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EDUCATION

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Proposed new classification for acute coronary syndrome: Acute coronary syndrome requiring immediate reperfusion

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1 | INTRODUCTION

Cardiovascular disease remains the leading cause of mortality globally, with coronary heart disease being responsible for more than 40% of cardiovascular deaths in the United States.[1] Despite great advances in the management and treatment of acute coronary syndromes (ACS), the classification of ACS has remained relatively unchanged.

Among the different presentations of ACS, the initial approach depends on the ST-segment changes on the electrocardiogram (ECG). For ST-elevation myocardial infarction (STEMI) the initial treatment is an immediate coronary reperfusion strategy (within 30–120 min depending the selected strategy), usually in the form of either primary percutaneous coronary intervention (PCI) or fibrinolysis or bypass surgery depending on availability, accessibility, transfer time to a center that can perform primary PCI, coronary artery disease complexity and severity among other variables.[2–4] This is in contrast with the non-ST-elevation acute coronary syndrome (NSTE-ACS), where immediate coronary reperfusion strategy as an initial approach is not typically recommended for all.[5,6]

This difference in approach is fundamentally based on the knowledge that we have had for almost 30 years from data provided by a large meta-analysis at the beginning of the reperfusion era. This meta-analysis demonstrated that the use of a simple, easy, accessible, and low-cost ECG, identified patients with STEMI who benefited from a significant reduction in mortality when they were treated immediately with a coronary reperfusion strategy.[7] This ECG pattern of ST-segment elevation correlated with the presence of at least one acute coronary occlusion, that required immediate reperfusion.[2,3] Thereafter, the classification of myocardial infarction moved away from Q-wave myocardial infarction versus non-Q-wave myocardial infarction to the current one of STEMI versus NSTE-ACS.[8]

There have been changes in other terminology in ischemic heart disease (moving from stable coronary disease to chronic coronary syndrome),[9] as well as evolving definitions of myocardial infarction more recently.[10] Nonetheless, the terminology in ACS has remained unchanged for more than two decades, as has the initial management of STEMI and NSTE-ACS.

2 | ACUTE TOTAL CORONARY OCCLUSION THAT COULD REQUIRE IMMEDIATE REPERFUSION IN THE ABSENCE OF STEMI

It is well established that most acute total or nearly total coronary occlusion results in ST-elevation on an ECG,[11] which guides the need for immediate reperfusion.[2,3] Nevertheless, there are other electrocardiographic patterns in patients with NSTE-ACS that are associated with acute occlusive coronary lesions in whom, an immediate reperfusion strategy may improve prognosis (Table 1).

It is estimated that approximately one in four patients with NSTE-ACS present an acute occlusive thrombotic lesion in the artery responsible for the coronary event.[12,13] A meta-analysis that included seven studies from 2008 to 2014 examined the association of all-cause mortality and major cardiac adverse events (MACE) after primary PCI based on the presence or absence of an acute coronary occlusion. This analysis included 40,777 NSTE-ACS patients, with a mean age between 58 and 73 years, most were men (64%–76%), and the mean time to PCI was greater than 24 h.

TABLE 1 NSTE-ACS scenarios associated with acute total coronary occlusion and/or increased cardiovascular risk.

Scenarios	Prognosis
Acute total coronary occlusion that could require immediate reperfusion	
NSTE-ACS	One in four patients has an acute coronary occlusion. The risk of death increases in the short term by 60% and in the long term by 47%–72%.[12,13]
A-Any ST-elevation in lead III but not in other inferior leads AND B-ST-depression in any of leads V4 to V6 (but not in V2) with a positive or terminally positive T-wave AND C-ST in lead V1 higher than ST in V2	54% have acute coronary occlusion. Increases the risk of death during hospitalization 5-fold and in the long term 3.67-fold.[15]
Isolated ST-depression in leads V1–V4	One in four patients has an acute coronary occlusion. Patients with this electrocardiographic pattern and acute coronary occlusion have 2.3-fold higher risk of death during hospitalization than those without acute coronary occlusion.[16]
Hyperacute T waves	It is considered an early sign of STEMI in the context of a patient with symptoms of acute coronary syndrome.[17,18,26]
J-point deviation and ST-upslope in V1–V6 with symmetrical tall, positive T waves, often with 1–2 mm ST-elevation in aVR (de Winter pattern)	High probability of occlusion of the left anterior descending artery.[20,21,27]
ST-elevation in lead aVR	Could be associated with total or nearly total coronary occlusion of the left main in patients with ACS.[21]
Non-total coronary occlusion that could require immediate reperfusion	
NSTE-ACS + heart failure	48% reduction in cardiovascular complications with early invasive strategy.[28]
Very high-risk NSTE-ACS (hemodynamic instability, cardiogenic shock, refractory and/or recurrent chest pain, or life-threatening arrhythmias)	Immediate reperfusion strategy recommended.[5]
Biphasic or deep negative T wave in anterior leads (Wellens pattern)	Associated with severe or critical lesion of the left anterior descending artery.[27,30]

Abbreviations: ACS, acute coronary syndrome; NSTE-ACS, non-ST-elevation acute coronary syndrome.

An acute coronary occlusion was identified in a quarter of the NSTE-ACS and was determined to be an independent prognostic marker. Those with an acute coronary occlusion in the setting of NSTE-ACS had a significant increase in the risk of MACE and all-cause in-hospital or 30 days mortality (41% and 60%, respectively) as well as 6–12 months follow-up (32% and 47%, respectively), when compared to those without an acute coronary occlusion.[12] In another large, international meta-analysis of 60,898 patients with NSTE-ACS from 25 studies between 2002 and 2016, 34% had an acute coronary occlusion. The mean age was between 58 and 69 years, and the proportion of women varied between 21% and 40%. This analysis also demonstrated that those with an acute coronary occlusion had a 72% increase in all-cause mortality at 1 year.[13]

In both meta-analyses, the vessels that most frequently presented an occlusive lesion were the circumflex and right coronary arteries. The occlusion of these vessels may not always manifest with ST-elevation in the standard 12-lead ECG,[24] so these occlusions will be interpreted as NSTE-ACS and will not be treated with an immediate reperfusion strategy. Although in cases of an occluded circumflex artery, the use of novel ECG strategies employing a multiplicity of leads may be helpful because this type of study increases the sensitivity for the detection of the occlusions of this vessel in patients with NSTE-ACS compared with the standard 12-lead electrocardiogram,[25] it is also important to keep in mind that it may not be available in most centers and that it requires trained personnel to interpret it.

One possible hypothesis regarding why acute occlusions in NSTE-ACS are associated with increased MACE and mortality, is simply the result of the prolonged time from the first medical contact to time to PCI because they are not diagnosed as a STEMI. This was demonstrated in a retrospective study of 727 patients, who were categorized as (1) STEMI with the total coronary occlusive lesion, (2) NSTE-ACS with the total coronary occlusive lesion, or (3) acute myocardial infarction without total coronary occlusive lesion. The median time between first medical contact and PCI was 55 min, 175 min, and 2139 min, respectively. In-hospital mortality was 3.3%, 7.6%, and 2.4%, respectively,[14] meaning that those with a total coronary occlusive lesion in the setting of an NSTE-ACS had more than a two-fold increased risk of death and underwent PCI approximately 120 min later when

compared with those diagnosed with STEMI with the total coronary occlusive lesion.

A retrospective study identified high-risk electrocardiographic patterns composed of (a) any ST-elevation in lead III but not in other inferior leads, (b) ST-depression in any of leads V4–V6 (but not in V2) with a positive or terminally positive T-wave, and (c) ST in lead V1 higher than ST in V2. In a study of 966 patients with NSTE-ACS, 61 patients presented with the electrocardiographic patterns described above. Those with these high-risk ECG features had no significant differences in time from performing the ECG and PCI, when compared to those without the high-risk ECG findings (3450 vs. 2460 min; $p = 0.2$), but did have a greater risk of an acute coronary occlusion in one vessel (54% vs. 27%; $p < 0.001$). The culprit artery was most often the circumflex artery (50%), followed by the right coronary artery (32%), and was generally accompanied by a severe lesion in another coronary artery. When compared with those without the high-risk ECG patterns identified, those with the high-risk ECG features had a significantly greater risk of in-hospital (5% vs. 1%; $p = 0.03$) and long-term mortality (11% vs. 3%, $p = 0.002$).[15]

A sub-analysis of the TRITON-TIMI 38 study also had similar findings. This study examined 1198 patients who presented with isolated ST-depression in leads V1–V4, and observed that 26% had an acute coronary occlusion, which was again seen more frequently in the circumflex artery (48%), followed by the right coronary artery (34%). Similarly, those patients with acute myocardial infarction and total coronary occlusion (TIMI 0/1 flow) had the highest in-hospital mortality (8.6%), compared with 6.3% in patients with acute myocardial infarction and TIMI 2/3 flow, and 2.9% in patients with unstable angina and TIMI 2/3 flow ($p = 0.006$).[16]

Another of the electrocardiographic manifestations associated with an acute coronary occlusion without ST-elevation is hyperacute T waves which are associated with an occlusion of the left anterior descending artery,[17,18,26] and this scenario may also benefit from an immediate reperfusion strategy.

Additionally, it is important to recognize that there are electrocardiographic patterns of STEMI that can be misinterpreted as NSTE-ACS and result in delayed reperfusion.[19] There can also be electrocardiographic patterns in patients with ACS that do not present as classic ST-elevation but are associated with an acute occlusive coronary lesion, such as the well-described de Winter's pattern (ST-elevation in lead aVR), among others.[20,21,27]

There is a proposed classification of occlusive myocardial infarction (OMI) versus non-OMI,[22] but it only considers different electrocardiographic patterns that express acute coronary occlusion without considering certain clinical conditions of the patients (acute heart failure at admission, cardiogenic shock, refractory sustained ventricular tachycardia, among others) or other electrocardiographic patterns without total coronary occlusion (e.g., Wellens' pattern). Therefore, such a classification would not be inclusive of all patients who might benefit from the immediate coronary reperfusion strategy.

3 | NONTOTAL CORONARY OCCLUSION THAT COULD REQUIRE IMMEDIATE REPERFUSION

There are other scenarios where patients with an NSTE-ACS might benefit from immediate reperfusion, even in the setting where there is not a total coronary artery occlusion. (Table 1) In an observational study of 160 patients with NSTE-ACS and heart failure in whom an invasive strategy was planned at admission, there was a significant reduction in the combined primary endpoint of cardiac mortality, life treating arrhythmia and nonfatal myocardial infarction in patients with an early invasive strategy (median 2 h) compared with a delayed strategy (median 240 h), both in the univariate analysis (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.30–0.87; $p = 0.01$) and multivariate analysis (HR, 0.44; 95% CI, 0.23–0.78; $p = 0.004$).[28]

At this time, the guideline for the management of patients with NSTE-ACS recommend an immediate invasive strategy only in those with hemodynamic instability, cardiogenic shock, refractory and/or recurrent chest pain, or life-threatening arrhythmias[5,29] based on expert opinions because all these groups are not usually included in randomized studies but such clinical settings are associated with poor clinical outcomes.[23]

Another ECG finding that is associated with non-total coronary occlusion that could require immediate reperfusion is the Wellens pattern. This pattern is associated with a critical lesion in the left anterior descending artery which, as originally described, develops acute anterior myocardial infarction in 75% of cases if they are not reperfused and could develop a STEMI in the next few hours.[30–32]

4 | A NEW APPROACH TO ACUTE CORONARY SYNDROME

Mounting evidence exists to support these important electrocardiographic patterns and/or clinical conditions in patients with ACS who do not meet criteria for STEMI but would benefit from an immediate reperfusion strategy. Current delays in reperfusion are associated with an increase in morbidity and mortality. It is for this reason, we suggest a new approach to ACS, beyond the ST segment changes. Identification of the correct patients who require immediate reperfusion (RIR) versus those who do not (non-RIR) is essential, and ST elevation alone may not completely identify those at the highest risk[33] (Figure 1). In some cases, complementary tools that are immediately available may be useful to approach the diagnosis of ACS and reperfusion strategy. In those scenarios, transthoracic echocardiography may help visualizing (or not) ventricular wall motion abnormalities, and coronary computed tomography angiography may allow identifying a total occlusion in a coronary artery.[34] Those complementary studies, among others, may be useful when type 2 myocardial infarction is suspected as well[35] where the initial treatment strategy should be targeted to resolve the cause of type 2 myocardial infarction such as atrial fibrillation with rapid ventricular rate, hypertensive crisis, gastrointestinal bleeding with anemia and

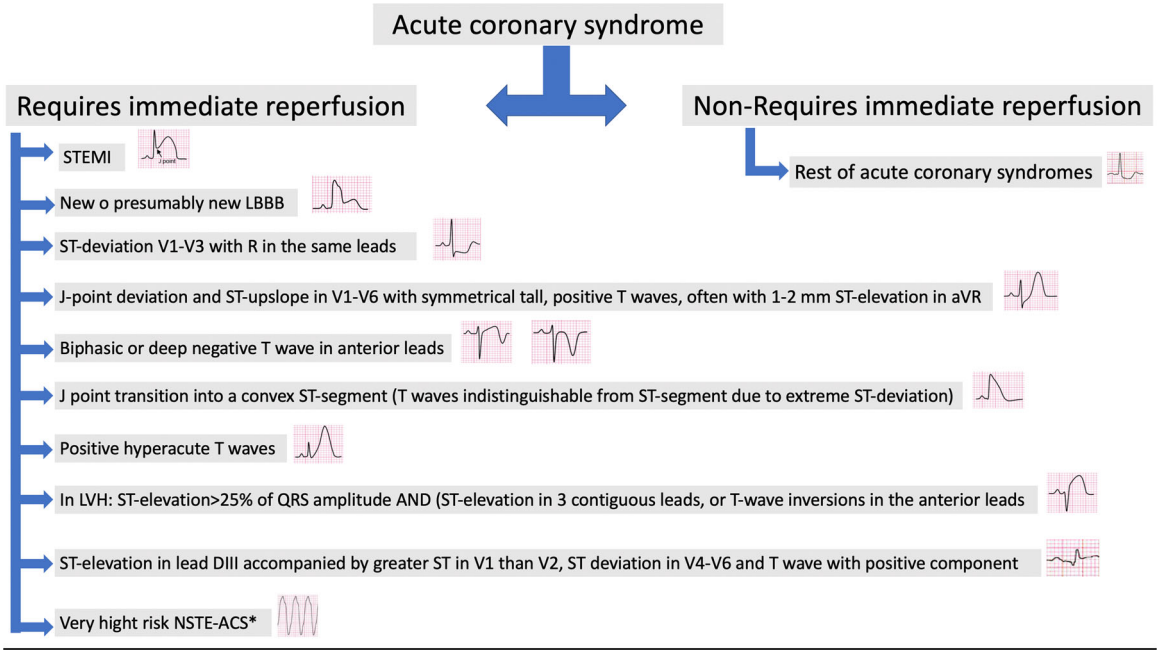

FIGURE 1 Proposed new classification for acute coronary syndrome. *Very high risk: hemodynamic instability, cardiogenic shock, recurrent/refractory chest pain despite medical treatment, life-threatening arrhythmias, a mechanical complication of myocardial infarction, acute heart failure clearly related to NSTE-ACS. STEMI, ST-elevation myocardial infarction; LBBB, left bundle branch block; LVH, left ventricular hypertrophic; NSTE-ACS, non-ST-elevation acute coronary syndrome. [Color figure can be viewed at wileyonlinelibrary.com]

sinus tachycardia, etc. and an immediate reperfusion strategy would not be required.

It is necessary to further refine the classification for ACS that will facilitate the appropriate initial therapeutic approach to improve the prognosis of ACS patients.

Finally, given the high PCI revascularization success rates in the current stenting era, together with modern pharmacotherapy for intracoronary thrombi, earlier rather than late angiography with revascularization may be appropriate for many patients with NSTE-ACS provided system resources are available (cath lab availability for NSTE-ACS after hours and weekends) especially if ACS with acute coronary occlusion is suspected. Of note, resource availability, including 24/7 cath lab, is limited in developing countries where 80% of global cardiovascular mortality occurs, and we need a robust stratification strategy outlined above to reduce system demands and burdening healthcare systems.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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