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Research Article

Prasugrel and Clopidogrel in Patients with STEMI Undergoing Primary PCI in the Prasugrel Core Population in Clinical Practice. Results from the Prospective ALKK PCI-Registry

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Abstract

Aim: In the randomized TRITON TIMI 38 trial prasugrel compared to clopidogrel reduced the combined endpoint of cardiovascular death, myocardial re-infarction and stroke (MACCE) in patients with STEMI without an increase in bleeding complications. Therefore we evaluated the use of prasugrel and its impact on outcome in patients with primary PCI for STEMI in real life in a large number of patients in the so-called prasugrel core population.

Methods and Results: We used the data of the ongoing prospective German ALKK-PCI registry and included patients with PCI for STEMI < 24h duration treated in 37 centres using both clopidogrel and prasugrel. We excluded patients with prior stroke, weight < 60 kg and age more than 74 years. Between 2009 and 2013 a total of 10267 patients with primary PCI for STEMI were included. In total, prasugrel was used in 3591 patients (35.0%) with a significant increase over the time. After adjusting for confounding variables in a propensity score model the rate of MACCE was significantly lower in prasugrel treated patients (MACCE prasugrel patients 2.8% vs. clopidogrel patients 3.5%, p-value 0.04; odds ratio 0.79, 95% CI 0.62 - 0.99) while more bleeding complications were observed (Bleeding complications prasugrel group 0.6% vs. clopidogrel group 0.3%, p-value 0.03; odds ratio 2.05, 95% CI 1.04 - 4.05).

Conclusion: In accordance with the randomized trial prasugrel was in real life associated with an improved in-hospital outcome. However, this was associated with an increase in bleeding complications.

Keywords: *Acute Coronary Syndrome; Ischaemic Heart Disease; Clinical Trial: Antiplatelet Drugs; Acute Myocardial Infarction*

Introduction

Worldwide coronary artery disease (CAD) remains the leading cause of death in both men and women. ST elevation Myocardial Infarction (STEMI) is still a life threatening disease with an overall in-hospital mortality of 7 - 10%.

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy in patients with STEMI. Dual antiplatelet therapy has become the standard of care for patients with acute STEMI [1,2] since it has been shown that acetyl salicylic acid and the thienopyridine clopidogrel improve the in-hospital [3], the short-term [4] and the long-term outcome after STEMI [5]. As clopidogrel is a prodrug that needs two metabolic steps to become the active compound the onset of inhibition of platelet aggregation is delayed [6]. Prasugrel, a third generation thienopyridine prodrug, results in a more effective, faster and more predictable inhibition of platelet aggregation compared to clopidogrel [6,7].

The TRITON TIMI 38 trial has demonstrated that in patients with acute coronary syndrome (ACS) undergoing PCI prasugrel was associated with a reduction of the combined endpoint of cardiovascular death, re-infarction and stroke compared to clopidogrel with an increase in bleeding complications [8]. Retrospectively a so called prasugrel core population (patients < 75 years, ≥ 60 kg of bodyweight, no prior stroke) has been identified that benefited from prasugrel without an increased rate of bleeding complications [9,10].

Aim of the Study

The aim of the present analysis was to assess the use, efficacy and safety of prasugrel and clopidogrel in patients with STEMI undergoing primary PCI in clinical practice. Here we report the results of the above mentioned "prasugrel core population".

Material and Methods

The ongoing ALKK PCI Registry (Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte) was initiated in 1992 to monitor quality control. It contains all consecutive and interventional procedures of the participating hospitals. The presented data were obtained by standardized questionnaires in 37 hospitals including information concerning the baseline characteristics of the patients, the medical history, indication for the procedure, adjunctive antithrombotic therapy, procedural characteristics and in-hospital complications. The ALKK PCI Registry is limited to the in-hospital phase. A long-term follow up was not conducted.

All data were centrally collected and analysed at the Institut für Herzinfarktforschung, Ludwigshafen, Germany. The registry has been approved by the Landesärztekammer Rheinland-Pfalz, Mainz, Germany.

All consecutive patients with STEMI of < 24 hour duration undergoing primary PCI and treated with either clopidogrel or prasugrel were included. According to the concept of the so called prasugrel core population we excluded patients aged ≥ 75 years, body weight of < 60 kilograms and those with a history of stroke. Patients who received fibrinolysis or ticagrelor were excluded as well.

ST-segment elevation myocardial infarction was diagnosed by the presence of the following criteria: 1) ST-Segment elevation of 1 mm in ≥ 2 standard leads or 2) ≥ 2 mm in ≥ 2 contiguous precordial leads, or 3) the presence of a left bundle branch block.

Cardiogenic shock was characterized by systolic blood pressure of < 90 mmHg, heart rate > 100 per minute and clinical signs of end organ hypoperfusion.

Stroke was defined as a persistent loss of neurological function for > 24 hours caused by cerebral ischemia or a hemorrhagic event. A major bleeding was defined as any non-CABG related bleeding requiring any transfusion of whole blood or red blood cells or bleedings requiring surgical interventions. In addition access site related bleeding complications were recorded. Major adverse cardiac and cerebral events (MACCE) were defined as death, non-fatal infarction and non-fatal stroke.

The analysis population was divided in two treatment groups: The first group consisted of those patients who received prasugrel peri-interventionally, the second group of those who received clopidogrel but no prasugrel. Categorical data are presented as absolute numbers or percentages. The distribution of metrical variables is characterized by median and quartiles, and that of age by mean with standard deviation. These values were calculated from the available cases. The frequencies of categorical variables in the two treatment groups were compared by Pearson–Fisher χ^2 test. Continuous variables were compared by Mann–Whitney–Wilcoxon test. For the comparison of TIMI flow generalized estimating equations were used in order to take clustering of lesions within the same patient into account.

The differences in baseline characteristics between the treatment groups were adjusted by using propensity score methods [11]. In the prasugrel core population, the propensity score was estimated as the probability to receive prasugrel in a multiple logistic regression model. For the subjects in the clopidogrel group, sampling weights were calculated as the odds of the propensity score. This weighting is meant to neutralize the selection induced by the differential allocation to treatment groups. As in randomized trials, the estimated treatment effect is an average over the included population, in our case over the prasugrel group (ATT, average treatment effect on the treated). The achieved covariate balance was assessed by the standardized mean difference, considering absolute values ≥ 0.1 to be indicative of potential relevant confounding [12]. This measure is especially appropriate to assess balance, as it does not depend on the sample size [13].

In the propensity model, variables associated with both treatment and outcome were included [14]: age, gender, diabetes mellitus, impaired renal function, prior revascularisation, presentation with heart failure, cardiogenic shock, significant coronary disease, occluded vessel, peripheral arterial disease, current smoking, medication with glycoprotein-IIb/IIIa antagonists, access via radial artery. The equality of event rates in the weighted groups was tested by the Rao-Scott test, distributions of continuous variables were compared by the weighted Kolmogorov-Smirnov test. The variance of the odds ratio estimates was calculated using Taylor series linearization.

All p-values are results of two-tailed tests. P-values ≤ 0.05 were considered significant, without adjustment for multiple testing. The statistical computations were mainly performed using the SAS© statistical package, Version 9.3 (SAS Institute, Cary, North Carolina, USA). For the weighted Kolmogorov-Smirnov test and the validation of the propensity score calculations the "twang" package in R version 3.2.3 was used.

Results

Between January 2009 and December 2013 a total of 17,643 consecutive patients with STEMI were included by 39 of the participating centers in the ALKK-PCI registry. We excluded 431 patients of two centres that did not use prasugrel at all. Another 336 patients were excluded because they underwent thrombolysis, 2.705 patients were left out because they were treated with ticagrelor and therefore neither with clopidogrel nor with prasugrel. Moreover, we excluded 3.265 patients that were ≥ 75 years old, 566 patients that had a body weight < 60 kilograms and 578 patients that had a history of prior stroke. In the remaining 10.267 patients 3.591 (35%) were treated with prasugrel and 6.676 (65%) were treated with clopidogrel. The average duration of the in-hospital stay was 6 days in both groups. The proportion of patients treated with prasugrel and clopidogrel changed during the study period. Figure 1 shows the alternation over the time starting from 2009 to 2013. Table 1 shows the baseline characteristics of the two groups.

Demographics	Prasugrel (n: 3.591)	Clopidogrel (n: 6.676)	P-value
Mean age [years]	57.3 ± 9.6	59.5 ± 10.0	< 0.001
Female Gender	19.7	20.7	0.20
Patient history and concomitant diseases			
Prior myocardial infarction	11.9	14.6	< 0.001
Prior PCI	12.4	14.0	0.026
Prior CABG	1.7	3.2	< 0.001
PAD	3.5	6.2	< 0.001
Impaired renal function (GFR < 60 ml/min)	7.3	10.3	< 0.001
Risk factors for coronary artery disease			
Hypertension	68.8	74.3	< 0.001
Current Smoker	59.8	53.0	< 0.001
Diabetes mellitus	17.9	19.9	0.020
Hypercholesterolemia	61.2	65.7	< 0.001
Findings on admission			
Heart failure	11.4	10.7	0.31
Cardiogenic shock	4.3	5.8	0.001

Table 1: *Baseline characteristics of patients with STEMI treated with clopidogrel or prasugrel. CABG: Coronary Artery Bypass Graft; GFR: Glomerular Filtration Rate; PAD: Peripheral Arterial Disease; PCI: Percutaneous Coronary Intervention; TIA: Transient Ischemic Attack*

Data are percentages of patients unless stated otherwise.

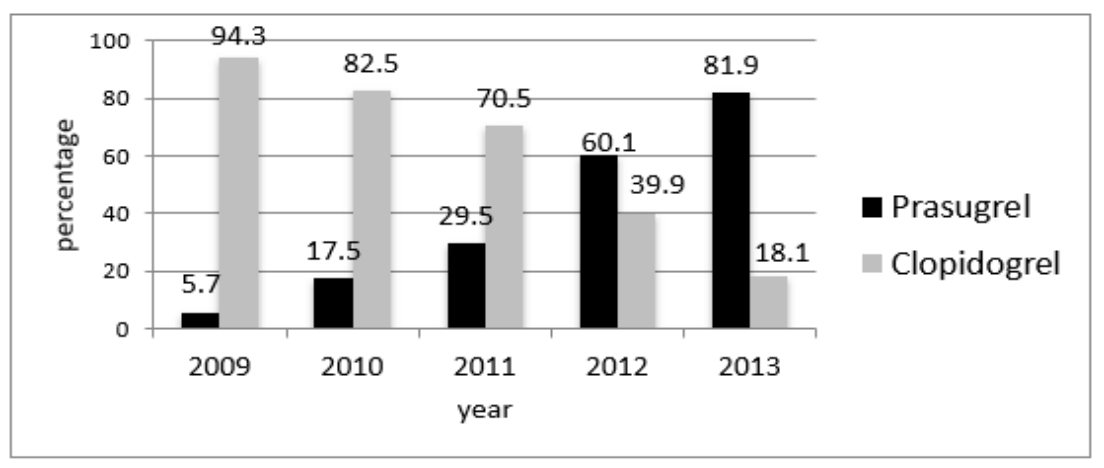

Figure 1: *Use of prasugrel and clopidogrel during the study period.*

Clopidogrel and prasugrel were administered prior to PCI in 74.2% and 51.4% of patients respectively. The majority of the patients was treated with a loading dose of either clopidogrel 600 mg (91.0% of clopidogrel patients) or prasugrel 60 mg (97.2% of prasugrel patients).

Primary PCI was performed in all consecutive patients. Information on the angiographic findings and procedural features are provided in table 2. Drug eluting stents were implanted more often in patients treated with prasugrel. Despite similar angiographic findings in both groups, clopidogrel treated patients required more often haemodynamic support (intraaortic balloon pump required in patients treated with clopidogrel 2.8% vs. 1.1% in the prasugrel group, $p < 0.001$).

	Prasugrel (n: 3.591)	**Clopidogrel (n: 6.676)**	**P-value**
Extent of CAD			
1-Vessel Disease	44.4	42.9	0.17
2-Vessel Disease	31.6	31.1	0.58
3-Vessel Disease	24.0	26.0	0.031
Left main coronary artery disease	3.8	4.9	0.023
Treated vessel			
RCA	41.8	43.8	0.047
LAD	45.4	42.9	0.016
LCX	17.3	17.3	0.99
Left-Main	1.5	2.0	0.065
CABG	0.8	1.4	0.008
Stent implantation			
Drug eluting stent	73.3	40.3	< 0.001
TIMI patency before PCI			
Infarct-related artery occlusion (TIMI 0 + 1)	60.2	59.9	
TIMI 2	19.6	19.6	
TIMI 3	20.3	20.5	
TIMI patency after PCI			
TIMI 0	1.5	2.9	
TIMI 1	0.8	1.3	
TIMI 2	5.3	4.7	
TIMI 3	92.4	91.1	
IABP	1.1	2.8	< 0.001
Manual thrombectomy	28.6	15.3	< 0.001
Femoral access	72.7	86.9	< 0.001
Radial access	27.0	12.8	< 0.001

Table 2: *Angiographic findings, procedural features and results of patients with STEMI treated with prasugrel or clopidogrel.*

CAD: Coronary Artery Disease; CABG: Coronary Artery Bypass Graft; PCI: Percutaneous Coronary Intervention; RCA: Right Coronary Artery; LAD: Left Anterior Descending Artery; LCX: Left Circumflex Artery; IABP: Intraaortic Balloon Pump; TIMI: Thrombolysis in Myocardial Infarction

Data are percentages of patients or treated lesions.

Details concerning the adjunctive antithrombotic medication administered to patients undergoing PCI are given in table 3a and 3b. GPIIB/IIIA Inhibitors were given more often in patients treated with clopidogrel, while bivalirudin was used more frequently in patients treated with prasugrel.

	Prasugrel (n = 3.591)	Clopidogrel (n = 6.676)	P-value
Aspirin	98.1	97.1	0.005
GP IIb/IIIa Inhibitors	41.0	59.4	< 0.001
Unfractionated heparin	95.0	96.0	0.017
Low molecular weight heparin	2.3	1.5	0.003
Bivalirudin	15.6	3.2	< 0.001

Table 3a: *Acute adjunctive antithrombotic therapy in patients treated with clopidogrel or prasugrel.*
GP: Glycoprotein

	Prasugrel (n = 3.591)	Clopidogrel (n = 6.676)
Long-term medication	1.4	3.5
> 6h before PCI	1.1	3.1
< 6h before PCI	48.9	67.7
After PCI	48.6	25.8

Table 3b: *Timing of study drug administration.*

In-hospital clinical events observed in both groups are shown in figure 2. Bleeding complications occurred slightly more often in patients treated with prasugrel (0.6% prasugrel patients and 0.4% clopidogrel patients, p = 0.1). In-hospital mortality was lower in patients treated with prasugrel compared to clopidogrel (2.6% vs. 4.3%, p < 0.0001). Non-fatal strokes and in-hospital recurrent myocardial infarctions were rarely observed in both groups without significant differences. MACE and MACCE were both observed less frequent in prasugrel treated patients (MACE prasugrel patients 2.7% vs. MACE clopidogrel patients 4.4%; MACCE prasugrel patients 2,8% vs. MACCE clopidogrel patients 4.5%).

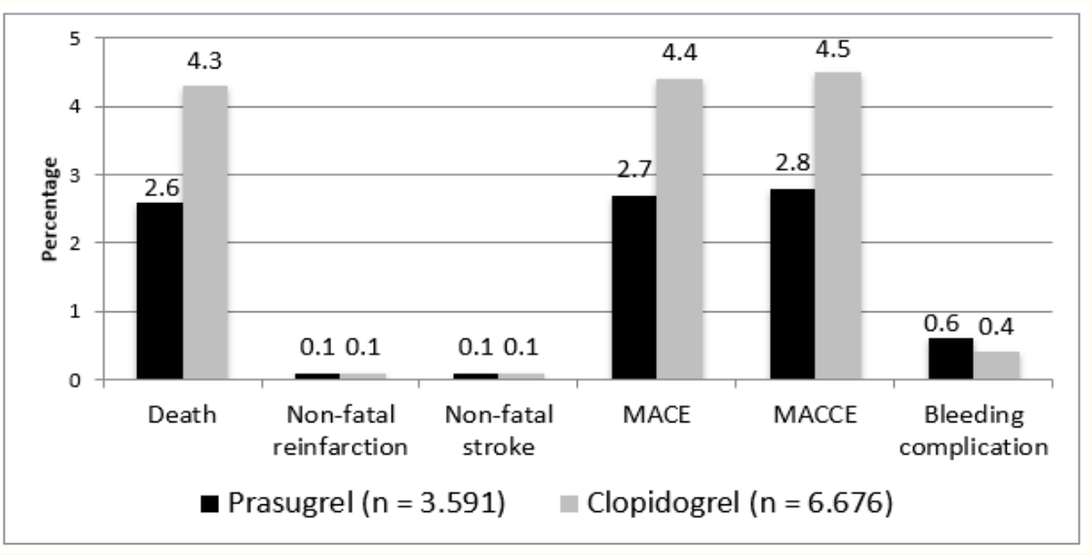

Figure 2: *Univariate analysis. In-hospital clinical outcomes in patients treated with prasugrel and clopidogrel.*

Appropriately balanced distributions of the baseline variables have been achieved by propensity score weighting of the clopidogrel group. Table 4 shows the relevant confounding variables in the weighted population. The frequencies of observed clinical events in this balanced comparison are presented in table 5. After adjustment for confounding variables the MACCE rate was significantly lower in prasugrel treated patients while a significantly higher rate of bleeding complications was observed (MACCE in prasugrel treated patients 2.8% vs. clopidogrel treated patients 3.5%, p-value 0.04; Odds ratio 0.79, 95% CI 0.62 - 0.99; Bleeding complications in prasugrel treated patients 0.6% vs. clopidogrel treated patients 0.3%, p-value 0.03; Odds ratio 2.05, 95% CI 1.04 - 4.05).

	Prasugrel (n: 3.591)	**Clopidogrel (n: 3.609)**	**SMD**	**P-value**
Mean Age	57.3 ±9.6	57.2 ± 10.3	0.01	0.76
Female Gender	19.7	19.8	0.00	0.20
Patient history concomitant diseases and risk factors for coronary artery disease				
Prior CABG	1.7	2.3	-0.04	0.049
Prior PCI	12.4	12.9	-0.01	0.52
Diabetes mellitus	17.9	18.0	0.00	0.86
Impaired renal function (GFR < 60 ml/min)	7.3	7.6	-0.01	0.60
Impaired renal function with Dialysis	0.2	0.1	0.00	0.93
Peripheral artery disease	3.5	3.7	-0.01	0.63
Current smoker	59.8	61.1	-0.03	0.25
Findings on admission				
Cardiogenic shock	4.3	4.5	-0.01	0.79
Heart failure	11.4	11.5	0.00	0.86
Angiographic findings and procedural features				
1-Vessel coronary artery disease	44.4	45.3	-0.02	0.44
Radial access	27.0	28.0	-0.02	0.35
Occluded vessel before PCI	58.0	57.4	0.01	0.58
Left main PCI	1.5	1.6	-0.02	0.47
PCI of CABG	0.9	1.1	-0.01	0.48
Antithrombotic therapy				
GPIIb/IIIa inhibitors	41.0	40.4	0.01	0.60

Table 4: *Confounding variables in propensity score weighted treatment groups. GFR: Glomerular Filtration Rate; PCI: Percutaneous Coronary Intervention; GP: Glycoprotein; CABG: Coronary Artery Bypass Graft; SMD: Standardized Mean Difference*

	Prasugrel (n = 3.591)	Clopidogrel (n = 3.609)	p-Value	OR (95%)
Death	2.6	3.3	0.062	0.79 (0.62 - 1.01)
Non-fatal reinfarction	0.1	0.1	0.81	0.85 (0.22 - 3.24)
Non-fatal stroke	0.1	0.1	0.51	0.64 (0.16 - 2.50)
MACE	2.7	3.4	0.061	0.79 (0.62 - 1.01)
MACCE	2.8	3.5	0.049	0.79 (0.62 - 0.99)
Bleeding Complication	0.6	0.3	0.034	2.05 (1.04 - 4.05)
Net benefit (MACCE and bleeding)	3.3	3.7	0.37	0.90 (0.72 - 1.13)

Table 5: *In-hospital outcomes in patients treated with prasugrel or clopidogrel. In the propensity score analysis.*

MACE: Major Adverse Cardiac Events; MACCE: Major Adverse Cardiac and Cerebrovascular Events: OR: odds-ratio

Discussion

The main findings of our analysis in a large cohort of patients with STEMI treated with primary PCI are as follows:

- From 2009 to 2013 even in the core population prasugrel was used in only about one third of the patients. However, there is a significant increase of a higher use of prasugrel with more than 80 percent of prasugrel treated patients in 2013.
- After adjustment for confounding factors prasugrel was associated with an improved in-hospital outcome but more bleeding complications.

The safety and the efficacy of prasugrel vs. clopidogrel has been evaluated in the large randomized TRITON TIMI 38 trial [8]. Retrospective analyses have identified three subgroups without benefit of prasugrel over clopidogrel: patients ≥ 75 years, body weight < 60 kg, history of stroke or TIA [9]. At the same time the STEMI subgroup within the so called "prasugrel core population" showed a significant reduction of the primary end point from 11.1% to 8.5% without a significant increase in TIMI non-CABG related major bleeding complications (1.4% vs. 1.6%) [10]. Therefore, in this randomized trial this subgroup of patients especially benefited from prasugrel.

In our analysis of the ALKK registry we found that in current every day clinical practice from 2009 to 2013 prasugrel was used less frequently than clopidogrel in patients presenting with STEMI and undergoing primary PCI. As prasugrel was only introduced in 2009, there was a strong trend towards a broader use of prasugrel over the time. In 2013 over 80 percent of eligible patients were treated with prasugrel. If used, prasugrel was administered predominantly to younger patients with less comorbidities. Despite these distinct differences concerning the baseline characteristics the angiographic findings were similar in both groups. Nevertheless clopidogrel treated patients required more often haemodynamic support (intraaortic balloon pump required in patients treated with clopidogrel 2.8% vs. 1.1% in the prasugrel group, $p < 0.001$). The results of our large real world registry showed a significantly reduced in-hospital mortality with 2.6% vs. 4.3% ($p = 0.00001$) in prasugrel and clopidogrel patients. Compared to the TRITON TIMI 38 trial we noted in our registry lower rates of bleeding complications in both groups with a trend towards more bleeding complications in prasugrel patients (0.6% prasugrel vs. 0.4% clopidogrel, $p = 0.11$). In general, bleeding could be a subject of underreporting in registries, but this is true for both clopidogrel and prasugrel and usually severe bleeding should not be missed.

In our study the use of radial access was quite low, but increased over the study period. The same was true for the use of drug-eluting stents, which are now the standard of care. However, there are no data that suggest that drug-eluting stents improve the in-hospital outcome in STEMI, therefore the differences in the use of DES should not have influenced the results.

Because of the inequality concerning the baseline characteristics within the two groups we adjusted for confounding factors using a propensity score model. After adjustment, MACCE were observed less often in the prasugrel population underlining the high efficacy of prasugrel. Another important finding of our registry is that after adjustment prasugrel treated patients had a higher rate of bleeding complications. This is especially interesting because such an effect was not observed in the TRITON TIMI 38 study.

Our registry is limited to the in-hospital phase with a median observation period of 6 days in both groups. However, in the TRITON TIMI 38 Study the greatest reduction of the primary end point was noticed within in the first days after randomization and persisted then for the total study period of 15 month.

Our data are in congruency with recently published results of the Swiss AMIS Plus registry. In this study prasugrel was administered predominately in STEMI patients < 75 years of age [15]. The in-hospital mortality was significantly lower in prasugrel treated patients (1.5% prasugrel vs. 3.7% clopidogrel, respectively) [15]. Bleeding complications tended to occur more often in prasugrel treated patients without significant difference (3.8% prasugrel vs. 3.2% clopidogrel, p 0.17) [15]. Interestingly, in the AMIS Plus registry there was a significant difference in the use of GPIIb/IIIa Inhibitors between the two groups [15]. In contrast to our data prasugrel treated patients received more frequently a co-medication with GPIIb/IIIa inhibitors (25.6% prasugrel vs. 16.0% clopidogrel, $p < 0.001$) [15].

Recently, another analysis was published that evaluated the efficacy and safety of prasugrel vs. clopidogrel in the so called "ideal" prasugrel core population presenting for PCI with STEMI [1]. The adjusted hazard ratio for all cause mortality for the prasugrel group was 0.47 (95% CI: 0.253 - 0.881; P = 0.018) [16].

In the Swedish SCAAR registry prasugrel was administered mainly to STEMI patients < 75 years [17]. Thirty-day mortality in the STEMI population was reduced from 5.0% with clopidogrel to 2.5% with prasugrel [17]. Major bleeding complications were observed in 2.5% with clopidogrel and 0.6% with prasugrel [17].

By nature registries have limitations due to a treatment assignment bias. Accordingly we cannot rule out that our results were influenced by imbalances concerning unobserved baseline characteristics between the two groups. No formal test hypotheses have been specified a priori and no power calculations have been made. Therefore, the inferential statistics should be interpreted in a descriptive, not in a confirmatory sense. Since the ALKK registry was planned for in-hospital quality control, we do not have follow up data. Therefore long-term effects of prasugrel on mortality and bleeding complications in our patient population remain uncertain.

Conclusion

The results of our registry show that in current every day clinical practice in patients with STEMI undergoing primary PCI in the "ideal" prasugrel core population, prasugrel became more and more the P2Y12 platelet-inhibitor of choice. It is more effective with significantly lower rates of MACCE. As it is known to be a highly potent platelet inhibitor bleeding complications occurred more often. The calculated clinical net-benefit (MACCE and bleeding complications) was only numerically superior in prasugrel treated patients.

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