coronary artery disease include a reduction in overall atherosclerotic plaque burden and high-risk plaque features. This reduction would translate, in theory, to less plaque rupture as well as a lower rate of thrombosis and negative arterial remodeling, which are the major contributors to obstructive CAD, STEMI, and mortality. Secondary prevention is the largest contributor to decreasing ACS mortality in multiple studies, ahead of revascularization or treatment for heart failure.[7,20] There has been a significant decrease in the prevalence of selected major cardiovascular risk factors over the years due to the increased public awareness with lower smoking rates, and the widespread implementation of guideline-directed medical therapy, including treatment of hypertension and dyslipidemia.[21-24] Conversely, the prevalence of obesity and diabetes is increasing.[25]

Using the coronary heart disease policy and prevention model, the IMPACT study (IMProving Adherence using Combination Therapy) showed that more than half of the estimated reduction in mortality came from risk factor reduction. Lowering total cholesterol concentrations, systolic blood pressure, and smoking prevalence were all associated with lowered mortality, while decreased physical activity and increased diabetes and obesity prevalence were associated with an estimated increase in mortality.[7] A study of the French registries over a 15-year period between 1995 and 2010 concluded that hospital mortality due to STEMI had decreased by more than 60%, which is consistent with other studies worldwide.[2,5,26,27] Of interest, the proportion of patients with AMI, particularly STEMI, was increasing at a younger age, more so in women than in men. This trend was hypothesized to be related to the improvement in aggressive medical therapy to patients with recognized obstructive CAD and the increased incidence of smoking among younger women in France over the study period.[10] In summary, these data suggest that, rather than a true reduction in ACS and stable IHD, we are observing a change in disease phenotype that is associated with lower mortality.

Sex differences

Men and women can have different ACS and stable IHD presentations and outcomes – there is a greater

proportion of STEMI in younger males, while females have a higher proportion of NSTEMI.[28,29] Women more often present with more atypical symptoms and suffer worse outcomes.[30] Our understanding of these differences and the complex mechanisms of ACS in women is improving. Women, in comparison to men, generally have a lower burden of coronary atherosclerosis angiographically and by IVUS[31]; however, they tend to have smaller coronary lumens and more coronary microvascular dysfunction and nonobstructing lesions.[32,33] Also, women tend to have less plaque rupture rates vs men, and, although the presence of thin-cap fibroatheroma (TCFA) was found to be similar in both sexes,[34] it was a stronger marker of plaque vulnerability in women.[35] Sex differences in STEMI and NSTEMI were studied in patients in the SCAAR registry (Swedish Coronary Angiography and Angioplasty Registry),[36] showing that significantly more women in both groups had nonobstructive CAD. STEMI rates are generally lower in women than in men[37]; the rates could potentially be lowered further in men by identifying sex differences in the mechanistic pathways. There is increasing interest in redefining the significance of coronary nonobstructive lesions on angiography in men and women, which may lead to improved therapeutic strategies and contribute to further reductions in ACS.

Conclusions

In recent years, the rates of ACS have been on the decline, with STEMI and mortality sharply declining, largely due to the widespread implementation of primary and secondary prevention strategies with aggressive risk factor modification. Modern technological advancements, as well as improvements in reperfusion therapy and treatments for heart failure also play a role. Developing sensitive diagnostic tests and identifying INOCA and nonobstructive CAD appear to be important. Contemporary data suggest that, rather than a true reduction in ACS and stable IHD, we are observing a change in disease phenotype, which is associated with lower mortality. This fact may be particularly relevant to women, due to the higher prevalence of nonobstructive CAD and coronary microvascular dysfunction. Work is ongoing to fill knowledge gaps needed for evidence-based guidelines for the changing face of ACS. ■

Funding disclosure: *This work was supported by contracts from the National Heart, Lung and Blood Institutes nos. N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, grants U0164829, U01 HL649141, U01 HL649241, K23HL105787, T32HL69751, R01 HL090957, 1R03AG032631 from the National Institute on Aging, GCRC grant MO1-RR00425 from the National Center for Research Resources, the National Center for Advancing Translational Sciences Grant UL1TR000124 and UL1TR000064, and grants from the Gustavus and Louis Pfeiffer Research Foundation, Danville, NJ, The Women's Guild of Cedars-Sinai Medical Center, Los Angeles, CA, The Ladies Hospital Aid Society of Western Pennsylvania, Pittsburgh, PA, and QMED, Inc., Laurence Harbor, NJ, the Edythe L. Broad and the Constance Austin Women's Heart Research Fellowships, Cedars-Sinai Medical Center, Los Angeles, California, the Barbra Streisand Women's Cardiovascular Research and Education Program, Cedars-Sinai Medical Center, Los Angeles, The Society for Women's Health Research (SWHR), Washington, D.C., The Linda Joy Pollin Women's Heart Health Program, and the Erika Glazer Women's Heart Health Project, Cedars-Sinai Medical Center, Los Angeles, California.*

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