Time for a new paradigm shift in myocardial infarction

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Abstract

The ST-elevation myocardial infarction (STEMI)/non-STEMI paradigm per the current guidelines has important limitations. It misses a substantial proportion of acute coronary occlusions (ACO) and results in a significant amount of unnecessary catheterization laboratory activations. It is not widely appreciated how poor is the evidence base for the STEMI criteria; the recommended STEMI cutoffs were not derived by comparing those with ACO with those without and not specifically designed for distinguishing patients who would benefit from emergency reperfusion. This review aimed to discuss the origins, evidence base, and limitations of STEMI/non-STEMI paradigm and to call for a new paradigm shift to the occlusion MI (OMI)/non-OMI.

Key words: acute coronary syndrome, coronary artery disease, coronary occlusion, electrocardiogram, myocardial infarction

Introduction

Surveying the history of myocardial infarction, the pre-reperfusion era is the dark ages for today's cardiologists. It may be easy to chuckle at the naivete of the management approach for patients with acute coronary occlusion (ACO) during that era (Fig. 1), and it may seem mysterious that the medical community reacted so slowly to the accumulating evidence (Fig. 2) (1-12). However, the physicians of the past were no less certain that they were providing the best possible treatment options available as are today's clinicians. Therefore, we must ask ourselves if we, too, are unaware of the obvious opportunities for improvement in the management of ACO, and what steps we can take to enact those improvements.

As the historical timeline shows, it has been more than a century since acute myocardial infarction (AMI) was linked to coronary occlusion (1) and half a century since acute thrombosis was blamed as the primary mechanism (7). Since then, it has been of the utmost importance to distinguish patients with ACO or near occlusion, whose myocardium is at imminent risk of irreversible infarction without immediate reperfusion, from those patients with myocardium that is at risk, but not imminently and who can be stabilized with medical therapy. Before the reperfusion era, and even well into that era, the established AMI paradigm used for this differentiation was the Q-wave/non-Q-wave AMI dichotomy (9). As clinicians had little to offer patients for opening acutely occluded arteries, this paradigm was actually used to retrospectively classify patients according to whether their subsequent ECG developed Q-waves, the ominous sign of the irreversible transmural loss of myocardium. However, the term "Q-wave MI" implicitly referred to ACO that clinicians had not been able to intervene upon.

At the end of the last millennium, as a result of large-scale randomized-controlled trials (RCTs) comparing fibrinolytics with placebo, there was a revolutionary paradigm shift from Q-wave MI/non-Q-wave MI to STEMI/non-STEMI (NSTEMI). The seminal Fibrinolytic Therapy Trialists' (FTT) meta-analysis (10), which pooled data from 58,600 patients who were enrolled in all 9 RCTs

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HIGHLIGHTS

- The STEMI/NSTEMI paradigm fails to diagnose nearly a quarter of acute coronary occlusions.
- ECG can detect acute coronary occlusion even when STEMI criteria are not fulfilled.
- We think that it is time to replace the STEMI/NSTEMI with a new OMI/NOMI paradigm.
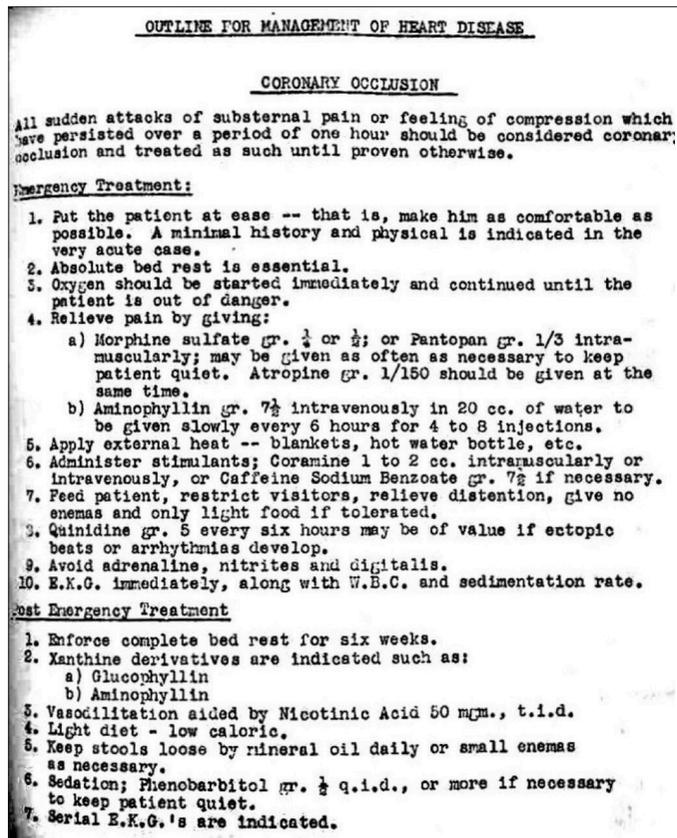- We believe this paradigm shift have the potential of improving the acute management of MI.

Figure 1. An old outline for management of acute coronary occlusion (Cook County Hospital Intern Manual, Year Book Publishers, Chicago, US, 1955).

of thrombolytics versus placebo of at least 1,000 patients, showed an impressive 3% absolute reduction in short-term mortality. This was an unmatched breakthrough in the entire history of cardiology, but one critical question was obscured by the elation over that great success. Although patients with ACO were the ones who were most expected to benefit from emergent reperfusion, how did these studies attempt to identify those with ACO from those without? Surprisingly, they did not. Angiography was not employed in these studies, either prior to or after therapy. Instead of enrolling patients with proven ACO, the researchers randomized patients with "suspected AMI" to thrombolytics versus placebo. In general, these were high-risk patients with acute chest pain and with concerning but unde-

fined electrocardiographic (ECG) findings. Overall, the group that received fibrinolytics had a significantly lower mortality. In a post-hoc analysis, the authors compared the effects of fibrinolytics in all patients to the effects in subsets of patients with ST-depression (STD), ST-elevation (STE), and "normal." Unfortunately, only 4 of the RCTs defined their version of STE, and these 4 had varying cutoffs and methods of measurement, usually not specified. Compared with giving fibrinolytics to all the patients regardless of ECG findings, using an undefined amount of STE as an arbiter of fibrinolytics administration produced an improvement in the number-needed-to-treat for short-term mortality from 56 to 43. Conversely, the subgroups of STD and "normal" ECG showed a non-significant trend to mortality harm. With these findings, the term STEMI became almost synonymous with ACO that necessitates acute reperfusion. Later, after fine-tuning of STE cutoffs by several investigators comparing the normal variant STE to STE in AMI (but, again, without the use of angiography) (13-16), "STEMI criteria" became a guideline-supported central dogma of cardiology (17-19).

At this point, we must ask ourselves the abovementioned foundational question: Are we perhaps unaware of errors in our current approach and thus ignoring opportunities for improvement in the management of ACO? Unfortunately, the answer seems to be yes.

Caveats of the STEMI/NSTEMI paradigm

The STEMI/NSTEMI paradigm is neither sensitive nor specific for the identification of ACO as it was flawed from the start. In the FTT meta-analysis (10), there were undoubtedly many patients with false positive STE (STE due to non-AMI conditions) who received thrombolytics, thus gaining no benefit despite the risk. Conversely, in the "normal" ECG and STD subgroups, there were doubtless many patients with ACO (including patients with "posterior" AMI, hyperacute T waves, and so on) whose benefit was confounded by those with a normal or STD ECG who did not have ACO (Fig. 3). Overall, without any ECG subgroup analysis, the group that received fibrinolytics had a lower mortality reflecting a high enough prevalence of ACO in the population with STE in whom benefit of administering fibrinolytics overweighs their harm.

As mentioned above, the STE cutoffs recommended in the 4th universal definition of MI (17) did not originate from these studies; instead, they were derived from studies comparing healthy individuals with those with AMI diagnosed by CK-MB, not by the presence of ACO (13-16). Thus, STEMI criteria were not originally derived or validated for the selection of patients with ACO who would most benefit from fibrinolytics or any other means of reperfusion intervention.

Because "STEMI" inappropriately became the term and concept used in place of ACO before ubiquitous cardiac catheterization was available, no study has ever questioned the benefit of emergent reperfusion therapies in ACO other than those manifesting the STEMI criteria. In the percutaneous coronary
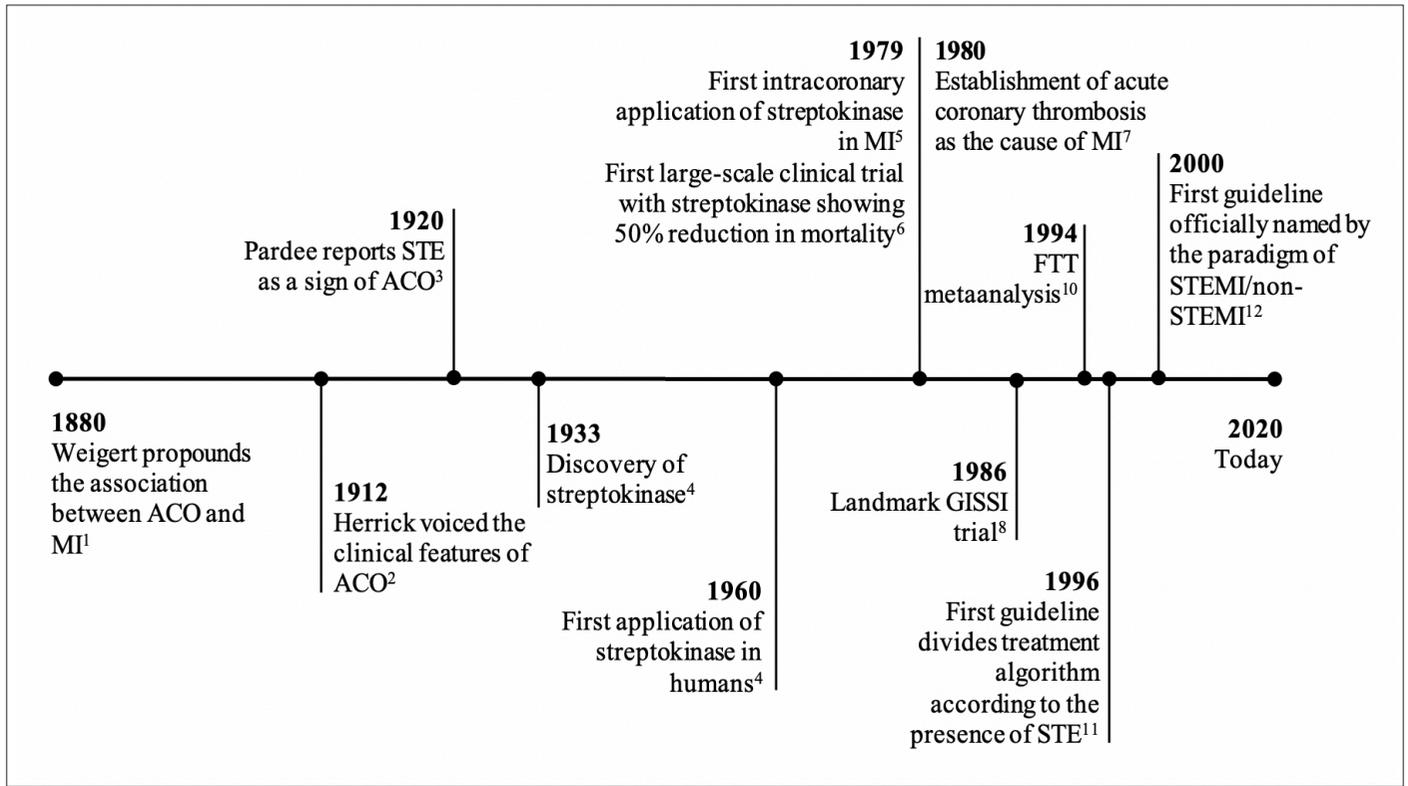
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Figure 2. A timeline of major events providing insights into the acute myocardial infarction pathogenesis and management.
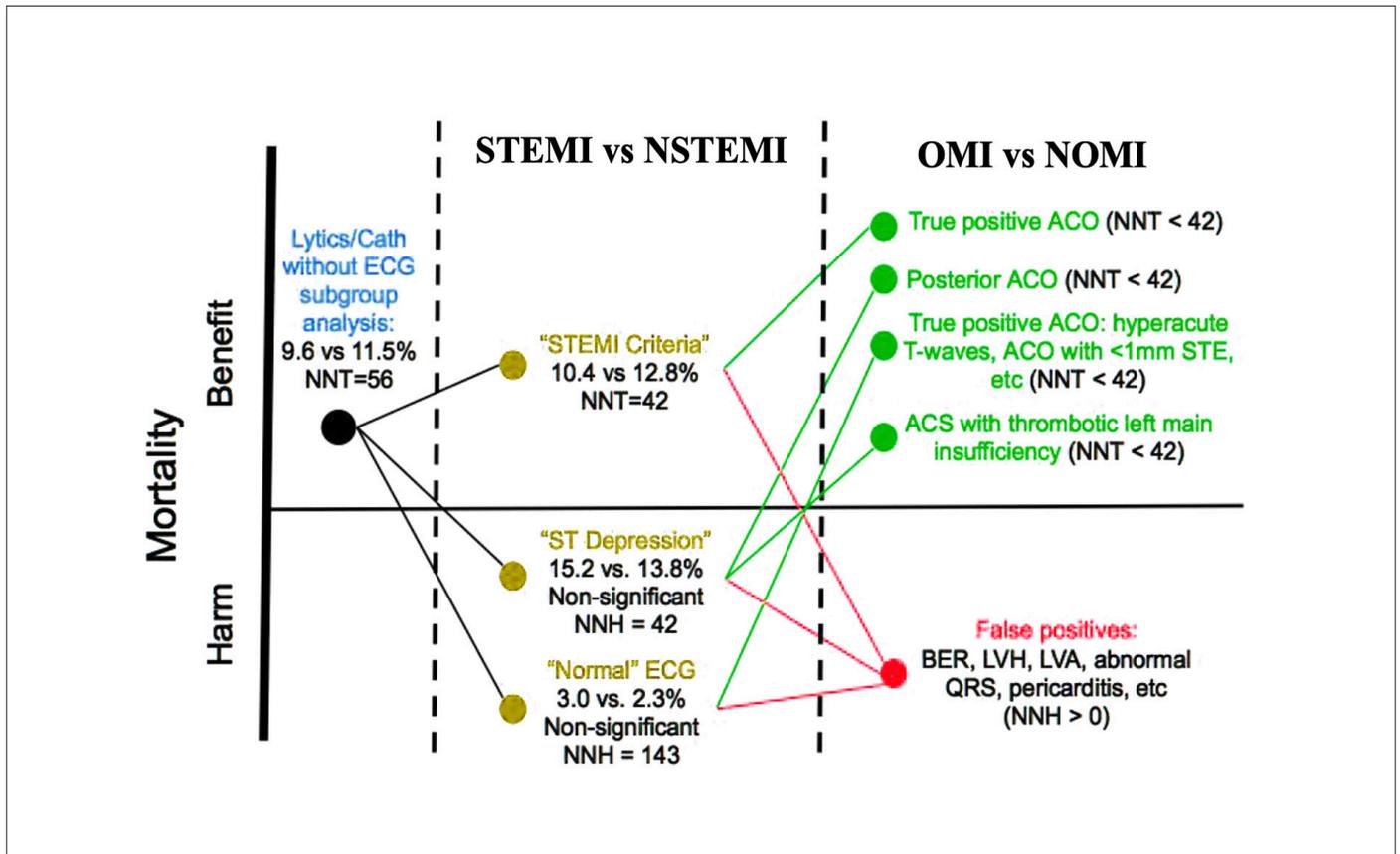

Figure 3. A comparison of ST-segment elevation myocardial infarction/ non-ST-segment elevation myocardial infarction and occlusion myocardial infarction/ non-occlusion myocardial infarction paradigms using the Fibrinolytic Therapy Trialists' meta-analysis mortality data.

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intervention era, STEMI criteria derived from studies of AMI as diagnosed by CK-MB are used, and their limited specificity for ACO cause a substantial amount of false catheterization laboratory activations (20-22). More importantly, the sensitivity is poor, missing at least one-third of the ACO (23-30) with the result that this unfortunate group of patients, labeled as NSTEMI, are deprived of emergent reperfusion therapy, just as they were in the old days of Q-wave/non-Q-wave MI approach. Marti et al. (23) have shown that approximately one-fifth of the patients with ACO had ≥1 mm of STE, including 12.7% of left anterior descending artery occlusions. Schmitt et al. (24) have found that 29% of the patients with ACO did not meet STEMI criteria, with circumflex occlusions being the most missed (50%). In the PARAGON-B trial (27) 27% of the patients with NSTEMI had completely occluded culprit vessels at the time of next day angiography. On average, these patients had a larger infarct size, worse left ventricular function, higher biomarkers, and higher long-term mortality than those of NSTEMI patients with open arteries. In a similar analysis of the TRITON-TIMI-38 (28), 26.2% of the patients with NSTEMI had completely occluded culprit vessels at the time of angiogram. A meta-analysis of 7 studies by Khan et al. (29) have showed that of the 40,777 NSTEMIs, 25.5% had ACO on angiography an average of 24 hours after presentation, and these patients with ACO but without STE had a 1.5 times higher relative risk of mortality compared with those without ACO. Of note, these numbers may underestimate ACO in NSTEMI as a large percentage of total thrombotic occlusions spontaneously reperfuse by the next-day angiogram; unfortunately, many only autolyse after a substantial loss of myocardium. Conversely, the occlusion might have also occurred later than the ECG decision point, but the recognition of this pathologic substrate that leads to ACO in the short term is still an important issue.

Some physicians who are unfamiliar with the source of the STEMI/NSTEMI paradigm might actually believe that patients with ACO but without STE on their ECG do not gain any benefit from reperfusion. Accordingly, many objections to the need for a paradigm change center around studies that purport to show that early angiography for patients with undifferentiated NSTEMI does not result in better outcomes (31-38). These objections fail to take into account that these studies excluded patients with persistent symptoms, and/or did not actually use very early intervention. In the largest such study, patients with persistent symptoms were excluded, and "early" angiography was at a mean of 16 hours; even so, patients with a GRACE score of >140 did indeed benefit from earlier intervention (31). In studies that did not exclude patients with persistent symptoms, and patients underwent truly early intervention, outcomes were indeed better (36-38). Even if all such trials were free of these methodological issues and had instead shown no benefit, they still would not be applicable to the question of whether the subset of NSTEMIs with ACO benefit from emergent reperfusion because these trials did not report the presence or absence of angiographic ACO, much less the outcomes in these patients.

These findings have 2 important messages with the same implication: We need to reshape our minds to understand that ACO needing reperfusion is clearly not synonymous with STEMI because NSTEMI with unrecognized ACO has higher short and long-term risk of mortality than NSTEMI with an open artery and similar to STEMI (39, 40). In addition, although the current guidelines recommend urgent (<2 hours) invasive evaluation "regardless of ECG or biomarker findings" in patients with persistent pain, hemodynamic compromise, severe heart failure, and/or arrhythmias to identify patients with ACO but without STE (17-19), these clinical parameters did not compensate for the silence of the ECG in the abovementioned studies. Furthermore, it is clear that there is a substantial deviation from the guidelines or there would not be so many occluded arteries in the 24-hour angiogram. It appears that even in the context of a highly observed setting of an RCT, physicians did not identify the patients with ACO among all the patients with undifferentiated chest pain.

STEMI/NSTEMI paradigm focuses only on ST-segment

The term "STEMI" is and has been a major obstacle to improvement. It cognitively inspires us to think that only the ST-segment matters. It leads us to ignore other ECG variables, such as the preceding QRS-complex, the T-wave, or even the morphology of ST-segment itself. However, ACO can be reliably recognized with the help of many ECG findings other than the STE cutoffs recommended by the 4th universal definition of MI, such as minor STE not fulfilling STEMI criteria (41), STE disproportionate to preceding QRS (42, 43), unusual patterns with contiguous leads showing opposite ST deviations (44, 45), and some patterns not showing STE at all (46, 47). The universal definition does in fact mention that there are other ECG findings of ACO than STE, which supports the argument that the name of ACO-MI should not be STEMI, but rather occlusion MI (OMI).

Furthermore, the differentiation of OMI from non-OMI (NOMI) and from non-cardiac chest pain does not end with the ECG. Not only may OMI have no STE, whatsoever; but OMI may also, in fact, present with a normal ECG (without even any subtle, non-diagnostic findings) and is sometimes only diagnosable by biomarkers, echocardiography (48, 49), or angiography, including CT angiography (50).

STEMI/NSTEMI paradigm does not focus on pathology, instead focuses on the test

The STEMI/NSTEMI paradigm uses a feature (STE) of a test (the ECG) as the name of an underlying pathology which is not accurately diagnosed by the test, which creates the "no false negative paradox." If there is no "diagnostic" STE, then there is no STEMI (even if there is ACO), and thus there can be no false negative test. Even in the presence of potentially fatal but reversible ACO, a negative test is a true negative for absence of STEMI! This has real consequences. When a patient is admitted with an NSTEMI and has an ACO on the next-day angiogram,

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that patient still gets a diagnosis of "NSTEMI," and the admitting physician does not get the feedback of "missed a STEMI" because, by definition, this was not a missed STEMI: the standard of care was followed. However, a great opportunity was missed to diagnose an ACO and save the patient's myocardium and possibly prevent heart failure and even death.

If we still use a surrogate sign paradigm (STEMI/NSTEMI) which does not accurately reflect the real underlying pathology (ACO), with the result that a large number of patients under our care helplessly infarct a large amount of myocardium, can we really boast that we have emerged from the dark ages? We should name the disease according to the pathologic substrate itself (ACO-MI, or OMI for short).

STEMI/NSTEMI paradigm is not our best option

Recently, Meyers et al. (51) performed a retrospective case-control study of 808 patients with suspected ACS symptoms and compared the accuracy of STEMI criteria with the structured expert ECG interpretation, which incorporates other findings of OMI, including hyperacute T waves, STD of posterior OMI, STE less than the STEMI criteria cutoffs, and so on. Both the interpreters had significantly higher sensitivity (86% versus 41% and 80% versus 36%) for the detection of OMI using the structured expert interpretation rather than using STEMI criteria, with similar specificity. Patients with STEMI (-) OMI had similar infarct size measured by peak troponin but greater delays to angiography compared with patients with STEMI (+) OMI. The interpreters had 94% agreement for the diagnosis of OMI and kappa value 0.849. A total of 55% of OMIs were correctly diagnosed a median of 1.5 hours earlier by structured expert ECG interpretation than by STEMI criteria.

Another study by Meyers et al. (40) compared the STEMI/NSTEMI with the OMI/NOMI paradigms in 467 consecutive patients with high-risk acute coronary syndrome. Among the 108 patients with OMI, only 60% had any ECG meeting STEMI criteria. Patients with STEMI (-) OMI had similar peak troponins, wall motion abnormalities, and clinical outcomes as the patients with STEMI (+) OMI but were much less likely to receive emergent catheterization (28% versus 76%, p<0.001). These data support the notion that patients with STEMI (-) OMI likely represent a missed opportunity under the STEMI/NSTEMI paradigm.

Similarly, the DIagnostic accuracy oF electrocardiogram for acute coronary OCClUsion resuLTing in myocardial infarction (DIFOCCULT) study (39) compared the OMI/NOMI approach with the STEMI/NSTEMI paradigm. This was the largest study specifically designed to challenge 20 years of unquestioned dominance of the STEMI/NSTEMI paradigm. In this study, a set of predefined ECG findings in addition to STEMI criteria were used, and the final outcome was a composite ACO endpoint. In accordance with the previous observations, over one-fourth of the patients initially classified as having NSTEMI were re-classified by the ECG reviewers as having OMI. This subgroup had a higher frequency of ACO, myocardial damage, and both in-hospital and long-term

mortality compared with those of the NOMI group. The OMI/NOMI approach to the ECG had a superior diagnostic accuracy compared with the STEMI/NSTEMI approach in the prediction of both ACO and long-term mortality. Furthermore, early intervention in patients with OMI-predicting ECGs was associated with lower long-term mortality, whereas early intervention increased long-term mortality in patients with NOMI-predicting ECGs.

Conclusion

The STEMI/NSTEMI paradigm shift was a major advancement when it was first proposed but is a major obstacle to advancement in the diagnosis and management of ACO. In recent years, there has been considerable incremental progress in the recognition of ACO by ECG findings other than STE, as well as by the use of other diagnostic tools, such as echocardiography (48, 49), CT angiography (50), and conventional angiography. Future studies are needed to better delineate how these modalities could be incorporated into fast diagnostic pathways in difficult cases. However, if we miss the opportunity to change our current paradigm before the next set of AMI guidelines is released, the failure to implement our current knowledge will cost many lives. Therefore, we call for a new AMI paradigm shift from STEMI/NSTEMI to OMI/NOMI.

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