

# Long-term outcome after normal myocardial perfusion imaging in suspected ischaemic heart disease

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## ABSTRACT

**INTRODUCTION:** Ischaemic heart disease (IHD) is the leading cause of mortality in the Western world. Therefore, to focus on those at risk of having IHD while at the same time avoiding unnecessary patient concern, it is important to have diagnostic tools capable of refuting an IHD diagnosis. Within the past 30 years, myocardial perfusion imaging (MPI) has been used increasingly to detect myocardial perfusion defects. MPI is a safe and non-invasive method with a sensitivity and specificity of > 90%. The aim of this study was to evaluate the long-term prognostic outcome after a normal MPI.

**METHODS:** The study population comprised patients referred for MPI from one single department of cardiology with invasive facilities, from 2008 to 2009. The patients' demographics and the results of the MPIs were collected from their medical records. Only patients without known IHD and with a normal MPI were included. After a follow-up period of 7.8 years (range: 6.8-8.8 years), a retrospective database search was performed. The major outcomes were all-cause mortality, cardiac events defined as nonfatal myocardial infarct or coronary revascularisation by percutaneous coronary intervention or coronary artery bypass grafting.

**RESULTS:** The risk of a cardiac event or death following a normal MPI was 9.6% during long-term follow-up, with an estimated annual death rate of 1.4% per year (95% confidence interval: 0.8-2.5%). This was not different from the background population.

**CONCLUSION:** A normal MPI predicts a favourable long-term prognostic outcome.

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Ischaemic heart disease (IHD) is the leading cause of mortality in the Western world. Therefore, to focus on those at risk of having IHD while avoiding unnecessary patient concern, it is important to use diagnostic tools capable of refuting an IHD diagnosis. Previously, the dominant diagnostic tool was exercise testing using either an exercise bicycle or a treadmill. The test was used to detect signs of myocardial ischaemia as reflected by electrocardiographic changes, chest pain or a decrease in systolic blood pressure during exercise. In

case of one or more of these signs of ischaemia, the patient was typically offered invasive coronary angiography (CAG) in the past to more precisely diagnose the extent of the disease. Within the past 30 years, myocardial perfusion imaging (MPI) has been used increasingly for the detection of myocardial perfusion defects. A perfusion defect on MPI often reflects one or more coronary stenoses or coronary occlusions due to IHD [1-4]. MPI is a well-known, safe and non-invasive diagnostic method to exclude flow-limiting coronary artery stenoses. Its sensitivity and specificity depend on various factors such as the tracer used, whether the "study" is gated, and which load protocol is used in the test. Gated MPI with <sup>99m</sup>Tc-MIBI is routinely used at our hospital, and the test has a sensitivity and specificity of > 90% [4].

Studies have demonstrated that patients with normal or nearly normal myocardial stress perfusion have an annual total cardiac mortality rate below 1%, which is the same as that of the normal age-matched population. Furthermore, there is a significant correlation between the extent of the myocardial perfusion defect and the number of subsequent fatal events [5, 6]. MPI is also known to be a reliable prognostic tool in patients with or without known coronary artery disease [7, 8]. Studies that have described the referral pattern for MPI show that the majority of patients referred for MPI are without previously known IHD [9, 10]. Nevertheless, not many studies exist on the prognosis following a normal MPI. The purpose of the present study is to describe the population referred for MPI directly from a cardiology department with on-site invasive cardiac catheterisation facilities, and to evaluate prognosis during a follow-up period after a normal MPI in patients with suspected IHD.

## METHODS

Data were collected from patients referred directly from the Department of Cardiology at Aalborg University Hospital from 1 January 2008 through 31 December 2009 for evaluation of myocardial perfusion by MPI. The overall study population consisted of 335 consecutive patients with known or suspected IHD. Excluded from the study were patients who were referred for MPI from

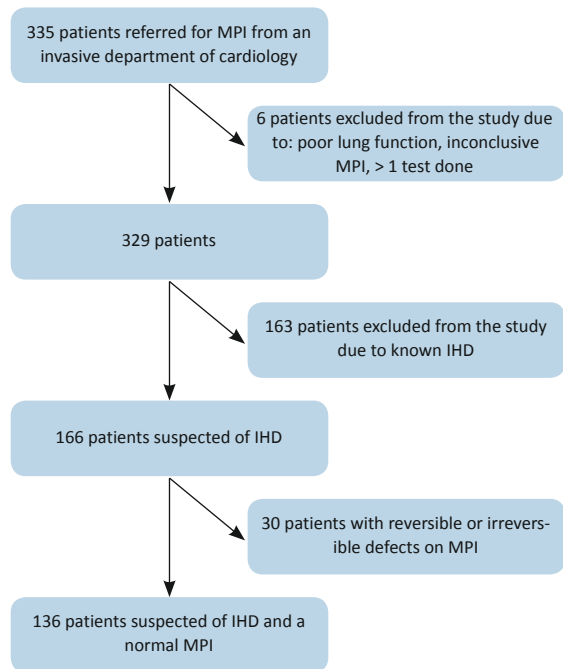
## ORIGINAL ARTICLE

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**FIGURE 1**

The selection of the study population consisting of patients with a normal myocardial perfusion imaging (MPI) and suspicion of ischaemic heart disease (IHD).



other departments or general practitioners, or those who had only a resting MPI study done due to poor lung function ( $n = 2$ ). Two more patients were excluded from the study. One patient had a positive stress MPI, but the subsequent resting MPI was cancelled for unknown reasons. The other patient had an inconclusive resting MPI due to noise artefacts. Two patients had two MPIs done during the two-year inclusion period, and only the first MPI was included in the present analysis. Consequently, the study population consisted of 329 patients. The selection of the final study population is demonstrated in **Figure 1**.

Prior to the MPIs, patient demographics (age, body weight, height, gender, and history of risk factors for coronary artery disease (CAD)) were recorded in an in-house clinical database. The patients were not contacted during follow-up. Follow-up was performed by searching national databases (The National Patient Register and the CPR Register).

Patients with known CAD were excluded from the analysis as were patients suspected of CAD who had reversible or irreversible perfusion defects during MPI; this left 136 patients with suspected IHD and a normal MPI for long-term follow-up.

Follow-up data were collected on 11 October 2016. The major outcomes were all-cause mortality, cardiac events defined as nonfatal myocardial infarct (MI) or

coronary revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). If the patients had more than one event during follow-up, only the first event was considered in the analysis; and if the patient had more than one event during the same admission, only the most severe event was included.

The present study is retrospective in nature and design, and thus no ethical approval was required according to Danish law. The study was approved by The Danish Data Protection Agency and The Danish Health Authority (FSEID-00002257).

### Myocardial perfusion imaging

All MPIs were performed in accordance with a two-day stress-rest standard protocol with a two-day interval between the two scans [11]. In case of a normal stress test, no resting scan was performed. All scans were evaluated blinded by experienced nuclear medicine physicians with no clinical or demographic information available. All MPIs were categorised as either normal or abnormal. Only normal scans were included in the analyses.

### Statistical analysis

Descriptive statistics are reported as frequencies and percentages, or means and ranges as appropriate. The analysis of mortality was performed following the methods described by Finkelstein et al [12]. The survival of the study population was compared to that of a reference population comprising the entire Danish population based on publicly available aggregated data on annual population size and death counts [13]. The comparison was performed among citizens of the same age and gender as the study population during the same calendar period. Based on these data, we calculated the expected number of deaths and compared this to the number observed in the study population using the  $\chi^2$ -test. Furthermore, we visualised the survival distribution in the study population compared with that of the reference population by estimating the survival function in the study population using the Kaplan-Meier estimator. The data search was performed on 13 January 2017.

*Trial registration:* FSEID-00002257.

### RESULTS

**Clinical characteristics** A total of 329 patients were referred for MPI from an on-site invasive department of cardiology. A total of 163 patients (50%) had a pre-existing history of IHD defined as; prior MI, CAG showing coronary arteriosclerosis, a prior PCI or a prior CABG. The remaining 166 patients (50%) were referred for MPI due to suspected cardiac symptoms.

The analyses of the MPIs were categorised into nor-



TABLE 1

Characteristics of patients with a normal myocardial perfusion imaging and suspicion of ischaemic heart disease (IHD).

Age, mean (range), yrs	56 (21-85)
Male/female, n	42/94
Active smoking, n (%)	41 (30)
Hypertension, n (%) <sup>a</sup>	67 (49)
Hypercholesterolaemia, n (%) <sup>a</sup>	62 (46)
Diabetes mellitus, n (%) <sup>a</sup>	12 (9)
Family history of IHD, n (%)	60 (44)
BMI, mean (range), kg/m <sup>2</sup>	28 (17-45)

a) Current medical treatment.



TABLE 2

Events during a mean follow-up period of 7.8 years in patients with suspected ischaemic heart disease (IHD) and a normal myocardial perfusion imaging (MPI) (N = 136).

	Suspected IHD and normal MPI, n (%)	Time to event, mean (range), days
Death <sup>a</sup>	13 (10)	1,430 (267-2,913)
Cardiac events <sup>b</sup>		
Myocardial infarct	3 (2)	1,166 (714-1,599)
Percutaneous coronary intervention	5 (4)	597 (47-1,448)
Coronary artery bypass grafting	2 (1)	1,500 (187-2,813)

a) Death covers all-over causes of death.

b) If the patient had > 1 cardiac event, only the 1st was included.

mal or abnormal.

The follow-up study included only the 166 patients who were referred due to suspected IHD. Of these, a total of 30 patients had abnormal MPIs and were consequently excluded from the follow-up study. Thus, the follow-up study population consisted of 136 patients suspected of IHD and having a normal MPI.

The following characteristics were registered; medically treated arterial hypertension, diabetes mellitus or hypercholesterolaemia, a family history of IHD defined as first-degree relatives with IHD before the age of 60 years of age, BMI and smoking status at the time of the MPI examination.

The 136 patients' demographics are presented in **Table 1**.

During a mean follow-up of 7.8 years (range: 6.8-8.8 years), a total of ten patients had a cardiac event and 13 patients died. The causes of death are unknown as the data were unavailable to the authors. Among the 13 patients who died during the follow-up period, none had a prior cardiac event. The time to event was 804 days (range: 47-1,568 days). In comparison to the background

population, there was no significant difference in observed total mortality (**Table 2**).

The risk of a cardiac event or death following a normal MPI was 9.6% during long-term follow-up, with an estimated annual death rate of 1.4% per year (95% confidence interval: 0.8-2.5%). Thus, after a normal MPI, the standardised mortality ratio was 1.17 (range: 0.58-2.38). This was not different from the age and gender-matched background population (**Figure 2**).

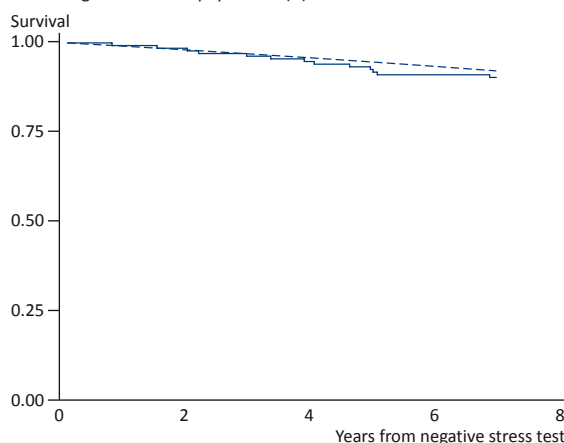
## DISCUSSION

The present study included a total of 329 patients referred for MPI from a department of cardiology with an on-site invasive unit in the course of a two-year-period. Of the 329 patients, 166 patients were referred due to suspected IHD. A large majority (82%) of these patients had a normal MPI. Obviously, it is of great interest to examine the extent to which a normal MPI in this large population reflects a low probability of subsequent major cardiac events, including death. Thus, in the present study, we performed a long-term follow-up based on national registers to show the prognosis compared with the matched background population. The overall outcome was favourable as no significant differences compared with an age and gender-matched background population was found during 7.8 years of observation. Non-invasive testing for ischaemia, such as MPI, is primarily used as a test prior to invasive CAG in patients with a low-to-intermediate predictive risk of having IHD [4]. During our follow-up period, no information on development of angina pectoris was available, nor was information available on medical treatment after the MPI. In the present population, a standardised mortality



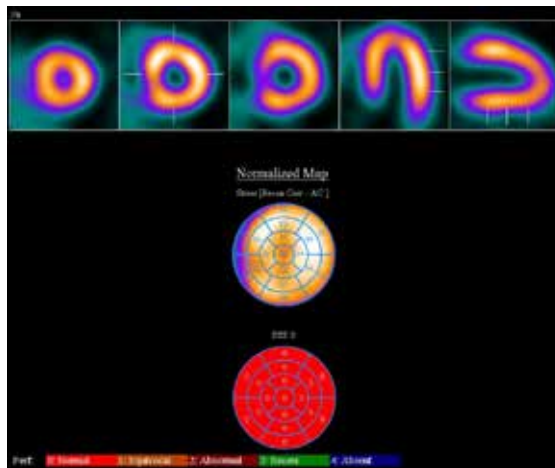
FIGURE 2

Comparison of survival of patients suspected of ischaemic heart disease with a normal myocardial perfusion imaging (—) and the age- and sex-matched general Danish population (---)<sup>a</sup>.



a) Standardised mortality ratio, mean (range): 1.17 (0.58-2.38).

## ! ABBREVIATIONS



A normal myocardial perfusion imaging.

death ratio in patients with a normal MPI and suspicion of IHD compared with a background population was 1.17. We assume that this small increase might be explained by the fact that almost half of the patients were medically treated for hypertension, hypercholesterolaemia or had a family history of IHD. In other words, the study population in total did have a risk profile indicating future events despite a normal MPI in the study. A total of ten patients had a cardiac event following a normal MPI, but this is not statistically significantly different from the background population. All of the ten patients had known risk factors for developing IHD. There is a gender difference in the study population, as two thirds of the patients were females. It is a fact that females develop IHD 10-15 years later than men. In the present study, the average age for the female patients with suspected IHD and a normal MPI was 59 years. Male gender is a well-known risk factor for early development of IHD, and referral for examination due to suspected IHD could be biased because the patients in question were all referred directly from a department of cardiology with an invasive centre. Thus, male patients might have been referred directly for CAG. Furthermore, the difference in symptomatology between females and males might influence the referral pattern. Moreover, the present study population was a highly selected group of patients. Several studies show that patients with a normal MPI have an excellent outcome, and that less than 1% will have a major cardiac event [2, 4-8].

A study by Shaw et al evaluated 4,728 patients with a normal or near-normal MPI, but one third had a prior history of IHD. During their 30-month follow-up, the annual cardiac death rate was 0.6%, which is clearly is lower than the rates reported in our study, but we in-

cluded the overall death rate. If we had divided mortality into cardiac and non-cardiac death, we might have had a similar result [14].

We found that patients suspected of IHD and with a normal scan have an annual event death rate of 1.4%. This finding is in line with the results reported by Schinkel et al in a study with a follow-up period similar to ours. The study by Schinkel et al also showed that the annual event rate increased with abnormal findings in MPI [7]. In our study, patients with abnormal scans were excluded as we intended to study the long-term prognosis after a normal MPI. We did this in order to study the diagnostic precision, as these patients will typically be discharged from hospital without further clinical cardiology follow-up after a normal MPI. Only a single study has previously included an even longer follow-up period of 15 years and that study also reported a favourable prognosis following a normal MPI [8].

The current study has a number of limitations that must be considered. A limited number of patients were studied, and the study is retrospective by design. It is also a selected study population. The causes of death are unknown as the data were unavailable to the authors. Moreover, data on medical treatment during follow-up were unavailable.

The main strength of the present study is that all consecutive patients were included. All patients were referred to MPI by a specialist in cardiology from a single invasive cardiology centre. The follow-up period was clinically relevant, almost eight years.

## CONCLUSION

Our study predicts a favourable long-term prognostic outcome in patients with suspicion of IHD and a normal MP.

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