Acute Coronary Events

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In the United States alone, >400 000 Americans die annually of coronary artery disease, and >1 000 000 suffer acute coronary events, ie, myocardial infarction and sudden cardiac death.[1] Considering the aging of our population and increasing incidence of diabetes mellitus and obesity, the morbidity from coronary artery disease and its associated costs will place an increasing, substantial burden on our society.[2] Between 2010 and 2030, total direct medical costs spent in the United States for cardiovascular diseases are projected to triple from $273 billion to $818 billion.[2] Although effective treatments are available and considerable efforts are ongoing to identify new strategies for the prevention of coronary events, predicting such events in an individual has been challenging.[3] In hopes of improving our ability to determine the risk of coronary events, it is prudent to review our knowledge of factors that lead to acute coronary events.

Coronary Atherosclerotic Disease as a Prerequisite for Coronary Events

Coronary atherosclerosis is the underlying condition for coronary events with few exceptions. Events are rarely caused by coronary dissection, arteritis, myocardial bridging, thromboembolism, or coronary vasospasm without obvious coronary artery disease.[4] In some of these instances, more sensitive tools for the detection of coronary artery disease revealed its presence after all.[5] Coronary atherosclerosis is known to develop in childhood and adolescence, as evident from fatty streaks seen in pathology studies of individuals who died of trauma or other noncardiac causes.[6] Depending on the constellation of genetic and environmental factors, coronary artery disease progresses throughout adulthood and is found in most middle-aged individuals in developed nations. Autopsy series in US communities among young adults (mean age, 36±14 years) who died of nonnatural causes revealed coronary atherosclerosis in >80% of the autopsy sample, with ≈8% having obstructive disease.[7] Thus, most individuals ≥40 years of age in our society have evidence of coronary atherosclerosis. However, the annual incidence of acute coronary events in the United States for individuals ≥40 years of age is 0.2% to 1%,[1] which is a relatively small number, considering the widespread prevalence of coronary artery disease. All of the above observations strongly suggest that factors other than the mere presence of coronary atherosclerosis need to be involved for an acute coronary event to occur.

Plaque Morphology Associated With Acute Coronary Events

Typically, 2 atherosclerotic plaque morphologies are associated with acute coronary events: plaque rupture and plaque erosion. A few cases (2% to 7%) are attributable to a third plaque morphology called calcified nodule.[8] In an autopsy series of 241 cases of sudden coronary death, plaque rupture accounted overall for 31% of culprit plaque morphology.[9] When cases with acute thrombus are considered, plaque rupture is found at the culprit lesion site in 59% to 75% of patients.[9,10] Denudation of the coronary arterial endothelium, also called erosion, is found in 19% of plaques in all patients with sudden coronary death and in 36% to 44% of plaques with acute thrombus (Figure 1).[9] Fresher thrombi are more frequently associated with plaque rupture than erosion, suggesting that the former is more frequently associated with acute presentation.[11]

The Vulnerable Atherosclerotic Plaque

Plaque rupture is most commonly associated with acute coronary events, and identification of coronary atherosclerotic plaques that are prone to rupture, called vulnerable plaques, is currently being investigated intensely. Pathology and clinical studies revealed that the atherosclerotic plaque type at the greatest risk of rupture is a thin-cap fibroatheroma, characterized by a large necrotic core covered by a thin layer of fibrous cap (Figure 2).[8,12–14] Early in the atherosclerotic process, only minimal fatty infiltration is evident in the arterial wall. The necrotic core increases in volume secondary to several mechanisms, particularly macrophage infiltration, the demise of macrophages, and intraplaque hemorrhage with free cholesterol derived from erythrocyte membranes.[15,16] The necrotic core is separated from the flowing blood by an ultrathin (mean thickness, 23 μm) layer of fibrous tissue that is depleted of smooth muscle cells, and is infiltrated by macrophages and T lymphocytes. Plaque growth, ongoing inflammation within the fibrous cap, external sheer stress, and other factors may particularly affect the thinnest region of

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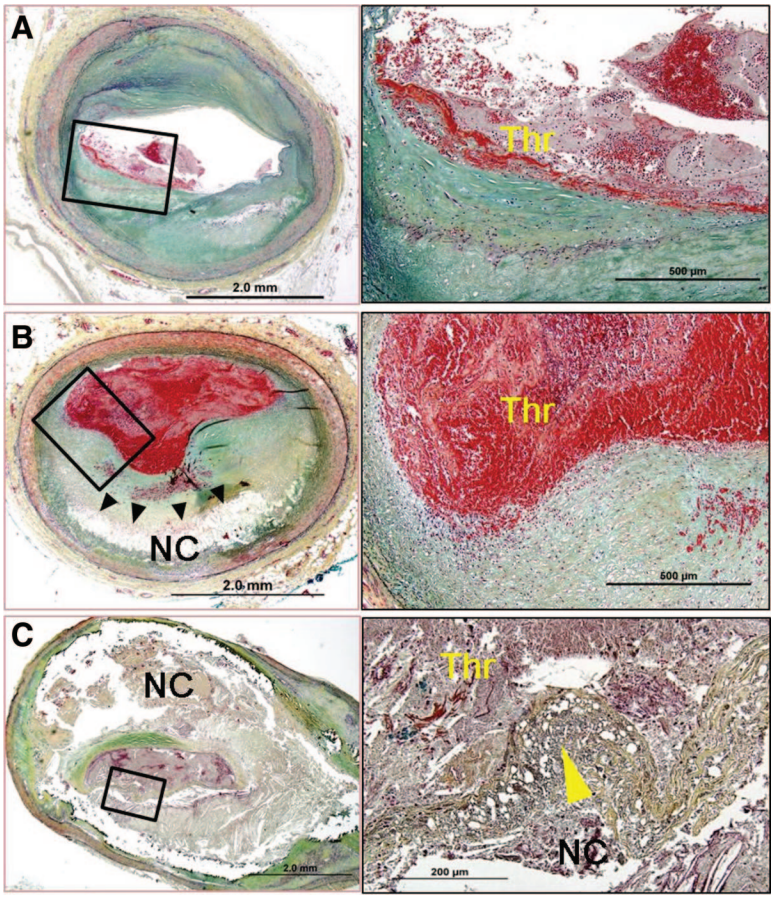

Figure 1. Histopathological images of partial and complete coronary arterial lumen occlusion caused by thrombosis. **A**, An example of plaque erosion with nonocclusive thrombus (Thr) in a 73-year-old man without a history of coronary artery disease who died suddenly. The plaque shown, located in the proximal left anterior descending artery (LAD), is the potential culprit lesion. The thrombus is adhering to a proteoglycan-rich intima, as demonstrated in the magnified section. Early organization of the thrombus is evident near the intima. **B**, Plaque erosion with occlusive thrombus in a 37-year-old man who suffered an unwitnessed sudden cardiac death. The plaque shown, located in the proximal LAD, is the likely culprit lesion. Although early necrotic core (NC) is present (black arrows), there is no connection between NC and thrombus. **C**, A ruptured plaque with occlusive thrombus in a 47-year-old man with no history of coronary artery disease who died suddenly. The plaque shown, located in the proximal LAD, is the likely culprit lesion. The fibrous cap is disrupted (yellow arrow), allowing exposure of the necrotic core to the bloodstream. All specimens were stained with Movat pentachrome.

the fibroatheroma, which may tear, exposing the highly thrombogenic material to the bloodstream (Figure 2).[8,12] Pathology and clinical studies using coronary angioscopy consistently documented thrombus formation at sites of plaque rupture and frequently at sites of plaque erosions.[8,11,17,18]

It is important to note that contrary to common perception, there is compelling evidence that plaque rupture and thrombus formation most often do not lead to coronary events.[19,20] Rather, both plaque rupture and thrombus formation are fairly frequent events that are instrumental in plaque progression and the development of lumen stenoses.[19,21] Postmortem studies in nonselected patients without a history of heart disease who died of noncardiac causes revealed evidence of coronary arterial plaque rupture in 8% to 11%.[22–24] In patients who died of noncardiac causes but had risk factors for coronary artery disease, 16% revealed coronary plaque ruptures,[19] and 31% of a similar patient population showed plaque ruptures in a study that used extensive coronary arterial sectioning.[25] Pathology and clinical studies showed that plaque rupture and thrombus formation are frequently present in the absence of associated symptoms.[17–19,24] In another autopsy study, investigators found evidence of prior plaque rupture and thrombus formation in the vast majority of coronary arterial stenoses, ≥50%, despite the absence of symptoms in many.[26] A different group of investigators confirmed these findings and revealed that multiple healed plaque ruptures are typically necessary for high-grade coronary arterial stenosis to develop (Figure 2).[27,28] Indeed, only 11% of plaque ruptures are virgin in nature; ie, they were not preceded by prior ruptures of the same plaque in these studies.[28] Finally, clinical studies using angioscopy or intravascular ultrasound (IVUS) found evidence of thrombus and plaque rupture remote from culprit sites in patients with unstable and stable symptoms, further confirming its frequent presence despite the lack of events originating from their sites.[18,29]

All of the above observations strongly suggest that an acute coronary event is not a necessary consequence of coronary plaque rupture but rather is an unusual correspondence of a plaque rupture or erosion (Figure 3). Most commonly, plaque ruptures or erosions occur without symptoms and lead to progression of plaque volume. These observations suggest that identifying plaques that are prone to rupture, ie, vulnerable plaques, may not be as significant as commonly perceived. This concept was recently confirmed in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, which followed up 697 patients after Virtual Histology IVUS for 3 years for the occurrence of adverse cardiac events.[14] Although 595 thin-cap fibroatheromas were identified by IVUS in 313 of 623 patients, only 26 of these plaques were sites of subsequent events at 3 years, and almost all (if not exclusively) events were related to rehospitalization for unstable or progressive angina. Indeed, of >3000 nonculprit lesions identified by IVUS at baseline in 673 patients with acute coronary syn-

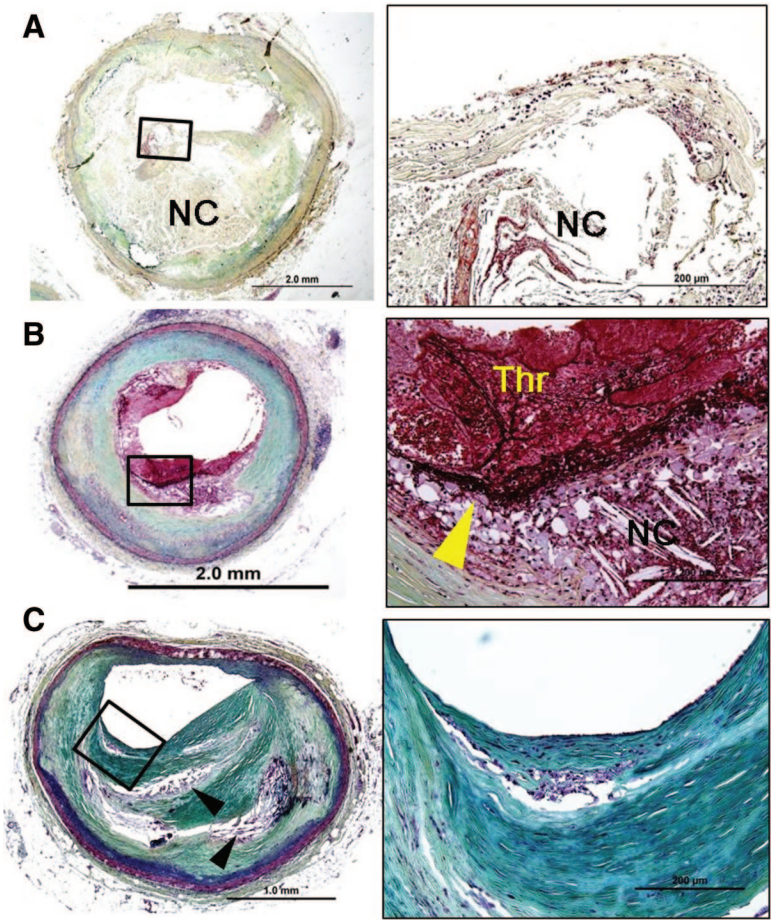

Figure 2. Histopathological images of thin-cap fibroatheromas at various stages. **A**, An example of an intact thin-cap fibroatheroma with large necrotic core (NC) in a 47-year-old man who died suddenly. The plaque shown, located in the proximal right coronary artery, resulted in 70% cross-sectional lumen narrowing. **B**, A plaque rupture with nonocclusive thrombus (Thr) in the left circumflex artery (LCx) of a 44-year-old woman without history of coronary artery disease who died suddenly. The yellow arrow marks the site of the disrupted fibrous cap. **C**, A coronary arterial cross section with evidence of several healed plaque ruptures in a 55-year-old man who died suddenly before scheduled cardiac catheterization. Autopsy revealed severe 3-vessel coronary artery disease. Shown is a plaque in the proximal LCx causing 80% lumen narrowing. The magnified section and black arrows highlight multiple necrotic cores (NCs), which ruptured at different points in time, leading to the multilayered appearance. All specimens were stained with Movat pentachrome.

drome, only 6 were subsequently related to myocardial infarction and death after 3 years.[14] The PROSPECT study confirmed smaller clinical investigations using optical coherence tomography[30] that suggested that the identification of a potentially vulnerable plaque may confer some increase in coronary event risk but that it is far less than generally assumed. Importantly, because PROSPECT used IVUS to predict events based on plaque characteristics confined to a lesion- but not patient-level analysis, it remains unclear whether individual plaque characteristics confer incremental predictive value over established risk factors, eg, total plaque burden assessment, for subsequent acute events in patients.

In addition to the aforementioned observations, there is intriguing evidence of the temporal instability of plaque morphology, which may further reduce the significance of identifying plaque characteristics at a given point in time. In a clinical study using IVUS, the majority of thin-cap fibroatheromas changed into thick-cap fibroatheromas after only 1 year of follow-up.[31] Conversely, some thick-cap fibroatheromas and some mild plaques described as intimal thickening at baseline changed into thin-cap fibroatheromas over 12 months. If confirmed, these data suggest that a plaque that appears vulnerable at a given time may be less vulnerable just months later, whereas another plaque, initially not vulnerable, may have developed vulnerable characteristics within the same time frame. More serial imaging data are needed to conclusively establish the temporal stability of plaque morphology, but the preliminary data available corroborate ob-

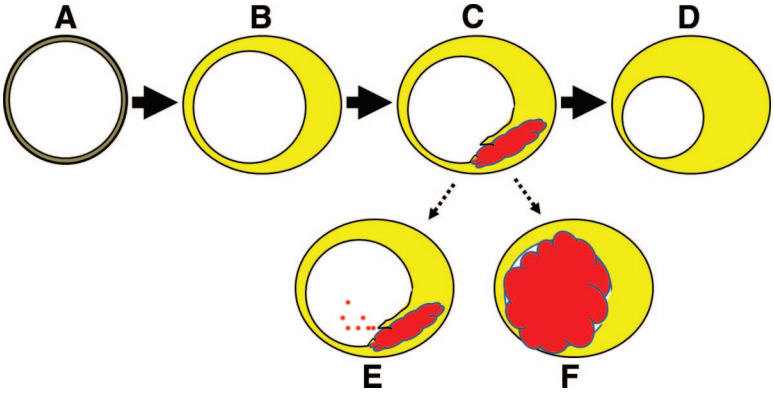

Figure 3. The progression of coronary artery disease. **A**, A cross section of a normal artery. **B**, Atherosclerotic plaque has accumulated, leading to external vascular remodeling to minimize lumen encroachment. **C**, Plaque rupture and plaque hemorrhage leading to intramural thrombus. In the vast majority of cases, plaque rupture will lead to plaque healing and growth (**D**). In some cases, thrombus material is embolized distally, which may cause symptoms of coronary arterial insufficiency or asymptomatic microinfarctions (**E**). If plaque rupture coincides with a thrombosis-conducive state at the site of plaque rupture or erosion, arterial thrombosis and occlusion may occur, which may trigger a coronary event (**F**).

Table. Factors and Conditions Associated With Increased Risk for Acute Coronary Events

Coronary Plaque Characteristics	Coronary Blood Flow Dynamics	Intrinsic Hemostasis Factors	Metabolic and Inflammatory Conditions	Neurohormonal Imbalance	Environmental Factors and Drugs
Plaque burden	Blood viscosity	Platelet function/volume	Diabetes mellitus	Stress	Smoking
Lumen encroachment	Shear stress	Circadian variation	Obesity	Catecholamine surges	Pollution
Lesion location	Reduced blood flow/low cardiac output	Factor V Leiden deficiency	Dyslipidemia	Depression	Climate
Plaque composition	Vascular tone and reactivity	Von Willebrand factor deficiency	Connective tissue diseases	Exertion	Legal drugs
Plaque biology	Arterial hypertension	Antiphospholipid syndrome	Infections	Autonomic dysfunction	Illegal drugs
Plaque configuration and remodeling			Renal disease	Endocrine imbalance	Diet
Endothelial dysfunction					Sedentary lifestyle

This table lists some of the established factors and conditions associated with increased acute coronary event risk. Note that there may be other, less well-established factors and unknown conditions that are not included.

servations from pathology studies that coronary artery disease is an active process that likely is constantly changing.

The Significance of Vascular Thrombosis

Pathology studies of sudden coronary death reveal the presence of an acute thrombus in 52% of cases that acutely or subacutely leads to partial or complete arterial occlusion (Figure 1).[9] However, this incidence increases to 74% if we include chronic total occlusions. Similarly, angiographic studies in patients suffering from acute coronary events show evidence of coronary artery disease and arterial thrombosis in most cases.[32,33] In the absence of an arrhythmia resulting from acute ischemia, the degree and location of coronary arterial thrombosis and the resulting lumen obstruction determine the severity of the event, ie, the development and extent of myocardial infarction. A pathology series found coronary intraluminal thrombus in 76% of patients who died suddenly of myocardial ischemia.[34] Healed myocardial infarctions were found in approximately half of those patients without obvious vascular thrombosis, suggesting that a coronary event in the past eventually led to myocardial scar formation and lethal arrhythmia. Thus, the vast majority (>80% to 90%) of sudden coronary deaths are either the immediate result or a sequela of acute coronary arterial thrombosis.

Factors and Conditions Associated With Increased Acute Coronary Event Risk

Because most plaque ruptures and erosions do not lead to symptomatic arterial thrombosis, other factors must be present for acute coronary events to occur. Numerous conditions are associated with an increased risk of acute coronary events (Table).[35] For many, it remains unclear whether they are associated with the development/progression of coronary atherosclerosis, with the frequency of plaque alterations, with conditions conducive to thrombotic vascular occlusion, or with a combination of these. Factors and conditions associated with increased acute coronary event risk may be further categorized into being related to coronary atherosclerotic plaque characteristics, coronary flow dynamics, intrinsic hemostatic/fibrinolytic dysfunction, neurohormonal dysregulation, and environmental factors and triggers (Table). Some of the most intriguing concepts are discussed here. Studies using both IVUS and computed tomography suggest that plaques with large volume (and presumably large lipid core) are of greater risk for triggering acute coronary events compared with plaques with smaller volumes, possibly because of the larger mass of thrombogenic material exposed to the bloodstream.[14,36] Furthermore, the location of such plaques is important. Autopsy and clinical studies revealed that culprit lesions occur predominantly in proximal coronary arteries near branch points where there is turbulent flow.[8,37] Certain shear stress and blood flow characteristics may promote "high-risk" plaques and thrombosis-favorable blood flow dynamics.[38,39] There has been particular interest in the intuitive notion that the larger the baseline lumen obstruction is, the greater the risk of an occlusive thrombus is in the setting of plaque rupture or erosion. This concept, however, has remained unproven. Although patients enrolled in the Coronary Artery Surgery Study (CASS) registry with >50% left anterior descending artery stenosis were at greater risk of subsequent anterior wall myocardial infarction compared with those with less severe lesions, the possibility that other lesions within the same vessel caused the event could not be excluded.[40] Both the PROSPECT and VH-IVUS in Vulnerable Atherosclerosis (VIVA) studies suggested that smaller luminal area at the plaque site is associated with increased event rates, but because rehospitalization or revascularization accounted for almost all end points, an association with acute myocardial infarctions or sudden death was not evident.[13,14] Angiographic studies established that patients with ≥50% stenosis have a much higher event rate compared with patients with nonobstructive disease.[41,42] However, at least 2 confounders may explain this phenomenon. First, patients with ≥50% stenosis are likely to have a greater total atherosclerotic plaque burden than patients with nonobstructive disease, which may explain the higher event rate rather than the actual 50% stenosis itself. Second, patients with ≥50% stenosis may be distinct from patients with mild disease by having more active, progressive coronary artery disease; ie, they have a higher frequency of plaque ruptures/erosions and hence have formed more advanced stenoses, so their likelihood of coinciding with an unfortunate constellation of thrombosis-promoting factors increases. On the other hand, several angiographic studies suggested that the majority

of myocardial infarctions arise from plaques with only mild to moderate lumen narrowing.[43–45] Pathology studies reported variable results for diameter stenosis (values were transformed from the original reported area stenoses) at the site of acute thrombus. Some studies found most such lesions to be <50% stenotic,[46] but others reported the majority to have >50% lumen narrowing.[24] Pathology studies are known to overestimate coronary artery stenoses by 25% to 30% compared with angiographic techniques because no lumen reference is used.[47] At present, therefore, we do not have good evidence supporting the notion that greater baseline lumen stenosis is an important factor for occlusive thrombus after plaque alteration. On the other hand, the above-referenced studies are in agreement that most acute events arise from plaques that are at least 25% to 50% lumen obstructive, suggesting that a certain plaque volume is necessary to trigger clinically significant thrombosis.

Of potentially pivotal importance are internal hemostasis function, platelet aggregation, and fibrinolysis at the time of plaque rupture/erosion. Patients with systemic alterations of their coagulation system, eg, antiphospholipid syndrome, von Willebrand factor, or factor V Leiden deficiency, are at increased risk for acute coronary events compared with normal control subjects.[48–51] Importantly, this association remains intact even after adjustment for inflammatory markers and other established risk factors.[50] Elevated platelet volume and high platelet reactivity also were found to be associated with increased acute coronary event risk.[52,53] For other disorders such as protein C and S deficiency, the data are less conclusive at present.[48] Several hemostatic proteins have been associated with increased risk of acute coronary events. Fibrinogen levels are independently predictive of myocardial infarction, even when accounting for inflammatory markers, eg, C-reactive protein.[54] Other factors such as D-dimer and tissue plasminogen activator also have been shown to be predictive of acute events.[55] Even in patients without obvious hemostatic deficiency, hemostasis functions, platelet reactivity, and fibrinolysis are influenced by numerous factors that may reduce or enhance their function throughout a given day. There is strong evidence for circadian variation of hemostasis and platelet function leading to relative hypercoagulability in the morning.[56] Several large clinical studies found a peak of myocardial infarction and sudden cardiac death in the early morning hours, suggesting a possible association with a thrombosis-conducive state during that time.[57] However, a causal relationship, although intuitive, is not proven, and other factors such as rising catecholamine and cortisol levels must also be considered. In addition to circadian variation, the ability of the coagulation system to prevent thrombosis in response to a stimulus varies throughout the day on the basis of diet, stress, comorbidity, exposure to toxins (eg, smoking, pollution), drug intake (legal and illegal), and local metabolic conditions.[58–64] Thus, because of the almost minute-to-minute variability of hemostasis function, it is exceedingly difficult to predict its performance at a given point in time, ie, at the time of plaque rupture/erosion.

A strong body of evidence supports a key role for inflammation in the development and progression of atherosclerosis.[15] Numerous cytokines, mediators, and proteins have been identified that influence cholesterol uptake into the arterial wall and the generation/accumulation of atherosclerotic plaque.[15] In addition, inflammation is involved in destabilizing the plaque and in promoting thrombosis.[65] Conditions associated with enhanced inflammation, eg, obesity and infection, are generally associated with increased coronary event risk.[66] It is interesting to note that similar to the variability of hemostasis functions, inflammatory processes show a circadian variability, which may contribute to states of temporary hypercoagulability.[67]

The Perfect Storm Scenario Leading to an Acute Coronary Event

Although numerous factors and conditions play a role in the pathophysiology of acute coronary events, it is very clear that their respective contributions in isolation are insufficient to predict events adequately. Available data for individual plaque characteristics, fibrinogen levels, C-reactive protein (as a marker for inflammation), cholesterol levels, diabetes mellitus, and numerous other factors and conditions indicate only small relative increases in acute coronary event risk for a given individual compared with control subjects.[14,36,54,68] The largest hazard ratios have been found in patients with high coronary atherosclerotic plaque burden as estimated by coronary calcium scoring.[69] In conjunction with traditional risk factors, eg, diabetes mellitus, hypertension, and hyperlipidemia, the area under the receiver-operating characteristic curve for calcium scoring increased to 0.83 for predicting myocardial infarction or cardiac death, which indicates good diagnostic accuracy but still is insufficient for accurate prediction.[69] Given the frequency of vulnerable plaque features and the very large number of subjects with evidence of plaque ruptures without apparent symptoms, it is apparent either that we have not identified a very important mechanism for triggering acute coronary events or that acute events are not caused by a single or a few factors but rather by the unfortunate constellation of numerous conditions. Given the complexity of factors involved, the latter situation is more likely; ie, a perfect storm scenario is necessary for an event to occur. The discussed variability of key processes such as hemostasis and inflammation further supports the hypothesis that an unfortunate constellation of occlusive thrombosis-promoting factors must coincide at the time of plaque rupture or erosion to cause an acute coronary event. Thus, the timing of an acute event appears to be influenced by the formation of multiple factors, which are poorly understood at this time, and likely by chance. Although this hypothesis is difficult to prove, it most satisfactorily explains the apparent variability in the occurrence of acute coronary events and our difficulties in predicting events in individuals.[70]

Therefore, coronary events likely occur with the unfortunate convergence of a nidus for thrombosis in a coronary artery (plaque rupture, erosion, or calcified nodule) combined with an inability of the patient to prevent clinically significant thrombus formation at a given point in time. The balance between these 2 factors may vary with time. The coronary arterial nidus, for example, may be relatively confined and limited but may coincide temporally with enhanced throm-

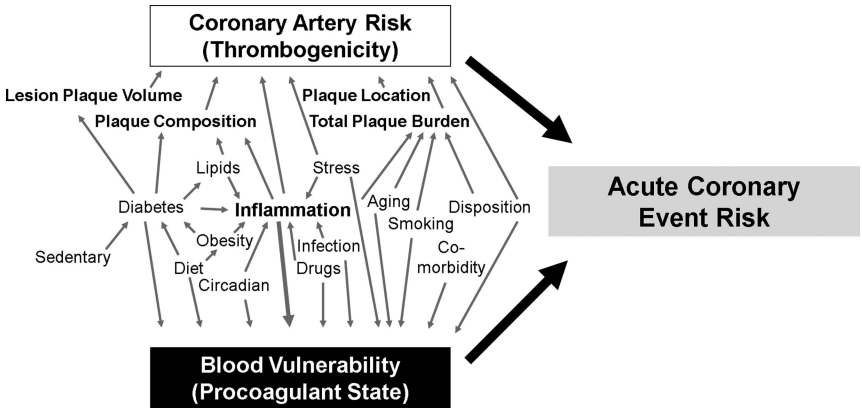

Figure 4. The complex interplay of factors contributing to acute coronary event risk. The purpose of this illustration is to convey the complexity of factors influencing event risk, not to provide a complete list of factors and associations involved. Both coronary thrombogenicity, ie, a stimulus for clinically significant arterial thrombosis, and a thrombosis-favorable condition need to be present for a coronary event to occur.

bogenesis. This combination might be seen in a subject (with an acute coronary event) who has mild, focal coronary arterial disease and no recurrent events. In contrast, the stimulus for thrombosis may be strong such as that which occurs with extensive plaque rupture, but the propensity for clinically significant thrombosis may be low such as seen in many patients with severe coronary artery disease who never experience myocardial infarction or sudden cardiac death. Furthermore, there is ample evidence that the balance between thrombosis-promoting and thrombosis-antagonizing factors is frequently fragile for days after a plaque alteration; any thrombus formation is conducive for more extensive thrombosis.[71,72] The severity of ischemia caused by an acute coronary event depends on the location of vascular blood flow restriction and its supplied myocardial territory, as well as collateral blood flow, current metabolic demands, and other factors. Finally, chance may also play a role in determining the severity of myocardial arrhythmia in that myocardial ischemia may coincide with membrane properties conducive to arrhythmia, eg, at a vulnerable point, within the cardiac cycle, and possibly paired with electrolyte imbalances.

Implications for Preventive Measures

The concepts presented in this review detail important implications for preventive strategies. Overall, an acute coronary event appears to result from an unfortunate coincidence of a coronary arterial stimulus for clinically significant thrombosis and a thrombosis-conducive state at the site of the plaque rupture or erosion (Figure 4). The probability of an event is influenced by the frequency and strength of thrombogenic stimuli within the coronary arteries and by the frequency and extent of the thrombosis-favorable condition. In general, the greater the plaque burden and the activity of the coronary artery disease are, the more plaque ruptures/erosions will occur, which increases the chance that a stimulus will coincide with a state that may permit the development of a vascular occlusive thrombus. This concept is supported by strong evidence of increased coronary event risk in patients with progressive coronary atherosclerotic plaque burden and accelerated plaque progression.[73,74]

Conversely, the absence of coronary atherosclerotic plaque, as confirmed on IVUS or computed tomography, essentially excludes the possibility of acute coronary events in the short term and midterm.[41,75,76] On the other hand, the more conducive the conditions are to thrombosis, the greater the event risk will be, even with mild coronary artery disease in the setting of plaque rupture or erosion, which is suggested by the increased risk of an event, in patients with hypercoagulable states.[77]

The available data suggest that the probability of a coronary event is fundamentally a function of the amount of potentially vulnerable substrate. A single, potentially vulnerable plaque is rather unlikely to cause an acute event; however, the more coronary atherosclerotic plaques are present, the greater the likelihood is that recurrent vulnerable features will develop, and rupture or erosion of any of these plaques will trigger an event in the setting of a vascular thrombosis–favorable state.

The requirement of plaque rupture or erosion coinciding with an occlusive, clinically significant thrombus-promoting condition hinders our ability to predict such an event because both occur with great variability. Similar to the "perfect storm" analogy, one may establish certain probabilities for plaque rupture/erosion and occlusive thrombus-favorable conditions to coincide, but a substantial residual component of uncertainty will remain. It appears intuitive that the more variables and factors that can be considered, the more accurate the estimate will be for the probability of an acute event to occur. Importantly, because coronary atherosclerosis essentially is a *conditio sine qua non*, assessing its extent, severity, and location must be considered fundamental for risk estimates. Furthermore, plaque characteristics, the extent of lumen obstruction, and the activity of coronary artery disease (rate of progression) appear to be promising for estimating coronary event risk. Factors influencing coagulation, eg, inflammatory states, comorbidity, disposition, and environmental factors, must be considered in conjunction with "coronary" risk factors to maximize our ability to predict events. The concepts described here underscore the need to recognize and address atherosclerosis as a systemic disease.[78,79] Intervening exclusively on single, potentially vulnerable plaques is unlikely to reduce the incidence of acute coronary events.[14,80] On the other hand, slowing or halting the activity of coronary atherosclerotic disease (eg, lipid-lowering therapy and risk factor modification),[81] decreasing the risk of coronary arterial thrombosis (eg, antiplatelet therapy),[82] and mitigating the effect on resulting ischemia (eg, cellular membrane stabili-

zation)[83,84] are prudent measures for reducing the risk of acute coronary events and their consequences. Unfortunately, despite contemporary preventive measures, studies such as Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) and PROSPECT demonstrate that events still occur with significant frequency.[14,85] More discriminating risk models may help us to direct advanced therapeutic measures, eg, anticoagulation or even implantable cardioverter-defibrillator placement, to individuals at the highest risk, which would be prohibitive in less well-defined populations. Conversely, patients at lower risk may be saved unnecessary medication and interventions. Ultimately, however, preventing the development of significant coronary atherosclerosis must be the most critical goal, which may be achieved by implementing policies for lifestyle/diet modifications and genetic profiling.[86,87]

The Potential Role of Noninvasive Imaging for Preventing Acute Coronary Events

Our review highlights the importance of the presence, distribution, extent, and severity of coronary atherosclerotic disease for the probability of acute coronary events to occur. Until recently, these features were assessable only with cardiac catheterization and invasive coronary imaging. Through technological advancements, particularly in the fields of magnetic resonance imaging and computed tomography, comprehensive coronary plaque assessment is now possible with noninvasive imaging.[88] Promising prognostic data, particularly for computed tomography coronary angiography, are available, which, importantly, have used only a fraction of the available information provided by these technologies.[41,89,90] For example, Ostrom et al[76] followed 2538 individuals for a mean of 6.5 years and found an area under the curve of 0.89, predicting total (not cardiac) mortality, on the basis of simple cardiac computed tomography categories of normal arteries, nonobstructive coronary artery disease, and obstructive coronary artery disease combined with a calcium score and traditional risk factors. It is conceivable that other characteristics such as individual plaque burden and composition and total atherosclerotic plaque burden further improve predictive power. In addition, molecular imaging using advanced biomedical engineering allows targeting of specific metabolic processes, eg, local inflammation, which may permit monitoring the activity of or even treating atherosclerotic disease.[12] Therefore, it appears that noninvasive vascular imaging has the potential to substantially affect our ability to identify and manage patients at risk of acute coronary events.[78,91,92]

For the reasons discussed, however, many individuals even with advanced coronary atherosclerotic disease will never experience acute coronary events. The challenge is to balance the costs and adverse affects of detecting and treating coronary artery disease with the reduction of coronary events and improved patient outcome.[3] This is particularly critical for using imaging for screening purposes among asymptomatic individuals in whom improved patient outcome must be weighed against risks from imaging and intervention.[93] Thus, a staged approach is likely necessary, with the least costly and most benign techniques applied to patients of seemingly low risk for screening purposes and advanced imaging reserved for those deemed at higher risk. For example, ultrasound imaging of carotid artery wall thickness provides prognostic information on acute coronary event risk incremental to traditional risk factors.[94] Many clinical investigations, some ongoing,[95] are necessary to define the appropriate role of imaging for the prevention of acute coronary events in patients.

The Potential Role of Biomarkers for Preventing Acute Coronary Events

Numerous biomarkers reflecting inflammatory and metabolic processes are associated with increased acute coronary event risk.[96] Nevertheless, despite intriguing data on their involvement in the atherosclerotic process, their respective contribution to the hazard for acute coronary events is small.[97] A prime example is C-reactive protein. The role of inflammation in the development, progression, and vulnerability of coronary atherosclerosis has been well established, but C-reactive protein is only modestly predictive of acute coronary events, and its effect can be largely attributed to associations with known risk factors for coronary artery disease.[54,96,98] Even biomarkers more specifically involved in the atherothrombotic process such as neopterin have not been shown to yield large hazard ratios for hard events, further supporting the hypothesis of a multifactorial mechanism for acute events to occur.[99,100] A promising target for biomarkers is to evaluate the metabolic activity of coronary atherosclerotic disease, but data to support such an application for clinical purposes are currently sparse and only modestly promising.[96,101] Another potential goal is to identify a predisposing coagulation system.[77] However, the varying function of human hemostasis makes it exceedingly difficult to predict a weakness that may be triggered by internal factors such as circadian variations and postprandial hyperlipidemia or external factors like stress and smoking.[102] At this time, the role of biomarkers for evaluating individuals for their coronary event risk appears to be supportive rather than leading.[96]

Conclusions

An acute coronary event is the result of a complex interplay of numerous factors that seems to include a component of chance, hindering our ability to assess the risk of such events to occur. Erosion or rupture of the coronary atherosclerotic plaque is typically required for an event to happen, but only when coinciding with a thrombosis-conducive state at the site of plaque rupture or erosion. In the majority of cases, plaque ruptures or erosions take place in the absence of symptoms and commonly lead to healing and progression of coronary arterial narrowing. The coronary atherosclerotic plaque burden and its metabolic activity, as well as conditions promoting vascular thrombosis, have the strongest evidence in support of their association with acute coronary events. Integrating coronary artery characteristics and thrombosis-promoting factors into a comprehensive model appears most promising for acute coronary event risk assessment in patients.

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