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After the Triumph of Cardiovascular Medicine Over Acute Myocardial Infarction at the End of the 20th Century

– Can We Predict the Onset of Acute Coronary Syndrome? (Con) –

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Predicting acute cardiovascular ischemic events is a crucial and urgent issue in the current cardiovascular field. An enormous effort to develop methodologies to achieve this purpose is being undertaken in cardiovascular institutes worldwide. However, currently, there is no established method of determining acute cardiovascular ischemic events in advance. This article reviews the latest progress on understanding how these events occur and how they can be detected. This goal represents a great dream that has realistic expectations. (*Circ J* 2011; **75:** 2019–2026)

Key Words: Acute coronary syndrome; Coronary risk factors; Molecular imaging; Vulnerable plaque

Currently there are no established clinical methods for detecting acute coronary syndrome (ACS) in advance. The prediction of ACS is a crucial and urgent issue in the cardiovascular field in the 21th century in which medical resources for intensive care of patients with acute myocardial infarction (AMI)/ACS and chronic heart failure following myocardial infarction (MI) have begun to become limited. Per patient, prediction costs less than treatment. Because of 2 emerging advances, 1 being characterization of the underlying pathophysiology of vulnerable plaques in human coronary arteries and the other being further understanding of risk stratification from the epidemiology in cohorts, the eventual identification of an individual who faces the onset of AMI/ACS could be realized in a decade.

The Treatment of AMI in 2000 Was a "Victory" for Cardiovascular Medicine

By the middle of the 20th century, cardiovascular disease had become the leading killer in the United States and other industrialized countries. With the outbreak of cardiovascular diseases, especially AMI and other vascular diseases, researchers and physicians in these countries began analyzing the mechanisms of disease, campaigning for risk control programs for citizens, and building clinical systems to treat patients with a life-threatening condition.[1] The introduction of coronary care units in the early 1960s immediately reduced the in-hospital mortality from approximately 30% to 15%, mainly from ventricular arrhythmias during the course of AMI.[2] Diagnostic imaging of the heart and coronary arteries, first performed by invasive techniques such as selective angiography and then by noninvasive techniques, especially ultrasonography, has greatly facilitated cardiac diagnosis. In the early 1980s, the introduction of thrombolytic therapy,[3] which was followed by other reperfusion techniques, including open-heart surgery, and catheter-based interventions such as coronary angioplasty and stenting, further reduced mortality. In addition, a number of pharmacologic agents, which includes aspirin, β-adrenergic blockers, angiotensin-converting enzyme inhibitors, and statins, were shown to be of benefit for hospital survivors of AMI/ACS.[4–6] Consequently, by the end of the 20th century, in-hospital mortality of AMI/ACS patients decreased to 5% (**Figure 1**).[1] This great achievement in cardiovascular medicine over AMI/ACS was featured in the Shattuck lecture by Braunwald.[7] However, at the same time, he emphasized that cardiovascular disease remains the number 1 killer. Indeed, because of an increase in the size of the population and the proportion of older people, the absolute number of deaths has remained almost constant over the past 25 years. Importantly, cardiovascular disease worldwide will climb from the second most common cause of death, with 29% of all deaths in 1990, to first place, with more than 36% of all deaths in 2020. To overcome this scenario, Dr. Braunwald believes that the current established knowledge and strategies for cardiovascular diseases need to be reconsidered by using both molecular and population-based approaches in tandem.[7]

Event Patterns of AMI Are Changing Towards the Atypical

Several lines of evidence have indicated that subjects with AMI/ACS by itself are being affected by alteration in populations, clinical strategies for diagnosis and treatment, and medications for their risk control. Investigators in Massachusetts

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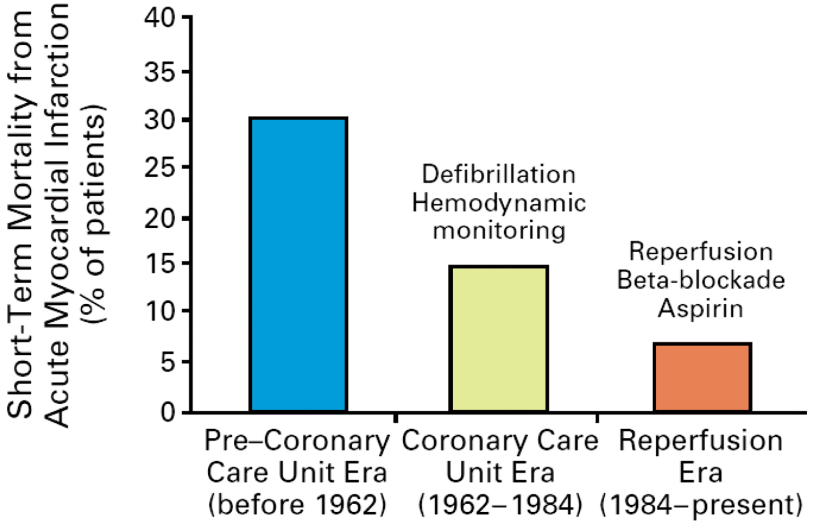

Figure 1. Estimated short-term mortality from acute myocardial infarction in the United States during the second half of the 20th century. (Modified from Antman and Braunwald with permission.[1] Copyright © 1997 Saunders Ltd. All rights reserved.)

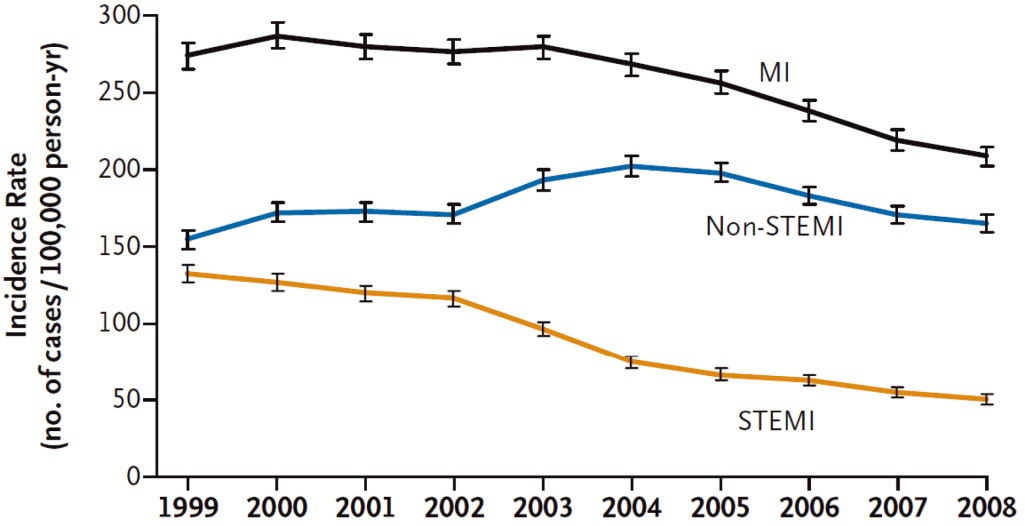

Figure 2. Age- and sex-adjusted incidence of acute myocardial infarction in the Boston area from 1999 to 2008. Vertical bars represent 95% confidence intervals. MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction. (Modified from Yeh et al with permission.[8] Copyright © 2010 *New England Journal of Medicine*. All rights reserved.)

General Hospital reported that, among 46,086 hospitalizations for MI during 18,691,131 person-years of follow-up from 1999 to 2008, the age- and sex-adjusted incidence of MI decreased from 287 cases per 100,000 person-years in 2000 to 208 cases per 100,000 person-years in 2008, representing a 24% relative decrease over the study period.[8] This finding is consistent with that in Braunwald's era. In fact, the age- and sex-adjusted incidence of ST-segment elevation MI (STEMI) has decreased year by year. However, in the same period, the incidence of non-STEMI (NSTEMI) has increased (**Figure 2**).[8] The MI population has shown a shift towards more aged people, females, and Hispanic/Asians, as well as those having a higher rate of hypertension, diabetes mellitus, and dyslipidemia. This population also has higher rates of previous stroke, coronary interventions, and peripheral artery diseases that were treated with more medications. Another recent study from the University of Massachusetts showed that an increase in NSTEMI during 2000–2003 was, at least in part, a consequence of the introduction of the troponin T assay for diagnosis.[9] Therefore, the basic characteristics of AMI/ACS patients, as well as the process of diagnosis, have drastically changed during the past decade. Compared with patients before 2000, these patients have more advanced atherosclerosis, more complex and multiple coronary lesions, more previous interventions, and more collateral resources. It is presumed that most of these patients would no longer show the typical onset of AMI/ACS, characterized as abrupt rupture of plaques in the major portion of the coronary tree, acute blood coagulation, and subsequent complete vessel occlusion with ST elevations on the ECG. In fact, the majority of these patients are asymptomatic or atypical in their complaints. Indications for diagnosis may be a small leak of myocardial-specific isozymes and

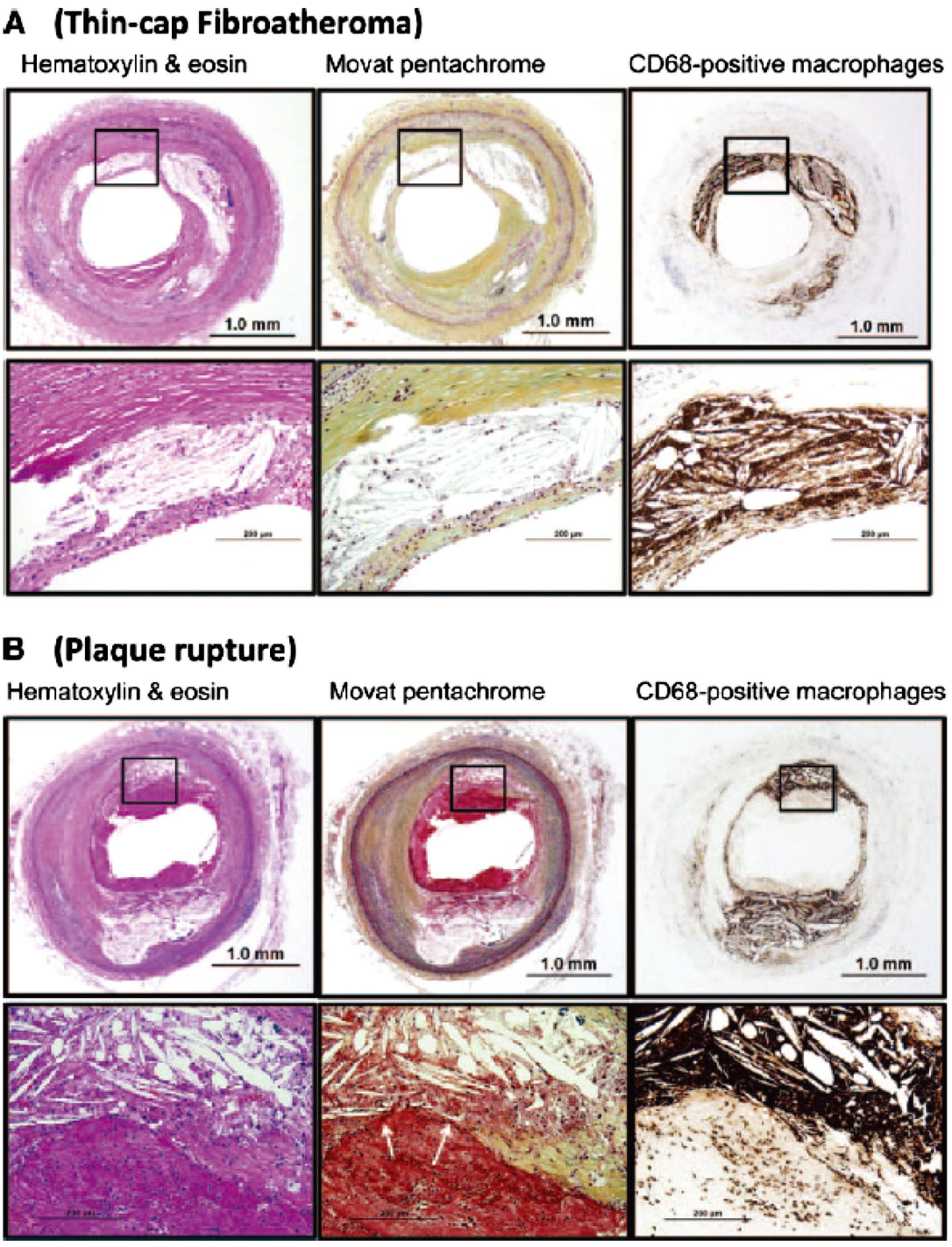

Figure 3. Morphological and histological similarities between thin-cap fibroatheroma (**A**) and plaque rupture (**B**). (Modified from Finn et al with permission.[19] Copyright © 2010 Walters Kluwer Health. All rights reserved.)

equivocal dyskinesis in a limited left ventricular (LV) area. Therefore, in this NSTEMI era we are facing more difficulties in the diagnosis and treatment of AMI/ACS patients. Currently, it is difficult to identify when, where, and how undisclosed coronary plaques in apparently healthy and asymptomatic individuals affect the transition to rupture and subsequent cardiovascular events.

Vulnerable Plaques and In Vivo Detection

Rupture of coronary plaque refers to the break down of a lesion consisting of a necrotic core with an overlying thin ruptured fibrous cap, leading to luminal thrombosis because of the contact of flowing blood with a highly thrombogenic necrotic core.[10] Consequently, the culprit lesion complicates

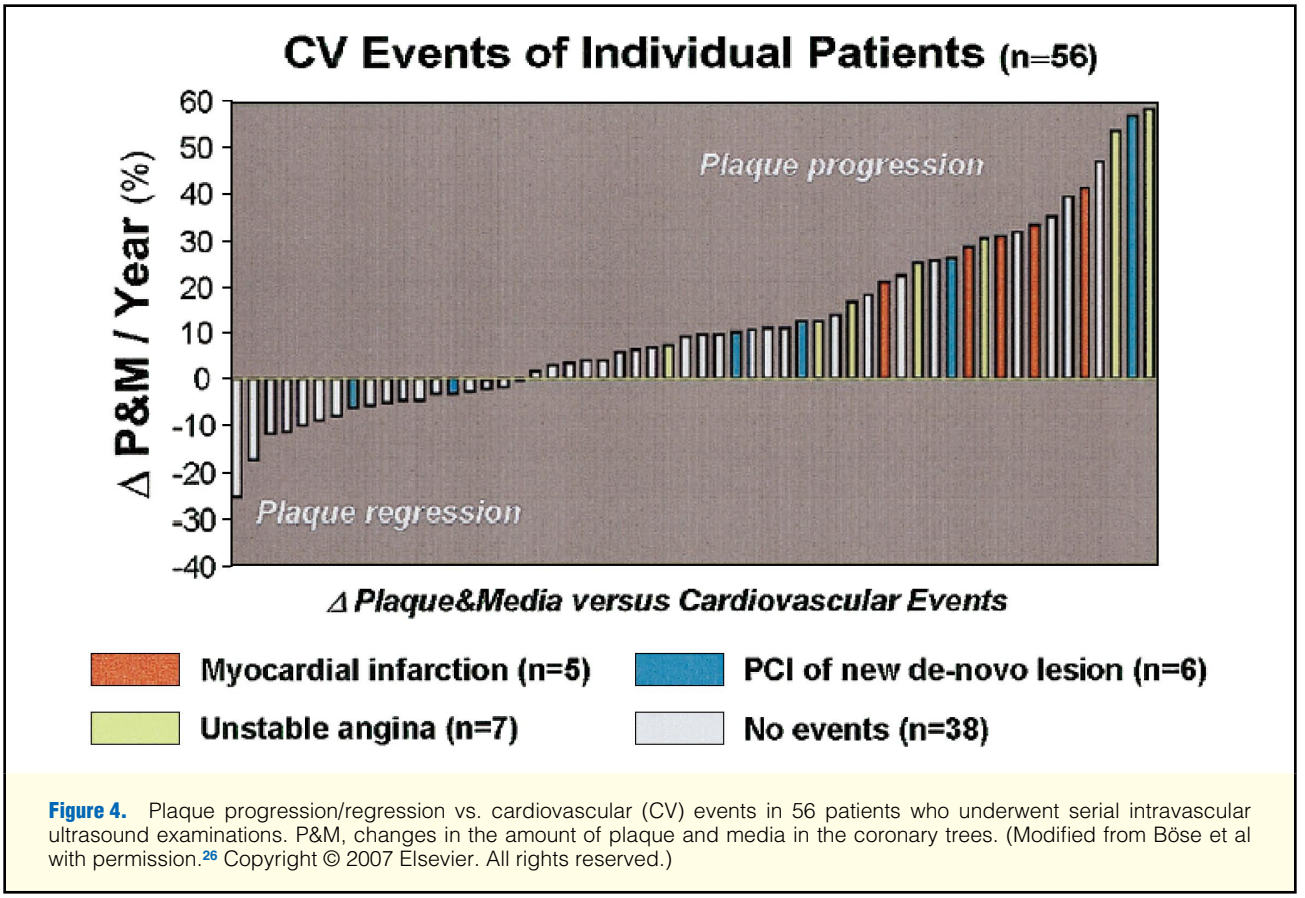

Figure 4. Plaque progression/regression vs. cardiovascular (CV) events in 56 patients who underwent serial intravascular ultrasound examinations. P&M, changes in the amount of plaque and media in the coronary trees. (Modified from Böse et al with permission.[26] Copyright © 2007 Elsevier. All rights reserved.)

the abrupt vessel occlusion, resulting in AMI/ACS. Ross et al describe the abundant infiltration of macrophages within the fibrous cap overlying lipid cores.[11] Thinning of an intact fibrous cap consisting of smooth muscle cells in a matrix rich in type I and III collagen results in vulnerability of the plaque to rupture. Degradation of this intact fibrous cap is caused by proteolytic enzymes and chemokines from macrophages[12,13] in combination with T cell-mediated inhibition of smooth muscle cell proliferation.[14] Based on this cellular and molecular identification, nuclear and non-nuclear approaches to visualizing a patient's atherosclerotic plaque burden are currently being developed, including visualization of macrophage accumulation (CD-68), apoptosis (annexin V), local molecular expression, such as lipid-related molecules (oxLDL, acLDL, LOX-1, and β-VLDL), cytokines (MCP-1, IL-2, and IL-8), and active platelets (P280 and DMP444) or fibrin (FBD and alpha-chain peptide).[15–19] There has been considerable progress in developing atherogenic animal models and human aorta and carotid arteries. However, molecular imaging of human coronary arteries is somewhat different because of (1) the small luminal size, (2) specific flow pattern, (3) the lack of human-relevant animal models showing plaque rupture, and (4) cardiac motion effects and the low signal to background noise ratio. Therefore, currently there is not a specific tracer that can be used as a diagnostic tool to diagnose prospective AMI/ACS in patients.[18]

It was a valuable discovery when acute plaque rupture was found to be the major cause of sudden coronary death.[20] From the examination of more than 800 cases of sudden coronary death at autopsy, Finn et al found that 55–60% of subjects had underlying plaque rupture as the etiology.[19] Another series of autopsy cases showed that plaque rupture was the predominant cause of death, occurring in 75% of patients with definitively-diagnosed AMI.[21] These autopsy studies also consistently showed that for 30–35% of cases, the etiology was not plaque rupture but plaque erosion with massive thrombi, which was common in women under the age of 50 years.[19] Therefore, plaque rupture is a representative but not the unifying cause of AMI/ACS. Additionally, in patients dying because of plaque rupture, 70% have additional lesion sites remote from the culprit plaque that typically appear to be thin-cap fibroatheroma (TCFA), which differs from ruptured plaques by the absence of cap disruption and thrombi, as well as having a thicker fibrous cap, smaller necrotic core, less calcification, and less macrophage infiltration (**Figure 3**).[19] It is highly likely that TCFA is a precursor to plaque rupture; however, not all TCFAs progress to rupture. Therefore, it is important to further define the essential surrogates of lesion instability at high risk of rupture.

Further complications to the understanding of the growth and progression of atheromatous plaques include (1) progressive plaques having several-year-long periods of positive remodeling that are responsible for the preservation of vessel luminal size[22] and (2) silent and repeated plaque ruptures being relatively common and leading to severe luminal narrowing.[23] Bulke et al supported this concept with their finding that in patients having sudden coronary death, plaques had progressed through repeated rupture and only 11% of acute plaque ruptures were "virgin".[24] These observations indicate that coronary plaque rupture could be an ordinal event in subjects having plaques, and only the small proportion of these lesions eventually causes clinical events. Plaque vulnerabil-

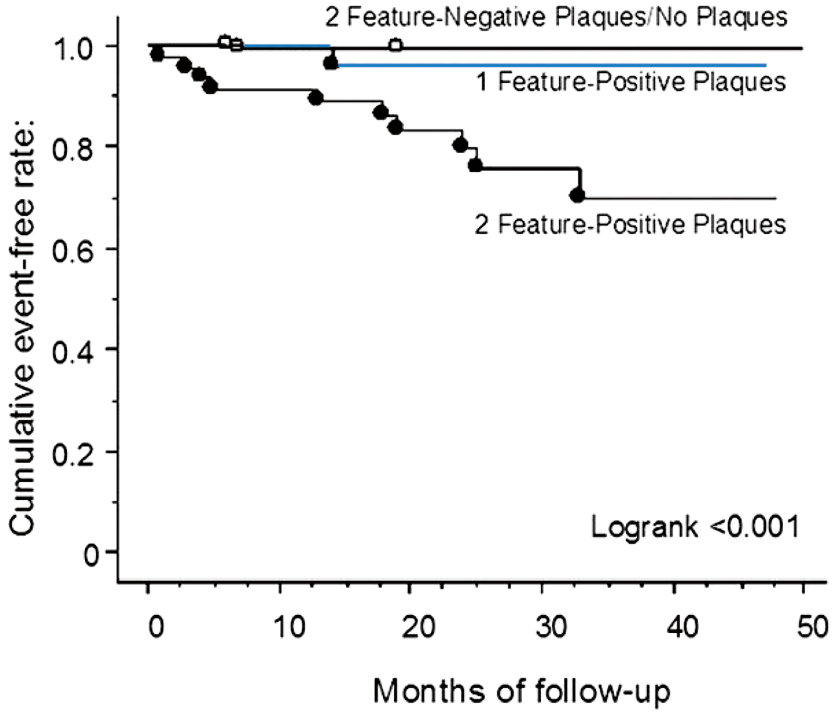

Figure 5. Kaplan–Meier curves for the development of acute coronary syndrome on the basis of plaque characteristics on coronary computed tomography angiography. (Modified from Motoyama et al with permission.[42] Copyright © 2009 Elsevier. All rights reserved.)

ity cannot be identified by luminal narrowing or by plaque rupture itself.

Taken together, these findings suggest that even though the major advances in elucidating the crucial roles of plaque rupture and TCFA in ACS/AMI, the critical factors for transition from TCFA to rupture or what causes a ruptured plaque to result in a critical cardiovascular event are still unknown.

Invasive Technologies to Visualize Vulnerable Plaques

The current catheter-based technologies for coronary angiography and sophisticated image modalities are used in laboratories worldwide to visualize atheromatous lesions. These include coronary angioscopy,[25] intravascular ultrasound (IVUS),[26] and optical coherence tomography (OCT).[27]

Via a miniature transducer that emits high-frequency ultrasound, IVUS provides transmural imaging of the entire coronary arterial wall and permits both detection of atheromatous lesions and accurate cross-sectional and even 3-dimensional quantification of the plaque mass. Because of its modest spatial resolution, it is controversial whether IVUS can accurately identify TCFA and plaque rupture. However, IVUS-guided quantification of plaque masses is well established as a risk stratification index of patients with ischemic heart disease.[26] When serially examined, patients with increased plaque volume show high rates of AMI/ACS and additional coronary interventions to new lesions, whereas patients with decreased plaque volume show few events (**Figure 4**).[26] The plaque volume measured by IVUS was used as a surrogate endpoint in several clinical trials, including CAMELOT,[28] ESTABLISH,[29] and REVERSAL.[30] OCT is a new technology with remarkable spatial resolution. Although its field of visualization is limited to the intima near the coronary lumen, OCT shows the precise morphological features of plaque in vivo.[31,32] Therefore, it is anticipated that OCT may further clarify the process of transition from TCFA to plaque rupture. A study using OCT has already raised questions regarding the threshold of thickness of the fibrous cap for rupture.[33] More recently, catheter-based near-infrared fluorescent spectroscopy has been developed.[34] Using cadaver hearts, a preliminary study showed that the correlation between the lipid core burden index with spectroscopy and that from a pathological examination was 0.86 in the area under the receiver-operator curve. In combination with molecular probes, such as detection of the proteolytic activity of matrix metalloproteinase 9, this novel technology successfully provides visualization of enzyme activity ex vivo.[35]

Taken together, these findings indicate that advances in these catheter-based technologies might provide further understanding of the local pathogenesis of lipid core growth, transition from TCFA to rupture, and thrombus formation. They may also identify surrogate markers that could replace hard endpoints in clinical trials. Because of their invasive nature, however, the clinical application is limited for individuals who are apparently healthy and asymptomatic.

Non-Invasive Technologies to Visualize Vulnerable Plaques

Compared with the invasive procedures, non-invasive modalities, such as magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (CT), ultrasound, and CT, have poorer spatial and temporal resolutions. However, because of their non-invasive nature, they have advantages in healthy individuals prior to the onset of cardiovascular diseases. These modalities have been extensively investigated for the prediction of ACS/AMI.

Among them, MRI emerges as the most promising for assessing plaque morphology. In particular, for the evaluation of aortic and carotid plaques at risk for atheromatous embolic stroke, MRI is well established in the current clinical setting. Its ability to quantify plaque size and composition

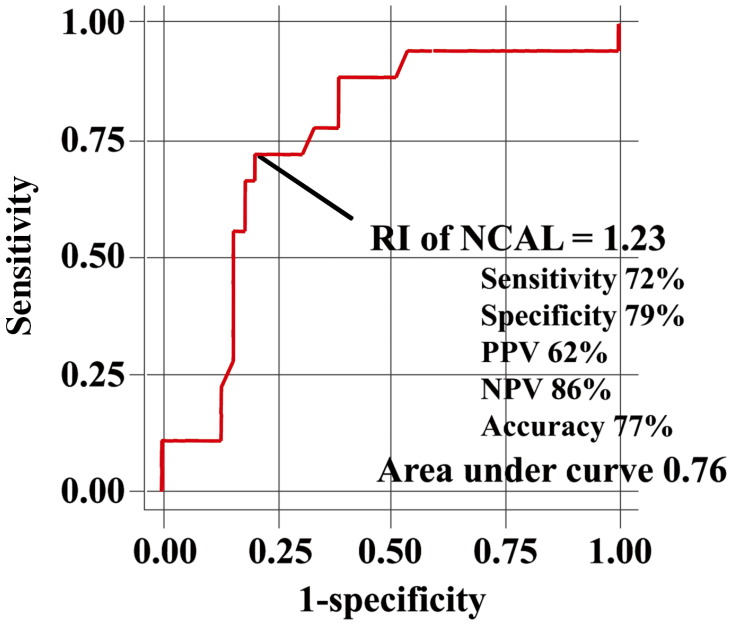

Figure 6. Receiver-operating characteristics curve analysis of the remodeling index of coronary arteries in computed tomography angiography for predicting culprit lesions of acute coronary syndrome. Plaques showing positive remodeling >1.23 (compared with the cross-sectional area of a nearby reference vessel) are the culprits, with a sensitivity of 72% and specificity of 79%.

with high reproducibility provides opportunities to study the relationship between plaque characteristics and subsequent cerebrovascular events. From prospective studies in patients with carotid plaques, cerebrovascular events correlate with thinned or ruptured fibrous caps, the presence of intraplaque hemorrhage, a larger lipid-rich necrotic core, and larger wall thickness.[36] Therefore, when MRI can compensate for the current hurdles in imaging the coronary vasculature, primarily because of cardiac motion artifacts, it will be the first-choice modality to screen apparently healthy individuals. MRI may have additional advantages, such as the use of magnetic nanoparticles. When nanoparticles are administrated, they are engulfed by macrophages and accumulate in those residing in an active lesion. Studies using such nanoparticles to focus on imaging vascular cell adhesion molecule-1 in animal models and human plaques have been performed.[37]

PET with fluorodeoxyglucose (FDG) is a highly sensitive and reproducible modality for detecting glycolytic tissue, especially tumors and inflamed lesions. Because a vulnerable coronary plaque is the locus of inflammation, FDG-PET might be able to provide images of the location and distribution. There are studies that have successfully shown the existence of this in the coronary vasculature.[38,39] However, cardiac motion and non-triggered signal acquisition substantially dampen image quality. Recently, using combined images of FDG-PET and cardiac CT spatially guided by an implanted stent in the left anterior ascending coronary artery, investigators reported improved localized information of FDG accumulation in patients with coronary artery disease. With substantial increases in the signal-to-noise ratio, recently-stented culprit lesions in patients with ACS have shown a significantly higher FDG uptake than that in patients with non-ACS or in remotely-stented patients.[40] Several practical hurdles need to be overcome before PET imaging can be available for general use, including a screening process for individuals at risk, and then PET has a strong potential for identifying local inflammation.

Although CT has less spatial and temporal resolutions than the other non-invasive imaging tools, it is the most commonly available modality in the current clinical setting. In particular, following technical advances towards multirow detector arrangement and high-speed gantry rotation less than 0.33 s, CT has rapidly improved for cardiac imaging including the epicardial coronary trees. According to the recent ACC/AHA/SCCT consensus report, cardiac CT has nearly the equivalent ability for diagnosing coronary luminal stenosis as invasive catheterization.[41] Two recent independent studies from Japan showed that a combination of low CT density (<40 Hounsfield units) and positive vascular remodeling at a site suggestive of plaque formation was predictive of predominant features differentiating ACS/AMI patients from stable and event-free patients[42,43] (**Figures 5**,**6**). Currently, in the practical clinical setting cardiac CT appears to be the most likely modality to achieve near-future detection of ACS/AMI in advance among patients at risk, those with symptoms, or those with known ischemic heart disease. It should be emphasized, however, that elucidation of the CT coronary images (especially images from curved planner reconstruction processing) and their pathological examination has not been achieved.[44] In addition, radiation and administration of contrast media are a matter of concern for routine application. Prospective multicenter studies are needed to confirm whether proposed features on CT images, such as low CT density and positive remodeling, are landmarks of future events as well as of the risk–benefit relation.

These remarkable advancements in non-invasive imaging of atheromatous vessels in humans might result in their clinical use for predicting cardiovascular events that could occur in the near future in particular individuals. Major hurdles that are still present include (1) image quality, which is greatly affected by cardiac motion, (2) risk-vs.-benefit or cost-vs.-benefit assessments and (3) identifying candidates for these clinical examinations, which might depend on known cardiovascular risks, age, sex, and race, as well as genetic background.

Mission of Cardiovascular Medicine in 2020

In this decade, we have obtained a deeper and more funda-

mental knowledge regarding the mechanisms of local coronary occlusion that occurs in certain people. This is an abrupt event requiring urgent emergency treatment. However, it is believed that it is caused by endothelial damage that begins several years earlier and is followed by macrophage infiltration, lipid accumulation, smooth muscle migration/proliferation, and subsequent morphological changes with activated inflammatory and proteolytic cytokines/enzymes, without any symptoms. Because cardiovascular disease is becoming the largest cause of death in the world's population, prediction before the actual event in individuals at risk is an urgent matter of attention worldwide. As reviewed in this article, an enormous effort has been made by engineers, molecular chemists, radiologists, and cardiologists, which has provided new opportunities to visualize both the coronary trees and the pathological changes in animals and humans. Currently, certain modalities, such as CT-based coronary angiography, have begun to be utilized in the clinical setting. To realize this prediction, further effort is required in a synergistic manner by specialists in different fields. However, cardiovascular physicians have the most important mission because they not only test new modalities and methodologies for candidates of cardiovascular disease but also contemplate who will benefit without risks or excessive costs. To achieve this aspect, Braunwald's belief that "we need to reconsider the current established knowledge and strategies for cardiovascular diseases by using both molecular and population-based approaches in tandem" may be appropriate.[7]

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Authors' Comments on the Pro-Side Authors

It is clear that both of Dr Kawasaki et al[44] and I essentially share the same perspectives on the prediction of coronary plaque rupture, which might play a central role in AMI/ACS. Differences between them and me may be in how we define fact and hypothesis. I believe, at least at the present time, that there is a working hypothesis, even though major advances in the results from multi-row CT-based coronary angiography are suggestive of vulnerable plaques before and after rupture.[42,43,45] I believe that CT angiography has the potential to realize this visualization for the first time in the clinical setting.[43] However, the majority of cardiovascular physicians and radiologists still do not agree on this issue, because of a lack of major prospective studies to prove this "hypothesis" (identifying the responsible vulnerable plaques before the onset of clinical coronary events).[41] I and my colleagues are currently conducting a multicenter, prospective, standardized registry named PREDICT (Plaque Registration, Evaluation, and Detection In Computed Tomography; NIH Clinical Trial ID: NCT00991835), which could provide discrete evidence on whether vulnerable plaques in CT images are the culprits of cardiovascular events, including AMI/ACS and cardiac death.