Optimization of secondary prevention and risk stratification in patients with coronary heart disease

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Chapter 3.

Myocardial infarction patients referred to the primary care physician after 1-year treatment according to a guideline-based protocol have a good prognosis

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Abstract

Introduction
ST-segment elevation myocardial infarction (STEMI) patients that could be referred to the general practitioner (GP) can improve patients tailored care. However, the long-term prognosis of patients referred to the GP is unknown. Therefore, the aim of this study was to assess the long-term prognosis of patients referred to the GP after treatment according to a 1-year institutional guideline-based protocol.

Methods
All consecutive patients treated between February 2004 up to May 2013 who completed the 1-year institutional MISSION! Myocardial Infarction (MI) follow-up and who were referred to the GP were evaluated. After 1 year of protocolized monitoring, asymptomatic patients with a left ventricular ejection fraction >45% on echocardiography were referred to the GP. Long-term prognosis was assessed with Kaplan-Meijer curves and Cox proportional hazards analysis was used to identify independent predictors for 5-year all-cause mortality and MACE.

Results
In total, 922 STEMI patients were included in this study. Mean age was 61.6 ± 11.7 years and 74.4% were male. Median follow-up duration after the 1-year MISSION! MI follow-up was 4.55 years (IQR 2.28-5.00). The event-free survival was 93.2%. After multivariable analysis, age, not using an ACE-inhibitor/AT2-antagonist and impaired LV function remained statistically significant predictors for 5-year all-cause mortality. Kaplan-Meijer curves revealed that 80.3% remained event free for MACE after 5-year. Multivariable predictors for MACE were current smoking and a mitral regurgitation grade ≥ 2.

Conclusion
STEMI patients referred to the GP have an excellent prognosis after being treated according to the 1-year institutional MISSION! MI protocol.

Introduction

Due to the implementation of various very successful treatments for ST-segment elevation myocardial infarction (STEMI), such as treatment with primary percutaneously coronary intervention (pPCI), adjunctive antithrombotic therapy and adequate secondary prevention medication,[1-6] the current 1-year and 5-year all-cause mortality rates in STEMI patients decreased the last decades to approximately 10%[7, 8] and 20%,[8, 9] respectively. In an era of growing economic pressure in healthcare, identifying low risk STEMI patients, can improve patient tailored care and could reduce healthcare costs. For example, several studies demonstrated that low risk STEMI patients can be safely discharged within two or three days after admission[10, 11], which resulted in a reduction of healthcare costs[10, 12]. However, to our knowledge, there are no recommendations as to the appropriate duration of follow-up in the outpatient clinic of a cardiologist after STEMI. According to the MISSION! myocardial infarction (MI) protocol[13], after 1-year follow-up, asymptomatic patients with a left ventricular ejection fraction (LVEF) >45% on echocardiography, are referred to the general practitioner (GP). The hypothesis of this study is that these patients can safely be referred to the GP after 1-year MISSION! MI follow-up. As the long-term prognosis of STEMI patients referred to the GP is unknown, the aim of this study was to assess the prognosis of patients referred to the GP after treatment according to the 1-year institutional MISSION! MI protocol in the Leiden University Medical Center.

Methods

Study population

All patients treated with a pPCI for STEMI in the LUMC are included in the prospective MISSION! MI registry.[13] For this current observational retrospective analysis all consecutive patients treated between February 2004 up to May 2013 who, after completion of the 1-year MISSION! MI follow-up were referred to the GP, were evaluated. Patients who died during the first year after their index infarction, or patients who were transferred during admission to another hospital due to logistic reasons were not included in this analysis. Logistic reasons were lack of available space for patients to admit, patient's preference or when patients were transferred back to the referring hospital after the pPCI. STEMI was defined as typical electrocardiographic (ECG) changes (ST-segment elevation ≥ 0.2 mV in ≥ 2 contiguous leads in V_1 through V_3, ≥ 0.1 mV in other leads, or presumed new left bundle branch block) and a typical rise and fall of cardiac biomarkers accompanied with chest pain for at least 30 minutes.[14] Since the data did not contain any identifiers that could be traced back to the individual patient and the data are obtained for patient care, the Dutch Central Committee on Human-Related Research permits the use of anonymous data without prior approval of an institutional review board. This study was

conducted according to the declaration of Helsinki.

Study procedure

The institutional, guideline-based MISSION! MI protocol is a standardized clinical framework which consists of a pre-hospital, in-hospital and an outpatient phase to optimize clinical decision making and treatment up to 1 year after the index event.[13, 15, 16] The MISSION! MI protocol is in accordance with the current STEMI guidelines and was changed when necessary.[15, 16] In the pre-hospital phase a high-quality 12-lead ECG was obtained. If a STEMI was diagnosed, patients were treated by the paramedics with a loading dose of clopidogrel or prasugrel, aspirin, heparin and intravenous glycoprotein IIb/IIIa inhibitors if appropriate. During the in-hospital phase patients were directly transferred to the catheterization laboratory for pPCI according to the current guidelines. If no contraindications existed, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins were administrated within 24 hours of admission. Dual antiplatelet therapy was additionally prescribed, consisting of aspirin 100mg daily for life and prasugrel 10mg daily or clopidogrel 75mg daily for 12 months if appropriate. The outpatient clinic phase consists of 4 clinic visits, where patients were treated in accordance to current guidelines to reach the secondary prevention targets. Furthermore, several functional tests, such as a stress echocardiography and Holter registration, were obtained and if necessary an intervention was performed. An important part of the outpatient clinic was to emphasize the need for drug compliance and was the education on and modification of lifestyle behavior (smoking cessation, healthy diet, exercise and weight management). Patients also participated in a professional cardiac rehabilitation program as part of the routine care where also a dietician, phycological worker and social worker where out at their disposal, as this is associated with better one-year outcome.[13, 17] After 1 year of intensive monitoring patients were, by protocol, referred to the general practitioner if they were asymptomatic with a left ventricular ejection fraction (LVEF) >45%.

Data acquisition/Clinical data

All patients risk factors, clinical features and laboratory measurements are systematically collected for each MISSION! patients in EPD-VISION, using a unique study code. Echocardiographic images were attained from patients at rest in left lateral decubitus position using a commercially available system (Vivid 7 and E9, GE, Healthcare, Horten, Norway). Standard M-mode and 2D (color, pulsed and continuous wave Doppler) images were obtained from the parasternal (long-and short-axis) and apical views (long-axis, 2- and 4-chamber), using 3.5-MHz or M5S transducers, and digitally stored for offline analysis (EchoPac BT13, GE Medical Systems, Horten, Norway). The LVEF, wall motion score index (WMSI) and the grade of mitral regurgitation (MR) were measured according to the current echocardiographic recommendations.[18, 19] Clinical follow-up data were prospectively collected in the electronical patients file by independent clinicians. Data from patients were gathered from either out-

patients chart review or by telephone interview. Information on the vital status was obtained from the Dutch Municipality Records registry. Cause of death was retrieved from the GP.

Study endpoint
The primary endpoint of this study is all-cause mortality. The secondary endpoint is a combined endpoint of coronary revascularization, recurrent myocardial infarction, implantation of an implantable cardiac defibrillator (ICD) or a pacemaker (PM), hospitalization due to heart failure, stroke and death. All these adverse events combined have been defined as major adverse cardiac event (MACE).

Statistical analysis
Data are summarized as means with standard deviation in case of normally distributed or as median with interquartile ranges in case of non-normally distributed data. Categorized data are shown as numbers with percentages. Univariable Cox proportional hazard regression models were used to assess the association of age, gender and pre-specified covariates, that are known associated variables in literature, with all-cause mortality or occurrence of time-dependent adverse events (MACE) in STEMI patients.[1-3, 20-23] Age, gender and other variables significant at $p<0.10$ were entered into a multivariable Cox model to calibrate a combined prognostic index to predict either all-cause mortality or MACE.[24] Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. To classify GP patients into either high or low risk groups based on these Cox regression models, we dichotomized the prognostic index using the median value. Stratified by these two groups, Kaplan-Meier curves were then used to estimate and verify survival expectations (time to either all-cause death or MACE). The log-rank test log-rank test was calculated to compare the cumulative incidences of the endpoints between the 2 groups. All statistical tests were 2-tailed, p-values <0.05 were considered statistically significant. Analyses were performed with SPSS 23.0 statistical analysis software (IBM, Armonk, NY, USA).

Results

Between February 2004 up to May 2013, 2943 patients were admitted to the LUMC and treated with pPCI for STEMI. During the first year after their index infarction 206 (7.0%) patients died and 964 (32.8%) patients did not follow the institutional MISSION! MI protocol for logistical reasons. In total, 1773 (60.2%) patients completed their 1-year follow-up according to the MISSION! MI protocol. Of these patients 851 (48%) received follow-up in the outpatient clinical of a cardiologist according to the MISSION! MI protocol.

Therefore, 922 (52%) patients were referred to the GP and selected for evaluation (Figure 1). Median follow-up duration after the 1-year MISSION! MI follow-up was 4.55 year (IQR 2.28-5.00).

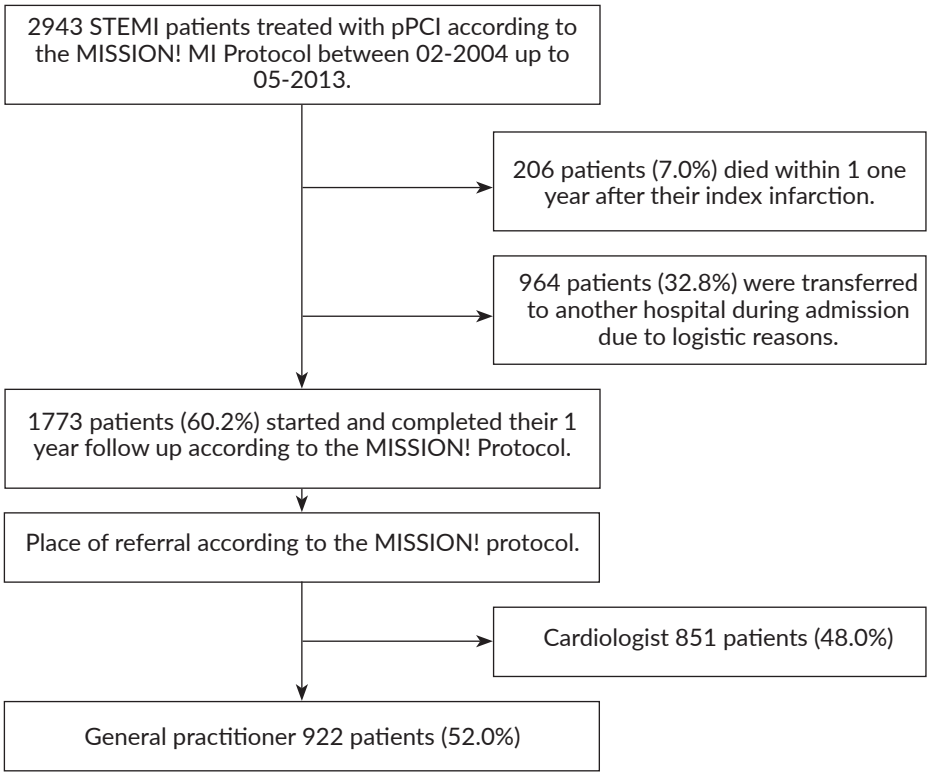

Figure 1. Overview of eligible MISSION! patients. Abreviations: STEMI, ST-elevation myocardial infarction; pPCI, primary percutaneously coronary intervention

Baseline characteristics

Patients characteristics, medication use and laboratory results after 1 year MISSION! MI follow-up are summarized in table 1. Mean age was 61.6 ± 11.7 year and 686 (74.4%) was male gender. The LVEF was in 70 (7.6%) patients below 45%.

Long-term survival analysis

In total, 48 patients deceased after 1 year MISSION! MI follow up. The cause of death was adjudicated as cardiac origin in 6 patients, likely cardiac in 3 patients, non-cardiac in 35 patients, unlikely cardiac in 2 patients and the cause of death was unknown in 2 patients.

The event free survival rate for the primary endpoint was 93.2% in the total GP group. Univariable Cox regression analysis revealed that age, history of a malignancy or stroke, not using a ACE-i/AT2-antagonist or aspirin, an impaired LVEF, a MR grade ≥ 2 and multivessel disease during pPCI were significant predictors for 5-year all-cause mortality. After multivariable analysis, age, not using a ACE-i/AT2-antagonist and an impaired LVEF remained statistically significant predictors for the primary endpoint (Table 2). Stratified by high and low risk GP patients, figure 2 showed that high risk GP patients (n=417) have a significant lower event free survival rate of 88.6% compared to 97.4% in the low risk GP group (n=416) (log rank <0.001).

Table 1. Patients characteristics after 1 year MISSION! follow up

Variable	GP (n=922)
Patient's characteristics	
Age, years	61.6 ± 11.7
Male gender	686 (74.4)
Current smoking	185 (20.1)
Diabetes mellitus	73 (7.9)
History of a malignancy	46 (5.0)
History of cerebrovascular disease	31 (3.3)
Medication use	
Betablocker	824 (89.4)
ACE-inhibitor/AT2-antagonist	877 (95.1)
Statin	887 (96.2)
Aspirin	859 (93.1)
Coumarin	40 (4.3)
Laboratory results	
Total cholesterol (mmol/L)	4.14 ± 0.92
LDL-cholesterol (mmol/L)	2.39 ± 0.75
HDL-cholesterol (mmol/L)	1.34 ± 0.42
Triglycerides (mmol/L)	1.54 ± 0.82
Echocardiographic parameters	
Left ventricular ejection fraction <45%	70 (7.6)
Mitral regurgitation grade ≥ 2	31 (3.4)
Wall motion score index	1.13 (1.00-1.25)
Clinical characteristics	
Number of vessel disease during pPCI >1[a]	451 (48.9)
Complete revascularisation during pPCI	560 (60.7)
Interventions	
Revascularization within 1 year FU	122 (13.2)

Data are expressed as number (%), mean ± standard deviation or median with interquartile range. Abbreviations: GP, general practitioner; ACE, angiotensin converting enzyme; AT, angiotensin; LDL, low density lipoprotein; HDL, high density lipoprotein; [a]A narrowed

coronary artery was defined as a stenosis of ≥ 50% on baseline coronary angiogram; FU, follow-up; pPCI, primary percutaneously coronary intervention

Table 2. Univariable and multivariable Cox proportional hazard regression analysis to identify independent predictors of 5-year all-cause mortality

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, y	1.085 (1.056-1.115)	<0.001	1.071 (1.040-1.108)	<0.001
Male gender	0.973 (0.506-1.870)	0.935	1.441 (0.678-3.064)	0.342
Current smoker	1.446 (0.757-2.764)	0.264		
Diabetes mellitus	1.725 (0.733-4.057)	0.212		
Comorbidities				
History of malignancy	2.812 (1.195-6.615)	0.018	1.896 (0.704-5.104)	0.205
History of cerebrovascular disease	3.359 (1.330-8.480)	0.010	1.077 (0.388-2.987)	0.887
Current medication use				
Betablocker	0.493 (0.230-1.054)	0.065	0.498 (0.221-1.124)	0.093
ACE-inhibitor/AT2-antagonist	0.301 (0.119-0.760)	0.011	0.294 (0.110-0.788)	0.015
Statin	0.627 (0.152-2.586)	0.519		
Aspirin	0.424 (0.180-0.998)	0.049	0.831 (0.327-2.116)	0.698
Coumarin	2.002 (0.718-5.584)	0.185		
Echocardiographic parameters				
Left ventricular ejection fraction <45%	3.088 (1.493-6.388)	0.002	2.807 (1.298-6.071)	0.009
Mitral regurgitation grade ≥ 2	3.712 (1.465-9.406)	0.006	1.747 (0.642-4.755)	0.275
Wall motion score index	1.655 (0.638-4.349)	0.307		
Clinical characteristics				
Number of vessel disease during pPCI >1[a]	2.043 (1.143-3.797)	0.017	1.540 (0.676-3.512)	0.304
Complete revascularisation during pPCI	0.585 (0.330-1.036)	0.066	1.041 (0.482-2.251)	0.918
Intervention				
Revascularization within 1 year FU	1.302 (0.610-2.782)	0.501		

Data are expressed as hazard ratios with 95% confidence interval

Abbreviations: CHD, cardiac heart disease; ACE, angiotensin converting enzyme; AT, angiotensin; pPCI, primary percutaneously coronary intervention; FU, follow up

Table 3. Univariable and multivariable Cox proportional hazard regression analysis to identify independent predictors of 5-year MACE

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, y	1.016 (1.002-1.030)	0.029	1.008 (0.991-1.026)	0.370
Male gender	1.179 (0.797-1.745)	0.409	1.374 (0.862-2.189)	0.181
Current smoker	1.460 (1.010-2.109)	0.044	1.788 (1.190-2.687)	0.005
Diabetes mellitus	1.739 (0.683-4.432)	0.246		
Comorbidities				
History of malignancy	1.778 (0.985-3.210)	0.056	1.534 (0.765-3.074)	0.228
History of cerebrovascular disease	1.788 (0.911-3.510)	0.091	1.362 (0.639-2.902)	0.424
Current medication use				
Betablocker	0.830 (0.49441.396)	0.483		
ACE-inhibitor/AT2-antagonist	0.659 (0.323-1.345)	0.252		
Statin	1.369 (0.436-4.296)	0.590		
Aspirin	0.529 (0.310-0.904)	0.020	0.381 (0.093-1.557)	0.179
Coumarin	1.757 (0.950-3.249)	0.073	0.562 (0.117-1.269)	0.471
Echocardiographic parameters				
Left ventricular ejection fraction <45%	1.987 (1.226-3.221)	0.005	1.649 (0.936-2.907)	0.083
Mitral regurgitation grade ≥ 2	2.759 (1.488-5.115)	0.001	2.463 (1.247-4.867)	0.009
Wall motion score index	0.870 (0.473-1.600)	0.654		
Clinical characteristics				
Number of vessel disease during pPCI >1	1.666 (1.194-2.325)	0.003	1.321 (0.794-2.197)	0.284
Complete revascularisation during pPCI	0.665 (0.478-0.926)	0.016	0.802 (0.490-1.314)	0.381
Intervention				
Revascularization within 1 year FU	1.074 (0.677-1.704)	0.763		

Data are expressed as hazard ratios with 95% confidence interval

Abbreviations: CHD, cardiac heart disease; ACE, angiotensin converting enzyme; AT, angiotensin; pPCI, primary percutaneously coronary intervention; FU, follow up

Long-term MACE analysis

In total, 147 reached the secondary endpoint. A recurrent myocardial infarction occurred in 36 patients, in 51 cases a patient was revascularized, 42 patients died, 15 patients had a cerebrovascular event, in 2 patients an ICD or PM was implanted and 1 patient was admitted for heart failure. In total, 80.2% remained event free after 5 years for the secondary endpoint. Table 3 demonstrates the univariable and multivariable predictors for MACE within 5 years. Patients with an unfavorable outcome according to the univariate Cox regression analysis were patients with an older age, current smoking, not using aspirin, a lower LVEF, a MR grade ≥ 2, multivessel disease during pPCI. Patients who underwent complete revascularization during pPCI had a favorable outcome in the univariate analysis. Current smoking and a MR grade ≥ 2 remained significant predictors for MACE after multivariable Cox regression analysis. Figure 3 showed the Kaplan-Meijer curves of the patients stratified by high and low risk GP patients. High risk GP patients (n=387) reached the secondary endpoint in 73.8% of the cases, compared to 88.3% in the low risk GP group (n=387) (log-rank <0.001).

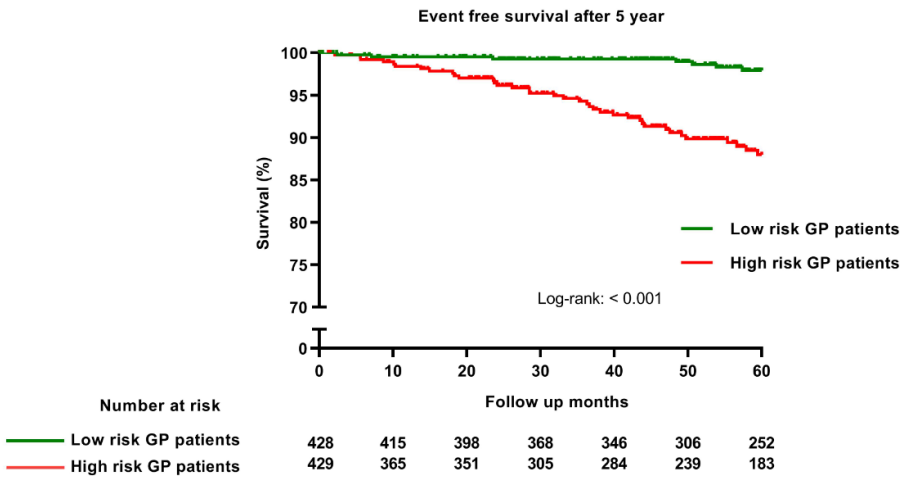

Figure 2. Kaplan-Meier analysis to evaluate the event free survival of experiencing the primary endpoint of 5-year all-cause mortality, stratified by high and low risk GP patients

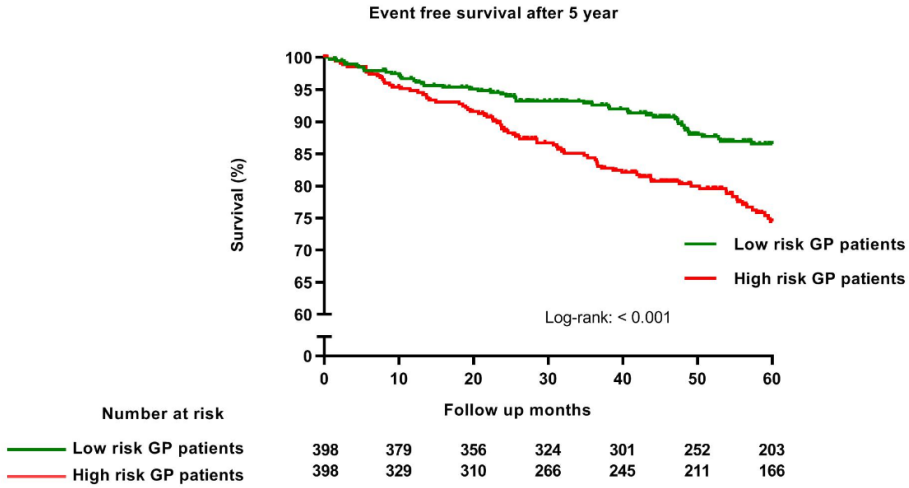

Figure 3. Kaplan-Meier analysis to evaluate the event free survival of experiencing the secondary endpoint of MACE, stratified by high and low risk GP patients

Discussion

In the present study, it is demonstrated that STEMI patients treated with pPCI and referred to the GP after being treated according to the 1-year MISSION! MI protocol have an excellent prognosis with a 5-year event free survival rate for all-cause mortality of 93.2% after 1 year MISSION! MI follow-up. Furthermore, 4 out of 5 patients remained event-free for MACE after they were referred to the GP. In an era of growing economic pressure in healthcare, identifying low risk STEMI patients, can improve patient tailored care and could reduce healthcare costs. Since there are no recommendations in international guidelines for the appropriate duration of follow-up in the outpatient clinic after a STEMI, this 1-year period might be applied in future guidelines.

The decision whether STEMI patients can be referred to the GP in the MISSION! MI protocol is mainly based on the LVEF measured after 1-year MISSION! MI follow-up. An impaired LV function in STEMI patients is strongly associated with worse outcome,[21, 22] and an EF of 45% seems to be a good discriminator between high and low risk patients.[21, 25]

There are several reasons in this study that support the idea that patients can be referred to the GP after 1-year MISSION! MI follow-up. First, in line with other large registry studies,[7-9] this study shows that after the first year after STEMI, the yearly risk of death decreases. In the current analysis, the annual mortality rate was slightly more than 1% after 1 year MISSION! MI follow-up. Secondly, cardiac death was observed in a very small number of patients. In the majority of the patients, 37 out of 48 patients, the cause of death was of non-cardiac origin,

mainly malignancies and pulmonary diseases, which is in line with results found by Pedersen et al.[8] Furthermore, according to the Central Bureau of Statistics (CBS) in the Netherlands the chance to survive for the next 5-year for a 61-year old healthy individual, which is the average age of the cohort referred to the GP, is 95.8%.[26] This is only slightly better than the observed risk of STEMI patients referred to the GP.

All patients in this study were treated according to the institutional MISSION! MI protocol. Other studies confirmed earlier that the extent of guideline implementation is associated with improved outcome.[27-29] The MISSION! MI protocol contains one structured patients-centered framework with a pre-hospital, in-hospital and an outpatient phase. An important part of the outpatient phase is to emphasize the need for drug compliance and is the education on and modification of lifestyle behavior. For example, a high percentage of patients still used their medication, prescribed during admission, after 1 year follow-up. Several studies indicated the importance of medication adherence that prevent CVD in patients with an AMI [30] which is associated with positive health outcomes.[30] Another possible explanation for the low event rate is the well-organized primary care in the Netherlands. In the region 'Zuid-Holland Noord' which also covers the Leiden region, the GP's use a uniform CVRM care program for all patients with CVD.[31] In this program, patients routine follow-up is performed by nurse specialists in primary care who monitor patients risk factors and adjust if necessary.

Several risk factors for a worse outcome were identified during this study. As this uncontrolled, observational study reflects the situation in the daily practice minor protocol deviations can be expected. A small percentage of patients referred to the GP had an LVEF < 45% or a mitral regurgitation grade ≥ 2. These patients were at higher risk of developing an adverse event. These results emphasize the importance that these patients stay in the outpatient clinic of a cardiologist where closer follow-up is available and where, for example additional treatment such as heart failure medication can get started when indicated or potentially the need for cardiac resynchronization therapy (CRT), ICD implantation or left ventricle reconstruction can be considered. Furthermore, current smoking and not using an ACE-inhibitor were identified as risk factors for developing an adverse event, which most likely reflects a surrogate marker for overall healthy behavior.[30] Before these patients are referred to the GP, addressing these issues to the GP are of importance.

There are several limitations that should be pointed out. First, since this is a retrospective observational single center study, with patients treated according to the MISSION! MI protocol, it is difficult to expand these results to other hospitals or countries. Secondly, this study may have introduced bias since a substantial part of the patients was referred to the referring hospital after treatment with a pPCI. However, these patients were not referred due to

medical reasons but due to logistic reasons such as lack of available space for patients to admit or patient's preference. So, a random cohort of patients was referred to the referring hospital thereby preventing selection bias. Thirdly, next to the LVEF, the presence of symptoms was a criterium to keep patients in the outpatient clinic of the cardiologist. In this study, no detailed information about patients' symptoms was available. Although it is not unquestionable, it is unlikely that there is a large proportion of patients with serious complaints referred to the GP since the number of adverse events in the GP group in the first year after referral was 4.4%. At last, this project did not focus on the 50% of the patients who stayed in the outpatient clinic of the cardiologist. Perhaps, amongst this group, there are patients who should considered to be low risk as well and could be referred to the GP. Future research is needed to optimize and identify all the patients eligible for referral to the GP after being treated according to the 1-year MISSION! MI protocol and should evaluate the possibilities the refer stable patients after a STEMI within one year to the GP as is already suggested in 2005 by Boomsma et al.[32]

In conclusion, STEMI patients referred to the GP after 1 year MISSION! MI follow-up have an excellent prognosis for 5-year survival and have a low risk for MACE. Patients with an impaired LV function or a mitral regurgitation grade ≥ 2 should be considered as higher risk patients and should stay in the outpatient clinic of a cardiologist.

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