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Silent myocardial infarction and risk of heart failure: Current evidence and gaps in knowledge ☆

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ABSTRACT

Coronary heart disease (CHD) is the most common underlying risk factor for heart failure (HF); up to one-third of the patients who are hospitalized for HF each year in the United States have a history of myocardial infarction (MI). Although silent MI (SMI) could account for up to one-half of all MIs, only a few studies examined the relationship between SMI and risk of HF. These few studies agreed on their conclusions that SMI is associated with increased risk of HF. However, there was less agreement on the magnitude of risk and the sex differences in the association between SMI and HF, which is probably due to the heterogeneity in how these studies defined SMI. This report summarizes and discusses the current evidence linking SMI to HF, the impact of the methods by which SMI is defined on the reported relationship between SMI and HF, the potential mechanisms for such relationship, the implications of these findings, and the gaps in knowledge that need to be addressed.

Introduction

Up to one-half of myocardial infarctions (MIs) go undetected at the time of occurrence then later discovered as part of routine clinical care, cardiac evaluation of emerging cardiovascular symptoms or as part of research studies [1,2]. Most of the studies examined the prognostic significance of these silent MIs (SMIs) or unrecognized MIs (UMIs) focused on investigating their associations with cardiovascular and total mortality, and only a few studies extended their investigations to include cardiovascular morbidity including heart failure (HF) [3–6]. Currently, 6.5 million patients suffer from HF in the United States, and projections show that this number will increase by at least 46% by 2030 [7]. Fueling this epidemic of HF is the improved survival of patients after acute MI making coronary heart disease (CHD) the leading underlying risk factor for HF [8]. This underscores the importance of studies investigating the link between SMI or UMI and HF.

Terminology

There is no consensus on whether SMI or UMI is a better term to describe the objective accidental finding of MI in an individual who denies having a prior MI. According to The Task Force for Third Universal Definition of Myocardial Infarction, in asymptomatic patients who develop new pathologic Q wavs criteria for MI detected during routine ECG follow-up, or reveal evidence of MI by cardiac imaging, that cannot be directly attributed to a coronary revascularization procedure, such MI should be termed “Silent MI” [9]. On the other hand, the term “Unrecognized MI” was the preferred term used by the American Heart Association (AHA) Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute in their statement on the definitions for acute coronary heart disease in epidemiology and clinical research studies [10]. The 2018 Fourth Universal Definition of Myocardial Infarction Task Force used "Silent/Unrecognized MI" which implies the appropriate use of both terms interchangeably [11]. Despite the lack of agreement on terminology, it is surprising to see that some healthcare providers and clinical investigators strongly argue for one term over the other to the extent that they totally dismiss the other term.

Generally, the “Unrecognized MI” terminology acknowledges the possibility of occurrence of symptoms at the time of the event that might have been too mild or atypical to push the patient to seek medical advice or to get the attention of the healthcare providers, and hence the MI went “unrecognized” to later be discovered. On the other hand, the “Silent MI” terminology makes a good contrast with the MI with full-blown picture that is hard to ignore by the patient and easy to pick by the healthcare providers.

☆ Conflicts of interest: None

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The term “Silent MI” , hence, overcomes any implied blame on the patients for misinterpreting their symptoms and not seeking timely medical advice, or on the healthcare providers who might have underestimated the symptoms. In research settings, it has been suggested that “Unrecognized MI” terminology should be reserved for MIs ascertained only in the cross-sectional studies. This is because “Unrecognized MI” is mostly defined in these studies as objective evidence of MI in the absence of self-reported history (lack of self-recognition) of MI. On the other hand, it has been suggested that the term “Silent MI” should be reserved for the longitudinal studies with multiple follow-up visits which have serial comparisons of cardiac investigations and the ability to objectively confirm the absence of clinical MIs. However, these suggestions have never been consistently applied, and both terms continue to be used interchangeably in studies using exactly the same definitions [3–6,12–15].

Regardless of the personal preferences and beliefs about which term is more appropriate, it must be realized that our current knowledge on this topic is derived from studies which used both terms interchangeably without distinction. Therefore, while it may be reasonable to prefer one term, it is not appropriate to totally dismiss the other. Also, it may not be practical at this point to standardize the terminology given the magnitude of prior studies and the evidence they generated using mixed terms. After all, when we say potato, potahto, tomato, tomahto we still know what each term means!

Current evidence of the link between SMI and HF

The PubMed, MEDLINE, Google Scholar, Web of Science databases were searched for published manuscripts until April 30, 2018 which include any of the terms “unrecognized”, “silent” or “subclinical” linked to “myocardial infarction” or “myocardial injury” . Only original research with reported results on the associations between SMI and HF as a separate outcome were considered. Table 1 provides a summary of these studies and their findings. In brief, the few studies which examined the risk of incident HF with SMI as a separate outcome reached a similar conclusion that SMI is associated with increased risk of HF. However, there have been differences in the strength of association and conflicting results regarding the sex differences in the association between SMI and HF.

The Framingham Heart Study reported on the risk of HF associated with SMI (referred to as UMI in the study) in 2,252 men and 2,818 women who were recruited in 1948 and followed for up to 34 years [3]. UMI was said to be present if routine biennial ECG showed a new MI that was not present in previous ECG tracings without either the patient or the attending physician raising the possibility that a clinical MI occurred in the time between the ECGs. The observed incidence of HF was 12.6% and 23.6% in women with UMI and recognized MI, respectively. In men, the incidence of HF was 34.4% and 23.3% for UMI and recognized MI, respectively. The increased risk of HF after UMI compared with recognized MI was significant in men but not in women [3]. Because the study was not intended to focus on only the relationship between UMI and HF, the authors reported the aforementioned incidence rates without reporting models adjusted for cardiovascular risk factors.

In the Rotterdam Study, UMI at the study baseline (1990–1993) was defined as the presence of ECG-evidence of MI in the absence of a self-reported history of MI in 2,581 men and 3,724 women who were followed until October 2006 [4]. ECG-evidence of MI was defined based on the Minnesota ECG Classification with some modifications [16]. Based on the presence of baseline UMI and history of MI, participants were classified as those with UMI, recognized MI, and those without MI. Participants were followed-up for incident HF for a median of 13.2 years. During follow up, 823 cases of HF occurred [403 (15.6%) in men vs. 420 (11.3%) in women]. Cumulative incidence rates of HF after 15 years of follow-up were 17% for no MI, 37% for UMI and 39% for recognized MI in men. These incidence rates were lower in women: 11% for no MI, 13% for UMI, and 28% for recognized MI. In multivariable-adjusted models, both recognized, and UMIs were associated with increased risk of HF in men [HR (95%CI) 2.6 (2.0, 3.3) and 2.1 (1.5, 2.9), respectively. In women, recognized MI was associated with HF [HR (95%): 2.8(1.9, 4.1)], but the association with UMI did not reach statistical significance [HR (95%CI): 1.1 (0.7, 1.7)].

In an early report from the ARIC (Atherosclerosis Risk In Communities) study, the risk of incident HF was examined in 7,659 women and 5,896 men who were free from self-reported history of CHD at baseline (1987–1989) then followed up until December 2002 [5]. SMI was defined as presence of old MI by Novacode ECG Classification [Novacode 5.1 to 5.4, major Q waves or minor Q waves with major ST-T abnormalities] at the baseline ECG [17]. During follow-up, 951 HF occurred [489 (6.4%) in women vs. 462 (7.8%) in men]. In a multivariable-adjusted model, the association between SMI with HF was significant in men [HR (95% CI):1.59 (1.04–2.44)] but not in women [HR (95% CI): 1.76 (0.85–3.62)] but the difference in hazard ratios (HRs) seemed to be non-significant [5].

In a more recent and detailed report from the ARIC study, the risk of HF was examined among 3,960 men and 5,283 women who were free of CHD at baseline (1987–1989) then followed up until December 31, 2010 [6]. Based on data from biennial ECGs recorded during four study visits as well as data on clinical MI obtained by review of hospital records, SMI was defined as presence of new MI by Minnesota ECG Classification in one visit in the absence of adjudicated clinical MI in the period before [16]. Participants were then classified as having SMI, clinical MI (CMI) or no MI. A total of 976 HF events occurred from the fourth visit (1996–1998) until the end of follow up in December 31, 2010. Although incident HF occurred more frequently in men than women [456 (11.5%) occurred in men vs. 520 (9.8%) in women], the association between MI [whether SMI or CMI] and HF was stronger in women than men. In women, incident HF occurred in 9.1% for no MI, 18.8% for SMI and 41.4% for clinical MI. On the other hand, men had incident HF of 10.1% for no MI, 16.9% for SMI, and 27.9% for CMI. In a model adjusted for demographics and HF risk factors, both SMI [HR (95%CI): 1.35 (1.02, 1.78), and CMI (HR (95%CI): 2.85 (2.31, 3.51)] were associated with increased risk of HF, compared with no MI. The risk of HF associated with SM was slightly stronger in women than that in men [HR (95%CI): 1.57 (1.05–2.35) vs. 1.19 (0.81–1.74)], which is opposite to that reported in the Framingham and Rotterdam Studies.

Methodological considerations in interpreting research on SMI

The reported rates of SMI varied widely among studies ranging from 4% to more than 57% of the total MIs [1,2]. Also, while some studies showed that SMI carries a worse prognosis than recognized MI, others showed the opposite [1]. Although these wide variations in the reported incidence rates and prognostic significance of SMI could be partially attributed to differences in populations at risk, it is unlikely that these differences among populations at risk are the main driving factors. This is because most of the studies that examined the epidemiology of SMI used age adjusted rates and adjusted for CVD risk factors such as diabetes, hypertension, obesity and smoking in their risk estimate models. Also, many of these factors are not significantly different among the studies listed in Table 1 that examined the associations between SMI and HF. For example, the prevalence of diabetes in the Rotterdam Study and ARIC Study (about 9% vs. 8%, respectively), and the prevalence of hypertension in the Framingham Heart Study and the ARIC study (about 28% vs. 30%, respectively) were not markedly different. On

Table 1
Studies investigating the association between silent myocardial infarction and heart failure.

Study	Sample		Methods of Defining MI		Risk of HF associated with MI by type		Comments
	Women	Men	Silent MI	Recognized MI	Women	Men	
The Heart Framingham Study [3]	2,818	2,252	New pathological Q wave ≥ 0.04 s during the biennial	Self-reported history and participants' physicians	**Incident HF in:** *UMI: 12.6%* *Recognized MI: 23.6%*	**Incident HF in:** *UMI: 34.4%* *Recognized MI 23.3%*	Up to 34 Y follow up The study reported only incident rates of HF. Proportion of age adjusted UMI out of total MIs: 37.6% in women; 28.8% in men.
The Rotterdam Study [4]	3,724	2,581	Baseline ECG evidence of MI using a modification of the Minnesota ECG Classification	Self-reported history and participants' physicians	**Incident HF in:** UMI: 13% Recognized MI: 28% **Adjusted HR (95%CI):** *UMI: 1.1 (0.7, 1.7)* *Recognized MI: 2.8 (1.9, 4.1) compared to no MI*	**Incident HF in:** UMI: 37% Recognized MI: 39% **Adjusted HR (95%CI):** *UMI: 2.1 (1.5, 2.9):* *Recognized MI: 2.6 (2.0, 3.3) compared to no MI.*	Median follow up 13 Y HF events: 403 (15.6%) in men; 420 (11.3%) in women Proportion of UMI out of total MIs: 65.1% in women; 36.8% in men.
The ARIC Study [5]	7,659	5,896	Baseline ECG evidence of MI using Novacode ECG classification	Self-reported history OF CHD which was an exclusion criteria	**Adjusted HR (95%CI):** *SMI: 1.76 (0.85, 3.62) compared to no MI*	**Adjusted HR (95%CI):** *SMI:1.59 (1.04–2.44) compared to no MI*	Mean follow up 14 Y HF events: 489 (6.4%) in women; 462 (7.8%) in men Participants with baseline CHD (n = 545) were excluded, and hence the exact proportion of SMI (n = 217) at baseline out of the total MI cannot be accurately calculated
The ARIC Study [6]	5,283	3,960	ECG-evidence of MI using the standard of Minnesota ECG Classification during four biennial study visits	Review of hospital discharge records by an adjudication committee	**Incident HF in:** *SMI: 18.8%* *Clinical MI: 41.4%* **Adjusted HR (95%CI):** *SMI: 1.57 (1.05–2.35)* *Clinical MI: 3.64 (2.58–5.14) compared to no MI*	**Incident HF in:** *SMI: 16.9%* *Clinical MI: 27.9%* **Adjusted HR (95%CI):** *SMI: 1.19 (0.81–1.74)* *Clinical MI: 2.54 (1.95–3.29) compared to no MI*	Median follow up 13 Y HF events:456 (11.5%) in men; 520 (9.8%) in women Proportion of age adjusted incident SMI out of total MIs: 60.5% in women; 41.3% in men.

UMI = Unrecognized myocardial infarction; ECG = Electrocardiogram; HR = Hazard ratio; CI = Confidence interval; ARIC = Atherosclerosis Risk In Communities, Y = Year.

the other hand, the method by which SMI is defined seems to play a more critical role.

SMI in its most straightforward definition is an MI that escapes clinical recognition at one point to be discovered later. Despite the simplicity of the definition, the "*devil is in the details*". The diagnosis of SMI requires two pieces of information. First, excluding patient's knowledge of or existence of documentation for a prior MI. Second, recent documentation of the occurrence of that prior MI despite lack of knowledge by the patient of its occurrence. Each one of those two pieces of information could be obtained using different methods that create heterogeneity among studies investigating SMI.

Excluding patient's knowledge of or existence of documentation for a prior MI could be done using self-reported history of a prior MI [13] or by review of hospitalizations records by a group of experts i.e. adjudication committee [18]. The self-reported history of a prior MI is liable to recall bias and misclassification, but it is a convenient and sometimes the only available method in population studies. On the other hand, review of hospitalization records by an adjudication committee is better but could be a logistically challenging approach. The Rotterdam Study [4] used baseline self-reported history supplemented by additional clinical information from the participant's physician but no review of hospital records. This process is similar to what was done in the Framingham Heart Study [3]. However, the Framingham Heart Study had the advantage of extending this process to multiple follow-up visits and not limiting it to the baseline visit only. On the other hand, the recent publication from the ARIC study [6] excluded the possibility of a prior recognized MI by reviewing hospital records by an adjudication committee during over ten years of follow up, which is the most accurate.

Similarly, documenting the occurrence of a prior MI could be obtained using different methods. Although ECG has been and remains the most common method for detection of SMI in both clinical and research settings, cardiac imaging such as echocardiography, nuclear imaging, or magnetic resonance imaging has been used to detect SMI [1,2]. Expectedly, different cardiac examination modalities could yield different SMI rates. Results from the Framingham Heart studies have shown that 10% of the anterior and 25% of inferior MIs lose their ECG signs within two years [3]. This means that many of the cases of SMI would go undetected with long intervals between ECG visits, and hence imaging would be a better method for these cases. This was proved true in a recent study showing low diagnostic accuracy of ECG to diagnose SMI compared to late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) [sensitivity = 9.7%, specificity = 98%, positive predictive value = 27%, and negative predictive value = 92%] [19].

Even with using the same cardiac investigation modality, heterogeneity in SMI ascertainment remains a major issue given lack of standard approaches to defining SMI. The ECG, which was used in all of the studies examining the association between SMI and HF, could be used in different ways to define MI. ECG-evidence of MI could be made based on the judgment of a cardiologist as a clinical diagnosis or based on specific standard criteria such as the Minnesota ECG Classification or Novacode ECG Classification [16,17]. Although all standard ECG classifications define MI based on predetermined criteria defining pathological Q, still there are differences in these criteria and how they are applied within the same ECG classification. For example, ECG-MI could be defined by Minnesota ECG Classification, the most commonly used ECG classification in population studies, as presence of a major Q/QS wave abnormality [MC1.1 or MC1.2] or minor Q/QS waves abnormality [MC 1.3] with major ST-T abnormality [MC 4.1, MC4.2, MC5.1 or MC5.2] [16]. Utilizing that definition, SMI could be defined as the presence of ECG-MI by Minnesota code at one point in time in the absence of a prior history of self-reported MI. This approach has been used in cross-sectional studies [12,13,20]. When multiple exam visits are available in longitudinal studies, the same ECG-MI definition also could be used to define new silent MI. In that case, new silent MI in a follow-up visit could be defined as the presence of evidence of ECG-MI by Minnesota code in that visit without evidence of a prior ECG-MI or clinical MI in a prior visit [6,18]. Another more specific approach that also uses Minnesota ECG Classification is called Q/ST/T serial changes [21,22]. This approach takes into account not only developing new ECG-MI by Minnesota code as previously defined in a follow-up visit but also requires significant changes in the amplitude and/ or duration of the Q/ST/T waveforms. Minor modifications to each of these approaches have also been reported. For example, instead of defining new MI from serial changes as codes Q1-Q7, using Q1-Q8 has been used [23,24].

In the Framingham Heart Study [3], MI from the ECG was defined as Q wave $\geq$ 0.04 s or loss of initial QRS in leads in which this could not have expected to occur. Interim myocardial infarction was said to occur when changes from a previous tracing showed clear loss of R-wave potential or the appearance of pathologic Q wave without another explanation. Notably, participants with UMI were further sub-classified as *SMI* if they do not recall any symptoms suggestive of acute coronary event or *atypical infarction* if they reported interim symptoms that could be MI [an alleged gallstone attack, peptic ulcer, or a hiatus hernia]. This means that not all UMI were indeed SMI.

On the other hand, the Rotterdam Study [4] used the Minnesota ECG classification to define MI [16]. The diagnosis of MI was driven by pathologic Q waves and secondary criteria such as QR ratio and R-wave progression. However, ST-T abnormalities were not considered but were taken into account by the clinicians validating the diagnosis of MI based on ECG. Omitting the ST-T abnormalities and depending on the clinicians for that part deviates from the basic principles of the Minnesota ECG Classification.

Unlike the Rotterdam Study, the recent publication from the ARIC study [6] applied the rules of Minnesota ECG classification in defining MI as supposed to be in each of the follow-up visits and not only at baseline. That is to say, ECG evidence of MI was defined as new appearance of a major Q/QS wave abnormality [MC 1.1 or 1.2] or minor Q/QS wave abnormality [MC 1.3] plus major ST-T abnormality [MC 4.1, 4.2, 5.1, or 5.2]. Notably, the study did not use the serial Q/ST/T changes which are more specific and would yield less rates of SMI. The earlier publication from the ARIC study [5] used only the baseline ECG and defined MI using Novacode [17], which explains the relatively different sex results even within the same study.

These differences in the MI definition among the Framingham Heart Study, Rotterdam Study, and the ARIC study could explain the differences in the magnitude of HF risk associated with SMI and the conflicting sex results. Without taking into account the method by which SMI is defined, our interpretation of the SMI research would not be complete and comparing studies would not be appropriate. There is no doubt that lack of standard methods to define SMI could hinder improving care of CHD and HF. Also, it is unclear whether the association of SMI would differ if a method other than the ECG is used. Identifying the ideal cardiac investigation modality that accurately detects SMI and predicts the risk of adverse outcomes such as HF is needed.

Mechanisms linking SMI to HF

SMI is an MI; the difference is the awareness and documentation of its occurrence. Therefore, the potential mechanisms linking SMI to HF could be similar to those mechanisms linking recognized MI to HF. That is to say, HF with reduced ejection fraction (HFrEF) could occur as a consequence of SMI due to loss of functioning myocytes and myocardial fibrosis and subsequent left ventricular

dilatation. The resulting neuro-hormonal activation and left ventricular remodeling could lead to progressive deterioration of the remaining viable myocardium. Also, chronic ischemia may result in hibernation and stunning with a further decline in left ventricular function [8].

Myocardial ischemia is one of the leading factors of HF with preserved ejection fraction (HFpEF) [8], and hence, HFpEF could also occur as a result of SMI. A previous report from the Framingham Heart Study showed that CHD accounts for more than half of patients with HFpEF [25], which further supports this notion. Nevertheless, the relationship between SMI and HFpEF is yet to be established, and it is not clear whether there is differential impact of SMI on HFpEF vs. HFrEF.

Another possible explanation for the reported association between SMI and HF is that both conditions share similar risk factors, and therefore they are the result of the same underlying pathology rather than being the result of one another. The reported significant risk factors for SMI include age, hypertension, and diabetes [2], which also are the reported significant risk factors for HF [26]. Nevertheless, the Rotterdam and the ARIC studies [4,6] adjusted for these risk factors in the models, and hence it is unlikely that the shared risk factors confounded the observed relationship between SMI and HF. To better prevent HF in the setting of SMI, more research is needed to identify the SMI risk factors that could be different from recognized MI and to shed light on the potential mechanisms for the links between SMI and HF.

Clinical and research implications

The accumulating evidence that SMI increases the risk of HF, and the fact that CHD is a significant risk factor for HF suggest that incorporating SMI in the HF prevention and management program is needed. With the increasing focus on addressing stage "A" HF (pre-HF) as the ideal approach of preventing the severe terminal forms of HF (stages C and D), attention needs to be directed towards screening risk factors such as SMI. However, the cost-effectiveness of screening for SMI as part of HF risk assessment need to be assessed. Although guideline-directed therapy has a definite role in preventing future HF among recognized MI patients and is part of a quality-of-care core measure [26], it is unknown whether such benefit exists for those with SMI.

Clinical trials examining the efficacy of novel HF therapies aimed at reducing future cardiovascular outcomes almost invariably include MI as one of the outcomes or part of the composite cardiovascular outcome. It seems reasonable that including SMI as an endpoint in the HF clinical trials that address adverse outcomes could significantly reduce the duration of these clinical trials, decreasing the cost and preventing undue harm to patients exposed to experimental therapies.

Gaps in knowledge

The literature on the association between SMI and HF provided reasonable evidence that SMI increases the risk of HF. This evidence is further supported by the known relationship between CHD and HF. However, still there are several gaps in knowledge in need to be addressed to better understand, diagnose, and treat SMI, and ultimately prevent HF in the setting of SMI. Examples of further research needed to fill the current gaps in knowledge include:

- Develop standard methods for defining SMI. This includes investigating whether ECG or imaging or a combination of both is a better approach for detection of SMI, and standardizing the criteria for such approach.
- Examine the impact of SMI size on the risk of HF
- Investigate the cost-effectiveness of screening for SMI as part of HF management.
- Identify SMI risk factors and whether they differ from recognized MI.
- Explore optimal risk factor modifications and treatment of SMI, as well as prevention of HF in the setting of SMI with emphasis on aspects that differ from recognized MI.
- Improve awareness of the adverse outcomes associated with SMI, and the potential benefits of detection of SMI in the prevention of HF.
- Examine whether there is a differential association between SMI and HF by type; HFpEF and HFrEF
- Investigate reasons for the sex differences in the association between SMI and HF.

Conclusions

SMI represents a significant proportion of all infarctions and is associated with increased risk of CVD and total mortality. The few studies that examined the relationship between SMI and HF have conclusively shown that SMI is associated with increased risk of HF. However, these studies reported conflicting sex differences in the association between SMI and HF, which is probably due to the heterogeneity in the methods by which SMI is defined. Developing standards methods for detection of SMI, examining the cost-effectiveness of routine screening for SMI as part of HF management, better understanding of the risk factors of SMI, and exploring optimal approaches for prevention HF in the setting of SMI are just a few of many gaps in knowledge that need further research.

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References

[1] Pride YB, Piccirillo BJ, Gibson CM. Prevalence, consequences, and implications for clinical trials of unrecognized myocardial infarction. Am J Cardiol 2013;111:914–18.
[2] Sheifer SE, Manolio TA, Gersh BJ. Unrecognized myocardial infarction. Ann Internal Med 2001;135:801–11.
[3] Kannel WB, Cupples LA, Gagnon DR. Incidence, precursors and prognosis of unrecognized myocardial infarction. Adv Cardiol 1990;37:202e14.
[4] Leening MJ, Elias-Smale SE, Felix JF, Kors JA, Deckers JW, Hofman A, et al. Unrecognised myocardial infarction and long-term risk of heart failure in the elderly: the Rotterdam Study. Heart 2010;96:1458–62.
[5] Rautaharju PM, Prineas RJ, Wood J, Zhang Z-M, Crow R, Heiss G. Electrocardiographic predictors of new-onset heart failure in men and in women free of coronary heart disease (from the Atherosclerosis in Communities [ARIC] Study). Am J Cardiol 2007;100:1437–41.
[6] Qureshi WT, Zhang Z-M, Chang PP, Chang PP, Rosamond WD, Kitzman DW, et al. Silent myocardial infarction and long-term risk of heart failure: the ARIC study. J Am Coll Cardiol 2018;71:1–8.
[7] Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018;20(137):e67–e492.
[8] Gheorghiade M, Sopko G, De Luca L, Velazquez EJ, Parker JD, Binkley PF, et al. Navigating the crossroads of coronary artery disease and heart failure. Circulation 2006;114:1202–13.
[9] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.
[10] Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation 2003;108:2543–9.
[11] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, The executive group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart

Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction. Circulation 2018;138 00–00. doi:10.1161/CIR.0000000000000617.
[12] Stiles MC, Seaquist ER, Yale JF, Green JB, Katz LA, Kempainen S, et al. Is silent myocardial infarction more common in women with type 2 diabetes than in men? J Diabetes Complications 2012;26:118–22.
[13] Levitan EB, Safford MM, Kilgore ML, Soliman EZ, Glasser SP, Judd SE, et al. Assessment tools for unrecognized myocardial infarction: a cross-sectional analysis of the reasons for geographic and racial differences in stroke population. BMC Cardiovasc Disord 2013;13:23.
[14] Davis TM, Coleman RL, Holman RR, Group UKPDS. Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. Circulation 2013;127:980–7.
[15] Kim HW, Klem I, Shah DJ, Wu E, Meyers SN, Parker MA, et al. Unrecognized non-Q-wave myocardial infarction: prevalence and prognostic significance in patients with suspected coronary disease. PLoS Med 2009;6(4):e1000057.
[16] Prineas RJ, Crow RS, Blackburn H. The Minnesota code manual of electrocardiographic findings. Littleton, MA: John Wright–PSG; 1982.
[17] Rautaharju PM, Park LP, Chaitman BR, Rautaharju F, Zhang ZM. The Novacode criteria for classification of electrocardiographic abnormalities and their clinically significant progression and regression. J Electrocardiol 1998;31:157–187.
[18] Zhang ZM, Rautaharju PM, Prineas RJ, Rodriguez CJ, Loehr L, Rosamond WD, et al. Race and sex differences in the incidence and prognostic significance of silent myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2016;133:2141–8.
[19] Amier RP, Smulders MW, van der Flier WM, Bekkers SCAM, Zweerink A, Allaart CP, et al. Long-term prognostic implications of previous silent myocardial infarction in patients presenting with acute myocardial infarction. JACC Cardiovasc Imaging 2018 pii: S1936-878X(18)30204-3.
[20] Rizk DV, Gutierrez O, Levitan EB, McClellan WM, Safford M, Soliman EZ, et al. Prevalence and prognosis of unrecognized myocardial infarctions in chronic kidney disease. Nephrol Dial Transplant 2012;27:3482–8.
[21] Prineas RJ, Crow RS, Zhang Z-M. The Minnesota code manual of electrocardiographic findings. London: Springer Science & Business Media; 2009.
[22] Crow RS, Prineas RJ, Hannan PJ, Grandits G, Blackburn H. Prognostic associations of Minnesota Code serial electrocardiographic change classification with coronary heart disease mortality in the Multiple Risk Factor Intervention Trial. Am J Cardiol 1997;80:138–44.
[23] Gupta M, Miller CJ, Baker JV, Lazar J, Bogner JR, Calmy A, et al. Biomarkers and electrocardiographic evidence of myocardial ischemia in patients with human immunodeficiency virus infection. Am J Cardiol 2013;111:760–4.
[24] Zhang ZM, Prineas RJ, Eaton CB. Evaluation and comparison of the Minnesota Code and Novacode for electrocardiographic Q-ST wave abnormalities for the independent prediction of incident coronary heart disease and total mortality (from the Women's Health Initiative). Am J Cardiol 2010;106:18–25.
[25] Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;26:1565–74.
[26] Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008;117:2544–65.