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ORIGINAL RESEARCH

Medical Therapy and Recurrent Ischemic Events in High Risk Patients Surviving their Myocardial Infarction for at Least 12 Months: Comparison of Patients with ST Elevation Versus Non-ST Elevation Myocardial Infarction

Uwe Zeymer · Katrin Riedel · Michael Hahn

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ABSTRACT

Introduction: Data about treatments and recurrent ischemic events in patients surviving their most recent myocardial infarction event-free for at least 12 months are scarce.

Methods: In a retrospective data analysis, charts of patients who had a myocardial infarction 1–3 years ago with an event-free period of at least 12 months after the index event and at least one high risk factor were centrally collected and analyzed. Here we compare patients with ST elevation myocardial infarction (STEMI) versus non-ST elevation myocardial infarction (NSTEMI).

Results: A total of 666 patients, 342 with STEMI and 324 with NSTEMI, were included. Revascularization procedures for the index event were performed in 89% of patients with STEMI and 72% of patients with NSTEMI. About 62% of patients were still on dual antiplatelet therapy after 12 months, predominantly with aspirin and clopidogrel. This rate declined to 30% after 18 months. Patients with STEMI had a higher mortality (19% versus 13%, $p = 0.04$) and major adverse cardiovascular and cerebrovascular event rate (MACCE; 33% versus 23%, $p = 0.03$) during follow-up up to 36 months, while there were no significant differences with respect to recurrent myocardial infarction or stroke. The number of high risk factors was closely linked to the rate of MACCE at follow up.

Conclusions: Patients surviving their myocardial infarction without any further event during the first 12 months have a high rate of recurrent ischemic events in both STEMI and NSTEMI cases during subsequent follow-up. Therefore, secondary prevention therapies should be continued even one year after myocardial infarction, which might improve outcomes.

Keywords: Acute myocardial infarction; Prognosis; Secondary prevention

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U. Zeymer (✉)
Klinikum Ludwigshafen and Institut für Herzinfarktforschung, Ludwigshafen, Germany
e-mail: uwe.zeymer@t-online.de

K. Riedel · M. Hahn
Astra Zeneca Germany GmbH, Wedel, Germany

INTRODUCTION

An acute myocardial infarction is the first manifestation of coronary artery disease in about 1/3 of patients [1]. These patients have an impaired long-term prognosis compared to patients with stable coronary artery disease [2, 3]. Therefore, intensified secondary prevention measures are recommended in the current European Society of Cardiology (ESC) guidelines, for patients with ST elevation myocardial

infarction (STEMI) and patients without persistent ST elevations (NSTEMI), to reduce recurrent ischemic events and improve long-term outcomes [4, 5]. While there is a lot of study evidence from randomized controlled trials about the optimal treatment within the first year after an acute myocardial infarction, less is known about the optimal long-term therapy in patients surviving the first year after their index event [4, 5]. Information about risk factors, treatment and recurrent ischemic events in these patients are of high clinical interest. Therefore we have performed a retrospective study in Germany to describe the disease and treatment characteristics of patients with an uneventful course for at least 12 months after their first myocardial infarction, treated by general practitioners or cardiologists in an outpatient setting.

METHODS

An eligible sample of German physicians recruited from the Lightspeed All Global (AG) physician panel conducted the retrospective medical chart review and abstraction. AG has built panels of physicians to conduct national and international online research. All physicians who are members of the AG panel have been telephone-recruited by AG recruitment teams and have actively opted in, i.e. explicitly stated their willingness to contribute to research studies, by providing opinions and access to treatment data on a regular basis. Validation procedures were implemented to ensure that the respondents are real, existing physicians. AG has a verification process in place in order to confirm a respondent's practicing status: all background data were checked and verified against medical directories. AG has confidentiality agreements, contracts and compensation procedures with panel members in place in order to facilitate study enrollment.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

AG maintains the panel members' personal details in the strictest confidence and uses the contacts for research purposes only. Therefore, the physician sample of this study is pseudonymous, meaning that while AG is familiar with personal details of enrolled physicians, Kantar Health (KH) received de-identified data. From the total of 341 participating physicians, 192 (56.3%) are general practitioners or internists and 149 (43.7%) cardiologists.

Patients were enrolled if they had experienced their most recent myocardial infarction >12 and <36 months ago and had survived the first 12 months after the index event without any further event. In addition, they had to have at least one of the following high risk factors: age >65 years, diabetes mellitus, second myocardial infarction, impaired renal function (GFR < 60 ml/min) or multi-vessel coronary artery disease. Information about the initial myocardial infarction, revascularization therapy, risk factors, medical treatment and recurrent ischemic >12 months after the index event were centrally recorded via an internet-based case record form.

Death was reported as all cause mortality. Major adverse cardiac and cerebrovascular events (MACCE) included death, recurrent myocardial infarction and stroke.

Statistics

Patients with STEMI or NSTEMI were compared regarding patient characteristics, treatment and procedures. Means (±standard deviation), numbers and proportions were calculated, respectively, p values were obtained from χ^2 test for categorical variables and outcomes and from t test for continuous variables.

Survival was defined as the time from 12 months after the date of diagnosis of myocardial infarction (index event) to the time of the occurrence of the first adverse cardiac and cerebrovascular event (MACCE). If MACCE was not recorded, the patient was censored. Survival probability was obtained by the Kaplan–Meier method, and statistical significance was assessed using the log-rank test.

RESULTS

Between April and June, 2015, a total of 666 charts of patient fulfilling the inclusion criteria

were reviewed and data were entered into the central data base.

The baseline characteristics of the patients with STEMI ($n = 342$) and NSTEMI ($n = 324$) as index event are given in Table 1 and did not show any significant differences between the two groups, except for gender (female higher in NSTEMI), hypertension (higher in STEMI) and smoking (higher in STEMI). There was a high use of invasive and revascularization procedures in both groups (Table 1), with more patients undergoing angiography and percutaneous coronary intervention (PCI) in the STEMI group.

Almost all patients were treated with some kind of antithrombotic therapy, while about 62% of patients received dual antiplatelet therapy, predominantly with aspirin and clopidogrel (Table 2). The rate of patients with dual antiplatelet therapy (DAPT) decreased steadily from around 62% after 12 months, to about 30% after 18 months, in patients with STEMI and NSTEMI (Fig. 1).

The use of other secondary prevention therapies was high, with statins in over 80%, ACE-inhibitor or ARBs in over 70% and beta-blockers in over 60% of patients. There was a higher use of beta-blockers after STEMI compared to NSTEMI (78.3% versus 64.8%).

MACCE and all cause and cardiovascular mortality were significantly higher after STEMI, while there were no significant differences in recurrent myocardial infarction and stroke rate (Table 3). The Kaplan–Meier curves MACCE after STEMI and NSTEMI are given in Fig. 2a.

Two hundred-ninety-nine (44.9%) patients had one, 244 (36.6%) two, 87 (13.1%) three, 25 (3.8%) four and 11 (1.7%) five high risk factors, respectively. As shown in Fig. 2b in the overall population there was increase of MACCE with an increasing number of high risk factors.

DISCUSSION

Our results indicate that patients surviving their myocardial infarction for at least 12 months without any event are still at ongoing risk of subsequent ischemic events during follow-up. This risk is closely related to the number of high risk factors, such as impaired renal function, diabetes, older age, multi-vessel disease and recurrent myocardial infarction.

The current guidelines of the European Society of Cardiology (ESC) for patients with STEMI [4] and NSTEMI [5] include firm recommendations about secondary prevention measures within the first year after the index event. However, in large clinical registries and clinical trials there has been a continuous rate of ischemic events beyond the first year after myocardial infarction. In the GRACE registry mortality was 15% after 12 months and 39% after 4 years [6]. In the TRA-2P trial the event curves did not differ between the first 12 months after myocardial infarction and after 12 months [7]. Further evidence is reported from the large REACH registry where patients with atherothrombotic diseases were followed for up to 4 years. Here patients with a history of myocardial infarction had a high event rate of about 18% [8].

All these data indicate that patients surviving their myocardial infarction have a high long-term risk for recurrent ischemic events, which is significantly higher than the event rate in patients with stable coronary artery disease [2, 3]. There are a number of registries available describing risk factors, treatment patterns and outcomes of patients within the first year after their myocardial infarction [9–11]. To gain some more insight into the patient profile, treatment patterns and event rates in patients with uneventful course for 12 months after their most recent myocardial infarction we performed a retrospective data analysis in an outpatient setting in Germany. Our patients had a high rate of invasive and revascularization procedures during their index hospitalization. These results are in concordance with reports from other registries in Germany in the same patient population [12] and with ESC Guidelines [4, 5]. Most likely due to the inclusion criteria requiring at least one high risk criterion [13] (the same used in the PEGASUS TIMI 54-trial), there was no age difference between the STEMI and NSTEMI population. This allowed a direct comparison of event rates without adjustment for age

Table 1 Baseline characteristics and revascularization procedures of the patients with STEMI and NSTEMI

	STEMI	NSTEMI	*p* value*
Patients	342 (51.04%)	324 (48.36%)	
Demographics			
Age (mean ± SD)	71.8 (±8.10)	72.4 (±8.22)	0.33
Age >65 years	294 (85.96%)	276 (85.19%)	0.77
Age >75 years	105 (30.70%)	105 (32.41%)	0.63
Female	94 (27.49%)	128 (39.51%)	0.001
Body mass index	28.7 (±4.09)	28.3 (±4.12)	0.17
Private health insurance	47 (13.74%)	47 (14.51%)	0.77
Coronary risk factors			
Hypertension	259 (75.73%)	220 (67.90%)	0.02
Dyslipidemia	148 (43.27%)	122 (37.65%)	0.13
Diabetes mellitus	143 (41.81%)	125 (38.58%)	0.39
Current smoker	110 (32.16%)	73 (22.53%)	0.005
Ex-smoker	159 (46.49%)	148 (45.68%)	0.83
Family history of coronary artery disease	128 (37.43%)	102 (31.48%)	0.10
Cardiac history and concomitant diseases			
Atrial fibrillation	43 (12.57%)	36 (11.11%)	0.55
Valve disease	15 (4.39%)	7 (2.16%)	0.10
Renal insufficiency (GFR[a] < 60)	52 (15.20%)	52 (16.05%)	0.76
Peripheral artery disease	22 (6.43%)	18 (5.56%)	0.63
Prior stroke/TIA	6 (1.75%)	9 (2.78%)	0.37
COPD	52 (15.20%)	37 (11.42%)	0.15
Chronic liver disease	9 (2.63%)	9 (2.78%)	0.90
Malignant disease	3 (0.88%)	13 (4.01%)	0.008
Anxiety/depression	34 (9.94%)	33 (10.19%)	0.91
Index event			
<24 months ago	250 (73.10%)	244 (75.31%)	0.51
>24 months ago	92 (26.90%)	80 (24.69%)	0.51
Coronary angiography	322 (94.1%)	262 (80.9%)	0.001
Multivessel disease	87 (25.4%)	82 (25.3%)	0.96
PCI	260 (76.0%)	206 (63.6%)	0.005

Table 1 continued

	STEMI	NSTEMI	*p* value*
CABG	42 (12.3%)	27 (8.3%)	0.09

COPD chronic obstructive pulmonary disease, *TIA* transitory ischemic attack
* *p* value obtained from χ^2 test for categorical variables and *t* test for continuous variables
[a] Creatinine clearance estimate by Cockroft–Gault

Table 2 Medical treatment at 12 months after the index event

	STEMI	NSTEMI	*p* value*
Antithrombotic therapy			
Aspirin	318 (92.9%)	302 (93.2%)	0.90
Clopidogrel	173 (50.5%)	181 (55.8%)	0.17
Prasugrel	59 (17.2%)	27 (8.3%)	0.006
Ticagrelor	46 (13.4%)	39 (12.0%)	0.58
Vitamin-K antagonist	21 (6.1%)	26 (8.0%)	0.34
Novel oral anticoagulant	25 (7.3%)	10 (3.1%)	0.01
Antithrombotic combination therapy			
Aspirin only	37 (10.8%)	54 (16.7%)	0.02
ADP-receptor antagonist only	8 (2.3%)	7 (2.2%)	0.87
Aspirin + ADP-receptor antagonist	213 (62.2%)	201 (62.0%)	0.94
VKA or NOAC only	8 (2.3%)	6 (1.8%)	0.66
VKA or NOAC + single antiplatelet[2)]	9 (2.6%)	10 (3.1%)	0.72
VKA or NOAC + dual antiplatelet	12 (3.5%)	5 (1.5%)	0.10
Concomitant therapy			
Statin	288 (84.2%)	260 (80.2%)	0.18
Beta-blocker	268 (78.3%)	210 (64.8%)	0.001
ACE-I/ARB	243 (71.0%)	246 (75.9%)	0.15
Calcium channel blocker	39 (11.4%)	39 (12.0%)	0.79

* *p* value obtained from χ^2 test for categorical variables
VKA vitamin-K-antagonist, *ADP* adenosine diphosphate, *NOAC* noval oral anticoagulant, *ACE-I* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker

between the two groups. We observed a higher mortality in the STEMI population that was statistically significant. Therefore, patients with STEMI seem to have a higher long term risk even after surviving the first year after their myocardial infarction. This is most likely due to the larger infarct and impairment of left ventricular function compared to patients with NSTEMI [14]. However, we do not have information about left ventricular function in our population to prove this hypothesis.

The rate of secondary prevention therapies at 12 months after the index event was quite high and in the range which has been reported from

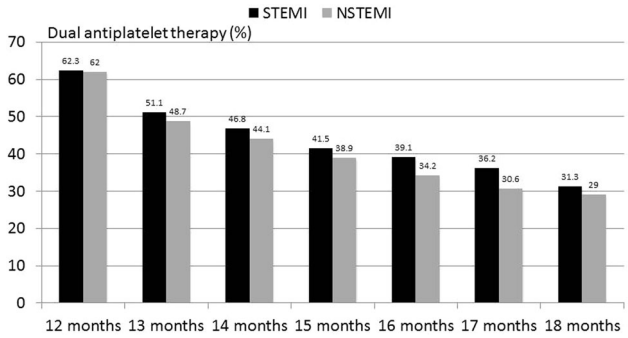

Fig. 1 Rate of patients treated with dual antiplatelet therapy >12 months until 18 months after the most recent myocardial infarction

Table 3 Cardiovascular events occurring >12 months after the index event up to 36 months follow-up

	STEMI	NSTEMI	*p* value*
Death	64 (18.7%)	42 (13.0%)	0.04
Non CV death	8 (2.3%)	13 (4.0%)	0.21
CV death	56 (16.3%)	29 (9.0%)	0.04
Recurrent MI (non fatal)	41 (12.0%)	27 (8.3%)	0.11
Stroke (non fatal)	13 (3.8%)	8 (2.5%)	0.32
MACCE	112 (32.7%)	74 (22.8%)	0.03

CV cardiovascular, *MI* myocardial infarction, *MACCE* major adverse cardiac and cerebrovascular events
* *p* value obtained from χ^2 test for categorical events

other registries. However, only about 80% of patients were on statins, a therapy which is recommended in every patient with coronary artery disease, especially those with myocardial infarction. We did not ask for reasons that statins were not prescribed, therefore the appropriateness of the therapy cannot be determined. Despite the clear recommendation in the current STEMI and NSTEMI guidelines to treat patients for at least 12 months after their myocardial infarction with DAPT, only 62% of patients received DAPT after 12 months. Furthermore, there was a continuous decrease in the rate of patients with DAPT over the next 6 months. This is in line with the observations of an international registry focusing on antithrombotic therapy after acute myocardial infarction [15].

The results of the PEGASUS TIMI 54-trial [13] and a recent meta-analysis [16] suggest that DAPT should be continued even over the 12--month period in high risk patients.

To guide decision making about the intensity and duration of secondary prevention therapy after myocardial infarction, risk stratification seems necessary. Most established risk scores included risk factors for the acute phase of myocardial infarction [17, 18]. However, they were linked to long-term risk as well. No prospective data are available to determine the risk of recurrent ischemic events if a patient had an uneventful course for 12 months after a myocardial infarction. Therefore, we used the criteria suggested by the PEGASUS investigators to determine high risk populations [13], which include age >65 years, impaired renal function, diabetes mellitus, a second myocardial infarction or multivessel coronary artery disease. As shown in Fig. 2b, the number of high risk factors is closely related to the MACCE rate at follow up. Therefore, it seems appropriate to treat patients with a higher risk, as indicated by these simple risk factors, more intensively and longer with secondary prevention measures.

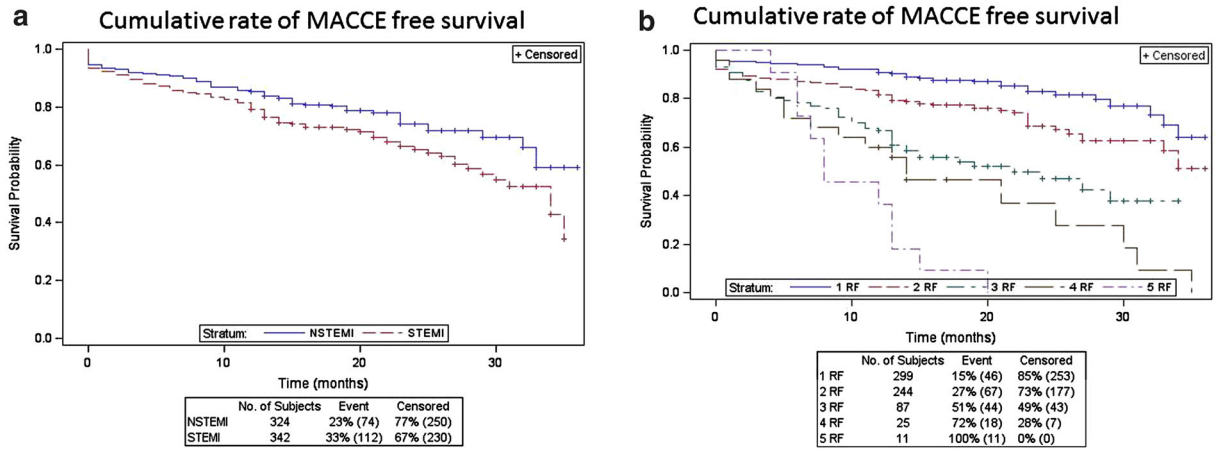

Fig. 2 a, **b** Cumulative rate of MACCE (non-fatal myocardial infarction, non-fatal stroke or death) >12 months after myocardial infarction in patients with STEMI versus NSTEMI (Fig. 1a) and in the total population according to the number of risk factors (age >65 years, type-2 diabetes mellitus, second myocardial infarction, impaired renal function = GFR < 60 ml/min) or multivessel coronary artery disease). In the *x*-axis 0 depicts 12 months after the index events

Limitations

This is a retrospective study which cannot assess the efficacy of secondary prevention therapies on outcome. Therefore the conclusion with respect to the prolonged therapies is hypothetical and should be investigated in dedicated prospective randomized trials. In addition, we do not have data on left ventricular function which would be helpful to further explain the differences in outcome between patients with STEMI and NSTEMI.

CONCLUSION

In summary, in this retrospective study we observed a high ischemic event rate in patients with an uneventful course for at least 12 months after their recent myocardial infarction. Despite a high rate of revascularization procedures with PCI or CABG and a high rate of guideline-recommended secondary prevention therapies, there was a continuous event rate, somewhat higher in the STEMI population. Therefore, secondary prevention measures, especially in patients with high risk features, should be continued even after 12 months after myocardial infarction, which might improve outcomes.

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Compliance with ethics guidelines All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and

national) and with the Helsinki Declaration of 1964, as revised in 2013.

Data availability The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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