Temporal Changes in the Current Practice of Primary Angioplasty: a Real Life Experience of a Single High-Volume Center

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Abstract

Background. In the last years, new techniques, drugs and devices have been introduced in the current practice of primary angioplasty (PPCI) and validated by pivotal studies The objective of our study was to evaluate if these studies have led to significant changes on the current practice of primary PCI in our center.

Methods. From March 2003 to December 2013 1980 patients with ST-segment elevation myocardial infarction underwent PPCI within 12-hours of onset of symptoms. We considered 2 periods of our activity: from 2003 to 2009 (P1) with 1078 patients and from 2010 to 2013 (P2) with 902 patients, and compared them in terms of pharmacological and arterial access strategies and of devices utilization.

Results. In P2 there was a significant increase of radial access (34.1% vs 1.5, p<0.001), as well as of the use of bivalirudin (22.7% vs 0.5%, p<0.001) and of new antiplatelet drugs (prasugrel or ticagrelor) (18.3% vs 0%, p<0.001) whereas the use of GP IIb-IIIa and of intraaortic balloon pump significantly decreased (from 82.3% to 52%, p<0.001 and from 17% to 7.5%, p<0.001 respectively). In the P2 there was a significant increase of the procedural efficacy (97.2% vs 95.1%, p=0.01) that persisted after the logistic regression adjustment (OR 2.09, CI 95%, 1.04-4.21).

Conclusions. Our study shows that in the last years, in a high-PCI center, after the publication of pivotal randomized trial and nationwide registries, there were significant changes in the PPCI current practice that could have had an impact on procedural efficacy.

Introduction

Primary angioplasty (PPCI) has been demonstrated to be superior to fibrinolytic therapy in the management of patients with ST-segment elevation myocardial infarction (STEMI) [1–3] becoming the leading treatment in this setting [4]. In the last years, new drugs and devices have been introduced in the practice of PPCI which have been validated by pivotal studies. In particular, the Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL) and the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) randomized trials [5,6], have demonstrated that the transradial artery access (TRA) can reduce bleeding complications and even the 30-days mortality, compared to transfemoral artery access (TFA) in patients with STEMI. The same result was achieved by a direct thrombin inhibitor, bivalirudin, in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial [7,8], compared to unfractioned heparin (UFH) plus Glicoproteins (GP) IIb-IIIa inhibitors, and these advantages were extended at 12 months. Finally, the Plateler Inhibition and Patient Outcomes (PLATO) and the Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) [9,10] showed that new antiplatelet drugs, ticagrelor and prasugrel respectively, reduced the cardiovascular and the total mortality compared to clopidogrel, even if they increased the bleeding complications at least in more frail patients. Furthermore, the Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) randomized trial [11] did not show any superiority of GP IIb-IIIa over UFH in terms of reduction of infarct size. As a result, the 2010 European Guidelines on revascularization put the bivalirudin use, as well as that of new antiplatelet drugs in class I, whereas they downgraded the upstream use of GP IIb-IIIa inhibitors in class III [12]. Yet, the net benefit effect demonstrated in randomized clinical trials (RCT) might not be the same as that observed in different clinical settings, because most RCT focus on the assessment of a single maneuver, and the investigated population might not be representative of the real-world

practice [13]. Therefore, large observational registries are needed in order to assessing treatment effectiveness in patients encountered in day-to-day clinical practice, undergoing everyday therapy. Aim of this large observational registry is to assess the impact of these recent pivotal studies in terms of changing the current practice of PPCI in an high volume hospital.

Methods

The Infermi Hospital in Rivoli, Italy, is a community hospital without cardiac surgery backup with a high volume catheterization laboratory (>900 PCI and >200 PPCI per year), which provides a 24-hour PCI service and is only 14 Km far from the nearest hospital with cardiac surgery backup. In 2008, the catchment area increased up to 583,000 inhabitants, including another hospital with intensive cardiac care unit, but without PCI facility.

Study population

The data of all consecutive patients with STEMI admitted to the Infermi Hospital hospital between march 2003 and December 2013 and treated by primary PCI within 12 hours of symptom onset were reviewed. Demographic, clinical and procedural data were prospectively collected in a dedicated database (Cardioplanet V.3.0.8, Ebit Aet S.p.A., Genoa, Italy).

The study protocol was approved by the Ethics Committee of our Institution (ASL 103, Piemonte Region, Italy) and informed consent was obtained in all patients.

Study definitions, procedures and medications

STEMI was defined as typical chest pain lasting more than 30 minutes associated with $\geq$0.1 mV ST-segment elevation in $\geq$2 contiguous electrocardiogram (ECG) leads or with new left bundle branch block. Door-to-balloon (D2B) time was defined as the time interval from arrival to the hospital (the initial referral hospital for transferred patients) to the first balloon inflation during PPCI. Total ischemic time was defined as the time interval from symptom onset to first balloon

inflation during PPCI. Lesion characteristics were evaluated according to the ACC/AHA classification [14].

All STEMI patients who complained symptoms for ≤12 hours were immediately transferred to the catheterization laboratory for urgent coronary angiography.

The indications to manual thrombus aspiration (TA) were driven by few parameters evaluated after diagnostic angiography as already reported [15]: a) visual estimation of infarct related artery (IRA) diameter ≥3 mm; b) the absence of severe proximal tortuosity and/or calcifications; c) complete vessel occlusion with distal convex contrast stain and the presence of visual thrombus in case of a patent IRA. However, the final decision to its use of TA as well as of intra-aortic balloon pump (IABP) support was left to the discretion of the operator.

A successful procedure was defined as a residual stenosis of treated vessels <30% associated with a Thrombolysis In Myocardial Infarction (TIMI) 3 grade flow [16].

All patients were routinely given aspirin (325 mg upon arrival, and then 100 mg daily) and an intravenous bolus of UFH (5000 U) in ambulance or in emergency room. The use of either bivalirudin (bolus of 0.75 mg/Kg and 1.75 mg/Kg/h thereafter), or UFH (100 U/Kg or 60 U/Kg if abciximab was used) or abciximab (bolus of 0.25 mg/Kg and 0.125 mcg/Kg/min for 12 hours) was left to the discretion of the operator. UFH therapy was stopped after the procedure, but, in case of IABP use, it was continued until its removal. When used, abciximab infusion was continued for 12 hours after the procedure. At the beginning of this use, we used to stop bivalirudin at the end of the procedure, but, since the publication of the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) randomized trial [17], it has been continued for 4 hours thereafter.

Until 2010, clopidogrel (loading dose 300 or 600 mg and 75 mg daily thereafter) was given as second antiplatelet drug but, afterwards, prasugrel (60 mg loading dose and 10 mg daily thereafter) and ticagrelor (180 mg loading dose and 90 mg bid thereafter) were used as well. Beta-adrenergic

blockers, ACE inhibitors and statins were used as in-hospital standard therapy, if not contraindicated.

Study Objectives

Two time-frames of activity were considered: from 2003 up to the end of 2009 (P1) and from 2010 up to the end of 2013 (P2). We chose this cut-off since our current practice did not have significant modifications up to the end of 2009 [18], whereas at the beginning of 2010, bivalirudin and the new antiplatelet drugs became available in our center. Furthermore, in the same year, a TRA intervention program in the urgency setting has been set up. We also took into account the differences in using TA, drug-eluting stents (DES) as well as of IABP support.

The aim of the study was to evaluate the changes in procedural characteristics in terms of vascular access, pharmacological treatment and device utilization. Thus we investigated the impact of these changes on procedural efficacy rate (defined as TIMI III grade flow and residual stenosis <30%) and in terms of in-hospital outcomes, defined as Major Cardiovascular Cardiac Events (MACE), i.e. death, recurrent myocardial infarction, stroke and target vessel revascularization. The rate of definite and probable stent thrombosis (ST) defined according to the Academic Research Consortium [19] and of bleeding complications acccording to Bleeding Academic Research Consortium (BARC) classification [20] were also taken into account.

Statistical analysis

Descriptive data are shown as absolute and relative frequencies of the different modalities for categorical data; as median and interquartile range (IQR) for continuous variables. Chi-square test for categorical variables and Wilcoxon test for independent data for continuous variables were carried out to assess whether significant differences could be demonstrated between time periods (before and after 2010).

Due to the observed differences in patients' characteristics between time periods, a propensity score analysis was carried out using a logistic regression model with time period as outcome. In the propensity score model, patient's characteristics which resulted associated with the time period (obesity, hypercholesterolemia, anterior location and transfer from other hospitals) were entered in the model.

Validation of the model was done through graphical examination of the residual diagnostics. Discrimination Index D (the higher the better) and the Somer's concordance index Dxy (the closer to 1 the better) were also computed. In absence of an external data source for model validation, to account for the degree of optimism in model accuracy induced by the use of the same data for training and testing purposes, goodness of fit indexes were computed using bootstrap (20 runs). Checking of the balance after the matching was performed using Chi-square and t test. Using individual propensity score, 876 patients in time period 2010-2013 were matched to 876 patients in time period 2003-2009; a caliper size equal to one-fifth of the standard deviation of the logit of the estimated propensity score was used. Finally, the analysis of the propensity score-matched sample was carried out using conditional logistic regression model, which accounts for correlation within matched pairs, including variables: period (pre-post 2010), hypercholesterolemia and total ischemic time (superior vs inferior to 3h). All tests were performed at a significance level of 5%. Analyses were done with R version 3.02 (R Core Team, Wien, Austria).

Results

From March 2003 to December 2013 1980 patients with STEMI underwent PPCI in our catheterization laboratory, whose 1078 in P1 and 902 in P2. The clinical characteristics of the two groups are shown in table 1. The patients of P2 were significantly more obese (body mass index $\geq$ 30 Kg per square meter), hypercholesterolemic, more likely to be transferred from another hospital without PCI facility and presented lower rate of anterior infarction. Furthermore, patients of P2 had

a significant longer D2B time and a lower rate of them underwent PPCI within 3 hours from the beginning of the symptoms.

Procedural characteristics are depicted in figure 1 showing a significant increase of TRA in P2, along with the use of bivalirudin, new antiplatelet drugs and DES implantation. In parallel, in the same period, the use of GP IIb-IIIa and of IABP significantly decreased. Furthermore, the rate of TA and multivessel PCI did not significantly change (table 2).

At 30-days (table 3) a significant increase of the procedural efficacy (from 95.1 to 97.2% , p=0.01) as well as a significant decrease of in-hospital mortality (from 6.3% to 3.9%, p=0.01), of ST (from 1.3 to 0.4%, p= 0.046) and of overall MACE (from 6.9% to 4.2%, p=0.01) occurred in P2 as compared to P1. The rate of bleeding complications remained almost unchanged (from 2.2% to 2.0%, p=0.7). Before matching with the propensity score (figure 2), the efficacy of the procedure was significantly associated to P2 (OR 1.81, CI 95%, 1.12-2.94) as well as MACE and mortality at 30 days resulted significantly reduced after 2010 (in P2). Logistic regression analyses on matched patients confirmed the before matching results for the efficacy of the procedure (OR 2.09, CI 95%, 1.04-4.21, figure 3), whereas MACE and mortality at 30 days did not result significantly associated to the time perdiod anymore. Moreover ST showed a trend towards a significant reduction (OR 0.3; 0.09-1.03).

Discussion

Our large observational registry showed that, after 2010, the current practice of PPCI in our centre significantly changed, with a significant increase of TRA, of the use of either bivalirudin or new antiplatelet drugs or DES and a significant decrease of the use of either GP IIb-IIIa inhibithors and IABP, whereas the rates of TA and multivessel PCI remained almost unchanged. Despite the

significant increase of the D2B time and the decrease of the number of the patients who underwent PPCI within 3 hours from the beginning of the symptoms (probably due to the widening of the catchment area), there was a significant increase of the efficacy of the procedure and a trend towards the significance of the reduction of ST. Our findings are in agreement either with randomized or non-randomized studies [5–10] or large registries [21–25]**.** Moreover, our study did not show significant differences in bleedings between the two study periods. This finding can further support the hypothesis that the decrease of cardiovascular events related to TRA and bivalirudin use can go beyond the simple reduction of bleeding complications [26,27]. More recent Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI) randomized trial [28], has raised concerns with regard to the increase of acute ST and even of the mortality. As a result, the last guidelines downgraded the bivalirudin use to a IIa class [29]. We did not find this relationship but rather a reduction, although not significant, of ST. The longer period of infusion at higher concentration, as stated by the EUROMAX [17] randomized trial, the use of new antiplatelet drugs and the UFH bolus given in emergency room or in ambulance, that has already shown to reduce the composite endpoint of death and ST compared to bivalirudin alone [30], can have overcome this negative effect.

Limitations

Our study offers the advantages and limitations of carefully performed observational registries: first, it is a retrospective analysis and is therefore subject to the limitations of such analyses. In particular, the procedural increase and decrease in rates of MACE cannot be attributed to a specific covariate. As a matter of fact our work was not powered, to find differences in the clinical outcomes, either because of the relatively small number of the patients, or of the non-randomized nature of the study. Secondly, the addition of a referral source with an intensive cardiac care unit but not PCI capability, could have somewhat changed significantly the referral population**.** For this reason, propensity score matching further enhanced the comparability of the patients**..**Third, the

data are derived from a single center, which limits their applicability. Finally, we analyzed only the 30-days oucomes. Therefore, it is not possible to extend the results beyond the acute phase.

Conclusions

Our large retrospective registry shows that in the last years, after the publication of pivotal randomized trial and large registries, there were significant changes in the current practice of primary PCI in a high primary PCI-volume catheterization laboratory, in particular either the increase of the TRA, bivalirudin, new antiplatelet drugs and DES, or the decrease of IABP and GP IIb-IIIa, These changes could have had an impact on procedural efficacy. However, due to the single centre retrospective evaluation, these findings need to be confirmed by further studies.

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Figure legend

Figure 1. Temporal changes trend in procedural characteristics between 2003 and 2013. Vertical axis represents the percentage of cases. DES: Drug Eluting Stents; IABP: Intra Aortic Balloon Pump; New Antiplatelet Drugs: Prasugrel or Ticagrelor

Figure 2. Multiple logistic regression analysis. OR: Odds Ratio; MACE: Major Adverse Cardiac Events

Figure 3. Individual propensity score matching analysis. OR: Odds Ratio; MACE: Major Adverse Cardiac Events

***Highlights (for review)**

- Net benefit effect demonstrated in randomized clinical trials (RCT) might not be the same as that observed in different clinical settings. Large observational registries are needed in order to assessing treatment effectiveness in patients encountered in day-to-day clinical practice, undergoing everyday therapy.
- After the publication of pivotal randomized trial and large registries, there were significant changes in the current practice of primary PCI in a high primary PCI-volume catheterization laboratory.
- We reported an increase of the trans-radial approach, of the use of either bivalirudin or new antiplatelet drugs or DES and a significant decrease of the use of either GP IIb-IIIa inhibithors and IABP. Conversely the rates of manual thrombus aspiration and multivessel PCI remained almost unchanged.
- These changes could have had an impact on procedural efficacy

Figure 1

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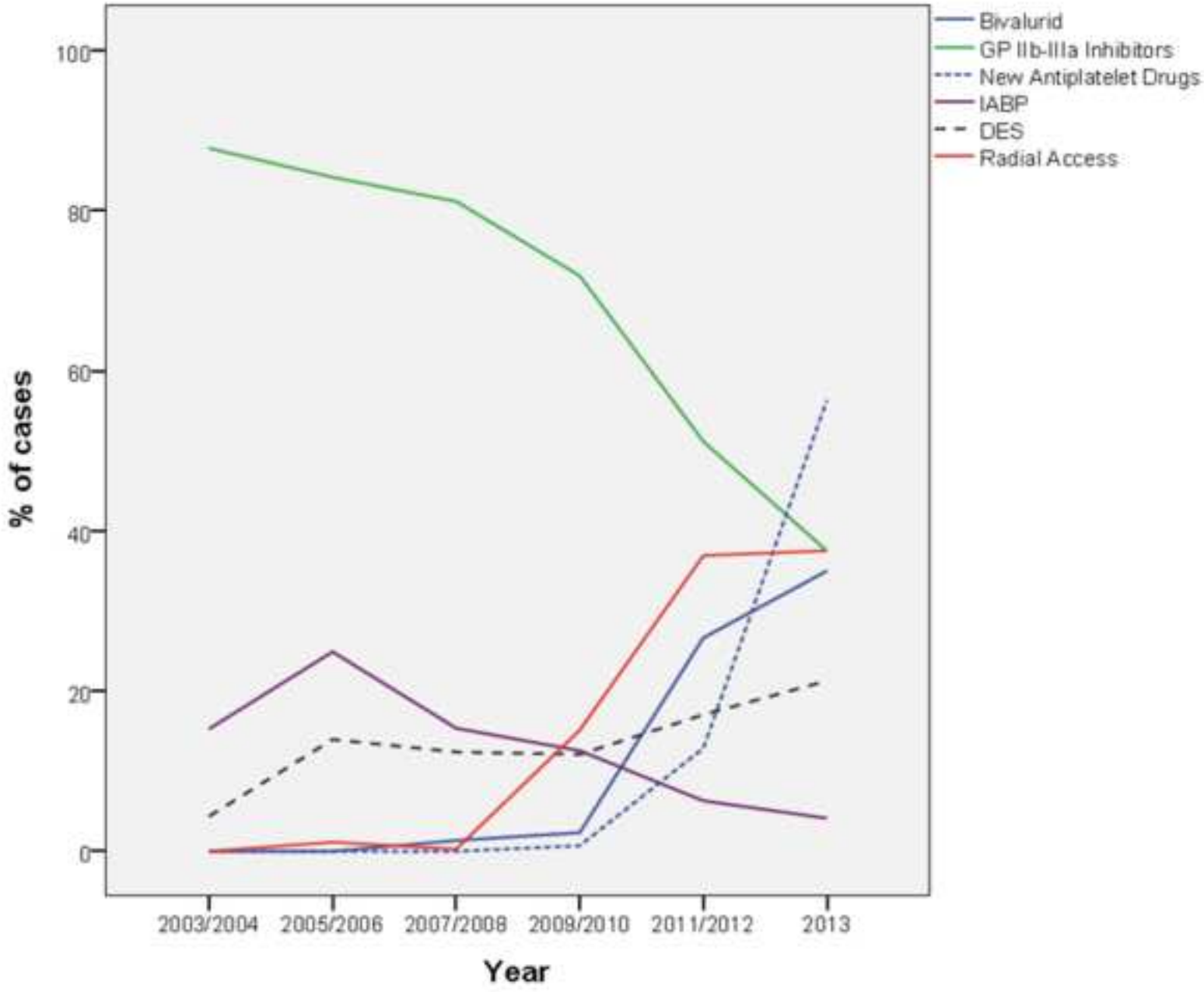

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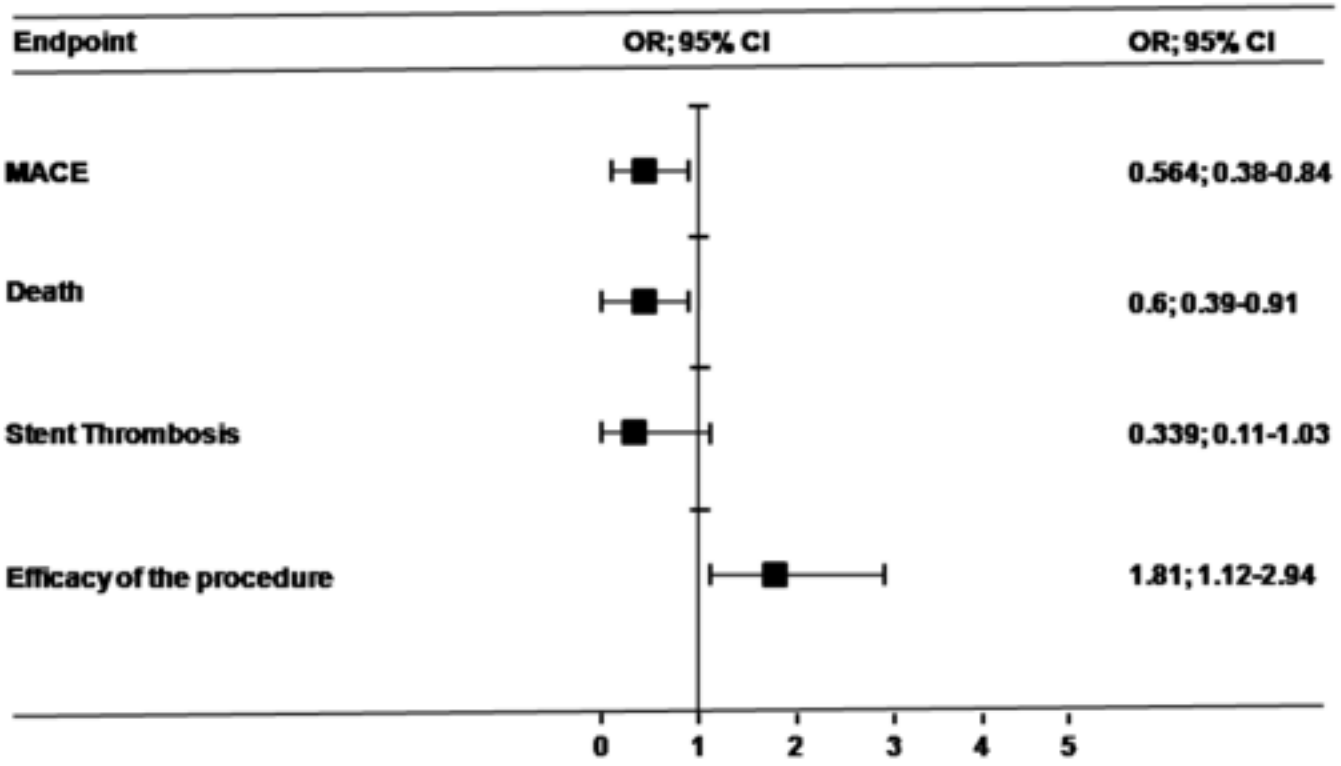

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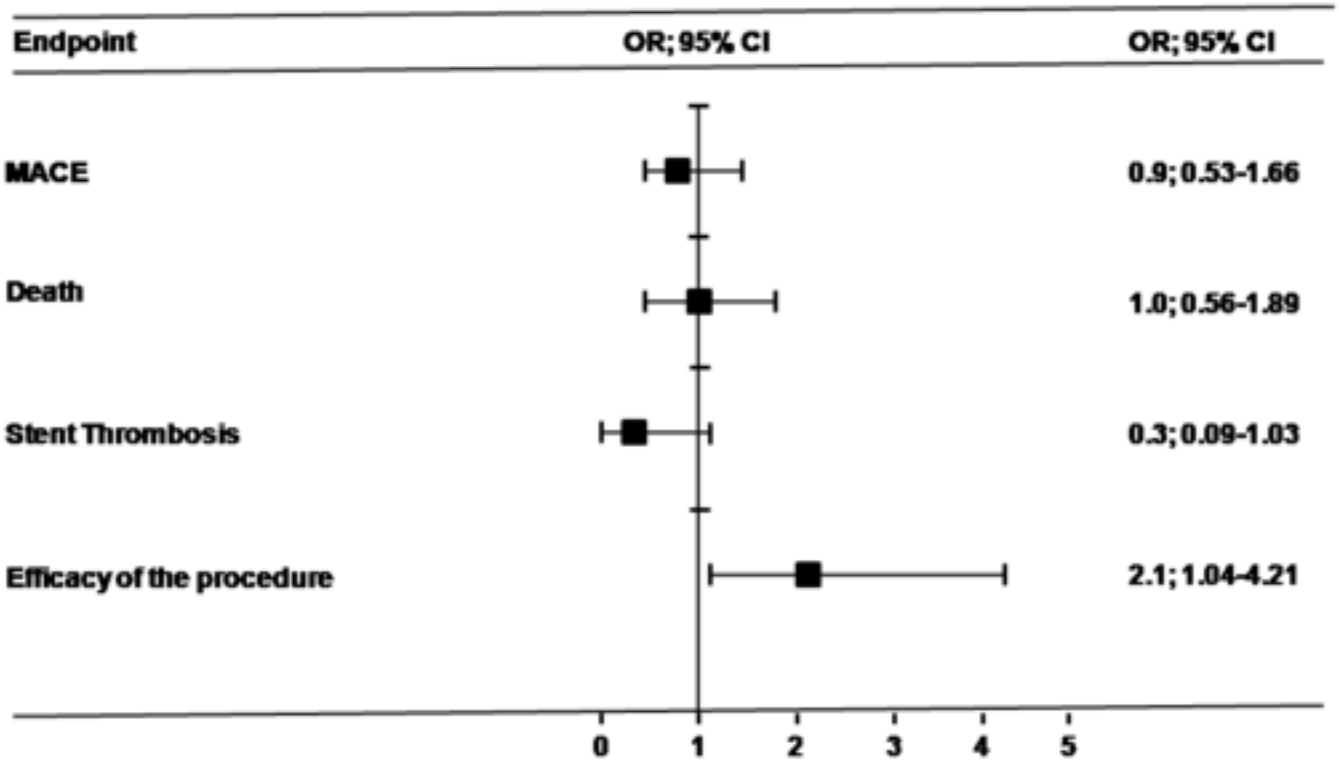

Table 1

Table I. General Characteristics

	P1 (2003-2009)	P2 (2010-2015)	p Value
Number of patients	1078	902	
Male Gender	801 (74.4)	695 (77.1)	0.17
Age (years)*	66 (56-75)*	65 (56-75)*	0.37
Age≥80 years	139 (12.9)	123 (13.6)	0.63
Transferred from another hospital	248 (23)	290 (32.2)	<0.001
Current Smokers	323 (30.0)	307 (34.4)	0.053
Hypertension	738 (68.5)	632 (70.1)	0.47
Hypercholesterolemia	324 (30.1)	418 (46.3)	<0.001
Diabetes	243 (22.5)	224 (24.8)	0.73
Obesity^	142 (13.2)	165 (18.3)	0.002
Renal Failure§	33 (3.1)	20 (2.2)	0.25
Anterior Infarction	490 (46.8)	357 (40.8)	0.008
LVEF (%)#	48.1±9.6**	48.9±8.3**	0.87
Killip Class ≥3	118 (11.0)	84 (9.3)	0.23
Symptom onset-to-door time (min)	121 (68-267)*	120 (72-239)*	0.64
Door-to-Balloon time (min)	59 (36-98)*	76 (53-119)*	<0.001
Total ischemic time≥3 hours	383 (55.9)	518 (61.6)	0.025

Data are n (%) unless otherwise stated.
* Median (interquartiles ranges)
** Mean ± SD
^ Body Mass Index ≥30
§ Renal failure defined as baseline creatinine ≥ 2.5 mg/deciliter.
# Left Ventricular Ejection Fraction

Table 2

Table II. Angiographic Findings and Procedural Characteristics

	P1 (2003-2009)	P2 (2010-2013)	P Value
Number of patients	1078	902	
Multivessel Disease	558 (52.0)	486 (54.1)	0.11
Radial Access	17 (1.5)	308 (34.1)	<0.001
Bivalirudin	5 (0.5)	205 (22.7)	<0.001
GP IIb-IIIa Inhibitors	887 (82.3)	469 (52.0)	<0.001
IABP	183 (17.0)	68 (7.5)	<0.001
Multivessel PCI	55 (5.2)	36 (4.0)	0.28
Thrombus Aspiration	601 (55.8)	500 (55.4)	0.89
DES	120 (11.1)	138 (15.3)	0.006
New Antiplatelet Drugs*	0	165 (18.3)	<0.001

Data are n (%) unless otherwise stated
IABP = Intra Aortic Balloon Pump
DES = Drug-Eluting Stents
*Prasugrel or Ticagrelor

Table III. 30-Days outcomes

	P1 (2003-2009)	P2 (2010-2013)	P Value
Number of patients	1078	902	
Efficacy of the procedure*	1025 (95.1)	877 (97.2)	0.015
In-Hospital Death	68 (6.3)	35 (3.9)	0.015
Bleeding Complications**	24 (2.2)	18 (2.0)	0.72
Re-AMI	1 (0.1)	2 (0.2)	0.46
Target Vessel Revascularization	5 (0.5)	1 (0.1)	0.15
Mechanical Complications	14 (1.3)	5 (0.6)	0.11
Stroke	6 (0.6)	2 (0.2)	0.30
MACEs	74 (6.9)	38 (4.2)	0.01
Stent Thrombosis§	14 (1.3)	4 (0.4)	0.046

Data are n (%) unless otherwise stated
*TIMI 3 grade flow and residual stenosis ≤ 30%
**BARC ≥ 3
MACEs = Major Adverse Cardiac Events
§ Acute and Subacute