

Long-Term Use of Antiplatelet Therapy in Real-World Patients with Acute Myocardial Infarction: Insights from the PIPER Study

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Abstract

The aim of this study was to assess long-term drug adherence and prognosis in real-world patients discharged on dual-antiplatelet therapy (DAPT) after acute myocardial infarction (AMI). A retrospective cohort analysis using administrative databases kept by eight local health units was performed. DAPT exposure (defined as ≥ 2 prescriptions), adherence, and the occurrence of major adverse events (MACE) were analyzed during a 36-month follow-up. The analysis included 11,101 patients who were discharged alive with a primary diagnosis of AMI. Of these, 5,919 patients (53.31%) were discharged on DAPT without a diagnosis of cancer or anemia, without transient DAPT discontinuation, and represented the study population. DAPT discontinuation occurred in 2,200 patients (37.2%) and in 1,995 (33.7%) after the first 6 and 12 months, respectively, whereas 423 patients (7.1%) were still on DAPT after 36 months. Patients who maintained DAPT up to 12 months had a significantly lower overall mortality, compared with patients who discontinued DAPT after 6 months. Exposure to DAPT at 3 years was associated with reduced all-cause mortality (hazard ratio [HR]: 0.067, 95% confidence interval [CI]: 0.027–0.162, $p < 0.001$) and reduced recurrent AMI (HR: 0.02, 95% CI: 0.003–0.173, $p < 0.001$). In conclusion, this study shows that prolonged DAPT over 12 months is maintained in a relevant number of patients after AMI. However, adherence to antiplatelet therapy in first 12 months after AMI is still unsatisfactory and efforts to enhance patients' compliance are warranted. Exposure to prolonged DAPT at 3 years seems to be associated with a significant reduction in all-cause mortality and AMI.

Keywords

- ▶ acute myocardial infarction
- ▶ antiplatelet therapy
- ▶ adherence to treatment

Introduction

Antiplatelet therapy represents the cornerstone therapy in patients with acute coronary syndrome (ACS). Prolonged dual-antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂

inhibitor is recommended up to 1 year after ACS both in patients submitted to revascularization and in patients medically managed.^{1–3}

Notably, only in the late years a mounting evidence for secondary prevention by intensified antiplatelet therapy has emerged after 1 year from ACS. It has been recently demonstrated that, in patients presenting with ACS, the ischemic risk can remain substantially elevated beyond the first 12 months, in spite of a successful revascularization. The DAPT⁴ and the

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PEGASUS-TIMI 54⁵ trials demonstrated that prolonged DAPT beyond 12 months can significantly reduce the incidence of major adverse cardiac events (MACE). In this setting, intensified antiplatelet therapy on top of aspirin has been shown to be an effective therapeutic strategy to prevent recurrent ischemic events. In selected patients at high thrombotic risk, prolonged DAPT beyond 12 months might be considered.¹⁻³

The need for prolonged DAPT might raise compliance issues, as long-term adherence to prescribed therapy after ACS is still challenging in real-world patients.⁶

Previous reports have shown that more than 10% of patients prematurely discontinue antiplatelet therapy within 30 days after stent implantation. Clinical trials reported a rate of premature discontinuation as high as 30% after 12 months.⁷ Premature antiplatelet therapy discontinuation raises safety concerns, as it is associated with a higher incidence of MACE.^{6,8} Nonadherent patients are at a substantially higher risk of death.⁹ Patients with ACS who discontinue all of their medications are more than three times as likely to die as those who remain adherent. Of note, the rate and clinical consequences of antiplatelet discontinuation beyond 12 months after ACS in real-world patients are still lacking.

The aim of our study is to assess long-term exposure and adherence to DAPT in patients with ACS in an Italian population. The occurrence of MACE in relation to maintenance of single- or dual-antiplatelet therapy has been investigated, as well.

Methods

Data Sources

The PIPER (Platelet-aggregation Inhibition: Persistence with treatment and cardiovascular Events in Real-world Study) is a retrospective, observational study, based on administrative databases of eight Italian Local Health Units (LHUs), in Lombardy, Tuscany, Puglia, and Campania, which includes approximately 5.6 million health-assisted individuals.

In particular, the following databases were used as data sources: the Health-Assisted Subjects' Database, containing patients' demographic data; Outpatients and Inpatients pharmaceutical drugs, providing information for each medication prescription, such as ATC (Anatomical-Therapeutic-Chemical) code of the drug purchased, number of packages, number of units per package, the dosages, unit cost per package, and prescription date; and Hospital Discharge Database, which includes all hospitalization data with discharge diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The patient code in each database permitted electronic linkage with all the other databases. No identifiers related to patients were provided to the researchers. Informed consent was not required for using encrypted retrospective information. This study was notified to the local ethics committee in each participating LHU according to the Italian law regarding the conduct of observational analysis, and the LHU Ethics Committees approved the study.¹⁰

Study Populations

This was a retrospective cohort study that included all consecutive beneficiaries of each LHU hospitalized and discharged alive with a primary diagnosis of acute myocardial infarction (AMI; ICD-9-CM: 410.xx) between January 1, 2010, and December 31, 2011 (enrollment period). The date of AMI discharge was identified as the index date, which represented the enrollment day of each individual patient, who was then followed up for 3 years after the index date (follow-up period).

Data on baseline characteristics, including demographics, risk factors, and medical history, were collected. Specifically, the treatments of interest were antihypertensive drugs (ATC codes: C02, C03, C08), oral hypoglycemic drugs and/or insulins (ATC code: A10), cardiac therapy (ATC code: C01), statins (ATC code: C10AA), beta-blocking agents (ATC code: C07), angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor antagonists (AAls; ATC code: C09). Previous cardiovascular hospitalizations were identified by ICD-9-CM codes: 410-414; history of percutaneous coronary intervention (PCI) (procedure codes: 00.66, 36.0x or absence of 36.04) and AMI of other than anterior wall (ICD-9-CM codes: 410.0 or 410.1) were also evaluated.

Patients were classified according to exposure to antiplatelet therapy during the follow-up period. A patient was defined as treated with antiplatelet therapy (ATC code: B01AC), if at least two prescriptions of these drugs during the follow-up period were found. In particular, all enrolled patients were stratified into four main categories: (1) monotherapy with acetylsalicylic acid (ASA); (2) DAPT (ASA + P2Y₁₂ inhibitors); (3) other drugs (only P2Y₁₂ inhibitors); and (iv) no antiplatelet therapy.

Patients with concomitant diagnosis at discharge of anemia or cancer were excluded, as these comorbidities might influence prescription and/or duration of DAPT.

Hospitalizations for AMI and all-cause mortality occurring during the 36-month follow-up period from discharge were considered. Multivariable analyses were conducted to check for possible confounders using a proportional hazards Cox regression model: demographic characteristics; other guidelines-recommended post-AMI therapies, including beta-blockers, ACE inhibitors/AAls, statin, and antiplatelet therapy; previous hospitalizations for cardiovascular disorders; and diabetes.

A patient was defined as antidiabetic, antihypertensive, or cardiac therapy if at least two prescriptions of antidiabetic agents, of antihypertensives, of cardiac drugs, respectively, were found at follow-up. A patient was defined as treated with statins, beta-blocking agents, or ACE inhibitors/AAls if at least two prescriptions of these drugs were detected during the observation period. Patients who were transferred to another LHU during the observational period were excluded from analysis.

A Pegasus score was calculated for each patient by the sum of the characteristics which constituted the inclusion criteria of the Pegasus trial.⁵

Statistical Methods

Continuous variables are given as means with standard deviations (mean ± SD); categorical variables are shown as percentages and absolute numbers.

Cox regression analysis has been used for the risk assessment. The impact of different variables on cardiovascular mortality and recurrent AMI was analyzed using the hazard ratios (HR) with 95% confidence interval (CI); a *p*-value less than 0.05 was considered statistically significant. Analyses were performed with Stata software version 12.1 (Stata Corp LP, College Station, Texas, United States).

Results

A total of 11,101 were discharged alive with a primary diagnosis of AMI. Of these, 5,919 patients (53.3%) were discharged on DAPT, without a diagnosis of cancer or anemia at discharge, without transient DAPT discontinuation, and represented our study population (► Fig. 1).

The demographic and baseline clinical characteristics of included patients are shown in ► Table 1. Among the enrolled patients, 55.6% presented hypertension at the baseline, followed by 43.9% with heart disease, 26.0% with diabetes, and 10.0% with previous hospitalization for cardiovascular disorders. Statins, ACE inhibitors/AAls, and beta-blocking agents were used in 79.4, 74.6, and 71.5%, respectively. PCI at the index hospitalization was performed in 52.9% of patients. ► Table 2 describes the type of DAPT.

Out of the 5,919 patients, 2,200 (37.2%) discontinued DAPT after the first semester and 1,995 (33.7%) discontinued DAPT after the second semester (► Supplementary Fig. S1). Of note, 423 patients (7.1%) were still on DAPT after 36 months.

Baseline clinical and demographic characteristics of patients in relation to exposure and type of antiplatelet therapy are summarized in ► Table 3. Compared with patients who were still on DAPT at 6 months, patients who were on DAPT at 12 months were younger (mean age: 62.5 ± 16.0 vs. 65.5 ± 17.0, *p* < 0.001), less frequently required blood transfusion (3.9 vs. 6.9%, *p* < 0.001), and

had less frequently chronic kidney disease (1.1 vs. 2.2%, *p* < 0.01). Patients who were still on DAPT at 3 years had more frequently a previous cardiovascular hospitalization (8.8 vs. 14.4%, *p* < 0.001) and were more frequently diabetic (38.5 vs. 25.5%, *p* < 0.001), compared with patients who discontinued after 12 months.

After controlling for possible confounders, patients who maintained DAPT up to 12 months had with a significantly lower all-cause mortality, compared with patients who discontinued DAPT after 6 months (HR: 0.531, 95% CI: 0.434–0.650, *p* < 0.001). Moreover, exposure to DAPT at 3 years (compared with no exposure to DAPT—no treated patients or patients in monotherapy with ASA/P2Y12) was associated with reduced all-cause mortality (HR: 0.067, 95% CI: 0.027–0.162, *p* < 0.001; ► Fig. 2) and recurrent AMI (HR: 0.02, 95% CI: 0.003–0.173, *p* < 0.001). PCI at the index hospitalization for AMI was found to be associated with reduced all-cause mortality (HR: 0.678, 95% CI: 0.557–0.825, *p* < 0.001), but was not associated with reduced AMI (► Table 4).

Discussion

The main findings of this study are the following: adherence to DAPT within the first 12 months after AMI is still sub-optimal; notably, a significant proportion of patients in Italy maintain DAPT up to 36 months after AMI; cessation of DAPT within the first 12 months is associated with increased overall mortality; prolonged DAPT beyond 12 months seems to be associated with a significant reduction in all-cause mortality and AMI.

The benefit of DAPT after an ACS was well demonstrated in the CURE,¹¹ COMMIT/CCS-28,¹² and CLARITY-TIMI 28¹³ trials. The association of aspirin and clopidogrel reduced the 1-year incidence of cardiovascular events by approximately 20% compared with aspirin alone. More potent and consistent

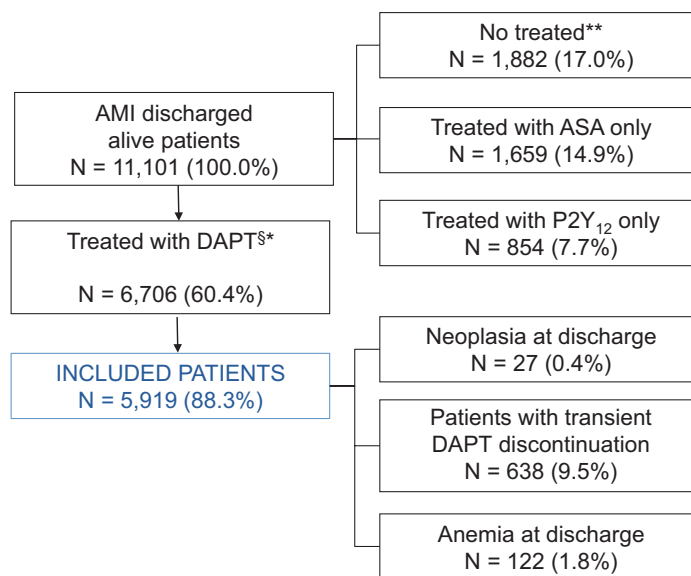


Fig. 1 Flow chart for patient selection and inclusion and exclusion criteria for study. DAPT, dual-antiplatelet therapy; AMI, acute myocardial infarction; ASA, acetylsalicylic acid. Notes: §DAPT = ASA + P2Y₁₂ inhibitors (clopidogrel, prasugrel, ticagrelor, ticlopidine); *At least one prescription of ASA and at least one prescription of P2Y₁₂ in the month following hospital discharge; **Any prescription of ASA or P2Y₁₂ in the 3 months following hospital discharge.

Table 1 Demographic and clinical characteristics of included patients

N, %	11,101
	100.0%
Age (y)	65.6 ± 17.6
Male	7,000
	63.1%
Previous cardiovascular hospitalizations	1,114
	10.0%
Diabetes	2,885
	26.0%
Hypertension	6,167
	55.6%
Heart disease	4,878
	43.9%
ACE inhibitors/AAls	8,285
	74.6%
Statins	8,819
	79.4%
Beta-blocking agents	7,942
	71.5%
Index MI: front/front-lateral	2,889
	26.0%
Index MI with PCI	5,872
	52.9%
Index MI with coronary angiography	5,821
	52.4%
CKD	232
	2.1%

Abbreviations: AAlI, angiotensin II receptor antagonist; ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

P2Y₁₂ receptor inhibition with either prasugrel or ticagrelor was superior to clopidogrel in the subsequent TRITON-TIMI 38¹⁴ and PLATO¹⁵ trials. Current guidelines recommend 12 months of DAPT after ACS.¹⁻³ These recommendations are made on the basis of early studies^{16,17} which demonstrated a sustained increased risk of thrombotic complications, including stent thrombosis and spontaneous cardiovascular events, beyond 6 months. Notably, the greatest absolute reductions in cardiovascular events with DAPT are seen in the first 3 months and since these studies, advances in drug-eluting stent technology have led to a substantially reduced incidence of late (>30 days) and very late (>1 year) stent thrombosis.^{10,18}

Although it has been fully elucidated that premature discontinuation of antiplatelet therapy is associated with a poor prognosis, patients' compliance remains low.^{6,7} Several reasons for noncompliance have been reported, such as excessive concerns about hemorrhagic complications or competing guidelines, complex treatment regimens, or lack of outcome expectancy.¹⁹ As anemia can be considered a marker for high bleeding risk, thus contraindicating prolonged DAPT, patients with anemia at discharge were excluded from the present analysis. Nevertheless, in this study, one out of three patients discontinued DAPT after 6 months. In routine clinical practice, poor medication adherence is one of the main factors that reduce the effectiveness of chronic drug therapies.²⁰ In accordance with data observed in other studies,^{6,21,22} in this study a considerable proportion of patients report low adherence to prescribed medications, particularly for non-monotherapy strategies.

Although many studies have evaluated the incidence or effect of antiplatelet therapy cessation on subsequent cardiovascular risk, most included selected cohorts of patients and were limited by lack of standardized definitions for therapy discontinuation that did not integrate the underlying context in which treatment was discontinued.^{23,24} The results presented here suggest that there are still numerous barriers to adherence to practice guidelines; therefore, encouragement to continue long-term therapy with lifestyle modifications and pharmacological treatments is needed to improve outcomes in patients at risk of cardiovascular events.²⁵

On the other hand, this study demonstrated that the number of patients who maintain DAPT up to 3 years after

Table 2 Type of antiplatelet treatment

Type of treatment			N	%	%
None			1,882	17.0	–
Treatment			9,219	83.0	100.0
	Monotherapy	ASA	1,659	14.9	18.0
		P2Y ₁₂	854	7.7	9.3
	DAPT	ASA + Clopidogrel	6,313	56.9	68.4
		ASA + Prasugrel	266	2.4	2.9
		ASA + Ticagrelor	10	0.1	0.1
		ASA + Ticlopidine	117	1.1	1.3
Total				100.0	–

Abbreviations: ASA, acetylsalicylic acid; DAPT, dual-antiplatelet therapy (ASA + P2Y₁₂).

Table 3 Demographic and clinical characteristics of patients by semester of DAPT interruption

	Patients who discontinued DAPT after semester 1	Patients who discontinued DAPT after semester 2	Patients who discontinued DAPT after semester 3	Patients who discontinued DAPT after semester 4	Patients who discontinued DAPT after semester 5	Patients still in DAPT at semester 6	p-Value
N, %	2,200	1,995	807	324	170	423	
	37.2%	33.7%	13.6%	5.5%	2.9%	7.1%	
Age (y)	65.5 ± 17.0	62.5 ± 16.0	61.4 ± 15.9	62.0 ± 17.6	61.8 ± 16.9	61.7 ± 17.9	0.001
Male	1,434	1,424	558	211	119	275	
	65.2%	71.4%	69.1%	65.1%	70.0%	65.0%	0.01
Previous cardiovascular hospitalizations	193	161	62	33	22	61	0.001
	8.8%	8.1%	7.7%	10.2%	12.9%	14.4%	
Diabetes	560	532	250	92	62	163	0.001
	25.5%	26.7%	31.0%	28.4%	36.5%	38.5%	
Hypertension	1,322	984	478	219	112	291	0.001
	60.1%	49.3%	59.2%	67.6%	65.9%	68.8%	
Heart disease	1,045	774	372	189	103	251	0.001
	47.5%	38.8%	46.1%	58.3%	60.6%	59.3%	
ACE inhibitors/AAls	1,806	1,718	726	283	156	382	0.001
	82.1%	86.1%	90.0%	87.3%	91.8%	90.3%	
Statins	1,946	1,938	793	320	164	413	0.001
	88.5%	97.1%	98.3%	98.8%	96.5%	97.6%	
Beta-blocking agents	1,736	1,710	693	282	154	365	0.001
	78.9%	85.7%	85.9%	87.0%	90.6%	86.3%	
Index MI: front/front-lateral	583	541	206	82	61	122	NS
	26.5%	27.1%	25.5%	25.3%	35.9%	28.8%	
Index MI with PCI	1,368	1,425	534	195	107	266	0.001
	62.2%	71.4%	66.2%	60.2%	62.9%	62.9%	
Index MI with coronary angiography	1,260	1,294	468	175	89	234	0.001
	57.3%	64.9%	58.0%	54.0%	52.4%	55.3%	
CKD	48	21	9	5	10	8	0.001
	2.2%	1.1%	1.1%	1.5%	5.9%	1.9%	
	0.3%	0.4%	–	–	0.0%	1.4%	

Abbreviations: AAl, angiotensin II receptor antagonist; ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; DAPT, dual-antiplatelet therapy; MI, myocardial infarction; NI, not issuable; PCI, percutaneous coronary intervention.

AMI is not trivial. It should be highlighted that the enrollment period was from January 2010 to December 2011, previous to the recent publication of data on prolonged DAPT beyond 12 months. This finding might be considered in the light of the attempt of clinicians to provide a further protection for ischemic events in patients considered high thrombotic risk, even without evidence of clear benefit. The DAPT trial was designed on the basis of this unmet need. In the DAPT trial,⁴ the largest and only double-blinded study, extended DAPT (30 vs. 12 months) reduced the risk of major adverse cardiovascular and cerebrovascular events (4.3 vs. 5.9%), myocardial infarction (MI; 2.1 vs. 4.1%), and stent

thrombosis (0.4 vs. 1.4%) but at a cost of increased moderate or severe bleeding (2.5 vs. 1.6%) and a borderline rise in all-cause mortality (2.0 vs. 1.0%; $p = 0.05$). The PEGASUS-TIMI 54 trial⁵ compared aspirin monotherapy to a combination of aspirin and ticagrelor in patients with a previous MI and at least one additional high-risk factor. At a mean of 33 months, ticagrelor (60 mg) reduced the incidence of cardiovascular death, MI, or stroke (7.77 vs. 9.04%) at the expense of increased thrombolysis in myocardial infarction (TIMI) major bleeding (2.30 vs. 1.06%) and a neutral effect on overall mortality. On the basis of these trials, combination antiplatelet therapy would appear to confer only a small ischemic

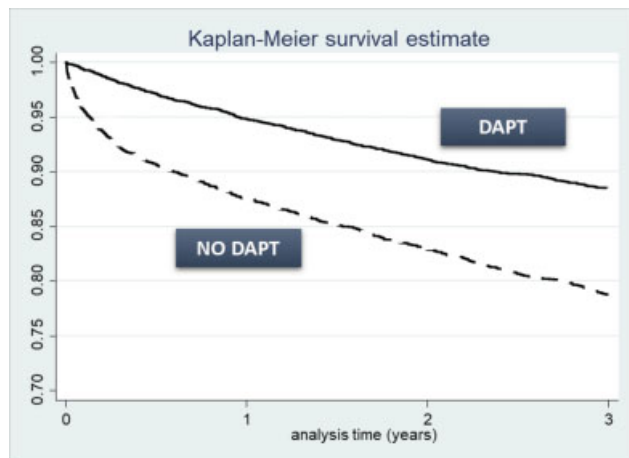


Fig. 2 Mortality at 36 months of follow-up (Kaplan–Meier). NO DAPT: N = 3,540, no. of events = 749 (21.2%); survivals after 3 years = 2,791 (78.8%); DAPT: N = 5,027, no. of events = 580 (11.6%); survivals after 3 years = 4,447 (88.4%). LHUs of Frosinone and Grosseto were excluded because data on deaths were not available.

Table 4 All-cause mortality at 3 years in relation to DAPT maintenance

	HR	95% confidential interval		p-Value
Age (y)	1.076	1.064	1.087	<0.001
Gender (ref. F)	1.576	1.316	1.886	<0.001
Previous cardiovascular hospitalizations (ref. no)	1.257	0.965	1.636	0.090
Diabetes (ref. no)	0.972	0.689	1.371	N.S.
Hypertension (ref. no)	0.820	0.579	1.160	N.S.
Heart disease (ref. no)	0.735	0.534	1.013	N.S.
ACE inhibitors/AAILs (ref. no)	0.235	0.168	0.328	<0.001
Statins (ref. no)	0.574	0.458	0.720	<0.001
Beta-blocking agents (ref. no)	0.417	0.301	0.578	<0.001
Index MI: front/ front-lateral (ref. no)	1.058	0.872	1.282	N.S.
Index MI with PCI (ref. no)	0.678	0.557	0.825	<0.001
Index MI with coronary angiography (ref. no)	0.950	0.783	1.153	N.S.
Neoplasia hosp. during obs. period (ref. no)	2.992	2.421	3.697	<0.001
Blood transfusion during obs. period (ref. no)	1.376	0.949	1.997	N.S.

Table 4 (Continued)

	HR	95% confidential interval		p-Value
DAPT maintenance				
Patients who discontinued DAPT after semester 1	1.000			
Patients who discontinued DAPT after semester 2	0.531	0.434	0.650	<0.001
Patients who discontinued DAPT after semester 3	0.455	0.330	0.628	<0.001
Patients who discontinued DAPT after semester 4	0.484	0.323	0.725	0.001
Patients who discontinued DAPT after semester 5	0.195	0.096	0.395	<0.001
Patients still in DAPT at semester 6	0.067	0.027	0.162	<0.001

Abbreviations: AAIL, angiotensin II receptor antagonist; ACE, angiotensin-converting enzyme; DAPT, dual-antiplatelet therapy; HR, hazard ratio; MI, myocardial infarction; N.S., not significant; PCI, percutaneous coronary intervention.

Notes: N = 5,027, no. of events = 580.

benefit at the cost of a significant bleeding risk. European²⁶ and North American²⁷ guidelines therefore do not recommend DAPT in patients with stable atherothrombotic disease but acknowledge that with careful consideration, combined antiplatelet therapy may be beneficial in some high-risk patients.

In this study, prolonged DAPT up to 3 years after AMI was associated with a significant reduction in overall mortality and AMI. Due to the retrospective nature of the study, this conclusion should be interpreted with caution and only as hypothesis generating. It should be highlighted that prolonged DAPT might identify patient at lower hemorrhagic risk, without noncardiac comorbidities which would have contraindicated long-term DAPT. To reduce a selection bias, patients with anemia of cancer at discharge were excluded, as well as patients who were not prescribed DAPT at discharge. An unexpected finding in the DAPT trial⁴ was a borderline-significant increase in overall mortality rate (0.5% absolute increase) with 30 months of DAPT versus 12 months of DAPT in DES-treated patients, which was due to significantly increased deaths from non-cardiovascular causes (most commonly cancer), with no increase in cardiovascular deaths, and no significant increase in fatal bleeding.

It should be highlighted that the prescription of DAPT at discharge was relatively low. This might be partly explained by the enrollment period, which was from January 2010 to December 2011, when P2Y₁₂ inhibitors in medically managed patients were still underused. Moreover, the analysis included not only type I but also type II MI patients, for whom

the benefit of DAPT may be controversial. The low use of beta-blockers and ACE inhibitors was evident, as well. The low use of ACE inhibitors might be due in some cases to preserved ejection fraction.

The results of this study should be interpreted in light of some strengths and limitations. The strength of the presented data includes its basis on the large size unselected population; our patients may represent a more representative sample of “real world” than those included in many of the randomized controlled trials that have previously evaluated antiplatelet use for mortality reduction. Limitations include, first, the absence of relevant clinical information in the data setting. It is plausible that patients’ risk profile might have conditioned DAPT duration. However, due to the nature of the study, which consists of a retrospective analysis from administrative databases, important clinical data are missing and confounding biases might have influenced the results. To overcome this limitation, we excluded patients with concomitant diagnosis at discharge of anemia or cancer, as these comorbidities might influence prescription and/or duration of DAPT. It cannot be ruled out if the reduced all-cause mortality associated with prolonged exposure to DAPT is related to a lower risk profile of patients (in terms of comorbidities), which allowed prolonged DAPT, or the protective effect of DAPT. Notably, prolonged DAPT was associated with a reduced rate of recurrent AMI, for which the protective effect of DAPT might be more evident. Second, adherence was estimated using pharmacy data on filled prescriptions, but no information on actual medication consumption was available. Third, the reasons for nonadherence were not retrievable from the dataset.

Despite these limitations, this study indicates prolonged DAPT beyond 12 months is maintained in a relevant number of patients after AMI. Notably, long-term exposure and adherence with antiplatelet therapy in patients with AMI still appear to be unsatisfactory in an unselected Italian population. Further efforts to enhance patients’ compliance to medical therapy are warranted.

Conflicts of Interest

L.D.E., V.P., C.V., and S.B. report no conflicts of interest in this work. Manuscript development was supported by an unconditional grant from AstraZeneca. R.R. reports payment as an individual for consulting fee or honorarium from Daiichi Sankyo, Inc, Astra Zeneca, Bayer, and Pfizer.

Authors’ Contributions

All authors contributed toward data analysis, drafting, and revising the manuscript and agree to be accountable for all aspects of the work.

Ethical Approval

This article does not contain any studies with animals performed by any of the authors.

Informed Consent

Informed consent is not required by the Local Health Unit (LHU) ethics committees for using encrypted retrospective

information. No identifiers related to patients were provided to the researchers. This study was notified to the local ethics committee in each participating LHU according to the Italian law regarding the conduct of observational analysis, and the LHU Ethics Committees approved the study.

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