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YEAR IN CARDIOLOGY SERIES

The Year in Acute Coronary Syndrome

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In this year's report on acute coronary syndromes (ACS), we have expanded the scope to include ST-segment elevation myocardial infarction (STEMI) in addition to non–ST-segment elevation ACS. In this report, we review selected highlights across the spectrum of ACS published between June 2012 and September 2013.

Background

It is estimated that there were over 1.1 million patients with diagnoses of ACS discharged from U.S. hospitals in 2010, of whom 74% were classified as having myocardial infarction (MI) (1). Despite improvements in the management of coronary heart disease risk factors, the annual rates of acute myocardial infarction (AMI) have been fairly stable in the United States over the past decade. The impact of enhanced prevention has been offset by the use of more sensitive biomarkers of cardiac necrosis, specifically cardiac troponin (cTn), to define MI (2), as well as the increase in comorbidities that increase the risk for developing ACS, including diabetes, metabolic syndrome, and chronic kidney disease, as well as the overall aging of the population. The percent of patients with ACS classified as having STEMI ranges from 29% to 47% in recent databases and registries, depending on the methods used to identify patients and the population being studied (1). This percent is decreasing relative to non-STEMI (NSTEMI), in part because of temporal changes in the risk factor profile (reductions in "classic" risk factors such as smoking and hypertension but increases in the aforementioned comorbidities) (3). With the broader acceptance of the third universal definition of MI (4) (Table 1), we expect these trends to continue.

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Indeed, as the sensitivity of cTn measurements has increased, the fraction of patients with unstable angina (UA) (i.e., those with non–ST-segment elevation ACS and no evidence of myocardial necrosis) is steadily declining (2). With the introduction of so-called high-sensitivity cTn (hs-cTn) into clinical practice in a number of countries (other than the United States), almost all patients with ischemic discomfort at rest consistent with ACS have elevations of hs-cTn and are being reclassified as having NSTEMI (5). Patients with chest pain at rest without elevation of hs-cTn on 2 measurements made 2 to 4 h apart most likely have nonischemic chest pain.

New Guidelines

New guidelines for the management of STEMI were released by the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) (6) and the European Society of Cardiology (7) during the past year. In addition, the ACCF and AHA published an update of the guideline for UA and NSTEMI guideline (8). Key changes in these guidelines are summarized in Table 2.

Two important updates to the STEMI guideline (6) include a new target of no more than 120 min from first medical contact to initiation of fibrinolysis (for those not undergoing primary percutaneous coronary intervention [PCI]) and the early initiation of therapeutic hypothermia in survivors of cardiac arrest, followed by immediate PCI when appropriate. Across the ACS spectrum, these updated guidelines (6–8) now recommend the use of the more potent oral antiplatelet drugs (prasugrel or ticagrelor) as alternatives to clopidogrel and provide specific advice on how to minimize bleeding, particularly among patients who require dual-antiplatelet therapy (DAPT) in addition to oral anticoagulation.

Pathophysiology

Three important reports extended the framework for understanding the basic mechanisms leading to ACS: 1) Libby (9) described an updated model in terms of cellular and molecular pathways that underlie the pathogenesis of ACS, with a central role for inflammation, which drives plaque disruption and thrombosis (Fig. 1). This more nuanced understanding of the pathophysiology of ACS has broadened our approach beyond management of a focal

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Table 1 Third Universal Definition of Myocardial Infarction

Definition of myocardial infarction
Criteria for acute myocardial infarction
The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI: • Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: ▪ Symptoms of ischemia. ▪ New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB). ▪ Development of pathological Q waves in the ECG. ▪ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. ▪ Identification of an intracoronary thrombus by angiography or autopsy. • Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. • Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. • Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. • Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Criteria for prior myocardial infarction
Any one of the following criteria meets the diagnosis for prior MI: • Pathological Q waves with or without symptoms in the absence of non-ischemic causes. • Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause. • Pathological findings of a prior MI.

Reprinted with permission from Thygesen et al. (4).
ECG = electrocardiogram.

intracoronary stenosis. 2) Crea and Liuzzo (10) classified ACS into 3 groups (Fig. 2): obstructive atherosclerosis with systemic inflammation, obstructive atherosclerosis without systemic inflammation, and ACS without obstructive atherosclerosis (e.g., Prinzmetal's angina, amphetamine-induced coronary spasm). 3) Falk and a group of cardiac pathologists (11) described 3 common coronary artery plaque morphologies resulting in thrombosis (plaque rupture, plaque erosion, and disruptive nodular calcifications protruding into the coronary artery lumen, known as "calcified nodules"). These latter investigators described several contributors to the "vulnerable plaque," including structural determinants of the plaque (size of the necrotic core, thickness and degree of inflammation within the fibrous cap), plaque neorevascularization and infiltration with hemoglobin-stimulated macrophages (both of which increase the risk for intraplaque hemorrhage), and the pattern of calcification (spotty calcification confers higher risk compared with dense localized calcification). It is hoped that continued work on the pathogenesis of ACS will lead to new diagnostic algorithms and therapeutic targets.

The search continues for interventions, other than prompt revascularization, to reduce infarct size in patients with STEMIs. An intriguing study in swine in which the left anterior coronary artery was occluded showed that unloading the left ventricle with left atrial–femoral artery bypass when added to coronary occlusion resulted in further reduction of myocardial infarct size (12). Although this approach cannot be applied routinely in the catheterization laboratory in all patients with STEMI, it could be lifesaving in those with large infarctions.

Risk Factors

Several reports published during the past year explored genetic risk factors for ACS. Micro-ribonucleic acids (miRNAs) are noncoding ribonucleic acid molecules, 21 to 23 nucleotides long, that regulate the expression of target genes. After multivariate adjustment, 3 circulating miRNAs (126, 233, and 197) were found to be risk factors for the development of future MI (13). Other miRNAs have been found to be associated with reduced myocardial salvage, more pronounced reperfusion injury, and left ventricular remodeling after first STEMI (14,15). The discovery of miRNAs represents a major advance in biology that is likely to aid in the elucidation of the pathobiology of many conditions (including ACS), may provide families of new biomarkers, and might open the possibility for the development of new therapies. For example, miRNAs can be "silenced" by specific antagonists, known as antagomirs, that might be designed to modify target proteins that predispose plaques to rupture.

New data on hormonal contraceptives and nonsteroidal anti-inflammatory drugs provided new insights regarding the increased risk for ACS with these classes of medications. In an analysis of over 1.6 million women the use of ethinyl estradiol was associated with increases in the risk for MI (16). A nationwide Danish cohort study of almost 100,000 patients alive at 30 days after first MI found that nonsteroidal anti-inflammatory drugs (prescribed to 44% of the cohort) within 5 years after the index MI increased the risk for coronary death or nonfatal MI by 30% after 1 year and 41% after 5 years (17). These findings provide additional support for the Class III recommendations (i.e., contraindications) for estrogen-containing hormones (6) and nonsteroidal anti-inflammatory drugs (6–8) present in current ACS guidelines.

Two reports call attention to specific groups of patients who are at high risk for initial and/or recurrent ACS events. 1) Mild psoriasis was associated with a 30% increase in the adjusted risk for MI, while severe psoriasis was independently associated with increased risk for MI and cardiovascular (CV) mortality of 70% and 40%, respectively (18).