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A novel and practical screening tool for the detection of silent myocardial infarction in patients with type 2 diabetes

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Disclosure Summary

The authors have nothing to disclose.

Abstract

Objective

Silent myocardial infarction (MI) is a prevalent finding in patients with type 2 diabetes and is associated with significant mortality and morbidity. Late gadolinium enhancement (LGE) by cardiovascular magnetic resonance (CMR) is the most validated technique for detection of silent MI but is time consuming, costly and requires administration of intravenous contrast. We therefore planned to develop a simple and low cost population screening tool to identify those at highest risk of silent MI validated against the CMR reference standard.

Methods

100 asymptomatic patients with type 2 diabetes underwent electrocardiogram (ECG), echocardiography, biomarker assessment and CMR at 3.0T including assessment of left ventricular ejection fraction and LGE. Global longitudinal strain (GLS) from 2 and 4 chamber cines was measured using feature tracking.

Results

17/100 patients with no history of cardiovascular disease had silent MI defined by LGE in an infarct pattern on CMR. Only 4 silent MI patients had Q waves on ECG. Patients with silent MI were older (65 vs 60, $p=0.05$), had lower E/A ratio (0.75 vs 0.89, $p=0.004$), lower GLS (-15.2% vs -17.7%, $p=0.004$) and higher NT-proBNP (106ng/L vs 52ng/L, $p=0.003$). A combined risk score derived from these 4 factors had an area under the receiver operating characteristic (ROC) curve of 0.823 (0.734-0.892), $P<0.0001$. A score of $\geq 2/5$ had 82% sensitivity and 72% specificity for silent MI.

Conclusions

Using measures that can be derived in an outpatient clinic setting, we have developed a novel screening tool for the detection of silent MI in type 2 diabetes. The screening tool had significantly superior diagnostic accuracy than current ECG criteria for the detection of silent MI in asymptomatic patients.

Abbreviations

ACR	Albumin creatinine ratio
BSA	Body surface area
CMR	Cardiovascular magnetic resonance
E/A	Early and late filling velocities ratio
ECG	Electrocardiogram
ECV	Extracellular volume
EDSR	Early diastolic strain rate
FT	Feature tracking
GLS	Global longitudinal strain
hs-CRP	High sensitivity C reactive protein
hs-cTnT	High sensitivity cardiac troponin T
LDSR	Late diastolic strain rate
LGE	Late gadolinium enhancement
NT-proBNP	Amino-terminal pro-brain natriuretic peptide
LV	Left ventricle
LVEF	Left ventricular ejection fraction
ROC	Receiver operating characteristic
MI	Myocardial infarction
SSFP	Steady-state free precession

SSR Systolic strain rate

TDI Tissue Doppler imaging

Introduction

Cardiovascular disease, primarily stroke and myocardial infarction (MI), account for the vast majority of mortality associated with type 2 diabetes (1, 2). Silent MI is a relatively common finding in patients with type 2 diabetes (3, 4) although the exact prevalence in contemporary asymptomatic populations is unknown (5).

Currently the most extensively validated method to assess for the presence and extent of silent MI is the late gadolinium enhancement (LGE) technique measured by cardiovascular magnetic resonance (CMR). Using this technique it is possible to establish the location and distribution of scar tissue. The prevalence of silent MI according to the presence of LGE in symptomatic patients with type 2 diabetes is reported to be between 21-28% (3, 4). In these cohorts the presence of silent MI was strongly associated with an increase in major adverse cardiovascular events (MACE) and mortality.

There has been a decrease in the rate of acute MI in patients with type 2 diabetes over the past two decades (6). This reduction is thought to reflect improvements in glycaemic control and modification of other concomitant risk factors such as smoking, dyslipidaemia and blood pressure. However, per definition, silent MI is usually undetected and affected patients therefore fail to benefit from aggressive risk factor management, which may explain the poor clinical outcome in this group.

The detection of patients with silent MI remains a challenge as the most accurate method relies on CMR, which has limited availability, is relatively time consuming, costly and requires administration of intravenous contrast making it a less than ideal population screening tool. Several imaging and biomarker tests have been shown to be able to detect the presence and determine the extent of clinically recognised MI measured by LGE including Q waves on 12 lead electrocardiogram (ECG) (7), ejection fraction (8), strain parameters (9), high sensitivity troponin (hs-cTnT) (10) and amino-terminal pro-brain natriuretic peptide (NT-proBNP) (11). However, the sensitivity and specificity of these tests to detect silent MI in type 2 diabetes is at present unknown.

In this study, we aimed to assess the diagnostic accuracy of several commonly measured parameters in asymptomatic patients with type 2 diabetes to detect silent MI. We hypothesised that a risk score

derived from a combination of these measurements could accurately predict the presence of silent MI on CMR.

Methods

Enrolment Criteria

100 asymptomatic patients with type 2 diabetes were recruited from 30 primary care health centres in West Yorkshire, UK. The study was approved by the local ethical committee (13/YH/0098) and individuals were enrolled onto the study after informed consent. Exclusion criteria were known cardiovascular disease (including ischaemic heart disease, heart failure or persistent atrial fibrillation), kidney disease (eGFR <30), uncontrolled hypertension (with latest BP >140/80mmHg (12)), treatment with insulin or ACE inhibitor/angiotensin receptor blocker (to avoid patients with occult evidence of renal or other end organ damage).

CMR protocol

All patients underwent an identical CMR study on a dedicated cardiovascular 3 Tesla Philips Achieva TX system (Philips, Best, The Netherlands) equipped with a 32 channel coil and MultiTransmit® technology. Data were acquired during breath-holding at end expiration.

From scout CMR images, the left ventricular long and short axes were determined. Cine images covering the entire heart in the LV short axis plane and orthogonal long-axis planes were then acquired (balanced SSFP, spatial resolution 1.2x1.2x10mm³, 50 cardiac phases TR/TE 2.6/1.3ms, flip angle 40°, field of view 300-420mm). Cines planned to cover the entire left atrium (LA) short axis plane in end systole were also acquired (as LV stack but slice thickness 5mm).

Late gadolinium enhancement (LGE) imaging was carried out more than 6 minutes after contrast injection (0.15mmol/Kg Gadovist, Bayer Schering) using inversion recovery-prepared T1-weighted echo. The optimal inversion time to null signal from normal myocardium was determined using a Look-Locker approach. Typical parameters are TR/TE 3.5/2.0 ms, flip angle 25°, acquired spatial resolution 1.54x1.76x10mm³ and performed in 10-12 short axis slices with further slices acquired in

the vertical and horizontal long axis orientations, phase-swapped or imaged in systole, if indicated based on LGE imaging obtained or wall-motion abnormality.

CMR interpretation

CMR data were assessed quantitatively using commercially available software (CVI42 v5.1.0, Circle Cardiovascular Imaging Inc. Calgary, Canada) blinded to clinical details. LV mass, ejection fraction (EF) and LA volume were measured from short axis cine images.

For feature tracking analysis endocardial and epicardial LV contours were drawn on long axis 4 chamber and 2 chamber cines using a semi-automated process. Peak global longitudinal strain, systolic strain rate, early and late diastolic strain rates were measured. Late diastolic strain rates were defined as peak rate during active atrial contraction.

The presence of silent MI was identified by 2 physicians experienced (5 and 15 years) in CMR interpretation based upon typical subendocardial distribution of LGE present. The mass of LGE was quantified by the Otsu method (13).

Echocardiography, Electrocardiography and 24 hour Blood Pressure monitoring

All patients underwent echocardiography (Vivid e9, GE Medical Systems, Milwaukee, WI, USA) focused on Doppler measurements of mitral inflow and tissue Doppler imaging (TDI) of the lateral and medial mitral annulus. E/A ratio (the inverse was used for the index), E', A' and S' are measured on the machine using inbuilt software. Diastolic dysfunction was graded 0-3 by an accredited echocardiographer blinded to clinical details according to international guidelines (14). 12 lead electrocardiography (MAC500, GE Medical Systems, Milwaukee, WI, USA) was analysed by 2 physicians blinded to clinical details for the presence of Q waves according to international guidelines (15). All patients underwent 24 hour blood pressure monitoring (6100, Welch-Allyn, Skaneateles Falls, NY, USA) set to inflate every 30 minutes in the day and every hour at night.

Blood tests

Blood was drawn from each subject at the time of CMR and tested for HbA1c. Serum was stored at -70°C and tested in one batch for hs-cTnT typical coefficient of variability 4.4% at 13.7ng/L and 3.6%

at 95.3 ng/L, NT-proBNP typical coefficient of variability 2.9% at 91 ng/L and 2.1% at 415 ng/L (Cobas 8000, Roche Diagnostics, Burgess Hill, West Sussex) and hs-CRP (Advia, Siemens Healthcare Diagnostics, Marburg, Germany). Fasting cholesterol and previous HbA1c values were recorded from review of electronic records.

Statistical analysis

Statistical analysis was performed using IBM SPSS® Statistics 22.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as means \pm standard deviation and compared using t-test or Mann Whitney U test depending on normality. Categorical variables were expressed as N (%) and compared using Fisher exact test.

Receiver operating characteristic (ROC) analysis was used to determine the diagnostic accuracy of parameters that had been significantly different in those with silent MI. The diagnostic accuracy is expressed as area under the curve (AUC) and 95% confidence interval. Optimal sensitivity and specificity were calculated using Youden index. Nested models were used to establish the best possible AUC from combining the variables associated with silent MI. AUCs were compared by using validated methods described by DeLong et al (16).

Using the cut offs derived from the Youden analysis of the ROC curves each significant variable was given a binary classification (0 or 1). These four categorical variables were summed to calculate a silent MI risk score (range 0-5). The AUC of the silent MI risk score was compared to the best possible AUC from the individual parameters derived from the nested risk model.

We estimated that for a screening tool to be clinically useful it would need sensitivity >80% and to be significantly superior to the current screening test of Q waves which has a sensitivity of 28% (7).

Assuming that the prevalence of silent MI in a diabetic cohort to be around 10% (4) using a 2 sided Fisher exact test with $\alpha=0.05$ and power 80% it was calculated 98 patients would be needed, including 10 with silent MI. $P<0.05$ two-sided was considered statistically significant.

Results

Seventeen of the 100 patients had evidence of silent MI defined as a subendocardial pattern of LGE identified by two experienced CMR reporters independently. Figure 1 shows examples from 3 patients. For the whole population mean \pm SD age was 60.7 \pm 10.9 years, duration of diabetes 5.0 \pm 4.4 years, current HbA1c 63.1 \pm 19.6 mmol/mol, median HbA1c since diagnosis 64.5 \pm 17.2 mmol/mol and 24 hour blood pressure 131.4 \pm 15.0/72.7 \pm 9.1 mmHg. Of the 100 patients 82 were male, 72 were white British, 19 South Asian, 6 Black, 1 Turkish, 1 Polish and 1 Latin American. Patient characteristics are shown in Table 1 according to silent MI status. There was a range in the extent of silent MI from 0.4g to 36.6g. Mean mass of infarction was 6.1 \pm 8.8g (5.8 \pm 8.5% of LV mass) and was predominantly subendocardial with mean transmural of 60.3 \pm 28.0%.

Patients with silent MI were older than those without silent MI (65.4 \pm 9.2 vs 59.8 \pm 11.0 years, P=0.05) but there was no significant difference in any other patient characteristic or use of medication. There was no significant difference in any cardiac risk factors including 24 hour BP, fasting cholesterol, duration of diabetes or smoking (P=0.24, 0.69, 0.24 and 0.28 respectively).

The mean number of previous HbA1c measurements included in the analysis was 9.7 \pm 5.7 per patient over 4.3 \pm 2.7 years. There was no significant difference between mean, median or highest HbA1c since diagnosis between those with and without silent MI (P=0.69, 0.77 and 0.28 respectively).

Electrocardiography

Pathological Q waves on ECG were only present in 4/17 with silent MI and 6/83 without silent MI (sensitivity 24%, specificity 93%). Other ECG abnormalities present in 19/100 patients were not associated with silent MI and included left axis deviation in 5, right bundle branch block in 5, left ventricular hypertrophy by voltage criteria in 4, left anterior hemiblock in 3, T wave abnormalities in 3 and trifascicular block in 1.

Echocardiography

Results of echocardiography are shown in Table 1. The only significant difference between those with and without silent MI was a lower E/A ratio (0.75 ± 0.30 vs 0.89 ± 0.30 , $P=0.03$) in patients with silent MI. Grade of diastolic dysfunction was not significantly different between those with and without silent MI (grade 0, 6 vs 19%; grade 1, 88 vs 75%; grade 2, 0 vs 5%; and grade 3, 6 vs 1% $P=0.24$).

Cardiovascular magnetic resonance

CMR results are shown in Table 1. LV mass index to BSA was higher in those with silent MI than those without (51.4 ± 6.5 vs $47.2\pm 8.7\text{g/m}^2$, $P=0.01$). There was no other difference in volumetric parameters. Of the longitudinal strain parameters measured by feature tracking, global longitudinal strain (GLS) -15.2 ± 3.7 vs $-17.7\pm 3.1\%$, $P=0.004$, peak systolic strain rate (SSR) -93.8 ± 31.8 vs $-111.2\pm 42\%$, $P=0.04$ and early diastolic strain rate (EDSR) 64.1 ± 16.6 vs $84.0\pm 33.1\%$, $P=0.02$ were all significantly lower in those with silent MI. There was no difference in late diastolic strain rate (LDSR) $P=0.89$.

Of the patient characteristics shown in Table 1 none had a significant association with quantitative mass of silent MI. Of the investigation findings shown in Table 1 the mass of silent MI only had significant correlations with LVEF ($R=-0.81$, $P<0.0001$), E/E' ($R=-0.58$, $P=0.02$) and hs-cTnT ($R=0.58$, $P=0.02$).

Biomarkers

NT-proBNP was significantly higher in those with silent MI (105.8 ± 132.2 vs $51.9\pm 100.8\text{ng/L}$, $P=0.003$). There was no difference in hs-CRP or hs-cTnT ($P=0.57$ and 0.42 respectively).

Development of a screening tool

The area under the ROC curve for age, Q waves, E/A ratio, GLS, and NT-proBNP are shown in Table 2 and Appendix 1. The AUC for the nested model of all 4 variables was 0.850 ($0.765-0.914$), $P<0.0001$ and the maximum possible sensitivity was 94% and specificity 71%. The nested model had higher diagnostic accuracy than Q waves, age, E/A ratio and GLS alone ($p<0.0001$, 0.02 , 0.02 and

0.006 respectively). The improvement over NT-proBNP showed a trend ($p=0.07$). The addition of Q waves did not significantly improve the AUC of the model.

The number of patients with silent MI according to their silent MI risk score is shown in Figure 2. The combined 4 variable silent MI risk score had an AUC of 0.823 (0.734-0.892), $p<0.0001$ and better diagnostic accuracy than Q waves, age and E/A ratio separately ($p<0.0001$, 0.001 and 0.02 respectively). The sensitivities and specificities for each possible silent MI risk score are shown in Table 3.

Discussion

The prevalence of silent MI (17%) detected by LGE imaging in this low risk asymptomatic population was high approaching 1 in 5 patients. We have found increasing age to be the only conventional risk factor associated with silent MI. We have identified several markers of silent MI that can be detected by cardiac imaging or blood test and have shown that these markers can be combined to develop a simple screening tool with good diagnostic accuracy.

We have demonstrated that a simple risk score can predict the presence of silent MI in patients with type 2 DM as shown by LGE on CMR. The risk score is composed of age, E/A ratio ≤ 0.79 , GLS $\geq -18.4\%$ and NT-proBNP $> 29\text{ng/L}$. These are all parameters that are often measured in a cardiology clinic or could easily be measured in community based screening. In the model we derived GLS from feature tracking of CMR cine images. However it is possible to measure GLS from standard echocardiography which has been demonstrated to show good agreement with GLS measured from CMR (17).

The decision about where to make the cut off to recommend further investigation depends on whether sensitivity or specificity is the predominant clinical priority (Table 3). If the cut off was set at a score ≥ 2 (100% sensitivity and 42% specificity) it would ensure that the vast majority of silent MI was detected with only 2.5 patients needing CMR to identify one patient with silent MI. Alternatively if the cut off was higher with a score ≥ 3 (82% sensitivity and 72% specificity) approximately 1 in 6 patients with silent MI would be missed but only 1.5 patients would need to be screened to detect one

patient with silent MI. Either of these two scenarios are vastly superior to our current screening test using Q waves that only had 24% sensitivity in our asymptomatic cohort and 28% sensitivity in a cohort of patients with clinically recognised non-ST elevation MI (7).

All of the measured components within the score namely impaired GLS (18), elevated NT-proBNP (19) and E/A ratio (20) have been associated with adverse outcomes in patients with type 2 diabetes without prior history of MI. It is likely that a proportion of the mortality reported in these patients is due to silent MI. It has also been shown that larger infarcts have greater impairment of GLS (9), higher NT-proBNP (11) and altered mitral inflow (21). Therefore all of the measured parameters have biological validity and prognostic significance that supports their inclusion in a risk score.

The imaging parameters associated with mass of silent MI were different from those included in the silent MI risk score and included LVEF, E/E' and hs-cTnT. These parameters are all recognised to correlate with extent of infarction and prognosis after symptomatic MI (8, 10, 22). However, we have demonstrated that they were insensitive for the detection of silent MI in type 2 diabetes and of limited value in this setting.

It was an unexpected finding that conventional risk factors including fasting cholesterol, 24 hour BP, smoking and even previous glycaemic control had no association with the likelihood of silent MI in our population, although this may reflect a relatively small sample size and appropriate use of primary prevention medication. However, it is unclear whether the pathological processes that lead to silent MI are identical to acute MI. The lack of association with conventional risk factors suggests that further research is needed to identify alternative risk factors specifically for silent MI.

To our knowledge this is the first study to assess silent MI by LGE CMR in a truly asymptomatic diabetic population. Previous studies have demonstrated that in patients with diabetes, silent MI detected on CMR is associated with increased mortality and adverse cardiovascular events (3, 4). Kwong *et al* reported an incidence of silent MI of 28% in symptomatic patients with diabetes undergoing clinical CMR (3). Schelbert *et al* reported a prevalence of 21% of silent MI of diabetic patients enrolled in the ICELAND MI study who underwent CMR between 2004 and 2007 (4).

However patients in both studies were not necessarily asymptomatic and in ICELAND MI 28% of those with silent MI had prior coronary revascularisation. The rate of infarction was similar between our study and the work of Schelbert *et al* despite patients in our study being younger, lower risk and asymptomatic.

Despite recommendations of aggressive risk factor modification in type 2 diabetes uptake remains variable (23) (with only 18% taking aspirin at time of recruitment to this study). Recognition of silent MI in these patients should prompt aggressive risk factor modification, which may improve long-term clinical outcome. Furthermore, the silent MI screening components that we have identified may help in future clinical studies by identifying those most likely to have silent MI who could be targeted with lifestyle, pharmacological or interventional management.

Limitations

There a number of limitations to this work that should be acknowledged. First, we have excluded certain higher risk patients, for example those on insulin or ACE inhibitors and therefore general applicability of the findings is uncertain. The silent MI risk model we propose would need to be validated in more varied populations to broaden its clinical use. Second, we have not performed coronary angiography to confirm that silent MI was caused by coronary disease. However in an asymptomatic cohort undertaking an invasive procedure would not be appropriate. Third, we have recruited a relatively low proportion of women. However previous data suggest that the rate of silent MI tends to be equal or lower in women (3, 4). Finally, the cut off points that we have used are based on Youden index which assigns equal importance to sensitivity and specificity. Depending on which of these is more important in clinical practice the thresholds would need to be altered accordingly. We have also assigned an equal score to each of the components which may oversimplify the complex nature of the disease process.

Conclusions

The rate of silent MI in this low risk asymptomatic cohort of patients with type 2 diabetes was higher than expected. No conventional risk factors other than age were associated with silent MI. Several

simple clinical parameters including ECG Q waves, E/A ratio, GLS and NT-proBNP were associated with silent MI. By combining them we were able to define a novel screening tool with good diagnostic accuracy for the detection of silent MI which can be used both clinically and for interventional studies.

Author Contributions

Guarantors of integrity of entire study PPS, SP; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, PPS, SP; statistical analysis, PPS, PH, and manuscript editing, all authors; Guarantor, SP.

References

1. **Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H** 2001 Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 44 Suppl 2:S14-21
2. **Mather AN, Crean A, Abidin N, Worthy G, Ball SG, Plein S, Greenwood JP** 2010 Relationship of dysglycemia to acute myocardial infarct size and cardiovascular outcome as determined by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 12:61
3. **Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, Davis RB** 2006 Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* 113:2733-2743
4. **Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, Dyke CK, Thorgeirsson G, Eiriksdottir G, Launer LJ, Gudnason V, Harris TB, Arai AE** 2012 Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. *JAMA* 308:890-896
5. **Davis TM, Coleman RL, Holman RR** 2013 Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. *Circulation* 127:980-987
6. **Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, Williams DE, Geiss L** 2014 Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med* 370:1514-1523
7. **Moon JC, De Arenaza DP, Elkington AG, Taneja AK, John AS, Wang D, Janardhanan R, Senior R, Lahiri A, Poole-Wilson PA, Pennell DJ** 2004 The pathologic basis of Q-wave and non-Q-wave myocardial infarction: a cardiovascular magnetic resonance study. *J Am Coll Cardiol* 44:554-560
8. **Ingkanisorn WP, Rhoads KL, Aletras AH, Kellman P, Arai AE** 2004 Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. *J Am Coll Cardiol* 43:2253-2259
9. **Biere L, Donal E, Terrien G, Kervio G, Willoteaux S, Furber A, Prunier F** 2014 Longitudinal strain is a marker of microvascular obstruction and infarct size in patients with acute ST-segment elevation myocardial infarction. *PLoS One* 9:e86959
10. **Nguyen TL, Phan JA, Hee L, Moses DA, Otton J, Terreblanche OD, Xiong J, Premawardhana U, Rajaratnam R, Juergens CP, Dimitri HR, French JK, Richards DA, Thomas L** 2015 High-sensitivity troponin T predicts infarct scar characteristics and adverse left ventricular function by cardiac magnetic resonance imaging early after reperfused acute myocardial infarction. *Am Heart J* 170:715-725 e712
11. **Garcia-Alvarez A, Sitges M, Delgado V, Ortiz J, Vidal B, Poyatos S, de Caralt TM, Heras M, Bosch X, Azqueta M, Pare C, Brugada J** 2009 Relation of plasma brain natriuretic peptide levels on admission for ST-elevation myocardial infarction to left ventricular end-diastolic volume six months later measured by both echocardiography and cardiac magnetic resonance. *Am J Cardiol* 104:878-882
12. **Sibal L, Home PD** 2009 Management of type 2 diabetes: NICE guidelines. *Clin Med* 9:353-357
13. **Vermes E, Childs H, Carbone I, Barckow P, Friedrich MG** 2013 Auto-threshold quantification of late gadolinium enhancement in patients with acute heart disease. *J Magn Reson Imaging* 37:382-390
14. **Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A** 2009 Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 10:165-193
15. **Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Apple FS, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow**

- JJ, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR 2012 Third universal definition of myocardial infarction. *J Am Coll Cardiol* 60:1581-1598
16. **DeLong ER, DeLong DM, Clarke-Pearson DL** 1988 Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44:837-845
 17. **Obokata M, Nagata Y, Wu VC, Kado Y, Kurabayashi M, Otsuji Y, Takeuchi M** 2015 Direct comparison of cardiac magnetic resonance feature tracking and 2D/3D echocardiography speckle tracking for evaluation of global left ventricular strain. *Eur Heart J Cardiovasc Imaging*
 18. **Holland DJ, Marwick TH, Haluska BA, Leano R, Hordern MD, Hare JL, Fang ZY, Prins JB, Stanton T** 2015 Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. *Heart* 101:1061-1066
 19. **Huelsmann M, Neuhold S, Strunk G, Moertl D, Berger R, Prager R, Abrahamian H, Riedl M, Pacher R, Luger A, Clodi M** 2008 NT-proBNP has a high negative predictive value to rule-out short-term cardiovascular events in patients with diabetes mellitus. *Eur Heart J* 29:2259-2264
 20. **From AM, Scott CG, Chen HH** 2010 The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction a population-based study. *J Am Coll Cardiol* 55:300-305
 21. **Nijland F, Kamp O, Karreman AJ, van Eenige MJ, Visser CA** 1997 Prognostic implications of restrictive left ventricular filling in acute myocardial infarction: a serial Doppler echocardiographic study. *J Am Coll Cardiol* 30:1618-1624
 22. **Naqvi TZ, Padmanabhan S, Rafii F, Hyuhn HK, Mirocha J** 2006 Comparison of usefulness of left ventricular diastolic versus systolic function as a predictor of outcome following primary percutaneous coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 97:160-166
 23. **Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW** 2013 Achievement of goals in U.S. diabetes care, 1999-2010. *N Engl J Med* 368:1613-1624

	Silent MI	No Silent MI	P value
N	17	83	
Age	65.4±9.2	59.8±11.0	0.05
Male gender, n (%)	16 (94)	66 (80)	0.30
Body mass index , kg/m²	27.8±3.1	28.9±4.6	0.32
Duration of diabetes, years	4.1±4.1	5.2±4.4	0.24
Current HbA1c, mmol/mol	57.1±12.5	64.3±20.6	0.23
Median HbA1c since diagnosis, mmol/mol	63.3±10.9	64.8±18.2	0.77
24 hr systolic BP, mmHg	135.3±15.9	130.8±14.7	0.24
24 hr diastolic BP, mmHg	72.5±10.1	72.7±8.9	0.89
Total cholesterol	4.3±1.2	4.4±1.1	0.69
Smoking, n (%)	4 (24)	11 (13)	0.28
Ethnicity			0.84
White British	12 (71)	60 (72)	
South Asian	4 (24)	15 (18)	
Black	1 (6)	5 (6)	
Other*	0 (0)	3 (4)	
Metformin, n (%)	13 (76)	74 (89)	0.23
Sulphonylurea, n (%)	5 (29)	28 (38)	1.0
Gliptin, n (%)	2 (12)	9 (11)	1.0
Exanatide, n (%)	0	1 (1)	1.0
Glitazone, n (%)	0	1 (1)	1.0
Repaglinide, n (%)	0	1 (1)	1.0
Dapagliflozin, n (%)	0	1 (1)	1.0
Insulin, n (%)	0	0	-
ACE inhibitor, n (%)	0	0	-
Beta blocker, n (%)	2 (12)	2 (2)	0.13
Calcium channel blocker, n (%)	4 (24)	6 (7)	0.06
Diuretic, n (%)	1 (6)	4 (5)	1.0
Statin, n (%)	14 (82)	56 (68)	0.26
Fibrate, n (%)	0	0	-
Ezetimibe, n (%)	0	0	-
Aspirin, n (%)	2 (12)	16 (20)	0.73

CMR				
LV EDV, ml	140.5±39.1	150.0±32.8	0.30	
LV EDV index, ml/m ²	70.4±17.1	74.5±13.4	0.27	
Ejection fraction, %	58.0±9.7	61.7±4.9	0.30	
LV mass, g	102.5±16.3	95.0±21.0	0.34	
LV mass index, g/m ²	51.4±6.5	47.2±8.7	0.01	
LA volumes, ml	89.0±31.6	88.5±16.8	0.93	
LA volume index, ml/m ²	44.9±15.9	44.2±7.7	0.87	
Feature Tracking				
GLS	-15.2±3.7	-17.7±3.1	0.004	
SSR	-93.8±31.8	-111.2±42	0.04	
EDSR	64.1±16.6	84.0±33.1	0.02	
LDSR	87.4±39.9	91.4±41.2	0.89	
Echocardiography				
E/A ratio	0.75±0.30	0.89±0.30	0.03	
E/E' average	7.4±2.4	7.1±2.1	0.96	
S' average, cm/s	9.8±2.2	9.5±1.8	0.72	
Electrocardiography				
Q waves (%)	4 (24)	6 (7)	0.06	
Biomarker findings				
hs-cTnT, ng/L	7.5±4.1	7.4±5.4	0.42	
NT-proBNP, ng/L	105.8±132.2	51.9±100.8	0.003	
hs-CRP, mg/L	3.5±3.5	3.7±5.9	0.57	

Table 1. Patient characteristics and investigation findings according to the presence or absence of silent MI. *Other ethnicities; 1 Turkish, 1 Polish and 1 Latin American.

	AUC	P value	Optimum cut-off	Sensitivity at cut-off	Specificity at cut-off
Q waves	0.582 (0.421-0.742)	0.29	categorical	24%	93%
Age	0.668 (0.522-0.803)	0.02	>62	76%	63%
E/A ratio	0.669 (0.526-0.813)	0.02	≤0.79	71%	59%
GLS	0.685 (0.542-0.829)	0.01	≥-18.4%	88%	41%
NT-proBNP	0.730 (0.604-0.855)	<0.001	>29ng/L	88%	57%

Table 2. Area under the curve (AUC) of Q waves and the 4 continuous parameters for detecting silent MI. Optimum cut-off, sensitivity and specificity derived from Youden index are also shown

Silent MI risk score	Sensitivity	95% CI	Specificity	95% CI
0	100.0	-	0.0	-
≥1	100.0	-	0.0	-
≥2	100.0	80.5 - 100.0	42.2	31.4 - 53.5
≥3	82.4	56.6 - 96.2	72.3	61.4 - 81.6
≥4	41.2	18.4 - 67.1	89.2	80.4 - 94.9

Table 3. Silent MI risk score calculated from age > 62, GLS \geq -18.4%, EA ratio \leq 0.79 and NT-proBNP > 29ng/L. The sensitivity and specificity to detect silent MI for each possible score is shown.

Figure 1. Examples of silent MI detected by LGE. Horizontal panels are from the same patient and white arrows denote the area of MI. A and B show basal and mid inferolateral subendocardial MI. C and D show apical and mid septal near transmural infarction. E and F show basal inferior subendocardial infarction.

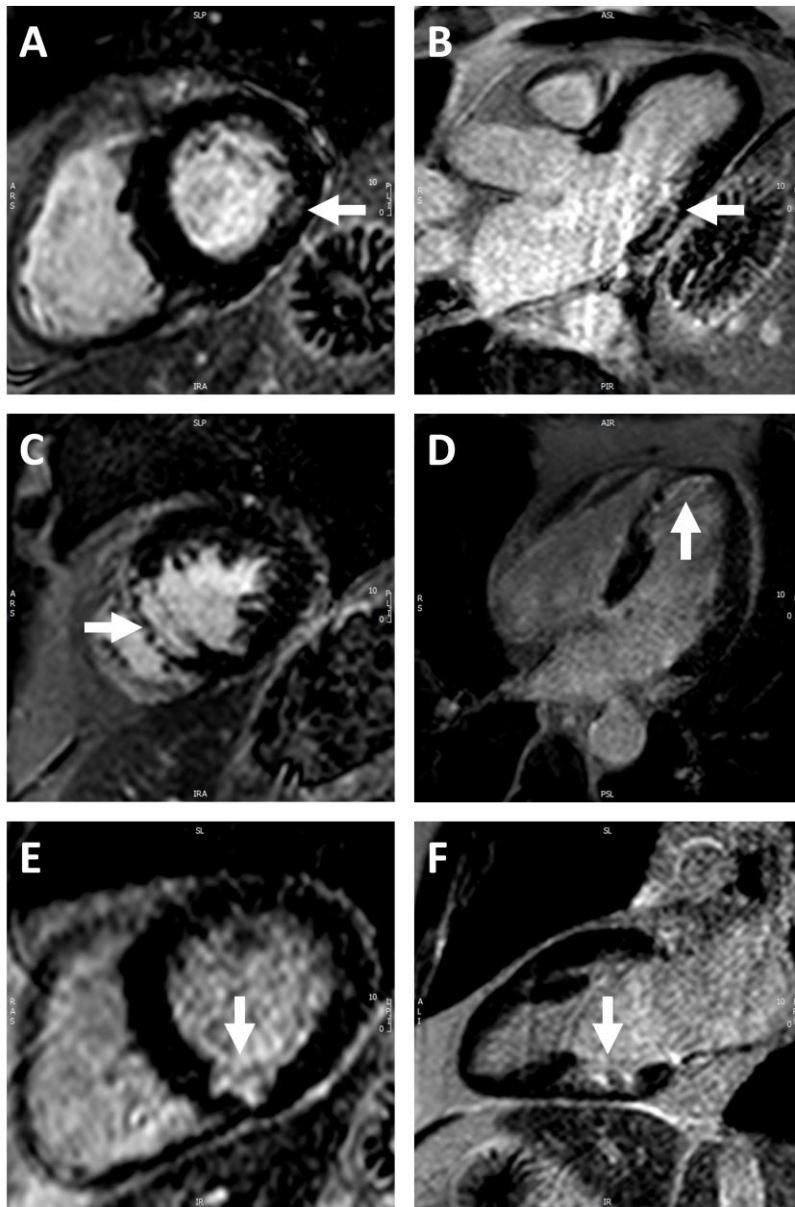
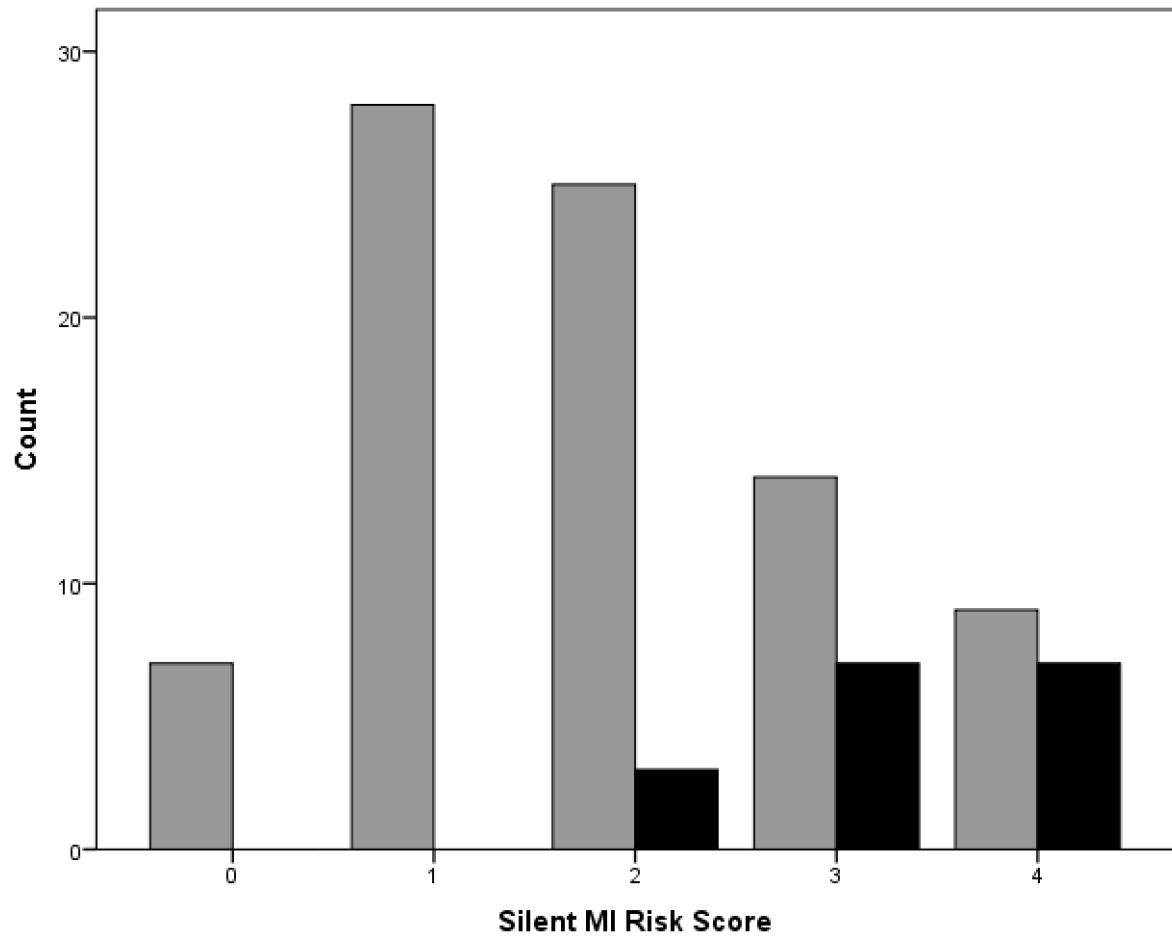


Figure 2. Number of patients with silent MI (black) and without silent MI (grey) according to their silent MI risk score.



Appendix 1. Receiver operator characteristic curves for age (AUC=0.668, P=0.02), average EA ratio (AUC=0.669, P=0.02), NT-proBNP (AUC= 0.730, P<0.001), global longitudinal strain (GLS) measured by feature tracking (AUC=0.68, P=0.01), the 4 variable nested model of age, Q waves, EA ratio, GLS and NT-proBNP (AUC= 0.85, P<0.0001) and the silent MI risk score using the same 4 variables (AUC=0.82, P<0.0001).

