



Dastidar, A. G., Baritussio, A., De Garate, E., Drobni, Z., Biglino, G., Singhal, P., Milano, E. G., Angelini, G. D., Dorman, S., Strange, J., Johnson, T., & Bucciarelli-Ducci, C. (2019). Prognostic Role of CMR and Conventional Risk Factors in Myocardial Infarction With Nonobstructed Coronary Arteries. *JACC: Cardiovascular Imaging*, 12(10), 1973-1982. <https://doi.org/10.1016/j.jcmg.2018.12.023>

Peer reviewed version

License (if available):
CC BY-NC-ND

Link to published version (if available):
[10.1016/j.jcmg.2018.12.023](https://doi.org/10.1016/j.jcmg.2018.12.023)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Elsevier at <https://www.sciencedirect.com/science/article/pii/S1936878X19300658> . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: <http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Prognostic role of Cardiac MRI and conventional risk factors in myocardial infarction with non-obstructed coronary arteries (MINOCA)

Amardeep Ghosh Dastidar^{1,2} *MBBS, MRCP*,
Anna Baritussio^{1,2} *MBBS, MD*,
Estefania De Garate^{1,2,3} *MBBS*,
Zsofia Drobni¹ *MBBS*,
Giovanni Biglino^{1,2} *PhD*,
Priyanka Singhal^{1,2} *MBChB*,
Elena Milano^{1,2} *MBBS, MD*,
Gianni D Angelini^{1,2,3} *MD, MCh, FRCS*,
Stephen Dorman¹ *MBBS, MRCP*,
Julian Strange¹ *MBBS, MRCP, MD*,
Thomas Johnson^{1,2} *BSc (Hons), MBBS, MRCP, MD and*
Chiara Bucciarelli-Ducci^{1,2,3} *MD, PhD, FRCP*,

¹Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

²School of Clinical Sciences, Faculty of Health Sciences, University of Bristol, Bristol, UK

³Bristol National Institute of Health Research (NIHR) Biomedical Research Centre (BRC), Bristol, United Kingdom

Word count: 4478 words (including figures legends and references)

Running title: Prognostic role of CMR and conventional risk factors in MINOCA

Disclosure: Chiara Bucciarelli-Ducci is a consultant for Circle Cardiovascular Imaging. All other authors have no relationships relevant to the contents of this paper to disclose.

Corresponding author:

Dr Chiara Bucciarelli-Ducci
CMR Unit, Bristol Heart Institute
Upper Maudlin Street
Bristol, BS2 8HW, United Kingdom
Email: Telephone: +44 117 342 5888
Email: c.bucciarelli-ducci@bristol.ac.uk

Acknowledgements

We thank Mr Chris Benny Lawton (superintendent radiographer) and the team of CMR Radiographers in the Bristol Heart Institute for their help in acquiring the CMR studies. We also thank Mr Alan Davies, Clinical data manager at UHBristol NHS Foundation Trust, for providing the mortality data. CBD is supported by the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Abstract:

Objective: Assess the prognostic impact of Cardiovascular Magnetic Resonance (CMR) and conventional risk factors in patients with Myocardial infarction with non-obstructed coronaries (MINOCA).

Background: MINOCA represents a diagnostic dilemma and the prognostic markers have not been clarified.

Methods: 388 consecutive MINOCA patients undergoing CMR assessment were identified retrospectively from registry database and prospectively followed up for a primary clinical endpoint of all-cause mortality. 1.5T CMR was performed using a comprehensive protocol (cines, T2-weighted, and late gadolinium enhancement sequences). Patients were grouped into 4 categories based on their CMR findings: myocardial infarction (MI) (embolic/spontaneous recanalization), myocarditis, cardiomyopathy and normal CMR.

Results: CMR(performed at a median of 37days from presentation) was able to identify the cause for the troponin rise in 74% of the patients (25% myocarditis, 25% MI and 25% cardiomyopathy), whilst a normal CMR was identified in 26%. Over a median follow-up of 1262days(3.5years), 5.7% patients died. Cardiomyopathy group had the worst prognosis (mortality 15%, log rank 19.9 p<0.001), MI had 4% mortality, and 2% in both myocarditis and normal CMR. In a multivariable cox regression model (including clinical and CMR parameters), CMR diagnosis of cardiomyopathy and ST-segment elevation on presentation ECG remained the only 2 significant predictors of mortality. Using presentation with ECG ST-elevation and CMR diagnosis of cardiomyopathy as risk markers, the mortality risk rates were 2%, 11% and 21% for presence of 0, 1 and 2 factor respectively(p<0.0001).

Conclusion: In a large cohort of MINOCA, CMR(median 37days from presentation) identified a final diagnosis in 74% of patients. Cardiomyopathy had the highest mortality, followed by MI. The strongest predictors of mortality were a CMR diagnosis of cardiomyopathy and ST-elevation on presentation ECG.

Keywords: MINOCA, Myocarditis, ACS unobstructed coronaries, CMR, Takotsubo cardiomyopathy, myocardial infarction

Abbreviations:

ACS – Acute coronary syndrome

CMR – Cardiac magnetic resonance

LGE – Late gadolinium enhancement

MINOCA – Myocardial infarction with non-obstructed coronary

NSTE-ACS – Non ST-segment elevation - Acute coronary syndrome

RWMA – Regional wall motion abnormality

STEMI – ST-segment elevation myocardial infarction

Introduction

Acute coronary syndrome (ACS) is one of the leading causes of mortality and morbidity worldwide.(1) Definite diagnosis of ACS is crucial for ensuring appropriate patient management. As per the international guidelines, patients presenting with ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation-acute coronary syndrome (NSTEMI-ACS) proceed to immediate or inpatient coronary angiography, respectively, with the aim to identify and treat a culprit coronary artery occlusion or stenosis.(2,3) However, in 1-14% of these patients no significant coronary obstruction is identified, thus being classified as MINOCA (Myocardial infarction with non-obstructive coronary arteries).(3) MINOCA represents a diagnostic dilemma, with subsequent uncertain clinical management. A recent registry study has shown beneficial effects of treatment with statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on outcome in patients with MINOCA.(4)

The underlying pathophysiological mechanisms occurring in MINOCA are complex and multifactorial. (5) Patients with MINOCA are thought to have a better prognosis, and consequently do not receive appropriate secondary prevention medications.(6) However, recent studies suggest that all-cause mortality may be as high as 4.7% at 12 months.(7,8) The latest ESC guidelines on the management of STEMI and the recent ESC/ACC/AHA/WHF Fourth universal definition of myocardial infarction has included MINOCA suggesting a potential role for cardiovascular magnetic resonance (CMR) in this cohort.(3)(9)

Confirmation or exclusion of myocardial infarction (MI) by CMR facilitates tailoring of medical therapy, ensuring appropriate long-term secondary prevention and modification of risk, and also minimizing exposure to anti-platelet therapy and the associated bleeding risks for those with a non-coronary aetiology for the MINOCA presentation.(10). Few previous studies have shown that CMR can identify the underlying diagnosis, most commonly: acute/chronic myocarditis,

acute MI with spontaneous recanalization/embolus, stress cardiomyopathy (Takotsubo) or other cardiomyopathies.(11–17) Only in a small proportion of cases, no abnormality is identified by CMR. The variable proportion of normal cases in the different studies may be due to the time delay between the acute presentation and CMR, (18) suggesting that the time between acute presentation and CMR can play a role in identifying the early reversible abnormalities that may resolve when patients are scanned later. Recent studies have demonstrated the prognosis in the individual diagnostic categories like myocarditis and Takotsubo cardiomyopathy. (19–21) However, there is no evidence in the literature on the prognostic significance of the CMR findings and conventional risk factors in MINOCA. The only study which looked at mid-term mortality was by Mittal et al. (22) However, they looked at patients presenting via the primary percutaneous coronary angiography pathway with non-obstructed coronaries. 60% of the study population had normal troponin thereby not strictly meeting MINOCA criteria. Our study aims to assess the prognostic impact of CMR and conventional risk factors in patients with MINOCA.

Methods

Study population

In this longitudinal observational study, consecutive patients presenting with MINOCA (chest pain, elevated troponin and non-obstructed coronary arteries) as per the new ESC STEMI Guideline(3) and undergoing CMR were identified retrospectively and followed up prospectively (Figure 1). We excluded patients admitted with suspected heart failure or arrhythmic events at presentation. The study was performed at a large cardiothoracic tertiary centre in the South-West of England; data were collected on consecutive patients scanned from September 2011 to December 2015. Patients were identified either presenting with STEMI or NSTEMI. Non-obstructed coronaries were defined as: TIMI III flow; <50% stenosis in any

coronary artery.(3) Troponin T level <14ng/L was considered normal. The typical rise and/or fall of Troponin T was used for the diagnosis of acute MI. (9)'False positive' troponin possibilities: a single troponin elevation (<5x upper limit of normal), which was not repeated during the admission or if a single elevated troponin was followed by a second normal troponin level within 24 h were excluded from study. (2)

The study was reviewed and approved by the local Institutional Review Board.

CMR protocol

CMR was performed at 1.5T (Magnetom Avanto, Siemens Healthineers, Erlangen, Germany). A comprehensive CMR protocol was carried out including cine, T2-weighted (myocardial oedema), early and late gadolinium enhancement imaging. (23) In particular, cine images were performed using a steady-state free-precession sequence acquired in three long axis planes and a stack of short axis images covering the left ventricle (LV) and T2-weighted (T2-STIR) sequence images were acquired in the same short-axis and long-axis planes as the cine images with standard parameters, as previously described.(24,25) Intravenous gadolinium-chelate contrast agent (gadobutrol) was administered at a dose of 0.1 mmol kg⁻¹ of body weight. Images were acquired 2-3min after contrast injection (early gadolinium), whilst late gadolinium enhancement (LGE) images were acquired 15-20minutes after contrast injection using a standard inversion recovery segmented gradient echo sequence, as previously described. (24,25)

CMR analysis

All CMR studies were analysed and reported by a consultant with >15 years of CMR experience and with ESC CMR level 3 certification (CBD). Diffuse and focal myocardial oedema was analysed using both the early gadolinium and the T2-STIR images. Myocardial oedema was considered present when the ratio of signal intensity between the myocardium and the mean

signal intensity of the skeletal muscle was >2 on T2-STIR images, according to the Lake Louise criteria. (26) Early gadolinium enhancement ratio used for assessment of hyperaemia was evaluated as previously described. (26) Patients were grouped into 4 categories based on their CMR characteristics: myocardial infarction (MI) (embolic/spontaneous recanalization), myocarditis, cardiomyopathy and normal CMR. The latter corresponded to a structurally normal heart, defined as no regional wall motion abnormality (RWMA) (except for dyssynchrony secondary to bundle branch block), no myocardial oedema, and no myocardial LGE (scarring) (except non-specific LGE in LV/RV insertion points). Myocarditis was diagnosed based on fulfilling two out of three Lake Louise Criteria: T2- STIR sequences detecting myocardial oedema; early gadolinium sequences detecting hyperaemia; epicardial or mid-myocardial LGE, as previously described (26). MI was diagnosed based on territorial subendocardial and/or transmural LGE. Takotsubo cardiomyopathy was diagnosed based on the T2- STIR images detecting myocardial oedema and regional wall motion in the mid-cavity or apical distribution with no myocardial LGE, all in accordance with the modified Mayo Clinic criteria.(27) Dilated cardiomyopathy, hypertrophic cardiomyopathy and cardiac amyloidosis were detected based on specific tissue characterization characteristics and were all grouped under cardiomyopathy together with Takotsubo cardiomyopathy.(15) The extent of LGE and myocardial oedema was quantified by calculating the number of segments involved.(20)

Study primary end-point

The end-point of the present study was all-cause mortality.

Patient related data were collected directly from medical records. Follow up was performed centrally by analysing the mortality data obtained from the NHS summary care records. Data

was collected and interpreted by one of the primary investigators (AGD, AB, EDG, GB) in all cases.

Statistical analysis

Baseline patient characteristics, conventional risk markers and CMR findings are described according to the diagnostic groups. Data for continuous variables are presented in mean \pm standard deviation or medians as appropriate. Categorical variables are presented as frequencies and percentages. Normally distributed continuous variables were compared using one-way analysis of variance with (ANOVA) with Bonferroni correction for multiple comparisons. Continuous variables that were not normally distributed were compared by Kruskal–Wallis tests. In univariate analyses the association of time variables to mortality was assessed using Kaplan–Meier curves and the log-rank test. Univariable and multivariable associations of risk covariates with mortality were assessed using Cox proportional hazard regression analyses. Only variables with a p value <0.05 in univariable analyses were used in multivariable model. SPSS Version 23 (IBM Corp, Armonk, NY) was used for statistical analysis. Probability values were two-sided, and values of $p < 0.05$ were considered significant. Due to paucity of mortality data on the MINOCA subgroups post-hoc power calculation was performed based on the study findings.

Results

11,757 patients underwent emergency or urgent coronary angiography during the recruitment period, out of which 410 patients with suspected MINOCA underwent CMR assessment. 2% (n=8) were excluded due to incomplete protocol and 3% (n=14) due to coronary artery disease which were deemed $>50\%$ stenosis thereby leaving a study sample size of 388. CMR was able to identify a cause for the troponin rise in 74% of cases. Clinical characteristics of the overall population (n=388) and for separate patients' groups based on the CMR diagnosis are

summarized in **Table 1**. There was a low prevalence of cardiovascular risk factors (hypertension, diabetes, hyperlipidaemia, smoking and family history), with no difference across the groups. The median time delay between acute presentation and CMR was 37 days. 37% of our patients underwent the scan within 2 weeks from presentation. In a median follow up of 1262days(3.5years), the overall all-cause mortality was 5.7%.

Conventional risk factors

Age: The mean age of the total population was 56±17years.

Kaplan-Meier curves were drawn showing the risk of mortality according to the different age categories (<40years, 40-59years, 60-79years and >79years). There was a strong association between increasing age and mortality (Log rank 23.2, p<0.001) **Figure 2a**

Gender: 48% of the total cohort was female. 98% of the patients diagnosed with Takotsubo cardiomyopathy were female. There was no significant association between gender and mortality in the overall cohort (log rank 2.5, p=0.1).

ECG at presentation (STEMI or NSTEMI-ACS): 19% of our study population presented with ST-segment elevation on the 12-lead ECG.

Kaplan-Meier curves were drawn showing the risk of mortality according to the ECG presentation as ST-elevation or no ST-elevation. There was a strong association between ECG presentation as ST-elevation and mortality (log rank 7.4, p=0.007). **Figure 3**

CMR characteristics and diagnosis

The CMR characteristics are described according to the diagnosis groups. **Table 2**

MI was the most prevalent diagnosis (25%, 97/388 patients), followed by myocarditis (25%, 96/388) and cardiomyopathy 25%, whilst 26% had a structurally normal heart and were grouped into the 'normal CMR' category.

LV volumes: In the overall cohort the mean indexed end-diastolic volume (iEDV) was 81ml/m². On Bonferroni correction the iEDV in the cardiomyopathy was significantly higher than MI and normal CMR category.

LV ejection fraction: The mean LV ejection fraction for the whole cohort was 61%. On Bonferroni correction the LVEF in the cardiomyopathy was significantly lower than MI, myocarditis and normal CMR category. In addition, the LVEF in the myocarditis was significantly lower than normal CMR category.

Regional wall motion abnormalities: Overall 39% of patients had RWMA. The normal CMR category had RWMA secondary to bundle branch block on ECG.

Myocardial oedema: The overall prevalence of focal myocardial oedema was 34% based on T2 STIR and/ or early gadolinium enhancement. Focal myocardial oedema was absent in patients with normal CMR. Additional analysis of the normal CMR cohort revealed no evidence of diffuse myocardial injury in any of the patients.

Late Gadolinium Enhancement: LGE was present in 58% of the entire cohort. 6% of patients with normal CMR had evidence of LGE only in the LV/RV insertion points, currently considered a non-specific finding.

Cardiomyopathy subgroup analysis

In the cardiomyopathy group, 43% had Takotsubo cardiomyopathy, 29% dilated cardiomyopathy and 18% hypertrophic cardiomyopathy. The remaining comprised of infiltrative cardiomyopathy (amyloidosis)(n=4), hypertensive heart disease(n=4) and valvular heart disease(n=2) and were grouped as 'other'. There was no statistically significant difference in the mean age and presentation as STEMI, however there was a significant difference in the gender among the

different cardiomyopathy subgroups. There was a significant difference in the CMR parameters among the different cardiomyopathy subgroups. **Table 3**

Treatment prior to CMR

The use of aspirin, other antiplatelet, ACE-Inhibitor/angiotensin receptor blocker, beta-blocker and statin use in the overall cohort was 93%, 61%, 66%, 65% and 57% respectively. There was no significant difference in the use of medications among the different diagnostic categories.

Table 4.

Prognosis in different CMR categories

In a median follow up of 1262 days (3.5years), the overall all-cause mortality was 5.7% with worst prognosis identified in the cardiomyopathy group (15% mortality). The mortality rate in the different groups was: cardiomyopathy 15%, MI group 4%, myocarditis group 2%, and the normal group 2% (p=0.001).

Kaplan-Meier curves were drawn showing the risk of mortality according to the different CMR diagnosis, showing a strong association between CMR categories and mortality (log rank 19.9, p<0.001). **Figure 4a**

An additional Kaplan-Meier curve was drawn for Takotsubo cardiomyopathy, showing a significantly higher mortality in Takotsubo group compared to any other diagnosis (log rank 7.3, p=0.011). **Figure 4b**

Predictors of all cause mortality

Age, presentation with ST-elevation on ECG, iEDV, log troponin, LV ejection fraction and CMR diagnosis of cardiomyopathy were significant univariable predictors of mortality (p<0.05 considered significant for univariate analysis). In a multivariable model only CMR diagnosis of

cardiomyopathy (hazard ratio 3.0, 95% CI 1.08-8.37, $p=0.034$) and ECG presentation with ST-elevation (hazard ratio 3.1, 95% CI 1.27-7.68, $p=0.013$) remained significant. **Table 5.**

Mortality risk markers (ECG presentation with ST-elevation + CMR diagnosis)

A risk assessment tool for predicting mortality was constructed on the basis of the 2 variables: CMR diagnosis of cardiomyopathy and ECG presentation with ST-elevation. A first group was defined as 242 patients with any other CMR diagnosis except cardiomyopathy and presentation as NSTEMI-ACS. A second group consisted of 122 patients with only one of the factors altered i.e. either a CMR diagnosis of cardiomyopathy or ECG presentation with ST-elevation. Finally, the third group included 24 patients with CMR diagnosis of cardiomyopathy and ECG presentation with ST-elevation. The mortality rates in these 3 groups were (4/242) 1.6%, (13/122) 10.6%, and (5/24) 20.8%. respectively. Kaplan-Meier curves were drawn showing the risk of mortality in these 3 groups, showing a strong association between number of risk marker and mortality (log rank 23.6, $p < 0.001$). **Figure 5.**

Post-hoc power calculation

Using the mortality of 15% in the cardiomyopathy group vs 3% for the rest of the cohort with an alpha of 0.05 our study demonstrated 95% power.

Discussion

This is the largest to date cohort of MINOCA patients assessed with CMR, and the first study to assess the prognostic role of CMR and conventional risk factors in patients with MINOCA. The main findings are as follows: 1) CMR can identify a diagnosis in 3/4 patients presenting with MINOCA and suitable for CMR assessment, 2) CMR diagnosis of cardiomyopathy (imaging) and ECG presentation with ST-elevation (conventional risk marker) were the strongest predictors

of mortality, 3) a combined risk assessment tool using the 2 parameters (cardiomyopathy and ECG presentation with ST-elevation) provides further risk stratification in these patients.

Diagnostic role of CMR in MINOCA

It is important to identify a cause for MINOCA in order to guide ongoing management and provide patient's guidance. As a non-invasive imaging technique, CMR (done at median of 37 days from presentation) is able to identify a diagnosis in these patients in up to 3/4 cases. The diagnostic role of CMR in this patient group has been demonstrated in a small number of previous studies with smaller sample sizes. (11–17) However, the diagnostic yield of CMR in the literature was disparate, ranging from as low as 30% to as high as 90%. (11–17) The variation in the diagnostic yield in the literature can be explained by the use of incomplete CMR protocol (oedema imaging not always included) as well as the timing of the test, sometimes occurring several months after the acute event leading to the resolution of the reversible cardiac abnormalities. (13,18)

In our cohort, the most common diagnosis was MI (25%, n=97), closely followed by myocarditis (25%, n=96) and cardiomyopathy (25%). However, the literature suggests myocarditis to be much more common than MI (10-13, 15), contrary to our result. The mean age in our study was much higher compared to the other studies on MINOCA which may have contributed to the higher prevalence of MI.(14,15) Another possible explanation could be the use of established criteria (Lake Louise Criteria) for diagnosing myocarditis(26), as well as an inclusion cut-off of <50% coronary artery stenosis.(10-15)

Prognostic role of CMR in MINOCA

Of all the CMR parameters examined (including LV size, LV function, LV mass, myocardial oedema, LGE and the overall CMR diagnosis), a CMR diagnosis of cardiomyopathy was

associated with the worst prognosis (15% mortality). On a multivariable analysis involving both traditional markers and CMR characteristics, CMR-derived diagnosis of cardiomyopathy remained significant as an independent predictor of mortality.

Among the other CMR parameters assessed, LV ejection fraction and LV indexed end-diastolic volume were significant univariable predictors of mortality but not in multivariable analysis. These findings are particularly useful in justifying the role of CMR tissue characterization in MINOCA.

The cardiomyopathy group in our study was a heterogeneous group with Takotsubo cardiomyopathy being the most common (43% of the cardiomyopathy group). Takotsubo cardiomyopathy had the worst prognosis over a median follow up of 3.5 years (15% overall mortality) when compared to any other CMR diagnosis. The findings are comparable to the recent study by Templin et al. in which Takotsubo cardiomyopathy had a mortality of 5.6% per patient-year in long term follow up.(21) CMR not only helps in diagnosis but it may also help in identifying the high risk Takotsubo cardiomyopathy cases by delineating the amount of myocardial oedema, RV involvement, thrombus, LV outflow tract obstruction. CMR derived apico-basal myocardial oedema gradient may be used as a marker of malignant arrhythmia risk.(28)

Conventional risk factors for prognosis assessment

Out of all the risk factors assessed, ECG presentation with ST-elevation was an independent predictor of mortality. Age and log peak troponin were univariable predictors of mortality but not in multivariable analysis. Gender was not associated with mortality. The finding on peak troponin is particularly important as it is in contrary to the regular practice. High peak troponin level is often used as an arbitrary prognostic marker due to its evidence from acute coronary

syndrome trials. (29) The importance of the presentation ECG is a novel finding as it is often overlooked while managing patients with MINOCA.

Clinical implication

Our findings strengthen the evidence that CMR is a clinically relevant non-invasive imaging modality for the assessment of patients presenting with MINOCA. In a previous study we have demonstrated that CMR in MINOCA leads to a change in diagnosis in 54% and change in management in 41%. (18) The current study reinforces the impact of CMR, as a diagnosis of cardiomyopathy is associated with worst prognosis. Any other diagnosis except cardiomyopathy had a relatively low mortality (2-4%) thereby putting them in a good prognostic category. Currently, there is no risk stratification algorithm for patients presenting with MINOCA. The results of our study suggest that ECG at presentation and CMR diagnosis might be useful predictors for risk stratification. This should be explored further and confirmed in larger multicenter studies.

Limitations

Several limitations merit consideration. This is a single centre study with relatively limited sample size. Although our study was designed to represent a real-world population, we potentially might have excluded higher-risk patients with contraindications to CMR (e.g., creatinine clearance <30 ml/min and intracardiac devices). However, our study included a broad range of consecutive MINOCA patients from a large catchment area, and only a limited number (2%) of patients were excluded from CMR. There may have been a referral bias as the study included MINOCA patients, referred for a CMR by the physician providing the care. However, our regular clinical practice at the Bristol Heart Institute includes CMR in patients presenting with MINOCA. The CMR was performed at a median of 37 days from presentation and this may

have impacted the diagnostic pick up rate as well as the prevalence of myocardial oedema, as not all patients were imaged in the acute phase. Nevertheless, our study showed a significant prognostic impact irrespective of the timing of scan. Also, newer mapping techniques were not performed in this patients' cohort. The normal CMR group had few patients with bundle branch block and LGE in the insertion points which may not be classed as entirely normal, however the presence of diffuse myocardial injury was excluded on the basis of both the early gadolinium enhancement and T2 weighted images analysis. Lastly, myocardial biopsy was not carried out in these patients. However, well-established and clinically validated CMR criteria were used for the diagnosis of the individual cases.

Conclusion

In a large cohort of MINOCA, CMR (median 37days from presentation) established a diagnosis in almost 3/4 of cases. Among the conventional risk factors and CMR characteristics, ST-segment elevation on presentation ECG and CMR diagnosis of cardiomyopathy were independent predictors of mortality. Combined analysis of CMR diagnosis and ECG at presentation may allow stratification of patients with poor outcomes.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

CMR (median 37days from presentation) enabled in establishing a diagnosis in 74% of patients presenting with MINOCA. Patients presenting with ST-elevation on ECG and CMR diagnosis of cardiomyopathy have worse prognosis.

TRANSLATIONAL OUTLOOK:

- Clinical relevance: MINOCA is common and often represent a clinical dilemma
- Current ESC/ACC guidelines suggest some diagnostic tests but there is no recommended work up and management of MINOCA
- CMR is useful for both diagnosis and prognostication in MINOCA
- Large multicentre prospective trial is warranted to confirm these results and thereby enabling a tailored treatment strategy in this heterogeneous cohort

References:

1. Vedanthan R, Seligman B, Fuster V. Global perspective on acute coronary syndrome: a burden on the young and poor. *Circ Res.* 2014;114(12):1959–75.
2. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2016;37(3).
3. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2018;39(2):119–77.
4. Lindahl B, Baron T, Erlinge D, et al. Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery DiseaseClinical Perspective. *Circulation.* 2017;135(16):1481–9.
5. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. *Eur Heart J.* 2015;36(8):475–81.
6. Maddox TM, Ho PM, Roe M, Dai D, Tsai TT, Rumsfeld JS. Utilization of secondary prevention therapies in patients with nonobstructive coronary artery disease identified during cardiac catheterization: insights from the National Cardiovascular Data Registry Cath-PCI Registry. *Circ Cardiovasc Qual Outcomes.* 2010;3(6):632–41.
7. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation.* 2015;131(10):861–70.
8. Gehrie ER, Reynolds HR, Chen AY, et al. Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary

- artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early. *Am Heart J.* 2009;158(4):688–94.
9. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol.* 2018;25285.
 10. Dastidar AG, Rodrigues JCL, Ahmed N, Baritussio A, Bucciarelli-Ducci C. The Role of Cardiac MRI in Patients with Troponin-Positive Chest Pain and Unobstructed Coronary Arteries. *Curr Cardiovasc Imaging Rep.* 2015;8(8):28.
 11. Collste O, Sörensson P, Frick M, et al. Myocardial infarction with normal coronary arteries is common and associated with normal findings on cardiovascular magnetic resonance imaging: results from the Stockholm Myocardial Infarction with Normal Coronaries study. *J Intern Med.* 2013;273(2):189–96.
 12. Mahmoudi M, Harden S, Abid N, et al. Troponin-positive chest pain with unobstructed coronary arteries: definitive differential diagnosis using cardiac MRI. *Br J Radiol.* 2012;85(1016):e461-6.
 13. Monney PA, Sekhri N, Burchell T, et al. Acute myocarditis presenting as acute coronary syndrome: role of early cardiac magnetic resonance in its diagnosis. *Heart.* 2011;97(16):1312–8.
 14. Leurent G, Langella B, Fougerou C, et al. Diagnostic contributions of cardiac magnetic resonance imaging in patients presenting with elevated troponin, acute chest pain syndrome and unobstructed coronary arteries. *Arch Cardiovasc Dis.* 2011;104(3):161–70.
 15. Assomull RG, Lyne JC, Keenan N, et al. The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries. *Eur Heart J.* 2007;28(10):1242–9.

16. Chopard R, Jehl J, Dutheil J, et al. Evolution of acute coronary syndrome with normal coronary arteries and normal cardiac magnetic resonance imaging. *Arch Cardiovasc Dis.* 2011;104(10):509–17.
17. Laraudogoitia Zaldumbide E, Pérez-David E, Larena JA, et al. The value of cardiac magnetic resonance in patients with acute coronary syndrome and normal coronary arteries. *Rev española Cardiol.* 2009 ;62(9):976–83.
18. Dastidar AG, Rodrigues JCL, Johnson TW, et al. Myocardial Infarction With Nonobstructed Coronary Arteries. *JACC Cardiovasc Imaging.* 2017;10(10):1204–6.
19. Gräni C, Eichhorn C, Bière L, et al. Prognostic Value of Cardiac Magnetic Resonance Tissue Characterization in Risk Stratifying Patients With Suspected Myocarditis. *J Am Coll Cardiol.* 2017;70(16):1964–76.
20. Aquaro GD, Perfetti M, Camastra G, et al. Cardiac MR With Late Gadolinium Enhancement in Acute Myocarditis With Preserved Systolic Function. *J Am Coll Cardiol.* 2017;70(16):1977–87.
21. Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med.* 2015;373(10):929–38.
22. Mittal TK, Reichmuth L, Ariff B, et al. Imaging diagnoses and outcome in patients presenting for primary angioplasty but no obstructive coronary artery disease. *Heart.* 2016;102(21):1728–34.
23. Dastidar AG, Rodrigues JC, Baritussio A, Bucciarelli-Ducci C. MRI in the assessment of ischaemic heart disease. *Heart.* 2015;102(3):239–52.
24. McAlindon EJ, Pufulete M, Harris JM, et al. Measurement of Myocardium at Risk with Cardiovascular MR: Comparison of Techniques for Edema Imaging. *Radiology.*

- 2015;275(1):61–70.
25. McAlindon E, Pufulete M, Lawton C, Angelini GD, Bucciarelli-Ducci C. Quantification of infarct size and myocardium at risk: evaluation of different techniques and its implications. *Eur Heart J Cardiovasc Imaging*. 2015;16(7):738–46.
 26. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. *J Am Coll Cardiol*. 2009;53(17):1475–87.
 27. Kawai S, Kitabatake A, Tomoike H. Guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy. *Circ J*. 2007;71(6):990–2.
 28. Dastidar AG, Frontera A, Palazzuoli A, Bucciarelli-Ducci C. TakoTsubo cardiomyopathy: unravelling the malignant consequences of a benign disease with cardiac magnetic resonance. *Heart Fail Rev*. 2015;20(4):415–21.
 29. Kontos MC, Shah R, Fritz LM, et al. Implication of different cardiac troponin I levels for clinical outcomes and prognosis of acute chest pain patients. *J Am Coll Cardiol*. 2004;43(6):958–65.

Figure legends:

Figure 1. Study flow-chart

Figure 2. Age as a marker of mortality.

Kaplan-Meier curves showing the risk of mortality according to age group.

Figure 3. ECG at presentation.

Kaplan-Meier curves showing the risk of mortality according to presence or absence of ST segment elevation on the presenting ECG

Figure 4. Cumulative Mortality According to CMR diagnosis.

4a: Kaplan-Meier curves showing the risk of mortality according to CMR diagnosis (MI vs Myocarditis vs Cardiomyopathy vs normal), 4b: Kaplan-Meier curves showing the risk of mortality according to CMR diagnosis of Takotsubo cardiomyopathy vs any other diagnosis

Figure 5: Prognostic role of CMR diagnosis and ECG in MINOCA.

(Left) In a population of patients presenting with MINOCA, CMR identified 4 main categories – Cardiomyopathy (Takotsubo), Myocarditis, Myocardial infarction and normal, Right: Kaplan-Meier curves showing the risk of mortality according to risk group (Group A - Any CMR diagnosis except cardiomyopathy & presentation as NSTEMI-ACS, Group B - CMR diagnosis of cardiomyopathy or presentation as STEMI, Group C - CMR diagnosis of cardiomyopathy & presentation as STEMI)

Table 1. Demographic characteristics.

Characteristics	Total n=388	MI n=97	Myocarditis n=96	Cardio- myopathy n=96	Normal n=99	Global p-value
Mean age in yrs (SD)	56 (17)	62(12)	42(17)	64(12)	54(16)	<0.001
Female sex %	48	56	23	61	54	<0.001
Family history of IHD %	3	2	4	1	3	0.57
Diabetes %	6	8	5	6	4	0.64
Hypertension %	13	16	9	14	14	0.54
History of smoking %	7	4	5	10	7	0.32
BMI	26.5	27.3	26.5	25.7	26.4	0.18
Troponin T ng/L median	497	660	924	419	202	0.03
Presentation as STEMI %	19	19	19	25	14	0.29
Median interval in days (presentation and CMR)	37	37	21	12	47	<0.001
Median Follow up (days)	1262	1246	1336	1231	1276	0.09

All cause mortality						
%(n)	6 (22)	4 (4)	2 (2)	15 (14)	2 (2)	<0.001

MI- myocardial infarction, IHD – ischaemic heart disease, BMI – body mass index, STEMI- ST elevation myocardial infarction, CMR- cardiac magnetic resonance.

Table 2. CMR characteristics of the different diagnostic categories

CMR Characteristics	Total n=388	MI n=97	Myocarditis n=96	Cardiomyopathy n=96	Normal n=99	Global p-value
iEDV ml/m²	81	78	83	90	74	<0.001
iESV ml/m²	34	30	32	47	26	<0.001
iSV ml/m²	47	48	50	43	48	<0.001
LVEF %	61	63	62	52	67	<0.001
iLV mass gm/m²	66	63	67	75	59	<0.001
RWMA %	39	59	31	59	6	<0.001
LGE %	58	100	94	34	6	<0.001
No. of LGE segments(IQR)	1(0-2)	1(1-2)	3(2-4)	0(0-1)	0	<0.01
Myocardial oedema %	34	52	52	34	0	<0.001
No. of Oedema segments(IQR)	0(0-2)	1(0-2)	2(0-4)	0(0-5)	0	<0.01

iEDV- indexed end-diastolic volume, **iESV =**-indexed end-systolic volume, **iSV-** indexed stroke volume; **LVEF-** left ventricular ejection fraction, **iLV-** indexed left ventricular, **RWMA-** regional wall motion abnormality, **LGE –** late gadolinium enhancement

Table 3. Characteristics of the cardiomyopathy subgroups

Characteristics	TCM	DCM	HCM	Others	Global
Cardiomyopathy	n=41	n=28	n=17	n=10	p-value
Mean age (SD)	68(10)	63(13)	60(17)	60(12)	0.05
Female sex %	98	32	47	33	<0.001
STEMI %	38	18	24	0	0.07
iEDV ml/m²	77	128	67	81	<0.001
iESV ml/m²	35	87	20	36	<0.001
iSV ml/m²	42	41	48	44	0.298
LVEF %	56	33	70	59	<0.001
iLV mass gm/m²	61	85	87	88	<0.001
Mortality(n)	6	5	0	3	<0.01

TMC- Tako Tsubo cardiomyopathy, DCM- dilated cardiomyopathy, HCM -hypertrophic cardiomyopathy, iEDV- indexed end-diastolic volume, iESV -indexed end-systolic volume, iSV- indexed stroke volume; LVEF- left ventricular ejection fraction, iLV- indexed left ventricular

Table 4. Treatment prior to CMR

Pre-CMR Treatment	MI	Myocarditis	Cardiomyopathy	Normal	Global
	n=97	n=96	n=96	n=99	p-value
Aspirin	95	92	91	92	0.81
Other Antiplatelet	61	59	60	63	0.31
ACE-inhibitor/ ARB	65	66	69	66	0.92
Beta-blocker	65	64	71	62	0.58
Statin	62	53	59	56	0.66

CMR- cardiac magnetic resonance, MI- myocardial infarction, ARB- angiotensin receptor blockers

Table 5. Univariable and multivariable association for mortality

Variables	Univariate analysis				Multivariate analysis			
	Sig.	HR	95% CI		Sig.	HR	95% CI	
			Lower	Upper			Lower	Upper
Age group	0.008	2.046	1.203	3.48	0.1	1.645	0.908	2.978
Sex	0.302	1.564	0.669	3.659	-	-	-	-
BMI	0.484	0.968	0.884	1.06	-	-	-	-
Log-Peak Troponin	0.041	0.509	0.267	0.971	0.094	0.565	0.29	1.101
STEMI	0.01	3.059	1.307	7.157	0.013	3.125	1.271	7.684
iEDV	0.008	1.016	1.004	1.028	0.258	1.01	0.993	1.028
LVEF	0.001	0.958	0.936	0.981	0.851	.996	0.96	1.034
RWMA	0.132	1.905	0.823	4.41	-	-	-	-
LGE	0.161	0.544	0.233	1.274	-	-	-	-
Oedema	0.228	0.542	0.2	1.469	-	-	-	-
MI	0.472	0.672	0.227	1.986	-	-	-	-
Myocarditis	0.098	0.293	0.068	1.253	-	-	-	-
CM	0.001	5.628	2.361	13.417	0.034	3.013	1.084	8.373
Normal	0.091	0.285	0.067	1.219	-	-	-	-

BMI – Body mass index, STEMI- ST elevation myocardial infarction, LVEF – left ventricular ejection fraction, iEDV – indexed end diastolic volume, RWMA- regional wall motion

abnormality, LGE – late gadolinium enhancement, MI – myocardial infarction, CM -
cardiomyopathy

Figure 1.

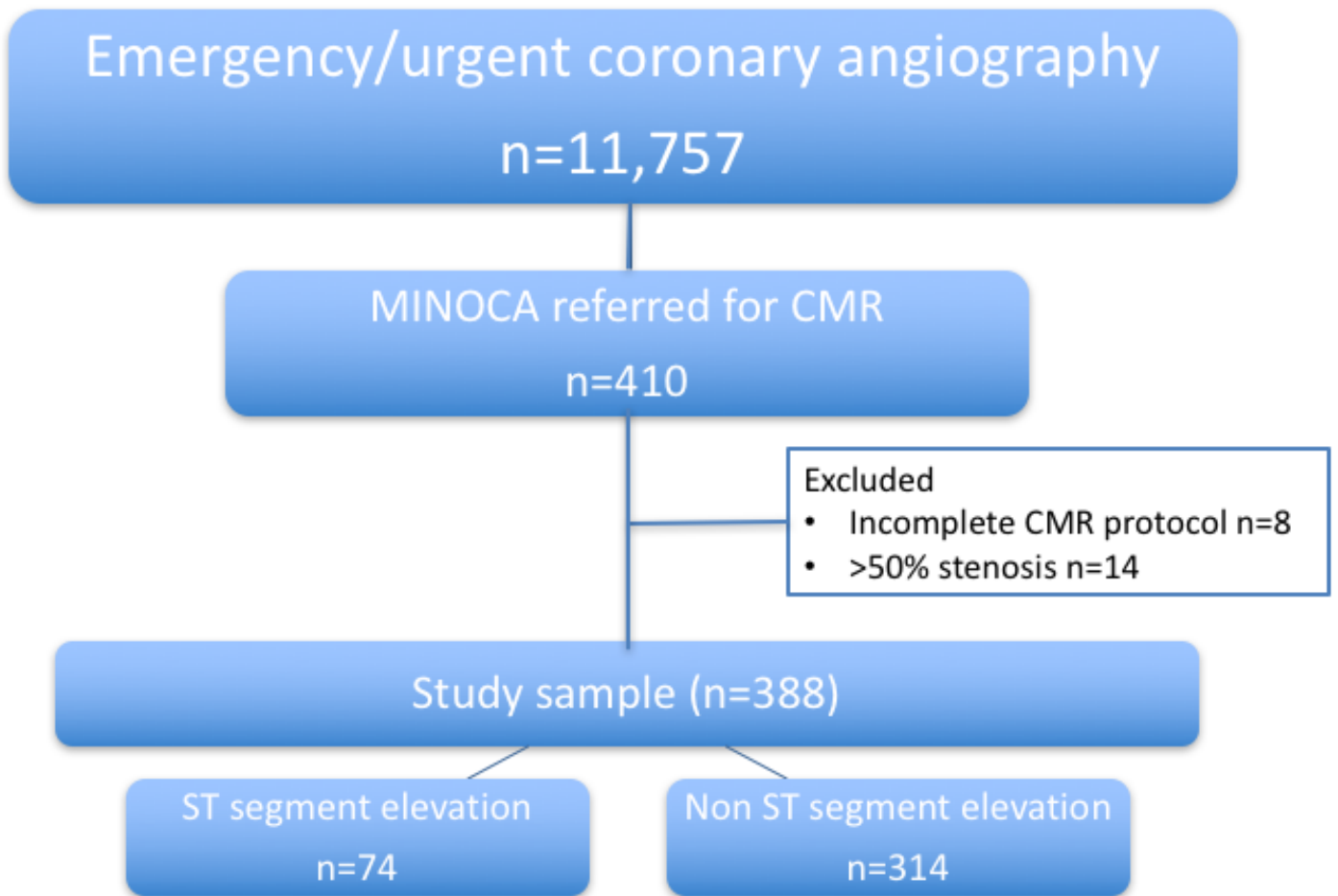


Figure 2.

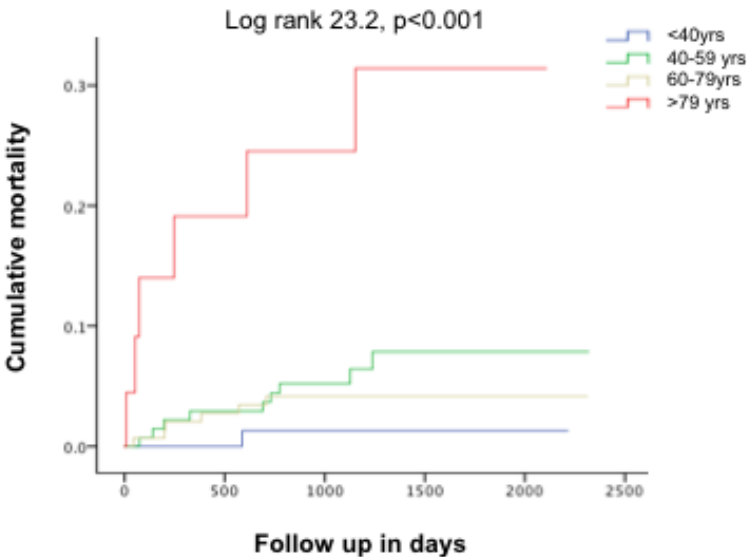


Figure 3.

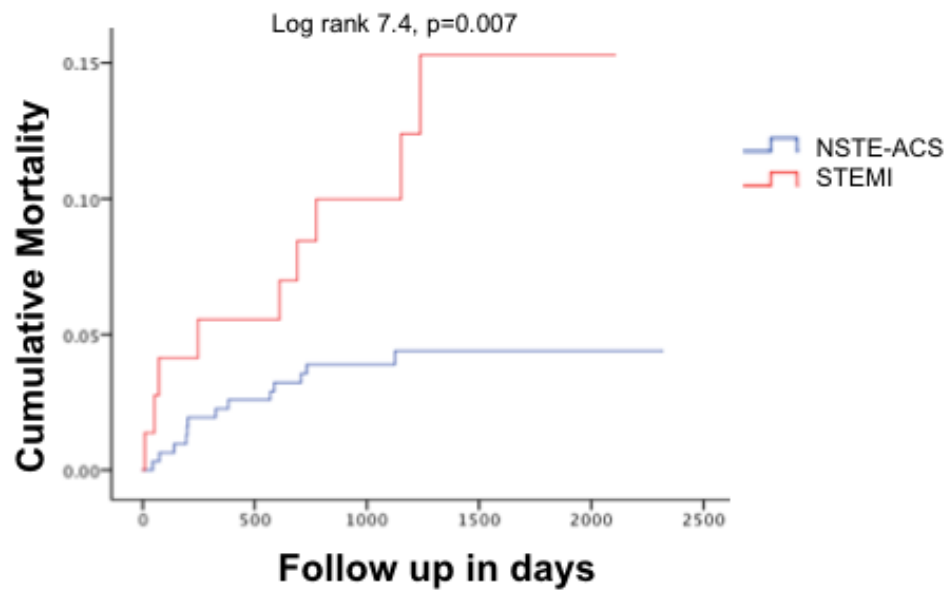


Figure 4a.

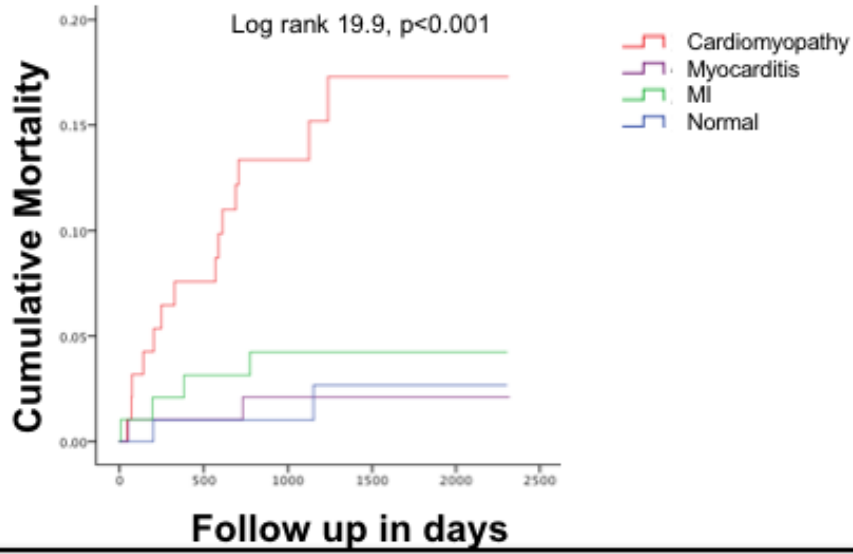
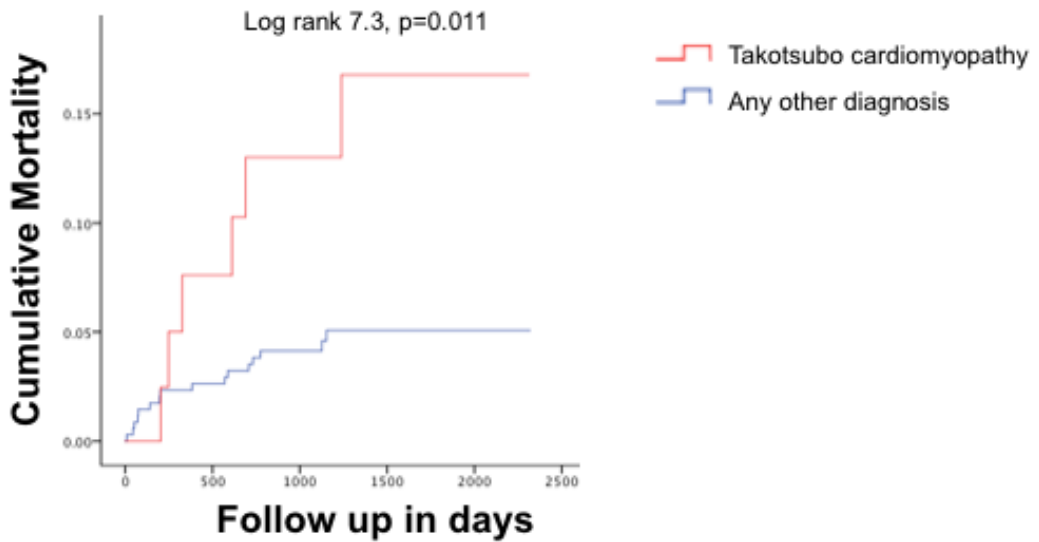
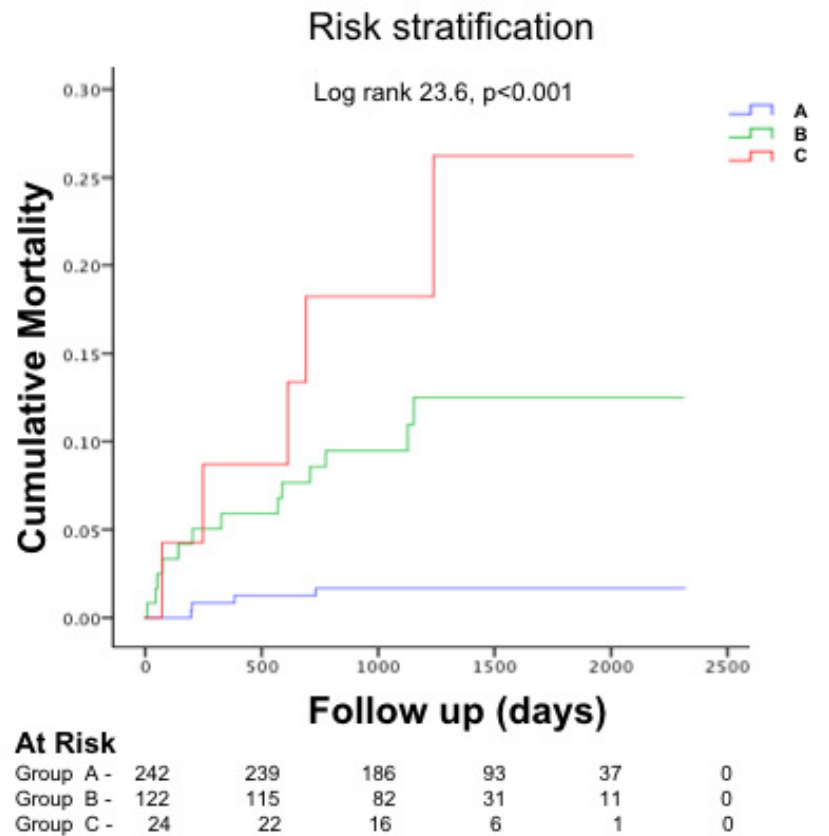
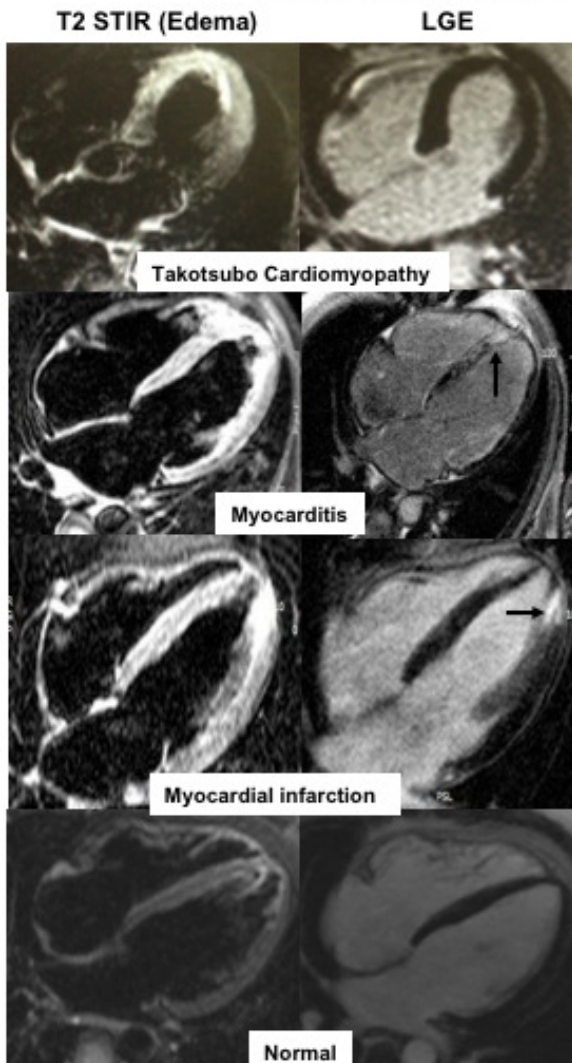


Figure 4b.



Prognostic role of CMR diagnosis and ECG in MINOCA



A - Any CMR diagnosis except CM & Presentation as NSTEMI-ACS
 B - CMR diagnosis of CM or Presentation with ST-Elevation on ECG
 C - CMR diagnosis of CM & Presentation with ST-Elevation on ECG