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Editorial commentary: Prior silent/unrecognized myocardial infarction and heart failure: Size/extent matters☆

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According to the recent (2018) expert consensus document on the fourth universal definition of myocardial infarction (MI), prior silent/unrecognized MI (UMI) is defined as any one of the three criteria that include pathologic Q waves, in the absence of left ventricular (LV) hypertrophy or left bundle branch block, with or without symptoms, imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology, or pathological findings of a prior MI [1]. Such MIs may be more common than previously thought; they are age-dependent, more frequent in diabetics and in hypertensives, or those with underlying cardiovascular disease, albeit with highly variable prevalence and incidence (4–55%), depending on the population and age groups studied, and the method used to detect prior MI [2,3]. Patients with UMI may differ in several aspects from patients with clinical MIs (Table 1). Several studies have indicated that patients who have had such MIs without prior clinical evidence of MI, thus having remained previously undetected/unrecognized/undiagnosed, have an increased risk of cardiovascular events during long-term follow up [4,5]. Among these events, heart failure (HF) has been associated with this type of MI [6]. Knowing the pathogenetic mechanisms of HF following clinical MIs, whereby the extent ($\geq$20–25%) of lost viable myocardium determines the subsequent development of HF, it is logical to consider that the extent of scarred myocardium produced by these undetected MIs would also be the decisive factor in the subsequent development of HF. Hence, the question arises whether these UMIs are large-, modest- or small-sized MIs. Unfortunately, the data in the literature, as nicely reviewed by Soliman in this issue of TCM [6], remain scanty on this matter. Of course, other risk factors may be present and play a role and contribute to the development of HF, such as hypertension and diabetes. However, some studies have indicated that such classical cardiovascular risk factors are less prevalent in participants with UMI [7].

In the recently reported ARIC study, both non-clinical MI (hazard ratio – HR, 1.35) and clinical MI (HR, 2.85) were associated with increased risk of HF compared with no MI, with a larger magnitude of HF risk associated with clinical MI than the risk associated with UMI [8]. The cumulative incidence of HF was 31.4% among patients with clinical MI, 17.7% among patients with UMI, and 9.5% among patients without MI. However, the study did not report on any data about the size of MI. Whether the higher risk conferred by clinical MI implies greater extent of MI remains unknown. The risk was higher in younger patients with non-clinical MI, perhaps indirectly indicating that due to lack of collaterals, these MIs might have been larger in this age group.

An important study reporting on MI extent indicates that this was limited to 10–12% of the LV in patients with prior UMI [3]. An echocardiography study (Olmsted County Heart Function Study) of UMI indicated that non-anginal cardiopulmonary symptoms (dyspnea, orthopnea, history of fluid overload) were associated with increased risk in UMI patients and UMI predicted mortality as a function of global cardiac dysfunction [9], with a less significant impact of regional wall motion abnormalities, indicating that UMI is associated with cardiac symptoms via global dysfunction, implying that only sizable MIs may produce HF. The results of this study also challenge the clinical practice of dispelling ECG-based MI as false positive in symptomatic adults in the absence of regional wall motion abnormalities. Despite the presence of Q waves in the ECG, regional wall motion abnormalities were detected in only 12% of patients with UMI compared with 53% of patients with clinical MI. This is in keeping with the findings of a cardiac magnetic resonance (CMR) study examining the relationship of contractile function to the transmural extent of infarction in MI patients, which needs to approach 50% before contractile dysfunction can be identified [10]. This can occur with large-sized MIs, but in patients with small MI ($\leq$5% of total LV mass), even segments with transmural extent of infarction > 75% have normal function as they are surrounded by normally moving adjacent segments.

More UMIs may be detected with use of CMR than with use of ECG, as CMR can also detect non-Q wave MIs, which may have a 3-fold higher prevalence compared to Q-wave MIs [4,11]; on the other hand, Q-wave regression over time has also been noted [1]. However, these UMIs are relatively small-sized MIs (mean 8% of LV mass), which would not be expected to significantly compromise LV function (mean ejection fraction 52%) and lead to HF [11]; nevertheless, even these small MIs have been associated with a higher incidence of major adverse cardiovascular events (MACE) [11,12]. Some investigators have indicated that the best predictor of Q waves on the ECG is a quantified > 17% infarcted (scar) tissue of the LV, with spatial extent of infarction as the next best predictor [13]. With regards to structural abnormalities, UMI patients manifest such abnormalities more commonly than do patients who have no MI but less commonly than do those who have recognized MI. Late gadolinium enhancement (LGE) on CMR has been reported

☆ **Conflicts of interest** None.

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Table 1
Features of prior clinical and non-clinical (Silent/Unrecognized) myocardial infarction.

Feature	UMI	Clinical MI	Comments
Proportion of incident MIs	Up to ~50% of all MIs	≥50% of all MIs	
ECG-defined (Q-wave)	5–30%	38–67%	Many MI patients do not develop Q waves, while some patients may lose them over time
CMR-defined	↑by 50% c/w ECG	↑by 50–75% c/w ECG	LGE sensitivity for detecting chronic MI: 86–99%
Echo/RWMA	12%	53%	The transmural extent of MI needs to be close to 50% for large MIs and > 75% for small MIs before RWMA can be identified by Echo
DM	43%	15%	
History of angina	~30%	~60%	
Incidence of HF (%/HR)	13–37% / 1.1–2.1	23–41% /2.5–3.6	Risk of HF a/w UMI appears stronger in younger patients (median age < 53 years), possibly in men, diabetics and hypertensives
MACE (HR) *	1.5–2.5	1.5–3.3	Even small-sized UMIs are associated with worse prognosis c/w those without MI
Mortality (HR) *	1.5–2.5	1.6–3.0	
CV mortality (HR) *	1.4–2.2	2.5	
AF (HR) *	2.2–2.4 (men)0.9–1.0 (women)	1.7 (men)1.4–1.6 (women)	
Mean size (% of LV wall)	6–12	>15–17	Non-Q wave MIs are smaller-sized c/w Q-wave MIs An MI involving ≥ 20–25% of the LV can result in HF
Coronary vessels narrowed	2.9	2.8	

a/w = associated with; AF = atrial fibrillation; CMR = cardiac magnetic resonance (imaging); CV = cardiovascular; c/w = compared with; DM = diabetes mellitus; HR = hazard ratio; LGE = late gadolinium enhancement; LV = left ventric-le(-ular); MACE = major adverse cardiovascular events; MI = myocardial infarction; RWMA = regional wall motion abnormalities; UMI = unrecognized myocardial infarction.
* vs those without MI.

in 28–33% of patients with UMI and in ~75% of patients with clinical MI [11,12]. As in patients with clinical MI, where a higher incidence of clinical events has been observed in the group with LGE, with HF being the most common cause (38.2% vs 7.4%, $P < 0.001$), patients with UMI and LGE on CMR suffer similarly higher morbidity compared to UMI without LGE. Furthermore, MI patients with LGE in other territories than the MI (an UMI subgroup) have poorer long-term outcome with higher risk of MACE compared to those with LGE limited to MI territories [14].

A pathology study of 61 patients (28 UMI) also showed smaller infarcts in patients with UMI compared with clinical MI (mean size 7% versus 17% of LV wall; $p < 0.001$) despite similar extent of coronary artery disease [15]. There was a non-significant trend of a lower incidence in the history of HF in UMI patients (32% versus 42%). There was a higher incidence of diabetes in UMI patients (43% versus 15%).

Although HF may occur without major compromise in LV function, e.g. due to ischemia-induced HF with preserved ejection fraction (HFpEF), as detailed in the review by Soliman [6], development of HF with reduced ejection fraction usually needs more extensive LV scars to produce LV dysfunction and UMIs do not appear to be associated with larger MIs as compared to clinical MIs. Thus, it is important for future studies to discern which UMIs are associated with HF by evaluating and associating the size/extent of MI with the development of HF, as some preliminary data indicate. In keeping with the notion of smaller-sized MIs in the UMI group, the results of the studies reviewed by Soliman indicate, albeit with some variation, a lower incidence of HF with UMIs compared with clinical MIs, with the exception of the Framingham study [6]. Other studies also have steadily shown a lower incidence of MACE in patients with UMI compared with those with clinical MI, including, as mentioned above, the presence of non-anginal cardiopulmonary symptoms of dyspnea, orthopnea, and history of fluid overload [9]. Some studies have indicated that the pathophysiology behind UMI and recognized MI may differ; UMI is more associated with small-vessel disease than with large-vessel disease compared to recognized MI [16]. This observation may go along with the notion of HFpEF in patients with UMI.

Patients with small MIs, whether clinical or non-clinical, still appear to have a high risk of future cardiovascular events, perhaps related to underlying coronary artery disease and ischemic events triggering ventricular arrhythmias, rather than producing HF [12]. Larger-sized UMIs can, of course, do both; one would expect an MI involving ≥20–25% of the LV to result in HF. A sub-analysis of the Rotterdam study suggested that the incidence of atrial fibrillation is higher in men with UMI compared to those without MI [17], which is another potential, albeit entirely hypothetical, cause of HF via tachycardia-induced cardiomyopathy from uncontrolled ventricular rates, if at all. At the end and as the investigators of the Rotterdam study, reporting a higher incidence of HF in men with UMI, state “in the light of the high incidence of both UMI and HF in the elderly, it may be worthwhile for both doctors and patients to improve responsiveness to typical and atypical symptoms of MI.” [5].

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