**Total coronary occlusion in Non ST Elevation Myocardial Infarction : Time to change our practice?**

**Running title : NSTEMI patients with total occlusion of coronary arteries**

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**UNSTRUCTURED ABSTRACT**

Based on 12-lead electrocardiogram (ECG) findings, myocardial infarction (MI) patients are dichotomized to ST-elevation MI (STEMI) and non ST-elevation MI (NSTEMI) in terms of management strategy. NSTEMI patients are increasing in numbers worldwide, among which an approximately 30% are associated with a total occlusion of a coronary artery. This review summarizes recent evidence in epidemiology, clinical, laboratory, ECG and prognostic characteristics of this NSTEMI sub-group. Patients with a diagnosis of NSTEMI and a total occluded coronary artery (TOCA) represent a sub-group of NSTEMI patients with total occlusion of coronary arteries and associated high-risk that are frequently not managed according to a STEMI-like pathway. The present review echoes a call for action in changing our everyday clinical practice. Therefore, we propose a new triage algorithm by which recognition of high-risk features in NSTEMI patients is central in order to identify STEMI ‘equivalents’ among NSTEMI patients in terms of similar pathology and high-risk who may benefit from immediate invasive strategy (<2 hours).

**KEYWORDS** Non-ST elevation myocardial infarction; total occlusion; ST elevation myocardial infarction equivalent; immediate invasive strategy

**INTRODUCTION**

Acute coronary syndromes (ACS) include three clinical syndromes, namely ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina. Based on 12-lead electrocardiogram (ECG), myocardial infarction (MI) patients are assigned to STEMI or NSTEMI categories for the implementation of established management strategies. Current clinical practice guidelines recommend an invasive strategy (door-to-balloon time within 90min) for patients with STEMI [1] whereas an early invasive strategy is reserved only for high-risk NSTEMI patients [2].

With the more frequent use of high sensitivity troponin assays in patients presenting with acute chest pain, an increase in the incidence rate of NSTEMI is being recorded worldwide [3]. Indeed, registries on both shores of the Atlantic have reported an increase in the proportion of acute MI patients presenting with a diagnosis of NSTEMI [4,5] to the point that in recent years, approximately two thirds (≈65%) of acute MI patients are classified as NSTEMI [6].

 STEMI results from acute total or nearly total occlusion of a coronary artery, being associated with the characteristic transient ST segment elevation on ECG [7]. However, totally occluded coronary artery (TOCA) has also been observed among patients with NSTEMI. [8]. Consequently, and as a result of current guideline recommendations, these NSTEMI patients will undergo a delayed revascularization procedure due to the lack of “appropriate” ECG findings, despite the presence of a total occlusion of a culprit artery[9]. The clinical implications, i.e. patient prognosis, of implementing current recommendations based mainly on ST segment changes and not on more global assessment of the patient, including angiographic findings, are not known and need to be investigated. Moreover, the management strategy of NSTEMI patients with TOCA, also needs to be defined [10].

 The present review aims to summarize the epidemiology and clinical and ECG characteristics of NSTEMI patients with TOCA, and describe the pathophysiological mechanisms underlying NSTEMI, as well as markers of risk. We propose a need for re-classifying MI post cardiac catheterization, as well as defining a rapid and effective triage strategy for the NSTEMI with TOCA subgroup.

**CHALLENGING THE CURRENT PARADIGM**

Conventional teaching is that in STEMI, acute total occlusion of a vessel causes transmural ischaemia due to complete interruption of blood supply to the territory supplied by the vessel [11]. This phenomenon results in ST-segment elevation on ECG leads relevant to the area of the non-perfused myocardium [12]. In NSTEMI, there is an acute partial occlusion of a coronary vessel causing an incomplete interruption of blood supply of the distal myocardial territory which causes non-transmural (subendocardial) ischemia [6]. The ECG in NSTEMI patients classically shows ST-segment depression and/or T-wave flattening or inversion, without ST-segment elevation) (**Figure 1**). However, NSTEMI can be associated with total vessel occlusion and therefore, the conundrum of a myocardial infarction without ST elevation (NSTEMI) albeit with a total occlusion of the culprit coronary artery has to have several possible explanations. Moreover, there may be important clinical implications of NSTEMI with TOCA and impaired clinical outcomes may be improved by targeted diagnostic strategies and treatment.

the nature and natural history of the acute occlusion and the myocardial area at jeopardy (**Table 1**).

**The ECG in NSTEMI.**

The ECG has reduced sensitivity to detect acute ischemia or necrosis affecting posterior or lateral myocardial walls, e.g. when the left circumflex artery (LCx) is the culprit artery [10]. Indeed, studies have shown that the inferolateral territory is more frequently involved among patients with NSTEMI with TOCA [10,13-17]. Acute total occlusion of the LCx may result in isolated posterior infarction with ST elevation which can be detected in leads V7–V9 only, which are rarely investigated in everyday clinical practice [10,18]. Furthermore, isolated posterior infarction is commonly missed [19] in everyday practice and is associated with longer revascularization times[20] and is less likely to be treated invasively [21]. Conceivably, this group of NSTEMI patients may really represent a subset of STEMI patients that are not diagnosed adequately by the ECG [9]. However, for this explanation to suffice, the occlusion of the culprit artery [(LCx or right coronary artery (RCA)] must be located distally so that the affected myocardial territory is restricted to the lateral or posterior wall.

Another possibility is that ST- segment elevation may be missed by the ECG performed on admission in patients who have an occlusive thrombus, which however resolves spontaneously before hospital arrival or in-hospital after medical therapy, rendering the ST-segment elevation transient and therefore not recorded [9,22]. In such patients, resolution of the ST-segment elevation would correlate with clinical improvement, angiographic reperfusion and improvement in TIMI flow [9,22]. However, this hypothesis is less appealing as the majority of these subset of NSTEMI patients have totally occluded arteries with TIMI flow 0-1 [9,10]. Additionally, we must underscore that there is published evidence for dynamic fluctuations in coronary artery patency and attendant ECG ST-segment changes in acute MI patients [23,24]. Spontaneous intermittent coronary recanalization and re-occlusion resulting from a variable combination of thrombosis and vasoconstriction are frequent during the early phase of acute MI [23]. Therefore, serial ECGs are strongly recommended after admission in order to capture these dynamic coronary flow changes.

Furthermore, a thrombus that develops slowly, allowing for the development of adequate collateral flow may lead subendocardial ischemia, as opposed to STEMI [9,25]. Indeed, the presence of collaterals at the time of complete occlusion of the culprit artery offers a logical explanation for why NSTEMI patients with TOCA and collaterals may have less myocardial damage and reciprocal ECG changes [11,25]. Two studies have described collateral artery status, reporting a higher incidence of angiographic collaterals in NSTEMI with TOCA [11,25]. Along similar lines, acute total occlusion in a territory with dual blood supply may result in NSTEMI with TOCA [10]. The most common clinical scenario is acute and total occlusion of LCx in the presence of a dominant or co-dominant RCA or vice-versa [21].

Other hypotheses include the possibility that chronic total occlusions are misclassified as acute occlusion especially in patients with delayed presentation [10]. When patient’s symptoms started long before hospital arrival, it is possible to postulate that ECG changes would not mirror angiographic findings. In such clinical settings, misdiagnosing a STEMI as NSTEMI is clearly possible [10]. Likewise, misclassifying a chronic total occlusion as the culprit lesion is possible in the presence of multivessel disease, prior myocardial infarction and prior coronary artery bypass grafting [10]. Finally, NSTEMI with TOCA may represent cases of total occlusion when the occluded coronary vessel is rather small and therefore associated with a small area of infarction [10].

In summary, possible explanations underlying the pathophysiology of NSTEMI with TOCA ‘oxymoron’ oscillates between a dipole : some researchers proposed this condition as a STEMI ‘equivalent’ [10,13,14,17,26] and others suggested that it may represent a ‘variant’ of the natural history of NSTEMI [11].

**Incidence OF NSTEMI with total occlusion and PATIENT CLINICAL characteristics**

Two recently published meta-analyses including 62,855 patients with NSTEMI from 26 studies reported that approximately 30% [95% Confidence Interval (CI) 23% to 38%] of the patients were diagnosed with NSTEMI albeit with TOCA [9,10]. Data from the cumulative 17,739 NSTEMI patients with TOCA showed that the majority were male (≈70%), middle-aged (mean age differed between 58 years to 69 years) and that associated left ventricular ejection fraction (LVEF) was worse than that of the NSTEMI patients without culprit artery occlusion [9,10].

 Hypertension was present in 35% to 86%, diabetes mellitus in 12% to 54%, dyslipidemia in 13% to 70% and smoking in 20% to 80% of NSTEMI patients with TOCA [9,10]. It is unknown nevertheless, if more than one CAD risk factor is more frequent in this NSTEMI sub-group.

 Severity of clinical presentation was not different in NSTEMI patients with TOCA as estimated by either Killip class in 5 studies or severity risk scores such as GRACE or TIMI [9,10]. However, presence of cardiogenic shock was more frequent in NSTEMI patients with TOCA compared to those with patent vessels (pooled odds ratio (OR) 1.66, 95% CI 1.35–2.04) [10]. Similarly, NSTEMI patients with cardiac arrest or hemodynamic instability as first symptom at presentation have frequently been associated with TOCA [27]. Of importance, it should be noted that in most studies, patients with cardiogenic shock were excluded from enrollment and furthermore, patients with significant co-morbidities (i.e. high risk of bleeding, chronic kidney disease) were also not included. As far as indirect measures of infarct size is concerned [i.e. markers of myocardial necrosis such as creatinine kinase (CK), creatine kinase MB fraction, (CK-MB), and Troponins], some studies reported statistically significant differences between the two groups, with increased biomarker levels found in NSTEMI patients with TOCA [9,10]. The magnitude of difference may be of importance as several studies reported differences between x1.2 to x2 [9,10]. However, there was significant variability in the levels of cardiac markers as measurement units varied across studies and biomarkers were measured at different time-points [9].

 Numerous ECG findings were associated with NSTEMI presentation with TOCA. These include but are not limited to: transient ST-elevation, ST-depression > 1mm, total ST-segment depression measured in mm, number of ST-depression leads, Q waves, ST-segment elevation in right precordial leads (V4R), ST-segment elevation in posterior leads (V7-V8), de Winter’s sign and ST-segment depression in anterior leads (V1-V3), prominent R-wave in anterior leads (V1-V2) with upright T-waves in anterior leads (V1-V3), resting U-wave inversion, low QRS voltage [2, 24]. If the ECG finding of LBBB as well as of other conduction abnormalities are associated with myocardial infarction patients with TOCA is debatable, as patients with these presenting ECG features were excluded from most of the studies so far.

Finally, there were differences in the anatomical distribution of the culprit artery between the TOCA and the patent vessels NSTEMI groups. Khan et al., assessing data from 6 studies reported that the RCA (TOCA: 40%, non-TOCA: 27%, P <0.0001) was the most commonly involved culprit vessel in the TOCA group followed by LCx (TOCA: 32%, non-TOCA: 28%, P <0.0001) and left anterior descending (LAD) artery (TOCA: 28%, non-TOCA: 44%, P <0.0001) [9]. In contrast, Hung et al, using data from 6 studies, reported that the most common culprit artery in NSTEMI patients with TOCA was the LCx, with a pooled OR 1.65 (95% CI 1.15–2.37) [10]. Thus, findings from both meta-analyses including 8 studies in total, showed 4 studies identifying RCA, 3 studies the LCx and only 1 one study identified the LAD coronary artery as the most frequent culprit artery (**Figure 2**) [9,10]. It is evident that any anatomical coronary territories can be affected, albeit some of these will be more amenable to detection but the ECG than others. The occlusion of the LAD coronary artery, for example, which is likely to cause easily detectable ECG changes because of the "proximity effect" referring to the association of this coronary artery with the chest plane scanned by the precordial leads., has been found to be the culprit vessel in 3% to 47% of NSTEMI patients with TOCA. [9,10].

**risk Associated WITH NSTEMI WITH TOTAL CORONARY OCCLUSION**

The diagnosis of NSTEMI dictates that coronary angiography be performed during hospitalization, although often delayed relative to STEMI management. This delay is reflected in the reported time to coronary angiography; in most of the studies the mean time to angiography or PCI was more than 24 hours [9,10]. Another interesting observation from all studies assessing characteristics or management strategies of NSTEMI with TOCA is that there was no difference in time to coronary angiography or PCI between NSTEMI patients with or without TOCA [9]. This probably reflects the level of difficulty of diagnosing a NSTEMI with TOCA and the ascertainment that practicing physicians were not able to identify high-risk clinical features [9].

As NSTEMI with TOCA is actually a NSTEMI with myocardial tissue in jeopardy, it appears logical to postulate that a delayed invasive approach might have an impact on prognosis. Indeed, both of the meta-analyses utilizing data from 11 studies, reported that NSTEMI patients with TOCA have impaired clinical outcomes [9,10]. Specifically, Hung et al., reported that NSTEMI patients with TOCA have increased mortality ratios (OR 1.72 95%CI 1.49-1.98) and increased re-infarction rates (OR 1.7 95%CI 1.06 – 2.75) compared to NSTEMI patients with patent vessels [10]. Moreover, Khan et al., showed impaired prognosis in this sub-group of patients when assessed both at the short- or the long-term [9]. Short-term mortality (in-hospital or 30-day) was increased in the NSTEMI patients with TOCA [relative risk (RR) 1.67 95%CI 1.31 – 2.13] [9]. Short-term major cardiovascular events (MACE; death, re-infarction, hospitalization for unstable angina, or target vessel revascularization) were more common in NSTEMI patients with TOCA (RR 1.41 95%CI 1.17-1.70) compared to NSTEMI patients without TOCA [9]. Proportionally, long-term mortality (6 to 12 months) was increased (RR 1.42 95%CI 1.08 – 1.86) as well as MACE (RR 1.32 95%CI 1.11 – 1.56) [9]. Taken all of the data together, one can suggest that a “delayed” invasive approach may be detrimental for these patients with NSTEMI caused by total occlusion of coronary arteries.

In summary, it can be argued that (a) there is an unmet clinical need for reducing adverse cardiovascular events in this patient population, (b) NSTEMI patients in general and consequently this sub-group of patients (NSTEMI with TOCA) are increasing in numbers world-wide, and (c) current triaging practices lack the sensitivity to identify these “high-risk” NSTEMI sub-population [24].

**findings suggestIVE of NSTEMI with total CORONARY occlusion**

NSTEMI patients with TOCA present a great practical challenge and at present there is no clinical or ECG algorithm to identify this condition in everyday practice [24]. The main issue for this type of NSTEMI, if clinical management is to be altered, first the patients must be identified [24]. The identification of NSTEMI with TOCA as a “STEMI equivalent” is not without complication, as some studies suggest that neither GRACE nor TIMI risk scores were able to differentiate between ‘true’ NSTEMI patients and “STEMI equivalent” counterparts [9,10].

 Thorough assessment of the relevant published literature suggests that specific clinical and laboratory or imaging characteristics can be identified in this high risk NSTEMI sub-group. Age < 70 years, male gender, clustering of risk factors (more than one), reduced LVEF on echocardiography or severe left ventricular wall abnormalities, especially abnormal levels of myocardial necrosis markers and specific ECG findings have been identified as possible predictors in this setting. Furthermore, angina severity, in terms of duration of chest pain or number of episodes in a given period, have characterized NSTEMI patients with TOCA [28]. In NSTEMI patients experiencing ongoing ischemia represented by chest pain and even minimal ECG changes, these findings may identify a ‘high-risk’ sub-group of NSTEMI with total coronary occlusion. Unfortunately, most of these NSTEMI patients are symptom free by the time they attend the emergency department or are admitted to hospital. For these specific subgroup, ‘closer’ long term follow-up and optimization of prognostic medications may be of benefit.

Importantly, new or worsening mitral regurgitation or new ventricular septal defects as ‘structural’ adverse sequelae have been recognized as echocardiographic markers of severity in NSTEMI patients [2,29]. Although, cardiogenic shock, hemodynamic instability or cardiac arrest at presentation were associated with NSTEMI and TOCA these clinical presentations are indications for immediate invasive approach therefore, their inclusion in an emergency triage algorithm would be of no added value. This also holds true for similar ‘structural’ adverse events of NSTEMI. On the other hand, history of previous myocardial infarction or previous CABG increases the possibility of misclassification of a total occlusion as acute.

 Regarding ECG findings, clinicians should look for distinctive features of acute coronary occlusion other than classical ST-segment elevation (**Table 2**) [2,24]. There are non-coronary artery specific ECG signs that have been shown to be associated with NSTEMI patients with TOCA, such as number of ST-depression leads affected [28] and total ST-depression score in mm [30]. Reviewing the existing literature regarding the use of these two ECG markers as risk indicators in non-selected NSTEMI patient population, ST-depression leads > 3 and total ST-depression score ≥ 6mm were identified as significant cut-offs [31]. Magnitude of ST-depression was also identified as a predictor of a totally occluded artery in NSTEMI patients, especially when depression was greater than 2mm [11]. The 2020 updated European Cardiology Society Guidelines for the management of NSTEMI patients suggested that ST -segment depression >1mm in 6 leads plus ST-segment elevation in aVR and/or V1 to be a criterion for high-risk requiring immediate (<2 hours) invasive intervention [2]. Similarly, presence of pathologic Q waves in at least 2 contiguous leads are helpful in patients with TOCA; they may be attributed to late presentation and misclassification of a non-acute total occlusion as acute [17]. Finally, hyper-acute T waves are widely recognized as a precursor sign of imminent coronary occlusion and found often in NSTEMI patients with TOCA as coronary artery occlusion is a dynamic process and therefore ECG presentation evolves rapidly [32]. They are generally described as broad-based, asymmetrical, and tall compared with the preceding R-wave, are most apparent in the precordial leads associated with total occlusion of LAD although it can be seen also and in other coronary territories. The following criteria were added to hyper-acute T waves [(a) a J-point position/T-wave amplitude ratio >25%, (b) T-wave amplitude/QRS amplitude ratio >75%, and (c) J-point elevation >0.3 mV] [33]. Therefore, serial ECGs, or continuous ECG monitoring is important due to the dynamic and short-lived nature of this ECG feature. Similarly, shark-fin appearance of the QRS wave is also an ECG finding associated with total occlusion of a coronary vessel which is more commonly appreciated, however not restricted, either on all ECG leads (LM) or on anterior precordial leads (LAD). Triangular QRS-ST-T waveform (TW) pattern or ‘shark-fin’ sign is defined as a unique, giant wave (amplitude ≥ 1 mV) resulting from the fusion of the QRS complex, the ST-segment and the T-wave and showing a “triangular” morphology with a positive polarity in the leads exploring the ischemic region [34]. Furthermore, transient ST-segment elevation, poor QRS voltage, and resting U-wave inversion have been identified as ECG criteria of high risk in the recent NSTEMI guidelines by the European Society of Cardiology [2].

 A review of coronary-specific ECG signs is presented as **Supplementary material**.

**Need for A change in clinical practice**

Based on the information reprted in this manuscript, there is a considerable number of NSTEMI patients with underlying totally occluded coronary arteries who are at a higher risk and cannot be identified by contemporary triage risk scores such as the GRACE risk score or the TIMI risk score. Conceivably, these patients would benefit from urgent revascularization,as their STEMI counterpart do. However, current NSTEMI guidelines suggest an immediate (<2 hours) invasive strategy only in a sub-group of NSTEMI patients with hemodynamic instability or cardiogenic shock, recurrent or ongoing chest pain refractory to medical treatment, life-threatening arrhythmias or cardiac arrest, mechanical complications of MI, acute heart failure with refractory angina or ST-segment deviation, recurrent dynamic ST- or T-wave changes, particularly with intermittent ST-segment elevation or ST-segment depression >1mm in more than 6 leads plus ST-elevation aVR and or V1 [2]. These criteria, however, do not include the potentially large NSTEMI with TOCA patient subgroup. In addition, there is little awareness of this condition among practicing physicians, for a number o reasons, and therefore potentially useful intervention may be delayed or not carried out at all in these patients.

 One of the main issues of NSTEMI patients with TOCA is that they expose a limitation to current triage techniques that depend on the dichotomization of acute MI according to the presence or not of ST-segment elevation on the 12-lead ECG [24]. Furthermore, as these patients are treated mainly according to mainstream NSTEMI guidelines, a treatment gap emerges for patients with NSTEMI and TOCA as they are diagnosed as NSTEMI and are not managed using STEMI-like pathways, with emergent coronary angiography and reperfusion. It is logical to postulate that these patients will benefit from urgent invasive management provided these patients can be identified rapidly in the acute setting [24].

 According to the most recent European Cardiology Society guidelines for management of NSTEMI patients, a routine invasive strategy does not reduce all-cause mortality risk in the overall population of NSTEMI patients, increases the risk of periprocedural complications such as MI and bleeding. It does, however, reduce the risk of composite ischemic endpoints, particularly in high-risk patients [2]. Although very high-risk patients who may benefit from an immediate invasive approach (<2 hours) are very well defined (i.e. hemodynamic instability or cardiogenic shock, recurrent or ongoing chest pain refractory to medical treatment, life-threatening arrhythmias or cardiac arrest, mechanical complications of MI, acute heart failure with refractory angina or ST-segment deviation, ST-segment depression >1mm in more than 6 leads plus ST-elevation in leads aVR and/or V1), it is recommended that high risk patients may benefit from an early (<24 hours) invasive approach [2]. This benefit of an early invasive strategy is strongly associated with the patient’s risk profile and although it is not modified by ST-segment / T-wave changes, ECG changes have been consistently identified as a predictor for an adverse outcome [2].

 Therefore, we propose a possible novel triage algorithm to be used for assessment of NSTEMI to identify a larger number of high-risk NSTEMI patients who should benefit from an early invasive strategy (<2 hours) (**Figure 3**). In the proposed algorithm, the following risk score should be used after evaluation for a ‘true’ STEMI presence and after assessment of very high-risk features, as reported in the ESC NSTEMI guidelines. Specifically, we propose the use of a risk score (SAVE Score) incorporating clinical, electrocardiographic and echocardiographic characteristics based upon the aforementioned data from approximately 26 studies assessing NSTEMI with TOCA patients (**Figure 4**). The proposed algorithm and SAVE score is likely to increase the practicing physicians’ awareness regarding the identification of NSTEMI patients with TOCA who are at high-risk and may benefit from an immediate invasive strategy.

 Along these lines, several published studies support very early invasive strategies in high-risk NSTEMI patients, reflecting an unmet need to reduce the increased rate of major adverse events in patients with NSTEMI and unrecognized features of poor prognosis. Recently, the EARLY randomized trial showed that without pre-treatment, a very early invasive strategy (<2 hours) was associated with a significant reduction in the primary end-point of cardiovascular death and recurrent ischemic events at 1 month (hazard ratio (HR) 0.20; 95%CI 0.11 to 0.34), driven by a reduction in recurrent ischemic events in patients with intermediate- and high-risk NSTEMI [35]. Similarly, the VERDICT randomized controlled trial showed that in NSTEMI patients with high-risk (GRACE score > 140) a very early invasive treatment strategy (<12 hours) improved the primary outcome (all-cause death, nonfatal recurrent MI, hospital admission for refractory myocardial ischemia, or hospital admission for heart failure) (HR 0.81; 95% CI, 0.67–1.01) [36]. A recent meta-analysis by Barbarawi M et al., corroborated the above observations reporting that an invasive strategy within 24 hours versus an invasive strategy after 24 hours was associated with fewer major adverse cardiovascular events [37].

**CONCLUSIONS**

In conclusion, current trial data and everyday clinical practice indicate that there is an unmet need regarding the treatment currently offered to of high-risk NSTEMI patients. As the incidence of NSTEMI is increasing world-wide the number of NSTEMI patients with TOCA are also increasing and represent approximately 30% of all NSTEMIs (**Figure 5**). The present review calls for action regarding a change everyday clinical practice, which could have a significant impact on NSTEMI patients clinical outcomes. Herein we propose a new triage algorithm by which recognition of high-risk features in NSTEMI patients is central. Moreover we suggest the use of a novel risk score, the SAVE score, utilizing clinical, electrocardiographic and laboratory/imaging characteristics as a supplement to TIMI and GRACE risk scores, in order to identify NSTEMI with TOCA and poor prognosis. We believe that there is a need for increased awareness as to the identification of STEMIs being misclassified as NSTEMIs, for the use of additional ECG leads added to the classic 12-lead, and the implementation of an algorithm that helps in the identification of high risk NSTEMI patients and promotes a prudent use of cardiac catheterization facilities. Similar suggestions have been presented in the current literature suggesting a need for change in clinical practice [9,10,38] and proposing different diagnostic approaches such as use of artificial intelligence and big data networks for ECG interpretation in NSTEMI patients [24]. We are aware that the change in clinical practice suggested in this review has not been tested in randomized clinical trials and that an arbitrary points system and cut-offs have been used. However, we strongly believe that our proposal represents a reasonable hypothesis to be tested in future studies.

**FUNDING**

None

**COMPETING INTERESTS**

The authors have no competing interests to declare.

**FIGURE LEGENDS**

**Figure 1.** Myocardial infarction classification based on electrocardiographic findings and coronary artery occlusion.

Adapted from Michaud, K., Basso, C., d’Amati, G. et al. Diagnosis of myocardial infarction at autopsy: AECVP reappraisal in the light of the current clinical classification. Virchows Arch 2020;476: 179–194 with permission [Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0>)]

ECG; electrocardiography, NSTEMI; non-ST elevation myocardial infarction, STEMI; ST elevation myocardial infarction

**Figure 2.** Distribution of culprit artery in non-ST elevation myocardial infarction patients with totally occluded artery

Number of studies refer to the number that found each coronary artery as more frequent

Percentages refer to minimum to maximum observed distribution in all studies

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LAD; left anterior descending; LCx; left circumflex; RCA; right coronary artery

**Figure 3.** Suggested triage algorithm for detection of high-risk NSTEMI patients with totally occluded coronary arteries

Very high-risk features are hemodynamic instability or cardiogenic shock, recurrent or ongoing chest pain refractory to medical treatment, life-threatening arrhythmias or cardiac arrest, mechanical complications of MI, acute heart failure with refractory angina or ST deviation, recurrent dynamic ST- or T-wave changes, particularly with intermittent ST-elevation

h; hours INV; invasive, LBBB; left bundle branch block, STEMI; ST elevation myocardial infarction,

**Figure 4.** Proposed risk score for identification of NSTEMI patients with totally occluded coronary arteries

Points and risk score elements are arbitrary

\* Severely elevated cardiac enzymes were arbitrarily defined by an elevation of cardiac marker values more than five times the 99th percentile of Upper Reference Limit in patients with normal baseline values.

ECG; electrocardiogram, CABG; coronary artery bypass graft, DM; diabetes mellitus, DYSLIPID; dyslipidemia, FHx; family history of coronary artery disease, HTN; hypertension, LAD; left anterior descending; LCx; left circumflex, LM; Left main, LV EF; left ventricular ejection fraction, MI; myocardial infarction, NSTEMI; non-ST elevation myocardial infarction, RCA; right coronary artery, RF; risk factor

**Figure 5.** Patients with NSTEMI and total occlusion of coronary arteries

Adapted from Michaud, K., Basso, C., d’Amati, G. et al. Diagnosis of myocardial infarction at autopsy: AECVP reappraisal in the light of the current clinical classification. Virchows Arch 2020;476: 179–194 with permission [Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0>)]

ECG; electrocardiography, NSTEMI; non-ST elevation myocardial infarction, STEMI

**REFERENCES**

**[1].** Ibanez B, James S, Agewall S, et al.; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119-77.

**[2].** Collet JP, Thiele H, Barbato E, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2020:ehaa575. doi: 10.1093/eurheartj/ehaa575.

**[3].** Fuster V, Kovacic JC. Acute coronary syndromes: pathology, diagnosis, genetics, prevention, and treatment. *Circ Res.* 2014;114:1847–51.

**[4].** Khera S, Kolte D, Aronow WS, et al. Non-ST-elevation myocardial infarction in the United States: contemporary trends in incidence, utilization of the early invasive strategy, and in-hospital outcomes. *J Am Heart Assoc.* 2014;3:e000995. doi: 10.1161/JAHA.114.000995.

**[5].** Neumann JT, Goßling A, Sörensen NA, et al. Temporal trends in incidence and outcome of acute coronary syndrome. *Clin Res Cardiol.* 2020;10.1007/s00392-020-01612-1. doi:10.1007/s00392-020-01612-1

**[6].** Basit H, Malik A, Huecker MR. Non ST Segment Elevation (NSTEMI) Myocardial Infarction. [Updated 2020 Mar 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK513228/>

**[7].** DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med.* 1980;303:897-902

**[8].** DeWood MA, Stifter WF, Simpson CS, et al. Coronary arteriographic findings soon after non-Q-wave myocardial infarction. *N Engl J Med.* 1986;315:417-23.

**[9].** Khan AR, Golwala H, Tripathi A, et al. Impact of total occlusion of culprit artery in acute non-ST elevation myocardial infarction: a systematic review and meta-analysis. *Eur Heart J.* 2017;38:3082-89.

**[10].** Hung CS, Chen YH, Huang CC, et al. Prevalence and outcome of patients with non-ST segment elevation myocardial infarction with occluded "culprit" artery - a systemic review and meta-analysis. *Crit Care.* 2018;22:34.

**[11].** Warren J, Mehran R, Yu J, et al. Incidence and impact of totally occluded culprit coronary arteries in patients presenting with non-ST-segment elevation myocardial infarction. *Am J Cardiol.* 2015;115:428-33.

**[12].** Vogel B, Claessen BE, Arnold SV, et al. ST-segment elevation myocardial infarction. *Nat Rev Dis Primers*. 2019;5:39.

**[13].** Stribling WK, Kontos MC, Abbate A, et al. Left circumflex occlusion in acute myocardial infarction (from the National Cardiovascular Data Registry). *Am J Cardiol.* 2011;108:959-63.

**[14].** Krishnaswamy A, Lincoff AM, Menon V. Magnitude and consequences of missing the acute infarct-related circumflex artery. *Am Heart J.* 2009;158:706-12.

**[15].** Haeberlin A, Studer E, Niederhauser T, et al. Electrocardiographic ST-segment monitoring during controlled occlusion of coronary arteries. *J Electrocardiol.* 2014;47:29-37.

**[16].** Berry C, Zalewski A, Kovach R, et al. Surface electrocardiogram in the detection of transmural myocardial ischemia during coronary artery occlusion. *Am J Cardiol.* 1989;63:21-6.

**[17].** Wang TY, Zhang M, Fu Y, et al. Incidence, distribution, and prognostic impact of occluded culprit arteries among patients with non-ST-elevation acute coronary syndromes undergoing diagnostic angiography. *Am Heart J.* 2009;157:716-23.

**[18].** Matetzky S, Freimark D, Feinberg MS, et al. Acute myocardial infarction with isolated ST-segment elevation in posterior chest leads V7-9: "hidden" ST-segment elevations revealing acute posterior infarction. *J Am Coll Cardiol.* 1999;34:748-53.

**[19].** Khan JN, Chauhan A, Mozdiak E, et al. Posterior myocardial infarction: are we failing to diagnose this? *Emerg Med J.* 2012;29:15–8.

**[20].** Waldo SW, Brenner DA, Li S, et al. Reperfusion times and inhospital outcomes among patients with an isolated posterior myocardial infarction: insights from the National Cardiovascular Data Registry (NCDR). *Am Heart J.* 2014;167:350–4.

**[21].** Kim SS, Choi HS, Jeong MH, et al.; Korea Acute Myocardial Infarction Registry Investigators. Clinical outcomes of acute myocardial infarction with occluded left circumflex artery. *J Cardiol.* 2011;57:290-6.

**[22].** Meisel SR, Dagan Y, Blondheim DS, et al. Transient ST-elevation myocardial infarction: clinical course with intense medical therapy and early invasive approach, and comparison with persistent ST-elevation myocardial infarction. *Am Heart J.* 2008;155:848-54.

**[23].** Hackett D, Davies G, Chierchia S, et al. Intermittent coronary occlusion in acute myocardial infarction. Value of combined thrombolytic and vasodilator therapy. *N Engl J Med.* 1987;317:1055–59.

**[24].** de Silva R, Steg PG. Identifying patients with acute total coronary occlusion in NSTEACS: finding the high-risk needle in the haystack. *Eur Heart J.* 2017;38:3090–93

**[25].** Bahrmann P, Rach J, Desch S, et al. Incidence and distribution of occluded culprit arteries and impact of coronary collaterals on outcome in patients with non-ST-segment elevation myocardial infarction and early invasive treatment strategy. *Clin Res Cardiol* 2011;100:457–67.

**[26].** Kim MC, Ahn Y, Rhew SH, et al.; KAMIR Investigators. Impact of total occlusion of an infarct-related artery on long-term mortality in acute non-ST-elevation myocardial infarction patients who underwent early percutaneous coronary intervention. *Int Heart J.* 2012;53:160-4.

**[27].** Barbarawi M, Zayed Y, Kheiri B, et al. Optimal timing of coronary intervention in patients resuscitated from cardiac arrest without ST-segment elevation myocardial infarction (NSTEMI): A systematic review and meta-analysis. *Resuscitation.* 2019;144:137-44.

**[28].** Jung DH, Jeong MH, Kim KH, et al. Predictors of total occlusion of the infarct-related artery in patients with acute Non-ST elevation myocardial infarction. *Korean J Med.* 2008;74:271–80.

**[29].** White N, Wu G, Hanowitz C. Left Circumflex Artery Occlusions: (Electrically) Silent but Deadly. Available from <https://www.emra.org/emresident/article/left-circumflex-artery-occlusions-electrically-silent-but-deadly/>

**[30].** Daly M, Finlay D, Guldenring D, et al. Detection of acute coronary occlusion in patients with acute coronary syndromes presenting with isolated ST-segment depression. *Eur Heart J Acute Cardiovasc Care.* 2012;1:128-35.

**[31].** Savonitto S, Cohen MG, Politi A, et al. Extent of ST-segment depression and cardiac events in non-ST-segment elevation acute coronary syndromes. *Eur Heart J.* 2005;26:2106-13.

**[32].** Tzimas G, Antiochos P, Monney P, et al. Atypical Electrocardiographic Presentations in Need of Primary Percutaneous Coronary Intervention. *Am J Cardiol.* 2019;124:1305-14.

**[33].** Collins MS, Carter JE, Dougherty JM, et al. Hyperacute T-wave criteria using computer ECG analysis. *Ann Emerg Med* 1990;19:114–20.

**[34].** Cipriani A, D'Amico G, Brunello G, et al. The electrocardiographic "triangular QRS-ST-T waveform" pattern in patients with ST-segment elevation myocardial infarction: Incidence, pathophysiology and clinical implications. *J Electrocardiol.* 2018;51:8-14

**[35].** Lemesle G, Laine M, Pankert M, et al. Optimal Timing of Intervention in NSTE-ACS Without Pre-Treatment: The EARLY Randomized Trial. *JACC Cardiovasc Interv.* 2020;13:907-17.

**[36].** Kofoed KF, Kelbæk H, Hansen PR, et al. Early Versus Standard Care Invasive Examination and Treatment of Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. *Circulation.* 2018;138:2741-50.

**[37].** Barbarawi M, Kheiri B, Zayed Y, et al. Meta-analysis of optimal timing of coronary intervention in non-ST-elevation acute coronary syndrome. *Catheter Cardiovasc Interv.* 2020;95:185-93.

**[38].** Vetrovec GW. Increasing clarity for an early invasive strategy in NSTEMI. *Catheter Cardiovasc Interv.* 2020;95:194–95.

**TABLES**

**Table 1.** Possible causes for total occlusion of coronary arteries to present with a non-ST elevation myocardial infarction diagnosis

|  |
| --- |
| **Electrocardiography** |
| Poor sensitivity to detect infarction in posterolateral myocardial territory |
| **Thrombotic occlusion** |
| Spontaneous thrombus recanalization prior to hospital arrival or in-hospital after medical treatment |
| Slowly developing thrombus allowing the formation of collaterals |
| Misclassification of a total chronic occlusion as an acute occlusion due to delayed patient presentation  |
| Misclassification of a total chronic occlusion as the culprit in multivessel disease or prior coronary artery bypass grafting |
| **Myocardial area at jeopardy** |
| Presence of collaterals |
| Myocardial territory with dual blood supply |
| Small area myocardial infarct |

**Table 2.** Electrocardiographic signs indicative of non-ST elevation myocardial infarction with total occlusion of the culprit coronary artery

|  |
| --- |
| **Non-coronary specific signs** |
| Total number of leads showing ST-segment depression (>3) |
| Total ST-segment depression sum (≥ 6mm) |
| ST-segment depression > 2mm in any lead |
| Presence of q waves in ≥ 2 contiguous leads |
| Hyperacute T waves  |
| ‘Shark-fin’ – triangular waveform ECG pattern |
| Transient ST-segment elevation |
| Low QRS voltage |
| **LAD specific signs** |
| Hyperacute T waves |
| De Winter’s sign |
| Wellens’ sign (Type A & Type B) |
| ‘Shark-fin’ – triangular waveform ECG pattern |
| New RBBB |
| Resting U-wave inversion |
| **LCx specific signs** |
| ST-segment depression and / or T-wave inversion in inferolateral leads |
| ST-segment depression in V1-V3 leads |
| ST-segment elevation in V7-V8 leads |
| Prominent R-waves in V1-V2 (R/S > 1) with upright T waves V1-V3 |
| **RCA specific signs** |
| ST-segment depression and / or T-wave inversion in inferolateral leads |
| ST-segment depression in V1-V3 leads |
| ST-segment elevation in V7-V8 leads |
| Prominent R-waves in V1-V2 (R/S > 1) with upright T waves V1-V3 |
| ST-segment elevation in lead V4R |
| ST-segment elevation in lead V1 |
| Deep ST-segment depression in lateral leads (I + aVL ≥ 2mm & ST depression aVL > I) |
| QRS prolongation or epsilon wave in lead V4R |
| **LM specific signs**  |
| ST-segment elevation in aVR lead |
| ST-segment depression in all leads |
| ST-elevation in lead aVR ≥V1 |
| ‘Shark-fin’ – triangular waveform ECG pattern |
| **Other high-risk signs** |
| New RBBB |
| Myocardial infarction on previous LBBB using Scarbossa criteria |
| AV conduction abnormalities |

AV; atrioventricular, ECG; electrocardiogram, LBBB; left bundle branch block, RBBB, right bundle branch block

New LBBB is considered as STEMI by definition and requires urgent coronary angiography