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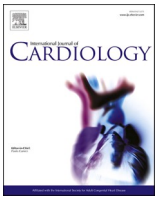

The Prognostic impact of treatments evolution in STEMI

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ABSTRACT

Objective: To evaluate in a real-world primary percutaneous coronary intervention (pPCI) registry the impact of the evolution of evidence-based treatments on prognosis.

Methods: STEMI patients undergoing pPCI at the University Hospital of Trieste, Italy, were enrolled. The first cohort (old treatments cohort) included STEMI patients treated between January-2007 and December-2012, and the second cohort (new treatments cohort), between January-2013 and December-2020. Inverse Probability of Treatment Weighting (IPTW) Cox regression models as well as multivariable Cox regression models were performed to assess the risk of a composite primary endpoint (PE) of all cause death, reinfarction and re-PCI at 5 years.

Results: A total of 2425 STEMI patients were enrolled. At multivariable Cox regression, the new-treatments cohort had lower risk of PE and mortality. Weighted (IPTW) Cox proportional hazard models confirmed the lower risk of the new treatments cohort for PE (HR 0.72; 95% CI 0.56–0.91, $p = 0.007$) and 5-year mortality (HR 0.70, 95%CI 0.54–0.91, $p = 0.009$). When considering both clinical and procedural variables, complete revascularization (HR 0.46, 95%CI 0.27–0.80, $p = 0.006$) and the administration of prasugrel or ticagrelor (HR 0.72, 95%CI 0.52–0.99, $p = 0.013$) were independent predictors of PE as well as of 5-year mortality. Patients receiving prasugrel or ticagrelor or drug eluting stent were at lower risk of 1-year stent thrombosis (HR 0.50, 95%CI 0.28–0.90, $p = 0.021$).

Conclusions: In a real-word STEMI population the prognosis of patients has improved in the last decades, and this was associated to the use of new antithrombotic treatments and to the implementation of complete revascularization.

1. Introduction

Cardiovascular diseases are still the major cause of death despite the continuous evolution of evidence based medical treatment [1] and ST-segment elevation myocardial infarction (STEMI) has remained a leading cause of death in patients hospitalized with acute coronary syndromes (ACS). In STEMI patients the primary goal is to rapidly restore blood flow to the acutely occluded coronary artery (ie, culprit artery) and the gold standard treatment for rapid reperfusion is represented by primary percutaneous coronary intervention (pPCI) [2].

In the last decades, based on the results of multiple randomized clinical trials, there has been an important evolution in the treatment of STEMI patients with substantial changes in the way of treating STEMI in clinical practice [2]. Second-generation drug-eluting stents (DES) have assumed a dominant role in PCI [3] to reduce the risk of stent thrombosis and improving clinical outcomes. Moreover, in order to reduce the rate of ischaemic events, dual antiplatelet therapy (DAPT) with aspirin and prasugrel or ticagrelor has become the standard of care [4,5], as well as the adoption, when possible, of the radial approach to decrease major bleeding events [6]. Moreover in multivessel disease patients the appropriate staged treatment of the non-culprit disease resulted in a significant reduction of hard outcomes [7]. Conversely manual aspiration showed no significant effect on prognosis [8] as well as the use of intra aortic balloon pump (IABP) for cardiogenic shock following myocardial infarction [9].

Whether these evolutions of treatment occurred in the last recent

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years have translated into improved outcomes and survival in the real world is unsettled. Because testing the results of randomized studies into clinical practice remains a fundamental process, we aimed to evaluate in a large real world pPCI registry the impact of treatment evolution on prognosis comparing different decades of treatment.

2. Methods

2.1. Study design and population

We conducted a retrospective study enrolling consecutive STEMI patients undergoing pPCI at the Cardiothoracovascular Department of the University Hospital of Trieste, Italy, between January 2007 to December 2020.

All STEMI patients were consecutively enrolled in a primary PCI-Registry. Clinical history, main demographic, clinical, laboratory, procedural data and reperfusion's times were included in a central database. STEMI diagnosis was made according to European Society of Cardiology (ESC) guidelines [2]. Patients enrolled received optimal medical therapy following guidelines during hospitalisation and after discharge.

In order to evaluate the prognostic impact of the changes of treatment occurred in the last decades, the population was divided in two cohorts: the first cohort (old treatments cohort) included STEMI patients treated between January 2007 and December 2012, and the second cohort (new treatments cohort), included STEMI patients treated between January 2013 and December 2020. This division was made considering that, from 2013 STEMI treatment was implemented with the use of new antithrombotic treatments (i.e prasugrel and ticagrelor) and with the use of DES in the majority of the patients, and conversely, they were rare or absent in the previous cohort.

2.2. Study end points

The study primary endpoint (PE) was a composite of major adverse cardiac events (MACE) at 5 years, which included: all cause death, re-infarction (re-MI) and re-PCI (non-staged). The secondary endpoint was all cause of mortality at 5 years. Moreover, we evaluated the incidence of stent thrombosis at 12 months.

2.3. Statistical analysis

Clinical, instrumental and laboratory variables were expressed as median and interquartile range (IQR) for non-normally distributed continuous variables; as average and standard deviation (SD) for normally distributed continuous variables or as percentage (%) for nominal variables. Comparisons between groups have been made by the Chi square test for the discrete variables; by the analysis of variance (ANOVA) test on continuous variables or by the non-parametric Mann-Whitney test when necessary.

For the PE analysis and all-cause mortality at 5 years, Cox proportional-hazards models were used. For stent-thrombosis, a cause-specific Cox model was fitted to take into account the competing risk of death.

Baseline variables of clinical importance and/or with difference between the cohort variable (old treatments cohort vs. new treatments cohort) were used as covariates in multiple Cox regression models. Since a main difference between the two cohorts regards procedural variables introduced after 2012, these substituted the cohort variable in a second set of models. Interactions between the two treatment cohorts and clinically relevant covariates were tested using the Likelihood Ratio Test. In case of significant interaction, sub-group analyses were performed. In the models, covariates were selected considering clinical relevance and the sample size available for the analysis.

From the Cox models, adjusted survival curves for two example patients having the same clinical presentation but different treatments cohort/procedures were obtained.

Moreover a matching through Inverse Probability of Treatment Weighting (IPTW) was performed to balance the two cohorts in terms of demographics, clinical presentation and ischemia time. The absolute standardised effect size was used as a balance metric to summarise differences between distributions of the variables in the cohorts before and after weighting. Covariates considered for balance were age, sex, previous MI, hypertension, smoker status, dyslipidaemia, diabetes mellitus, heart rate, Killip class 3–4, creatinine, haemoglobin, diastolic blood pressure, cardiac arrest presentation and ischaemia time. To define the IPTW, propensity score was estimated using multivariable logistic regression.

All statistical analyses were performed using IBM SPSS Statistical Package 25 and R Statistical Software.

3. Results

3.1. Patients' characteristics

In this study were included a total of 2425 consecutive STEMI patients, who underwent pPCI. The mean follow-up was 7.5 (± 3.9) years with a minimum of 10 months and a maximum of 14.8 years. The mean age of the population was 66 ± 12.5 years, 74.3% were males. More than half of the population presented hypertension (60.3%), dyslipidaemia (56.2%) and were smokers (53.7%). Others risk factors such as family history of cardiovascular disease (CVD) and diabetes mellitus were present in 27.6% and 20.2% of the population, respectively.

A summary of descriptive characteristics is presented in Table 1.

According to the study design, the number of STEMI patients treated before 2013 were 947 and the STEMI patients treated starting from 2013 were 1478. A summary of descriptive characteristics comparing the two cohorts is presented in Table 2.

Regarding the procedural characteristics, the old treatments cohort, compared to the new treatments cohort, presented a lower use of the radial approach (24.4% vs 83.1% $p < 0.001$), the near absent utilization of DES (1.0% vs 67.1% $p < 0.001$), the use of an higher number of stents during pPCI (1.34 ± 0.699 vs 1.25 ± 0.670 $p = 0.002$), a greater use of thrombectomy (72.4% vs 43.9% $p < 0.001$), gp IIb/IIIa inhibitor (34.3% vs 21.2% $p < 0.001$) and a lower use of complete staged revascularization (4.1% vs 13.1% $p < 0.001$).

As expected, antithrombotic therapy was different in the two cohorts: the old treatments cohort at discharge presented a higher prescription of aspirin (97.9% vs 95.5% $p = 0.002$) and clopidogrel (86.2% vs 24.3% $p < 0.001$) and a very lower prescription of prasugrel (8.0% vs 42.9% $p < 0.001$) and ticagrelor (0.0% vs 26.9% $p < 0.001$) compared to the new treatments cohort.

3.2. Study outcomes

The occurrence of the PE (MACE at 5-years) on the whole population was of 20.3%. All cause death at 5-years occurred on 17.2%. Instead, the incidence of stent thrombosis at 1-year was 2.0% in the whole population.

At 5-years of follow-up the old treatments cohort compared to new treatments cohort presented an higher rate of primary outcome (23.1% vs 18.5% $p = 0.006$), an higher rate of all-cause mortality (19.9% vs 15.5% $p = 0.006$). Moreover the old treatments cohort presented an increased rate of stent thrombosis at 1-year (2.7% vs 1.5% $p = 0.03$). All the outcomes comparison are presented in Table 2.

3.3. Baseline predictors of outcomes at 5 years

At Cox regression model the baseline variables associated with a lower risk of MACE at 5 years were: haemoglobin on admission (HR 0.888, 95% CI 0.828–0.951, $p = 0.001$), dyslipidaemia (HR 0.734, 95% CI 0.578–0.931, $p = 0.011$), and belonging to the new treatments cohort

Table 1
Baseline characteristics of the two cohorts.

VARIABLES	2007–2012 COHORT ($n = 947$)	2013–2020 COHORT ($n = 1478$)	*P* value
DEMOGRAPHIC DATA			
Age (year) ± SD	65.88 ± 12.48	66.14 ± 12.52	0.919
Age ≥ 75, n (%)	257 (27.1)	415 (28.1)	0.614
Male gender, n (%)	709 (74.9)	1093 (74.0)	0.614
RISK FACTORS			
Previous MI, n (%)	97 (10.3)	115 (7.8)	**0.033**
Previous PCI, n (%)	64 (6.8)	106 (7.2)	0.722
Hypertension, n (%)	592 (63.0)	862 (58.6)	**0.031**
Family history of CAD, n (%)	239 (25.5)	426 (29.0)	0.061
Diabetes mellitus, n (%)	191 (20.3)	296 (20.1)	0.894
Smoker, n (%)	477 (50.8)	818 (55.6)	**0.022**
Dyslipidaemia, n (%)	572 (60.9)	784 (53.3)	**<0.001**
CLINICAL FEATURES AT PRESENTATION			
Heart rate (bpm) ± SD	73.6 ± 18.0	75.8 ± 18.4	**0.002**
Systolic blood pressure (mmHg) ± SD	130.8 ± 28.3	132.1 ± 28.4	0.327
Diastolic blood pressure (mmHg) ± SD	73.73 ± 14.9	75.67 ± 15.3	**0.003**
Glycaemia (mg/dl) (IQR)	142 (119–178)	147 (122–186)	0.054
Haemoglobin on admission (g/dl) (IQR)	14.2 (13.1–15.4)	13.8 (12.6–14.9)	**<0.001**
Creatinine on admission (mg/dl) (IQR)	0.99 (0.84–1.16)	0.89 (0.76–1.08)	**<0.001**
Killip class 3–4, n (%)	105 (11.1)	186 (12.6)	0.281
Cardiac arrest, n (%)	64 (6.8)	167 (11.3)	**<0.001**
LVEF on admission (IQR)	51 (43–58)	50 (43–57)	0.265
LVEF <45% on admission, n (%)	219 (25.7)	402 (28.5)	0.156
CORONARY ANGIOGRAPHY DATA			
Culprit LAD, n (%)	426 (46.4)	703 (47.6)	0.435
Culprit CFx, n (%)	136 (14.8)	223 (15.1)	0.435
Culprit RCA, n (%)	350 (38.1)	526 (35.6)	0.435
Culprit left main, n (%)	5 (0.5)	14 (0.9)	0.435
Culprit venous graft, n (%)	2 (0.2)	9 (0.6)	0.435
Multivessel CAD, n (%)	417 (44.3)	672 (45.6)	0.514
PROCEDURAL CHARACTERISTICS			
Radial approach, n (%)	231 (24.4)	1221 (83.1)	**<0.001**
Contrast agent (mL) (IQR)	170 (130−230)	170 (130–230)	0.842
DES, n (%)	9 (1.0)	991 (67.1)	**<0.001**
Number of stent ± SD	1.34 ± 0.699	1.25 ± 0.670	**0.002**
Basal TIMI flow 2–3, n (%)	198 (22.1)	369 (25.2)	0.089
Final TIMI flow 2–3, n (%)	903 (95.6)	1404 (95.7)	0.860
Thrombectomy, n (%)	685 (72.4)	614 (43.9)	**<0.001**
Gp IIb/IIIa inhibitor, n (%)	325 (34.3)	296 (21.2)	**<0.001**
IABP, n (%)	63 (6.7)	68 (4.9)	0.064
Swan Ganz catheter (%)	32 (3.4)	18 (1.3)	**0.001**
RePCI staged, n (%)	39 (4.1)	193 (13.1)	**<0.001**
ISCHAEMIA TIME			
Patient time (hours.minutes) (IQR)	1.51 (0.54–3.35.)	1.13. (0.30–3.00)	**<0.001**
Ischaemia time (hours.minutes) (IQR)	3.45 (2.42–5.42)	3.05 (2.10–5.13)	**<0.001**
IN-HOSPITAL EVOLUTION			
Inpatient in UTIC (days) (IQR)	4 (3–6)	3 (2–5)	**<0.001**
Troponin I (ng/mL) (IQR)	44,500 (15000–95,000)	39,850 (13610–91,962)	0.292
Heart failure, n (%)	203 (22.0)	297 (20.4)	0.343
LVEF at discharge, n (IQR)	52 (44–58)	52 (44–58)	0.951
LVEF <45% at discharge, n (%)	179 (21.4)	324 (23.3)	0.293
MEDICATIONS AT DISCHARGE			
Aspirin, n (%)	855 (97.9)	1356 (95.5)	**0.002**
Clopidogrel, n (%)	749 (86.2)	345 (24.3)	**<0.001**
Prasugrel, n (%)	74 (8.0)	607 (42.9)	**<0.001**
Ticagrelor, n (%)	0 (0.0)	386 (26.9)	**<0.001**

Table 2
Outcomes comparison between the two cohorts.

OUTCOMES	2007–2012 COHORT (n = 947)	2013–2020 COHORT (n = 1478)	P value
In-hospital mortality, n (%)	57 (6.0)	76 (5.1)	0.355
30-day mortality, n (%)	70 (7.4)	85 (5.8)	0.107
30-day stent thrombosis, n (%)	19 (2.0)	22 (1.5)	0.335
1-year stent thrombosis, n (%)	26 (2.7)	22 (1.5)	**0.030**
5-year MACE, n (%)	219 (23.1)	274 (18.5)	**0.006**
5-year mortality, n (%)	188 (19.9)	229 (15.5)	**0.006**
5-year re-IMA, n (%)	37 (3.9)	57 (3.9)	0.950
5-year re-PCI n (%)	37 (3.9)	47 (3.2)	0.339

(HR 0.717, 95% CI 0.567–0.907, $p = 0.006$). Conversely the baseline variables associated with higher risk were: age (HR 1.050, 95% CI 1.037–1.062, $p < 0.001$), previous MI (HR 1.481, 95% CI 1.063–2.065, $p = 0.020$), cardiac arrest (HR 1.453, 95% CI 1.010–2.092, $p = 0.044$), Killip class 3–4 (HR 3.114, 95% CI 2.397–4.046, p < 0.001), heart rate (HR 1.008, 95% CI 1.003–1.014, $p = 0.004$) and creatinine on admission (HR 1.401, 95% CI 1.219–1.610, p < 0.001) (Table 3).

At Cox regression model the new treatments cohort was also associated with lower mortality at 5 years (HR 0.662, 95% CI 0.509–0.860, $p = 0.002$) (Table 4). Estimated adjusted survival curves from the Cox model for PE and mortality at 5-years are presented in Fig. 1.

3.4. Propensity IPTW analysis

After IPTW weighting for age, sex, previous MI, hypertension, smoker status, dyslipidaemia, diabetes mellitus, heart rate, Killip class 3–4, creatinine, haemoglobin, diastolic blood pressure, cardiac arrest presentation and ischaemia time, weighted (IPTW) Cox proportional hazard models showed that belonging to the new treatments cohort was associated with lower risk of MACE at 5 years (HR 0.72; 95% CI 0.56–0.91, $p = 0.007$) and 5 years mortality (HR 0.70, 95%CI 0.54–0.91, $p = 0.009$).

3.5. Baseline plus procedural predictors of outcomes at 5 years

Considering that the new treatments cohort was associated to a lower risk of the primary outcome independently from baseline clinical characteristics, and to better understand the potential impact of new procedural treatments, we performed a COX regression model including both baseline and procedural characteristics.

The variables associated with lower risk of PE at 5 years were: haemoglobin on admission (HR 0.870, 95% CI 0.815–0.928, $p < 0.001$), complete revascularization in case of multivessel disease (HR 0.459, 95% CI 0.265–0.796, $p = 0.006$) and the administration of prasugrel or ticagrelor as antithrombotic therapy (HR 0.721, 95% CI 0.524–0.992, $p = 0.013$).

Conversely the variables associated with higher risk of PE at 5 years were: age (HR 1.046, 95% CI 1.033–1.059, $p < 0.001$), Killip class 3–4 (HR 2.396, 95% CI 1.779–3.228, p < 0.001), heart rate (HR 1.007, 95% CI 1.002–1.012, $p = 0.009$), creatinine on admission (HR 1.247, 95% CI 1.115–1.396, p < 0.001), IABP (HR 1.784, 95% CI 1.193–2.668, $p = 0.005$) and implantation of >1 number of stent (HR 1.354, 95% CI 1.066–1.719, p = 0.013) (Table 3).

Table 3
Cox Regression models for predictors of 5 years MACE outcome.

PRIMARY ENDPOINT AT 5-YEARS							
BASELINE CLINICAL PREDICTORS				BASELINE CLINICAL PLUS PROCEDURAL PREDICTORS			
Variables	HR	95% CI	p value	Variables	HR	95% CI	p value
Age	1.050	1.037–1.062	**<0.01**		1.046	1.033–1.059	**<0.01**
Male gender	1.103	0.843–1.444	0.476		1.223	0.946–1.582	0.124
Previous MI	1.481	1.063–2.065	0.020		1.283	0.910–1.810	0.155
Hypertension	1.067	0.819–1.389	0.631		1.120	0.866–1.448	0.388
Diabetes mellitus	1.151	0.882–1.502	0.300		1.164	0.902–1.502	0.242
Smoker	1.071	0.841–1.364	0.577		1.148	0.908–1.452	0.249
Dyslipidaemia	0.734	0.578–0.931	**0.011**		0.805	0.639–1.016	0.067
Cardiac arrest	1.453	1.010–2.092	**0.044**		1.308	0.944–1.814	0.107
Killip class 3–4	3.114	2.397–4.046	**<0.01**		2.396	1.779–3.228	**<0.01**
Heart rate	1.008	1.003–1.014	**<0.01**		1.007	1.002–1.012	**<0.01**
Creatinine	1.401	1.219–1.610	**<0.01**		1.247	1.115–1.396	**<0.01**
Haemoglobin	0.888	0.828–0.951	**<0.01**		0.870	0.815–0.928	**<0.01**
Patient time	1.000	1.000–1.000	0.838	Ischaemia time	1.000	1.000–1.000	0.839
2013–2020 Cohort vs 2007–2012 Cohort	0.717	0.567–0.907	**0.006**	Radial approach	0.865	0.666–1.123	0.275
				Gp IIb/IIIa inhibitor	0.843	0.633–1.121	0.240
				IABP	1.784	1.193–2.668	**<0.01**
				Thrombectomy	0.867	0.681–1.103	0.245
				DES	0.887	0.663–1.186	0.420
				PCI staged	0.459	0.265–0.796	**<0.01**
				Number of stent >1	1.354	1.066–1.719	**0.013**
				Prasugrel or Ticagrelor	0.721	0.524–0.992	**0.045**

Table 4
Cox Regression models for predictors of 5 years mortaliy outcome.

MORTALITY AT 5-YEARS							
BASELINE CLINICAL PREDICTORS				BASELINE CLINICAL PLUS PROCEDURAL PREDICTORS			
Variables	HR	95% CI	p value	Variables	HR	95% CI	p value
Age	1.081	1.065–1.097	**<0.01**		1.072	1.056–1.088	**<0.01**
Male gender	1.109	0.827–1.488	0.490		1.258	0.954–1.660	0.104
Previous MI	1.334	0.920–1.936	0.129		1.146	0.778–1.687	0.491
Hypertension	1.130	0.832–1.534	0.435		1.168	0.870–1.568	0.303
Diabetes mellitus	1.326	0.994–1.770	**0.055**		1.350	1.026–1.777	**0.032**
Smoker	1.009	0.768–1.324	0.950		1.118	0.861–1.452	0.403
Dyslipidaemia	0.663	0.507–0.866	**<0.01**		0.714	0.551–0.925	**0.011**
Cardiac arrest	1.676	1.129–2.487	**0.01**		1.463	1.028–2.082	**0.034**
Killip class 3–4	3.449	2.609–4.561	**<0.01**		2.524	1.839–3.464	**<0.01**
Heart rate	1.010	1.004–1.015	**<0.01**		1.009	1.003–1.015	**<0.01**
Creatinine	1.489	1.289–1.720	**<0.01**		1.302	1.158–1.463	**<0.01**
Haemoglobin	0.886	0.821–0.956	**<0.01**		0.863	0.804–0.927	**<0.01**
Patient time	1.000	1.000–1.000	0.962	Ischaemia time	1.000	1.000–1.000	0.886
2013–2020 Cohort vs 2007–2012 Cohort	0.662	0.509–0.860	**<0.01**	Radial approach	0.908	0.683–1.208	0.508
				Gp IIb/IIIa inhibitor	0.862	0.620–1.200	0.379
				IABP	1.894	1.230–2.918	**<0.01**
				Thrombectomy	0.844	0.645–1.104	0.216
				DES	0.872	0.631–1.204	0.404
				PCI staged	0.461	0.240–0.885	**0.020**
				Number of stent >1	1.339	1.025–1.749	**0.032**
				Prasugrel or Ticagrelor	0.580	0.396–0.850	**<0.01**

The variables associated with lower risk of mortality at 5 years are presented in Table 4.

Estimated adjusted survival curves from the Cox model for PE and mortality at 5-years are presented in Fig. 2.

3.6. Predictors of stent thrombosis at 1-year

In order to establish which were the principal variables associated with the decreased rate of stent thrombosis at 1-year of in the new treatments cohort compared to the old treatments cohort, we performed a Cox regression model which considered the lower number of stent thrombosis. In this model, emerged two protective factors: age (HR 0.963, 95% CI 0.941–0.986, $p = 0.001$) and the combined variable represented by the administration of ticagrelor or prasugrel, as antithrombotic therapy, or the use of DES (HR 0.502, 95% CI 0.280–0.900, $p = 0.021$). Table 5. Estimated curves from the Cox model for stent thrombosis at 1-year are presented in Fig. 3.

3.7. Sub analysis of effect modification of new treatments cohort

We conducted a subgroup analysis according to age. New treatments cohort with an age ≤ the median (66 years) had a significant lower risk of primary endpoint at 5-years (HR 0.535, 95% CI 0.343–0.832) compared to patients with age > median (66 years) (HR 0.793, 95% CI

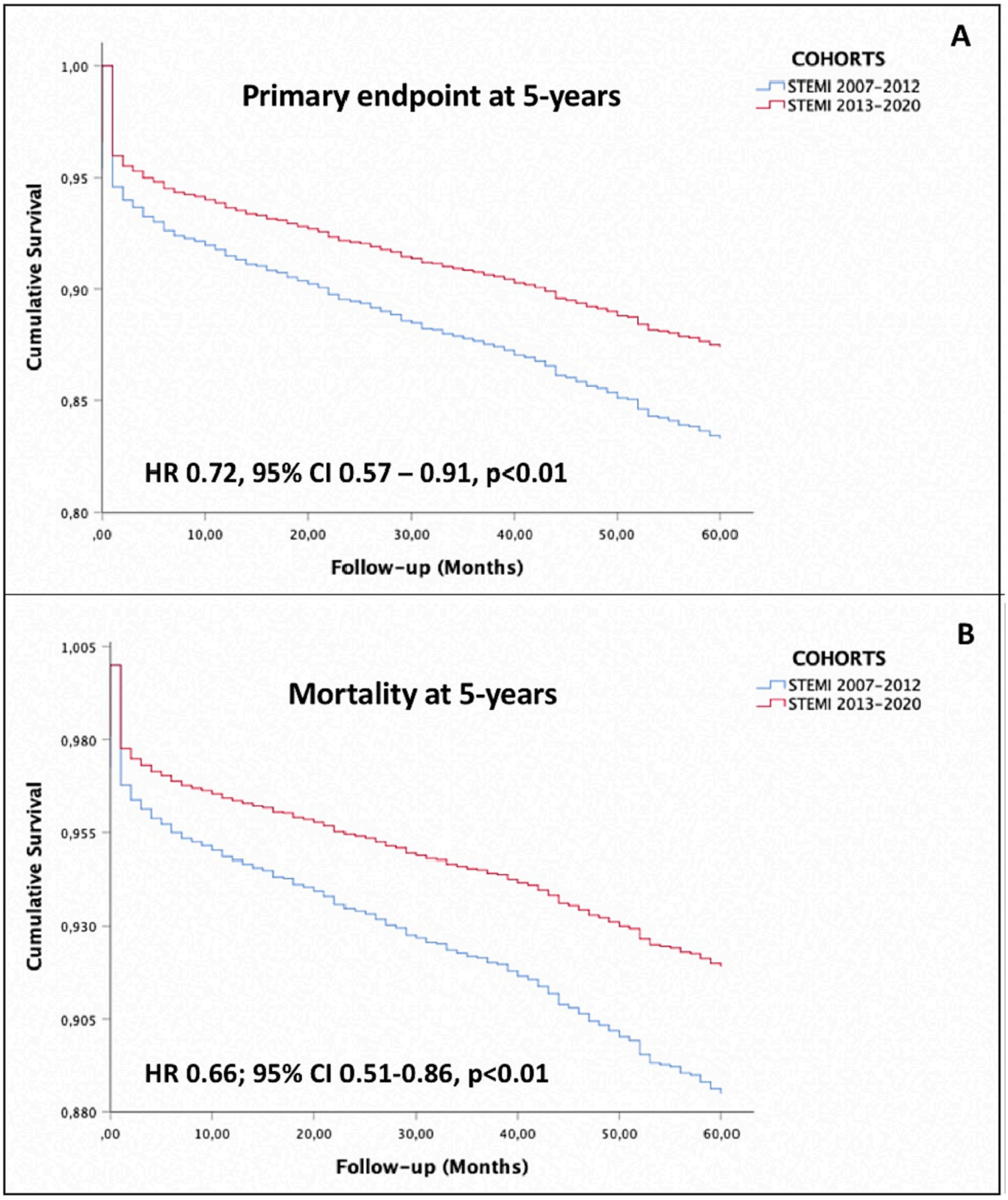

Fig. 1. Adjusted survival curves from the Cox model for primary endpoint at 5-years and mortality at 5-years.
In the panel A is represented the Cox model performed for two patients from different treatments cohorts. The clinical continuous variables: age, heart rate, creatinine on admission and haemoglobin on admission, were fixed at the mean value. Instead, the clinical categorical variables, such as previous MI, dyslipidaemia, cardiac arrest and Killip class 3–4, were considered absent. In the panel B is represented the Cox model performed for two patients from different treatments cohorts. The clinical continuous variables: age, heart rate, creatinine on admission and haemoglobin on admission, were fixed at the mean value. Instead, the clinical categorical variables, such as diabetes mellitus, dyslipidaemia, cardiac arrest and Killip class 3–4, were considered absent.

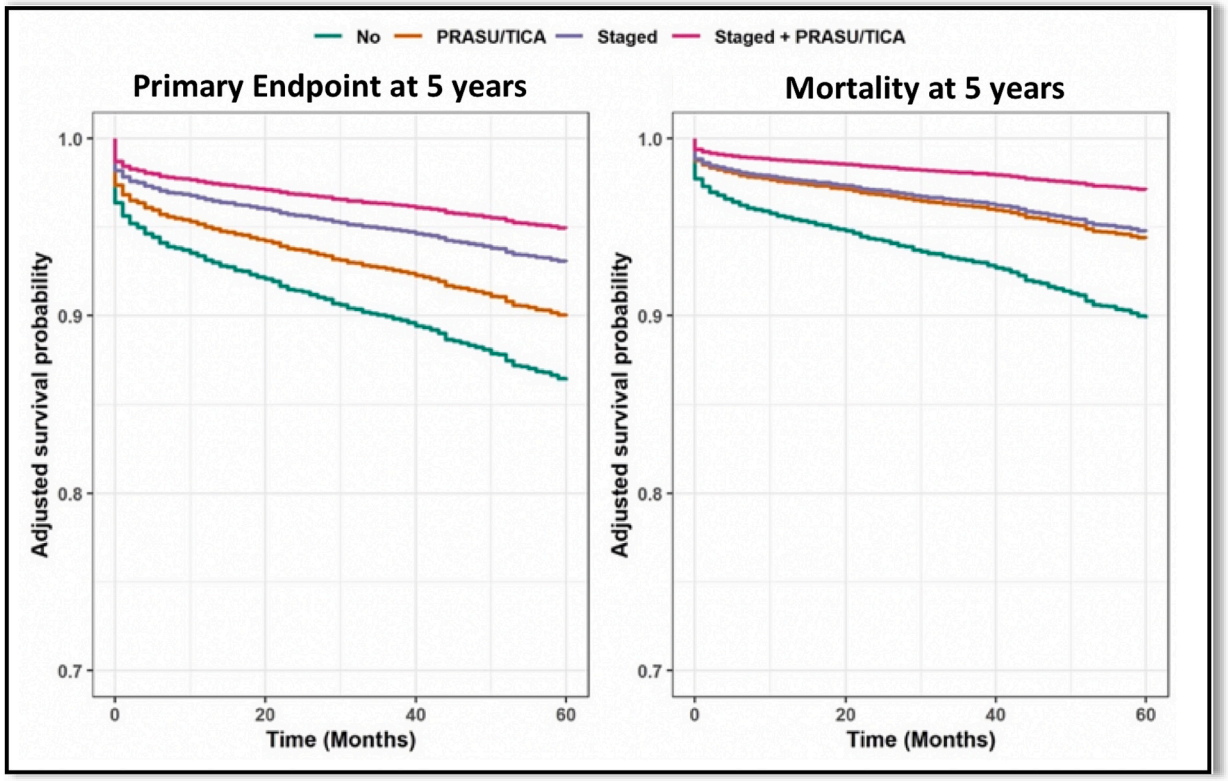

Fig. 2. Adjusted survival curves from the Cox model for primary endpoint and all-cause mortality at 5-years.
In the figure is represented the Cox model performed for four patients from four different treatments strategies (Culprit only revascularization and old antiplatelet agents vs implementation with prasugrel/ticagrelor vs implementation with staged revascularization vs implementation with both prasugrel/ticagrelor and staged revascularization) for MACE at 5 years (left panel) and for mortality at 5 years (right panel). The clinical continuous variables: age, heart rate, creatinine on admission and haemoglobin on admission, were fixed at the mean value for both panels. For MACE at 5 years, the clinical categorical variables, such as previous MI, dyslipidaemia, cardiac arrest and Killip class 3–4, were considered absent. For mortality at 5 years, the clinical categorical variables, such as diabetes mellitus, dyslipidaemia, cardiac arrest and Killip class 3–4, were considered absent.

Table 5
Cox Regression for clinical plus procedural predictors of stent thrombosis at 1-year.

VARIABLE	HR	95.0% CI	P value
Age	0.963	0.941–0.986	**0.001**
Male gender	1.016	0.491–2.104	0.966
Killip class 3–4	1.891	0.872–4.099	0.106
Prasugrel/Ticagrelor/DES	0.502	0.280–0.900	**0.021**

0.626–1.004), (P for interaction = 0.03) (Fig. 4). Furthermore, new treatments cohort with an age ≤ the median (66 years) had a significant lower risk of all cause death at 5-years (HR 0.425, 95% CI 0.226–0.798) compared to patients with age > median (66 years) (HR 0.728, 95% CI 0.569–0.932), (P for interaction = 0.04) (Fig. 4). This subgroup analysis suggests that the beneficial effect of the new treatments compared to the old treatments may be greater in younger patients.

4. Discussion

We analyzed an all-comers series of real-world STEMI patients, including different decades of treatments, and the principal findings of our study are: 1) In a real-word STEMI population the prognosis of patients significantly improved in the last decades also after adjustment for baseline clinical characteristics; 2) When considering both baseline and procedural variables potentially associated to outcomes, complete revascularization and the administration of prasugrel or ticagrelor were independent predictors of MACE as well as of 5-year mortality, suggesting that the better outcomes of the more recent cohorts are related to the use of new antithrombotic treatments and to the implementation of revascularization strategies; 3) Patients receiving prasugrel, ticagrelor or drug eluting stent (DES) were at lower risk of stent thrombosis at 1-year. In summary, this study showed that the implementation of new treatments, such as new antiplatelet drugs, and the strategy of complete revascularization in STEMI patients with multivessel disease, had an independent impact on the prognosis. Besides, even the risk of stent thrombosis was reduced by the contemporary use of treatments such as prasugrel, ticagrelor or DES implantation.

These results suggest that the benefits demonstrated by the new antiplatelet drugs in the randomized clinical trials as the landmark trials of prasugrel and ticagrelor, the TRITON TIMI 38 [5] and the PLATO [4] trials respectively, have translated into a benefit also in the real-world population. Indeed compared with clopidogrel, prasugrel and ticagrelor exhibit a faster onset of action, as well as more profound and consistent platelet inhibition [10]. Clopidogrel is now recommended only to patients who have contra indications to prasugrel and ticagrelor, and in patients receiving oral anticoagulants [2]. Antithrombotic therapy in STEMI patients will need to focus on both the development of novel antiplatelet medications and timing of antiplatelet administration [11], and the use of different antiplatelet regimens using currently existing drugs [12].

Our study demonstrated also the benefit of complete revascularization after culprit lesion treatment. This approach was more frequent in the recent cohort and was driven by the results of multiple trials as the PRAMI [13], DANAMI-3-PRIMULTI [14], CvLPRIT [15] and Compare-Acute [16] trials, as well as the COMPLETE trial [7] which showed that staged non-culprit lesion PCI resulted in a significant reduction of the primary composite outcomes of cardiovascular death (CVD) or new

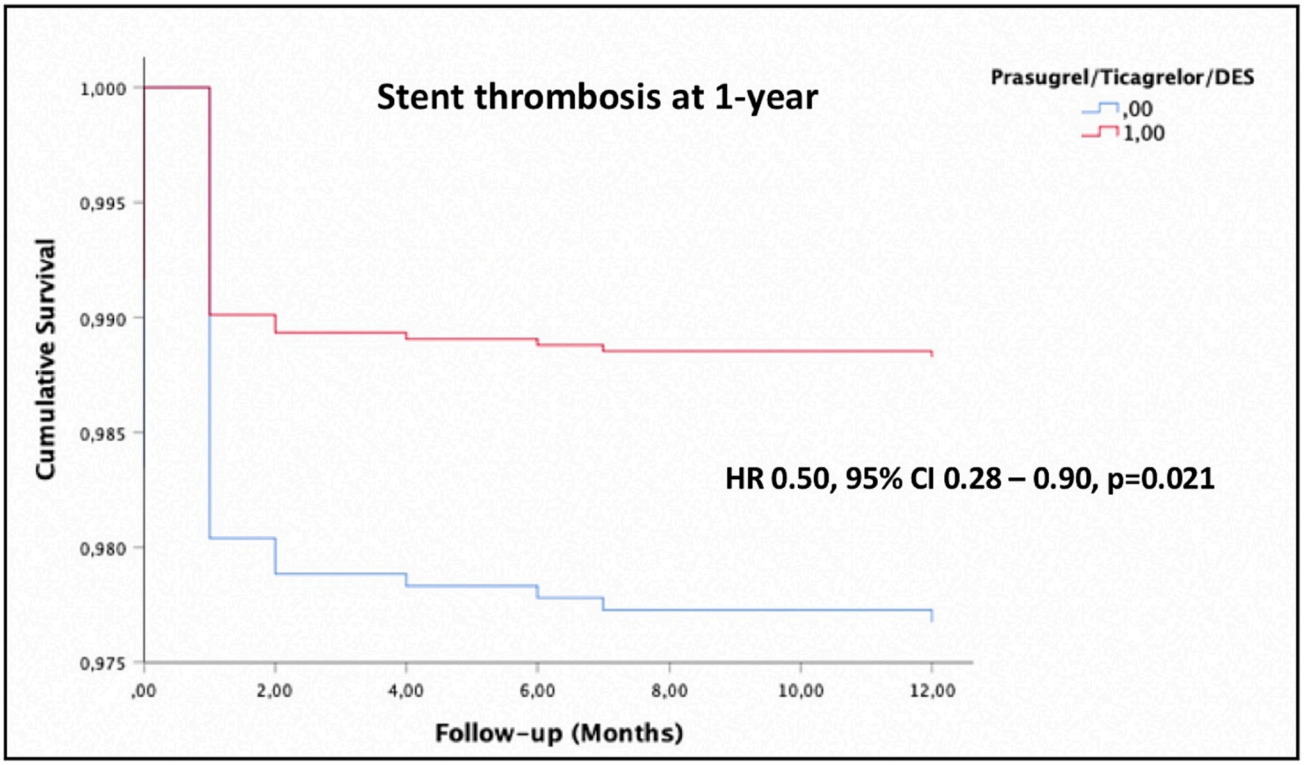

Fig. 3. Adjusted curves from the Cox model for stent thrombosis at 1-year.
In the figure is represented the Cox model performed for two patients from different treatments strategies (patients treated with prasugrel/ticagrelor or DES vs old antiplatelet therapy and BMS). The clinical continuous variable, age, was fixed at the mean value. Instead, for the clinical categorical variables: Killip class was considered to be 1–2, and for gender was considered the male one.

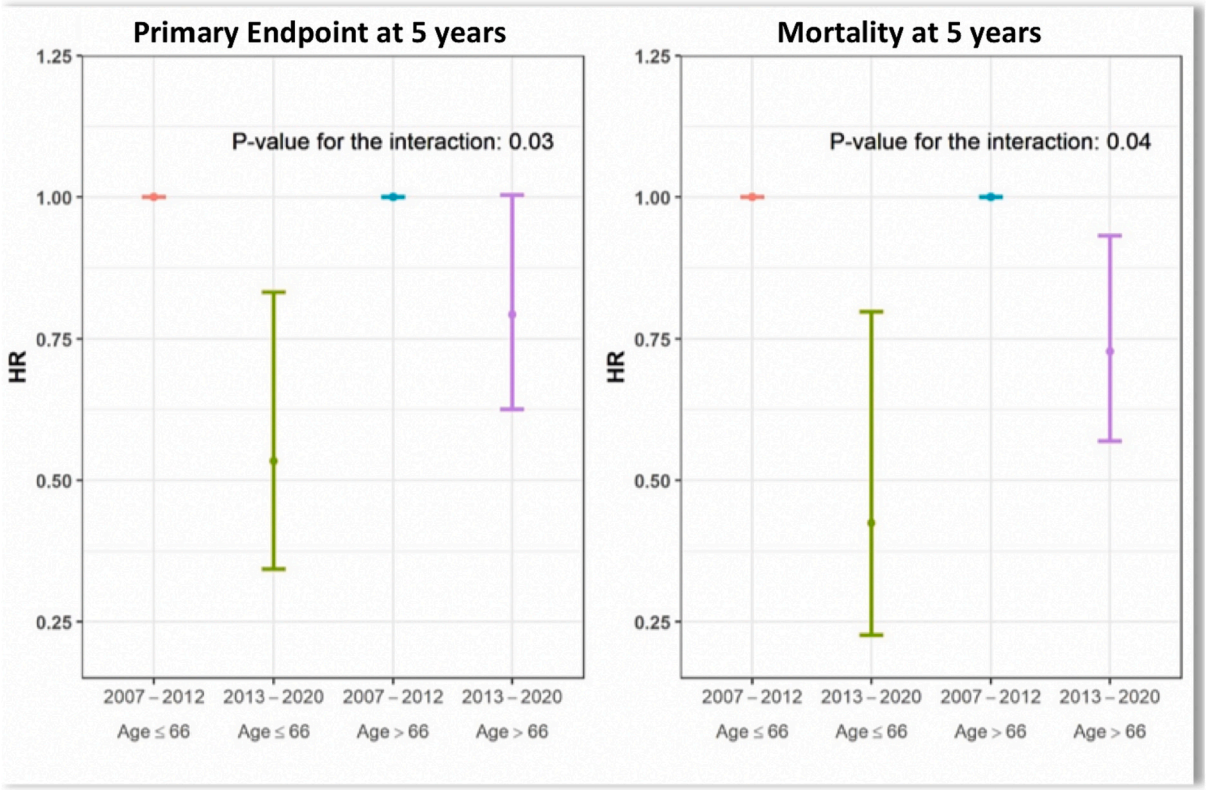

Fig. 4. Effect modification for 5-years MACE and 5-years all-cause mortality of new treatments cohort in subgroups according to age.

MI and the composite of CVD, new MI or revascularization compared with culprit-lesion only PCI. Moreover a recent metanalysis of randomized trial showed that complete revascularization was associated with a reduction in CV mortality with a consistent benefit of a fractional flow reserve– or angiography-guided PCI approach [17].

Our study confirmed in the setting of STEMI, the improved safety of DES in terms of stent thrombosis. Indeed the introduction of new generation DES has reduced the risk of ST as compared to bare metal stents [18] and also a shorter DAPT regimens after PCI with second-generation DES in STEMI has been shown to be safe [19].

The study showed the negative effect on prognosis of some common risk factors and clinical presentations. Indeed, the factors associated to a higher risk of MACE at 5-years were: increasing of age, history of previous MI, developing a cardiac arrest during clinical presentation of the STEMI, presenting higher Killip class (III-IV), higher heart rate and an increased creatinine value. These factors were also associated to a higher mortality at 5-years except for previous MI, while diabetes mellitus was an independent predictors of 5-years mortality. Surprisingly, dyslipidaemia resulted to be associated with better survival, however the reason of this association remains uncertain. At baseline patients with known dyslipidaemia could have been more frequently treated with statin compared to patients with unknow dyslipidaemia. Previous studies suggested favourable effects of statin use before PCI [20–22] and better myocardial perfusion in STEMI patients [23]. Moreover it is possible that the more stringent target of LDL recommended in the more recent years [24] may have resulted in more aggressive treatment in patients belonging to the more recent cohort, thus the better treatment of dyslipidaemia could have biased the association of dyslipidaemia with outcomes.

Timely myocardial reperfusion with pPCI is the central therapy for STEMI, because “time is muscle” and ESC guidelines consider the system delay an index of quality of care in STEMI that should be recorded and reviewed regularly [2]. In our study the ischaemia time was decreased in the more recent treatments cohort compared to the previous cohort, however it was not associated to PE or mortality. Despite the efforts to reduce “door-to-balloon” time over the past decade, an analysis from the Cath-PCI registry questioned the usefulness of decreasing door-to-balloon times in the contemporary era of STEMI treatment [25]. However door-to-balloon time is only one component of total ischaemic time. Considering that still a significant proportion of patients continues to delay seeking medical care, efforts should still be made to educate the general public to minimize this time as much as possible [26,27]. Moreover the early period after symptom onset represents a golden opportunity in the management of STEMI patients and in the effort to decrease the duration of ischaemia and to improve pre-hospital treatment new therapies are under development [11].

Another consideration is that the more recent cohort presented a more frequent use of radial approach, but radial approach did not impact the outcomes. It is possible that the size of our population was not big enough to demonstrate effect of radial approach on outcomes, and despite this result, radial approach should be the standard of care in pPCI given the benefits demonstrated in clinical trials [28].

The use of thrombectomy and of glycoprotein IIb/IIIa inhibitors has decreased in the more recent cohort in line with current ESC guidelines [2] which consider the use of thrombus aspiration only as a bailout therapy in case of large burden of thrombotic material. Similarly, in shocked patients IABP is not routinely recommended, however, although patients in the more recent cohort were less frequently treated with IABP, it is still used in clinical practise despite the low class of recommendation.

Lastly, in the more recent years the percentage of the population presenting with cardiac arrest was increased. This may be probably due to an improvement in STEMI diagnosis in patients who experienced cardiac arrest, coupled with a better pre-hospital care, that may have increased the proportion of patients who arrived still alive in the cath lab.

4.1. Limitations

This study has limitations. The results of this study should be interpreted in light of the common limitations of a registry-based cohort study. For the observational nature of the study, we were able to provide only correlation with the explored outcome, but not causation. We did not analyse the impact of bleeding events on outcomes, indeed the retrospective adjudication of bleeding events and their severity was considered unfeasible. However the newer and more potent antiplatelet therapy, as prasugrel and ticagrelor administration, was still associated to a better mortality outcome thus probably conserving a net clinical benefit on long term survival despite the potential increased risk of bleeding. Moreover cerebrovascular events were collected only in the short term and the number of events were too low to provide meaningful insights. Finally, this registry did not include data concerning long-term drug compliance, rates of discontinuation or new prescriptions, therefore we did not analyse the impact of discharge-medications other than antiplatelet agents.

5. Conclusions

In a real-word STEMI population the prognosis of patients has improved in the last decades, and this was associated to the use of new antithrombotic treatments and to the implementation of complete revascularization. The application of new evidence-based therapies in clinical practise is fundamental to improve patient prognosis because the benefits demonstrated by clinical trials have translated into a benefit in the real-world population.

Declaration of Competing Interest

None.

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