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A Novel Concept in the Progression of Acute Coronary Syndrome: Acute Coronary Continuum (ACC)

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Abstract

This review put forward a novel concept of acute coronary continuum (ACC), which described a continuous chain throughout the up and down stream of ACS. The cardiovascular continuum developed and formalized in late 1980s by Dzau and Braunwald contributed to various interventions targeting this chain at multiple sites and great improvements in both the primary and secondary prevention of coronary artery disease (CAD). As the central stage of the chain, acute coronary syndrome (ACS) is responsible for the large population of end-stage heart diseases and cardiovascular death. Through years of research, the authors come up with a similar specific pathophysiological process, including rupture of vulnerable plaque, acute myocardial infarction, microcirculation dysfunction and myocardial injury, which concludes to the novel concept of ACC. ACC is a novel concept which establish a comprehensive understanding of ACS. It links the initial pathophysiological process to clinical manifestations of ACS and its residual risks. The review summarizes what is newly known and what remains unknown about each event involved in this novel continuum. It describes the most common sequential clinical problems in ACS: what causes plaque rupture and how to identify plaque destabilization, what is the optimal reperfusion strategy for AMI, how to deal with microcirculation dysfunction, and how to identify myocardial injury and improve post-MI heart protection. The formalization of ACC will help enhance understanding of ACS and provide guidelines for future research.

Keywords: Acute coronary syndrome; Acute coronary continuum; Plaque rupture

Introduction

Ischemic heart disease has developed to be the top single health killer in the last 15 years, which caused over 8 million deaths in 2015 [1]. The concept of a progressive pathophysiological chain underling the disease - the cardiovascular continuum – was developed and formalized in late 1980s by Dzau and Braunwald [2]. In the past several decades, various interventions targeting this chain at multiple sites have emerged and contributed to great improvements in both the primary and secondary prevention of coronary artery disease (CAD). As the central stage of the chain, acute coronary syndrome (ACS) often occurs as a life-threatening event and leads to impaired heart function, responsible for the large population of end-stage heart diseases and cardiovascular death. Similarly, several crucial events play important roles in the progression of ACS, including rupture of vulnerable plaque, acute myocardial infarction, microcirculation dysfunction and myocardial injury. These specific pathophysiological processes constitute a continuous chain throughout the up and down stream of ACS, which comes to the novel concept of acute coronary continuum (ACC). ACC establish a comprehensive understanding of ACS. It links the initial pathophysiological process to clinical manifestations of disease and its residual risks. The chain holds the key to the prevention, treatment and rehabilitation of ACS and provides pathophysiological targets for innovative researches. Figure 1 depicted the sequential chain of ACC.

Despite the notable efforts that have been made in exploring the mechanism underlying the acute disease, challenges still exist at each level in the chain leading to irreversible heart dysfunction. The purpose of this review is to summarize what is newly known and what remains unknown about each event involved in this novel continuum. Although not all researches can be addressed or discussed in depth, the information presented here help better understand the novel concept of ACC and might help provide guidelines for future research.

Literature Review

Part I: Rupture of vulnerable plaque: The initiation of ACC

The concept of plaque rupture, known as the initial process of acute coronary events, was first reported in 1844 [3,4]. The connection between plaque stability with coronary thrombus had not been well demonstrated until the mid-20th century [5]. The vulnerable plaque is defined as a lesion consisting of a necrotic core with an overlying thin ruptured fibrous cap whose disruption exposes the highly thrombogenic material of the core to the blood. Plaque rupture reportedly contributes to 75% of the thrombi responsible for ACS and is widely accepted as the leading cause of coronary thrombus [6-8]. Thus, the mechanism underlying the conversion of the plaque from stable to vulnerable phenotypes is of great importance in understanding how the atherosclerotic lesions develop.

The absence of proper animal models has hampered the efficiency of basic research on plaque destabilization. An optimal animal model must bear close resemblance to the pathophysiological processes of human beings. Tremendous efforts have been devoted to generating an efficient model for vulnerable plaque with high rate of plaque rupture and luminal thrombus. In recent years, breakthrough occurred with the emergence of apolipoprotein E (ApoE) knockout mice [9,10]. With a high cholesterol diet, these mice experience development of

atheromata and mimic similar features to those of human advanced plaques, but plaque rupture and luminal thrombosis are rarely observed in murine atherosclerosis [11]. Hence, various approaches were studied to generate plaque destabilization. Surgical alteration of perivascular blood flow is the most common method [12-19]. Variants were established based on different combined use of common carotid artery ligation, local shear modification, tandem stenosis and surgical induced endogenous activation of Renin-angiotensin-aldosterone System (RAAS) [16-19]. Furthermore, models were extended by additional genetic manipulation. Overexpression of the proapoptotic protein p53, matrix metalloproteinase-9 (MMP-9), imposed hypercoagulability and human diphtheria toxin administration were reported to increase apoptotic cell accumulation, plaque inflammation and events of plaque disruption, intraplaque hemorrhage, or luminal thrombosis [5,13-15]. Despite the limited possibility of genetic modification that hampers the use of rabbit and porcine models in the understanding of plaque destabilization pathophysiology, these large animal models are suitable for the assessment of novel imaging techniques, stabilizing therapies, and cardiovascular surgical techniques [20-22].

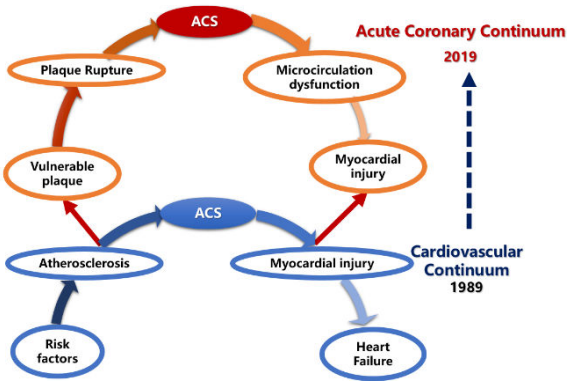

Figure 1: Acute coronary continuum.

Thanks to efficient animal models, mechanisms leading to plaque destabilization can be studied *in vivo*. Series of studies have demonstrated the cellular change during the lesion development. Smooth muscle cell (SMC) apoptosis triggers plaque vulnerability with reduced matrix protein deposition, aggravated plaque inflammation and expanded necrotic core (NC) [5]. As an alternative mechanism of SMC apoptosis, loss of cell matrix and cell-to-cell interactions are found after matrix metalloproteinase (MMP)-dependent degradation [23,24]. Meanwhile, autophagy death was also identified as a way of macrophage removal to prevent apoptosis and promote the clearance of reactive oxygen species production [25,26]. However, macrophages revealed opposite stage-dependent effects during the progression of atherosclerosis [25,27]. The continuous exposure to stressors inhibits autophagy in favor of an apoptosis-mediated macrophage death, contributing to enlarged NC size and plaque inflammation [25-27]. Data showed that unbalanced activity of endoplasmic reticulum (ER) stress pathways and nuclear receptors may be crucial in promoting macrophage apoptosis [25-36]. Deficiency of the homologous protein (CHOP), which mediates mitochondria- dependent apoptosis through the downregulation of Bcl-2 and triggers ER calcium release, critically reduces atheroma burden and lesional apoptosis [28-30]. GFP-Nur77 has been reported to inhibit differentiation of oxLDL-treated macrophages into DC [31-36]. Despite the increasing knowledge about mechanisms underlying macrophage apoptosis, the key molecules underlying its induction and phenotype differentiation remain elusive. During atherosclerosis, defective cell efferocytosis results in the accumulation of apoptotic cells and the delay of resolution of inflammation [37]. Apoptotic cells produce a plethora of find-me and eat-me signals that mediate phagocyte attraction, interaction, and, finally, engulfment [38]. Both efferocytosis- related receptor competition and impaired function of lesional macrophages during phagocytosis may hamper efferocytosis [39-43]. Protease-driven degradation of extracellular matrix (ECM) is a dominant process leading to mechanical weakening of the fibrous cap, which precedes plaque rupture and consequent secondary thrombotic events [44,45]. MMP family members, such as MMP-8, MMP-9, or MMP-12, correlate with plaque instability and risk for ACS [46,47]. However, results from studies using MMP transgenic or knockout mice indicated divergent effect of MMP family members. For instance, MMP-8MMP-9 and MMP-12 are related with the induction of a vulnerable plaque phenotype [45,48-50], while MMP-2 and MMP-3 represented beneficial function [45,51,52].

Clinically, early detection of vulnerable plaque in asymptomatic patients is of great importance to the prevention and treatment of ACS. The development of intravascular imaging provides new methods to identify high-risk plaques. The PROSPECT study demonstrated that most of the non-culprit lesions characterized by large plaque burden (>70%), small luminal area (<4 mm2), and presence of thin-cap fibroatheroma in virtual histology intravascular ultrasound (VH-IVUS) were associated with clinical events [53]. However, the predictive value of these features was low [53]. Near-infrared spectroscopy (NIRS) is able to discriminate lipid-rich atherosclerotic plaque with high sensitivity and specificity *in vitro* [54]. Hence, the combined use of NIRS and VH-IVUS provides the possibility of detecting lipid-rich atheroma *in vivo* [55,56]. Three intravascular ultrasound (IVUS) have been associated with coronary artery disease instability: echo attenuation, an intraplaque echolucent zone, and spotty calcification [57-61]. A recent study comparing IVUS with near-infrared spectroscopic detection of lipid core plaque and histopathology in vessel segments at necropsy demonstrated that echo-attenuated plaque, especially superficial echo attenuation, was the most reliable IVUS signature for identifying a high-risk plaque [62]. Molecular imaging enables the detection of key biological processes of plaque destabilization by MRI, X-ray CT, PET-CT80 or PET/MRI [63-66]. Successful imaging of destabilizing processes such as macrophage-rich plaques, neointimal cell death, protease activity or oxidative stress, have emerged as a promising complementary tool to identify subclinical lesions and have been evaluated in preclinical [67-73]. Encouraging results in these imaging researches require further clinical evaluation, especially prospective studies are needed.

Part II: Acute myocardial infarction: Core clinical consequences

The rupture of vulnerable plaque leads to acute myocardial infarction (AMI). As a common cardiac emergency and the core clinical process of ACC, AMI with or without ST-segment elevation (STEMI or non-STEMI) is associated with the potential for substantial morbidity and mortality. Ischemic heart disease has become the top single killer responsible for over 8 million deaths worldwide in 2015 [1]. Concurrently, the global burden of AMI has shifted from developed countries to low- and middle-income ones [74,75]. In the

past three to four decades, dramatic improvements have been made in the management of AMI.

STEMI is typically characterized by a totally occluding thrombus [76]. Thanks to the rapid development and evolution in devices and techniques, the acute mortality of STEMI has progressively declined from more than 20% to less than 5% [77,78]. Despite the improvement in survival during the acute phase, there is still a trend of increasing death rate among the whole population [1]. Huge efforts are made to further optimize current treatments. Traditionally, there are two main methods for emergency revascularization, thrombolysis and percutaneous coronary intervention (PCI). Both have their unique advantages. Thrombolysis can achieve fast reperfusion with a simple injection of fibrinolytic agents. However, only 50-60% patients could achieve complete reperfusion with thrombolysis alone, which increases the risk of recurrent ischemia [79,80]. PCI used to be considered prior to thrombolysis with the advantages of lower rates of early death, reinfarction, and intracranial hemorrhage. Undoubtedly, PCI prompt with door-to-balloon time ≤90 minutes as guidelines recommended is the preferred approach for STEMI with onset of symptoms within the previous 12 hours [76]. The development of chest pain center contributed to rapid diagnosis and treatment of AMI. Nevertheless, still a proportion of patients with STEMI cannot receive timely primary PCI due to lack of facilities or delays in patient transfer or catheterization team mobilization. The advantages of easy administration, widespread availability and early patency of the infarct-related artery (IRA) make thrombolysis an ideal alternative on the occasion where in-time PCI is unavailable. Hence, the concept of pharmaco-invasive emerges. Early routine post-thrombolysis has been proved to be a reasonable, useful strategy to bridge the time gap to complete revascularization [80-86]. In these patients, despite a propensity for more bleeding, pharmaco-invasive strategy was associated with similar clinical efficacy as compared with primary PCI, even in patients presenting within 3 hours after symptom onset and unable to undergo primary PCI within 1 hour [82,84]. Shorter symptom-to-reperfusion time, higher culprit-vessel patency, and similar clinical outcome were observed in STEMI patients receiving fibrinolysis followed by PCI [85]. Moreover, when PCI related delay is prolonged, the benefits of pharmaco-invasive strategy increase [83]. Now, thrombolysis followed by routine PCI within 2 to 24 hours is gradually accepted as a reasonable alternative reperfusion option when primary PCI is not readily available, especially in patients presenting early after symptom onset [76,87]. The pharmaco-invasive does not increase intramyocardial hemorrhage (IMH) and microvascular obstruction (MVO) according to cardiac magnetic resonance (CMR) [87]. The myocardial injury caused by the infarction decided the patient's outcomes. In daily practice, several indicators are used to evaluate myocardial injury, including functional (i.e., left ventricular ejection fraction, LVEF), symptomatic (i.e., NYHA classification) and clinical (i.e., age, sex, morbidities, etc.) characteristics. However, these factors may be arbitrary and changeable, or experiences dependent, so that the evaluation on the same patient may come to different conclusions with discrete method. Moreover, some of the indicators even lose their values in patients with little functional or structural changes, especially those who received timely reperfusion therapies. Undoubtedly, the stratification of myocardial injury after ACS is crucial for doctor's medical decision and patient's secondary prevention. The modern advancements of cardiac imaging technologies allow more precise determination of pathophysiologic changes during ACS. For example, CMR can visualize the tissue injury that is undetectable by traditional echocardiography and is able to identify different pathophysiological stages of ACS, including myocardial edema caused by ischemia, permanent myocardial necrosis resulting from prolonged blood blockage, microvascular obstruction (MVO)/intramyocardial hemorrhage (IMH) induced by microcirculation dysfunction, initial contracting dysfunction mostly due to myocardial stunning, compensatory cardiac remodeling triggered by extensive infarction, and the final cardiac decompensation [88,89]. Recently, a classification based on pathophysiological stages has been established with the combined use of CMR and echocardiography to make up the insufficient evaluations for less-injured patients and represent a more subtle and comprehensive stratification of cardiac detriments [90]. In this novel grading system, patients are classified as Grade 0: no detectable myocardial necrosis; Grade 1: myocardial necrosis without functional and morphological abnormalities; Grade 2: myocardial necrosis with reduced LVEF; Grade 3: reduced LVEF on the basis of cardiac remodeling; Grade 4: mitral regurgitation additional to the Grade-3 criteria [90]. The classification was documented as a good reflection of infarction size and a comparable predictor for outcomes [90], which would help improve information-interchange among doctors, self-awareness of the disease for patients and objective evaluation for post-STEMI labor capacity. Figure 2 introduced the novel evaluation system.

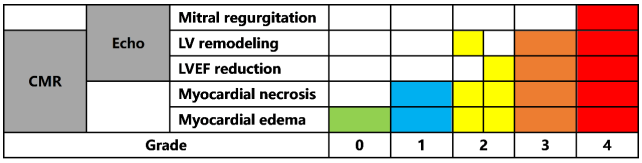

Figure 2: The novel post-MI grading system.

Partial coronary occlusion, or occlusion in the presence of collateral circulation, usually results in non-STEMI or unstable angina [91]. Patients presenting with NSTEMI is triaged to either an invasive strategy or an ischemia-guided strategy [91]. An invasive strategy is favored for the majority because of improved outcomes, and it has become consensus that the patients at higher risk benefits more from earlier revascularization [92]. With the development of antiplatelet agents, there is a trend for early intervention in NSTEMI patients. However, controversy remains on the definition of the time point. Too early may lead to complications without enough time for effective antiplatelet action, while too late can meet with ischemic risks during waiting. Series of clinical studies worked on this project, but the results were inconsistent. The underlying reason is that the definition of early or delayed timing varies [93-97]. Moreover, from 2007 to 2015, guidelines switched the time point from less than 72 hours to 24 hours [91,98-100]. Two recent meta-analysis based on the classic dual antiplatelet treatment revealed an early hazard phenomenon in intervention within 3 hours for NSTEMI, which should be taken seriously during decision [101,102].

With the increasing demand for early diagnosis and treatment of ACS, a new concept of chest pain center (CPC) has generally developed to be a safe, cost-effective, and rapid approach to the evaluation, triage, and management of patients presenting with susceptible symptoms of AMI or unstable angina [103]. The popularity of CPC has contributed to cost reduction by less hospitalizations, shorter lengths of stay and fewer unnecessary treatments and procedures [103,104]. Its initial target to decrease waiting time to

treatment for AMI fostered the protocol-driven mode in CPC. With the standard protocol, high- and low-risk patients can be identified on presentation and receive optimal therapeutic strategies. Nevertheless, challenges still sustain in various stages. Since that unlimited expansion of CPC is impossible, how to bridge the gap between areas with different qualities of public health system requires attention. First medical contact seems to be more and more important in the treatment of ACS. Pre-hospital thrombolysis is likely to be a safe and effective method to be added to current protocol for patients unfortunately faced with inevitable delay to primary PCI. Moreover, risk stratification of NSTEMI is of great importance for its decisive role in patients' treatment. What is the best assessment system to identify high risk patients? What is the optimal invasive time for NSTEMI at different risk levels? More works need to do to further enhance patient care in ACS.

Part III: Microcirculation dysfunction prevention: Key bridge from vessel to muscle

PCI has been well documented as the most effective method for epicardial revascularization for AMI [105-111]. However, successful epicardial reperfusion does not necessarily equate to effective myocardial perfusion, even in patients with TIMI 3 flow after successful PCI. In fact, still 20% - 40% patients with ACS remain impaired microvascular blood flow regardless of patent epicardial reperfusion [56,62]. The presence of abnormal microcirculation is associated with poor healing of the infarct and adverse left ventricular remodeling, which can result in detrimental impacts on survival [112-116]. Hence, the ultimate therapeutic goal is the complete restoration of myocardial perfusion [116-119], which calls for proper assessment methods and effective therapies.

Currently, there are two widely used myocardial perfusion angiographic parameters: TIMI myocardial perfusion grading (TMPG) [116] and myocardial blush grading (MBG) [119]. TMPG is an index that focuses on the velocity of contrast opacity clearance [116]. When damage occurs to the microcirculation, it will be evidenced by slowing of the contrast clearance and abnormal or absent myocardial blush. MBG is based on the intensity of contrast opacity of the infarcted area. These two angiographic methods are reported to have high predictive value in AMI [112,114-116,119]. However, both methods are categorical, subjective, and operator dependent [112-116]. Recently, a novel quantitative index of myocardial perfusion by angiographic frame counting, named TIMI Myocardial Perfusion Frame Count (TMPFC), that encompasses the filling and clearance time of contrast in the myocardium to evaluate the degree of myocardial perfusion has been established [120]. TMPFC allows quantification of TMPG and correlates well with these established parameters [120]. The new assessment method also represents ideal predictive value in patients undergoing primary angioplasty [120]. With the development of cardiac imaging techniques, non-invasive imaging such as gadolinium contrast magnetic resonance imaging (MRI), myocardial contrast echocardiography and nuclear imaging, have developed to effectively evaluate myocardial perfusion [121-123].

Lack of effective therapeutic methods has hampered the treatment of patients with suboptimal myocardial perfusion for decades. Vasodilator drugs was first attempted to deal with no-reflow by coronary injection during PCI. Various vasodilator agents have been tested for the coronary pharmacological therapy. Adenosine at a dose of 100 to 200 mg, nicardipine at a median dose of 400 mg, or nitroprusside at doses ranging from 50 to 300 mg, are the current standard of care [124-126]. No significant difference was observed between various pharmacological intervention strategies but resolved flow in myocardial tissue brought about significant clinical benefit [127]. Recently, intracoronary administration of glycoprotein (GP) b/a inhibitor has been reported to improve both angiographic and clinical outcomes of patients with ACS [128]. Since the traditional injection through the guiding catheter may have significant systemic effects and is considered less effective with only a small amount of agent reaching the microvascular bed, the authors recommended the use of micro infusion catheter to achieve distal coronary administration of agents. Local delivery is more likely to get better results. Predictably, along with the development of assessment system and devices, more and more effective medicines or techniques will be introduced to the treatment of microcirculation disorders.

Part IV: Ischemia/Reperfusion injury and heart protection: Final goal for salvage

Unfortunately, even if patients have received successful PCI with optimal epicardial and myocardial results, the induced reperfusion may not only contribute to the recovery of ischemic cardiac tissue but also lead to the paradoxical phenomenon of myocardial "ischemia/reperfusion injury" (IRI) [129]. IRI brings about excessive production of reactive oxygen species (ROS)/reactive nitrogen species, the activation of apoptotic pathways, and the induction of autophagy dysfunction, all of which contribute to post-ischemic cardiomyocyte death and injury expansion [129-131]. The severity of cardiac detriments is strongly associated with patient's outcomes [132-135]. The myocardial protection has become the final stage of ACS treatment. Numerous efforts have been made to figure out the underlying mechanisms and search for novel pharmacological or molecular therapeutic targets.

During IRI, large amounts of intracellular components as alarming compounds are released and trigger inflammation [136]. In particular, nuclear proteins, such as histones, heat-shock proteins, or amphoterin, as well as nuclear DNA [137], mitochondrial DNA [138-140], ribosomal RNA [141,142] and miRNAs, play a crucial role in this process [143-145]. For instance, extracellular RNA (eRNA), together with Tumor Necrosis Factor a (TNF-a), serve as damaging factors in experimental IRI [145]. Administration of RNase1 is documented to significantly reduce the infarct area and prevent cardiomyocyte death [145].

Discussion

Cardiomyocyte apoptosis plays an important role in the pathogenesis of heart dysfunctions related to IRI [129]. Increased apoptosis results in contractile tissue loss, compensatory hypertrophy, and reparative fibrosis, all aggravate the injury [129]. Several members of the nuclear receptors have been reported to regulate cardiac apoptosis, including the peroxisome proliferator-activated receptors (PPAR-α, β, γ), androgen receptor, retinoic-X-receptor (RXR), and farnesoid-X-receptor (FXR) [146-149]. Besides apoptosis, ROS and autophagy dysfunction also contributed to IRI. A recent study demonstrated that VDR served as an endogenous self-defensive and cardioprotective receptor against IRI, via reducing oxidative stress, as well as inhibiting apoptosis and autophagy dysfunction-mediated cell death [150]. Interestingly, different subtypes of Liver-X-receptor (LXR) have reportedly different function [151]. Knockout of LXRα, but not LXRβ, exacerbated IRI-induced oxidative/nitrative stress, and aggravated endoplasmic reticulum stress and mitochondrial

dysfunction [151]. The similar phenomenon was investigated in the overexpression study [151]. LXRα, but not LXRβ, protects myocardium against IRI [151]. These results indicate that the nuclear receptor superfamily may represent a potential molecular therapeutic target for the treatment of cardiac disease. Regeneration is a promising strategy to treat end-edge heart diseases, especially ischemic heart failure. However, damage to myocardium is irreversible as the mammalian heart loses its ability to regenerate after birth. Hence, mechanism underlying cardiomyocyte reactivation may have great potential to protect or improve heart function. For instance, Hippo signaling has been implicated in epicardial cell proliferation, epithelial-to-mesenchymal transition, and cell fate specification during cardiac organogenesis [152,153]. In the last decade, stem cell therapy has been introduced as a novel treatment for a (AMI) [154,155]. Intracoronary bone-marrow-derived stem cells (BMC) treatment was documented to improve both overall systolic function and mid-term diastolic function as well as exercise capacity after AMI [156,157]. Meanwhile, human-induced pluripotent stem cell (iPSC)-derived cardiomyocytes were used as a tool to study cardiac arrhythmias and to evaluate the cardiac toxicity of typical drugs *in vitro* [158]. These researches indicated the powerful iPSC technology as value creation for understanding the mechanisms of heart diseases and a potential therapeutic opportunity for cardiac regeneration. Despite the notable strides that have been made in recent years in understanding the pathogenesis of cardiac regeneration, this field is still at an early stage.

Conclusion

In the late 1980s, Dr. Braunwald put forward the famous concept of the cardiovascular continuum, which contributed to huge progress in the research and treatment of CAD in the following decades. Along with fast economic and social development, CAD has already become the heaviest health burden worldwide. As the most severe acute manifestation of CAD, ACS is responsible for a large proportion of end-stage heart disease and cardiac death. Similar to the cardiovascular continuum, the novel concept of ACC provides a comprehensive layout of series crucial processes during the development of ACS. Underlying this novel chain is a pathophysiological continuum. It describes the most common sequential clinical problems in ACS: what causes plaque rupture and how to identify plaque destabilization, what is the optimal reperfusion strategy for AMI, how to deal with microcirculation dysfunction, and how to identify myocardial injury and improve post-MI heart protection. The formalization of ACC will help enhance understanding of ACS and clearly indicate existing challenges at each level in the chain. Further efforts in interrupting these critical stages, perhaps at multiple sites, will probably contribute to therapeutic revolution and better patient care in the coming future.

Conflicts of Interest

There are no conflicts of interest for the present study.

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