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EVIDENCE-BASED POLYTHERAPIES AND LONG-TERM MORTALITY AFTER ACUTE MYOCARDIAL INFARCTION IN VERY OLD SUBJECTS COMPARED WITH ELDERLY AND ADULTS: A NESTED CASE-CONTROL STUDY

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This thesis is dedicated in loving memory to my grandfather, Lino, and my uncle, Maurizio.

1 INTRODUCTION

Clinical trials have demonstrated that selected secondary prevention medications for patients after acute myocardial infarction (AMI)—angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), β-blockers, antiplatelet agents, and lipid-lowering drugs (statins)—reduce cardiovascular mortality.[1] Yet, a gap still persists between the benefits demonstrated in clinical trials and the effectiveness of these medications in clinical practice.[2,3] There are two potential explanations for this discrepancy: first, these medications are generally underprescribed in the secondary prevention of patients;[4-7] second, older people are underrepresented or even absent from drug trials.[1,8] Elderly patients are the most vulnerable subgroup in the population, as they have higher cardiovascular risk, more comorbidities, poorer tolerability and compliance to medications,[9] and higher susceptibility to drug interactions.

Findings from observational studies indicate that secondary prevention medications after AMI are more effective and have synergistic benefits, when prescribed additively.[10-13] However, it is reasonable to assume that variations in compliance and tolerability profiles across younger and older age groups might alter the strength of association between adherence and survival. To the best of our knowledge, no population outcome study has attempted to determine whether polytherapy after AMI is effective on long-term mortality in very old patients.

Accordingly, the objective of this study was to examine the relationship between adherence to evidence-based drugs and mortality following AMI in a cohort from Emilia-Romagna region (Northern Italy), focusing on the effect of single therapy and polytherapy in very old patients (≥80 years) compared with elderly and adult patients (<80 years). The findings of this study may have practical implications for designing interventions to improve secondary prevention of older patients after AMI.

2 MATERIALS AND METHODS

The study was carried out in conformity with the regulations on data management of the Regional Health Authority of Emilia-Romagna, and with the Italian *Code of conduct and professional practice applying to processing of personal data for statistical and scientific purposes* (Art. 20–21, DL 196/2003) (http://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/1115480, published in the Official Journal no. 190 of August 14, 2004) which explicitly exempts the need of ethical approval for encrypted data (Preamble #8). Data were encrypted prior to the analysis at the Regional Statistical Office, where each patient was assigned a unique identifier. This identifier does not allow to trace the patient's identity and other sensitive data. As encrypted administrative data are used routinely for healthcare management, no specific written informed consent was needed to use patient's information.

2.1 Setting and study population

The study population comprised all residents of the Local Health Authority[a] of Bologna in Northern Italy (population size 866 000 in 2012) who were hospitalized for AMI between January 1, 2008 and June 30, 2011. Discharge diagnosis retrieved from hospital discharge records (HDRs)[b] was used to identify eligible patients; specifically, the diagnosis of AMI was based on the presence of one out of the 2 following criteria: a primary diagnosis of AMI (ICD-9-CM codes 410.x1) or a primary diagnosis of an AMI-related condition along with a

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[a] Local Health Authorities are vertically integrated organizations funded by the Italian regions through a capitated budget. They are responsible for a wide range of hospitals and community services in geographical areas with populations ranging 60 000 to 1000 000 inhabitants.

[b] Information contained in HDRs is transmitted by all public and private hospitals to their own region, and every 6 months from the region to the Ministry of Health. Since 1995, all HDRs have been entered in a Hospital Information System database. The database includes demographic characteristics, admission and discharge dates, admission referral source, discharge status, principal diagnosis, up to 5 secondary diagnoses, and up to 6 interventions. The HDR-DRG (Diagnosis Related Group) system is systematically used to allocate funds to hospitals and to monitor quality of care and outcomes.

secondary diagnosis of AMI (Table S1 in the Appendix). Fifth-digit 1 diagnoses were considered in order to include in the analysis only initial episodes of care of AMI.

Subsequent hospitalizations for any reason after the index discharge were investigated, and repeated admissions within 2 days of discharge were regarded as one single "episode". The reference date for the beginning of the follow-up period was thus the day of hospital discharge of the index episode, so as to investigate home care and outpatient follow-ups. The end of the observation period was considered to be either death by natural causes (ICD-9-CM codes 001–799), identified through the Regional Mortality System Database,[c] or end of the study period (December 31, 2012), whichever occurred first. In summary, the potential follow-up period varied between 1.5 and 5 years.

2.1.1 Exclusion criteria

Patients were excluded from the analysis if one of the following criteria was met:

1) Length of stay for episode of care >35 days (95th percentile); that is, very complex or instable cases;

2) Age <37 years (lower adjacent value of age), as drug prescription in very young patients might differ from standard therapy;

3) Individual follow-up <30 days, to give all patients the chance to achieve clinical stability and to guarantee a minimum observation period of one month.

4) Patients who spent more than 50% of their individual follow-up in the hospital, because drugs dispensed by the facility during inpatient treatment cannot be retrieved from the Outpatient Pharmaceutical Database, possibly leading to immeasurable time bias.[14]

[c] The Mortality Information System database includes patients' demographic characteristics as well as date, place and cause of death (classified in the ICD-9-CM).

2.2 Selection of cases and controls

Patients who experienced the study outcome (i.e., death by natural causes) during follow-up were defined as cases. Up to 8 controls were randomly selected and matched to each case with respect to age (5-year groups), sex, and duration of follow-up.[d] Thus, all controls had an equal duration of follow-up at the time of death. We chose this approach to ensure an equal time window for measuring drug exposure of cases and controls.

2.3 Drug exposure

Data on drug utilization were retrieved from the Regional Health Authority Outpatient Pharmaceutical Database, which contains information on patients (identification number, gender and age), prescriptions (substance name, Anatomical Therapeutic Chemical [ATC] Classification System code—version 2013, trade name, date of prescription filling, and number of packages) and prescribers. This register is limited to drugs prescribed out of the hospital and reimbursed by the healthcare system.

Data on filled prescriptions during the follow-up were linked with HDRs through the patient's identification code. Drugs were classified into 4 evidence-based ATC groups recommended for secondary prevention after AMI:

1) ACEIs/ARBs (ATC codes C09);

2) β-blockers (ATC codes C07);

3) Antiplatelet drugs (ATC codes B01AC);

4) Statins (ATC codes C10AA, C10BA, C10BX).

All these medications are included in the Outpatient Pharmaceutical Database, and equally available to all residents in accordance with the universal healthcare coverage provided to

[d] This technique is called "incidence density sampling". All subjects are eligible for selection as a control (including subjects who later become cases), and can also be used as controls on multiple occasions.

Italian residents. See Table S2 in the Appendix for essential information about therapeutic indications, side effects and main warnings of each of the 4 medication groups.

Drugs belonging to the same ATC group were cumulated throughout the individual follow-up, and adherence to each group was calculated using the proportion of days covered (PDC) on the basis of the Defined Daily Doses (DDDs). PDC is defined as the total number of days with possession of medication in a period of time; it avoids double counting when refills overlap with each other or oversupply of medications exists, but ignores the situations in which patients may refill their prescriptions before finishing the drug in hand and stockpile them for future use.[e]

For each of the 4 drug therapies considered, patients were subdivided a priori into 2 categories according to PDC: adherence (PDC ≥75%) and nonadherence (<75%).[12,13] Adherence to polytherapy was investigated dividing patients into 5 categories: no evidence-based drug therapy (<%75 PDC of any of the drugs), and therapy with 1, 2, 3, or 4 evidence-based drugs.

2.4 Potential confounders

We considered a number of potential confounders, measured before and at the index episode, known to be associated with mortality after AMI, and which might also influence the choice of secondary prevention medications. Specifically, we considered: index episode length of stay, ST-segment elevation (non-ST segment elevation [codes 410.71] vs. ST segment elevation [all remaining 410.x1 codes])[f] and revascularization procedures during the index episode (percutaneous coronary intervention [PCI] or bypass), as proxies of severity and intensity of care; 26 comorbidities retrieved from HDRs for both index episode and 2 years

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[e] We used PDC because physicians usually prescribe a new active ingredient when the post-AMI patient has still in hand a drug belonging to the same 4th level ATC code. We are aware that this choice can lead to an underestimation of adherence.

[f] The choice of combining ST segment elevation cases and AMIs of unspecified site was based on a preliminary Cox regression analysis.

before (Table S3 in the Appendix),[g] and use of specific drugs during the last 12 months prior to the index admission (defined as at least 3 filled prescriptions) (Table S4 in the Appendix). Comorbidities and previous drug treatments were investigated because the presence of certain conditions might increase the probability of receiving specific drug therapy, as they themselves require treatment with some of the ATC groups under study independently of AMI (e.g., statins for diabetic patients), and the presence of others might reduce drug prescription of specific ATC groups because of adverse effects and/or contraindications (e.g., β-blockers for patients with chronic obstructive pulmonary disease). Lastly, we considered the area-based index of socioeconomic position (SEP) based on 2001 Census block data (5 levels of SEP: high, medium-high, medium, medium-low, and low),[h] because some studies have demonstrated that it is associated with overall mortality and medication adherence.[15,16]

2.5 Statistical analysis

We analyzed the association between medication adherence and mortality using conditional logistic regression, which is appropriate for a time matched nested case-control design.[17] In addition to age and sex on which the logistic regression was conditioned, we considered for inclusion in the models the confounders described above. Specifically, we adopted a bootstrap backward procedure[i] to determine which factors were significantly associated with the outcome.[18] Using this approach, 200 replicated bootstrap samples[j] were selected from the original cohort. A backward procedure was applied to each replicated sample with a

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[g] Some conditions (diabetes, disorders of lipoid metabolism, hypertension, COPD) were not considered at the index episode, because they are not likely to be reported for very severe patients.

[h] SEP index considers various socioeconomic parameters (occupation, education, housing tenure and family composition). It is a composite indicator derived from factor analysis, and the 5-level classification is based on a quintile split.

[i] Bootstrap resampling allows including in the model only significant predictors which are not sensitive to a small change in the data.

[j] A bootstrap sample is a sample of the same size as the original dataset chosen with replacement. A given subject in the original cohort may occur multiple times, only once, or not at all in a specific bootstrap sample. Bootstrap methods assess the stability of models and are useful for determining the strength of the evidence that a given variable truly is an independent predictor of the outcome.

significance level of removal =5%, and only risk factors selected in at least 50% of the replicates were included as confounders in the conditional logistic regression models. The variables included in the final models are reported in table footnotes.

In the primary analysis, we compared patients adherent to 1, 2, 3 and 4 evidence-based medications with patients with no EB therapy (PDC <75% of any of the drugs). In secondary analysis, we investigated the role of each medication group under study (ACEIs/ARBs, β-blocker, antiplatelet drugs, and statins) in reducing mortality. In all these analyses, we examined the role of patient's age as an effect modifier by including interaction terms between age and drug adherence.

2.5.1 Sensitivity analyses

We carried out some sensitivity analyses to evaluate the robustness of the results. First, all analyses were replicated by restricting the study population to subjects who had not been hospitalized for AMI, other forms of ischemic heart disease, PCI, bypass, or surgery of the heart and great vessels in the 2 years before index admission (Table S3 in the Appendix). Second, we lowered the cutpoint for adherence from 75% to 60%. Lastly, the potential effect modification of time since index date was investigated: the observation period was subdivided into tertiles and an exposure by tertile interaction was included in the conditional logistic regression model.

All analyses were carried out using Stata software, version 13 (StataCorp. 2013. *Stata Statistical Software*: *Release 13*. College Station, TX: StataCorp LP).

3 RESULTS

Of the 5932 patients discharged after AMI, 4861 (81.9%) were enrolled in the study population (Figure 1). Patients' characteristics overall and by age group (<80 vs. ≥80 years) are presented in Table 1. Mean age was 72 years, 62.5% were men, and the median follow-up was 2.8 years. Forty-three percent of patients had an ST elevation AMI, 58.6% underwent PCI and 2.4% had bypass surgery. Some comorbid conditions were highly prevalent: 18.4% of patients had been previously diagnosed with hypertensive diseases, 12.3% had chronic nephropathies, 9.0% had diabetes, 8.8% had previous AMI, and 14.4% other forms of ischemic heart disease. More than two-thirds of patients (68.3%) had used antihypertensive drugs before the index AMI, while 7.7% had used drugs for obstructive airway diseases. When stratified by age group, we observed higher prevalence of prior drug therapies and comorbid conditions in very old subjects, while younger patients underwent more often PCI and bypass surgery (Table 1).

Figure 1. Patients' flow diagram

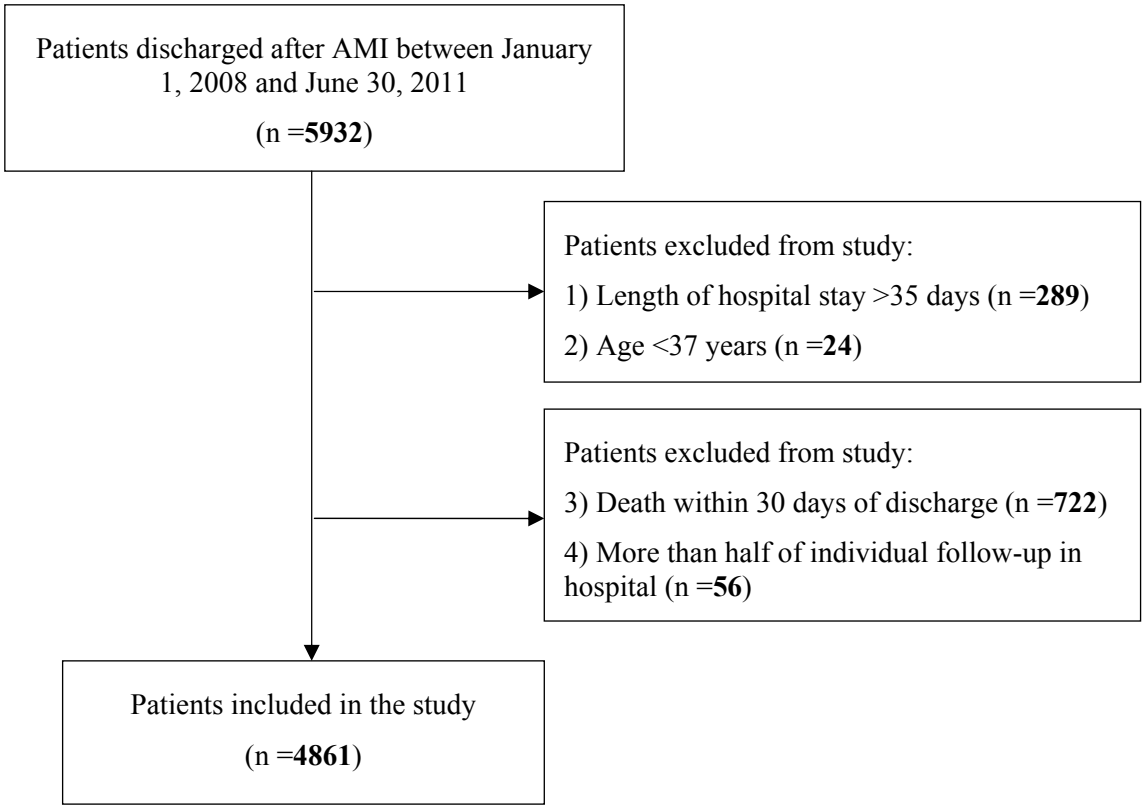


Table 1. Characteristics of post-AMI patients, overall and by age group

Characteristics	Age <80 years (n =3254)		Age ≥80 years (n =1607)		All patients (n =4861)		*P* value
	n	%	n	%	n	%	
Male	2347	72.1	692	43.1	3039	62.5	<0.001
Socioeconomic position							0.21
High	651	20.0	313	19.5	964	19.8	
Medium-high	519	16.0	257	16.0	776	16.0	
Medium	548	16.8	247	15.4	795	16.4	
Medium-low	579	17.8	295	18.4	874	18.0	
Low	711	21.9	393	24.5	1104	22.7	
Unknown	246	7.6	102	6.4	348	7.2	
ST segment elevation AMI	1552	47.7	537	33.4	2089	43.0	<0.001
Bypass surgery	97	3.0	18	1.1	115	2.4	<0.001
PCI	2240	68.8	608	37.8	2848	58.6	<0.001
Length of hospital stay							<0.001
<6 days	1384	43.2	280	17.7	1664	34.7	
6–9 days	1114	34.8	575	36.3	1689	35.3	
>9 days	707	22.1	731	46.1	1438	30.0	
Prior use of drugs							
Antidiabetic drugs	600	18.4	304	18.9	904	18.6	0.69
Drugs for cardiac therapy	376	11.6	510	31.7	886	18.2	<0.001
Drugs for obstructive airway diseases	219	6.7	153	9.5	372	7.7	<0.01
Antihypertensive drugs	1969	60.5	1350	84.0	3319	68.3	<0.001
Statins	736	22.6	382	23.8	1118	23.0	0.67
Antiplatelet drugs	1120	34.4	883	55.0	2003	41.2	<0.001
Comorbidities							
Malignant tumors	209	6.4	138	8.6	437	7.1	<0.01
Diabetes	276	8.5	162	10.1	438	9.0	0.07
Disorders of lipoid metabolism	215	6.6	87	5.4	302	6.2	0.11
Obesity	112	3.4	12	0.8	124	2.6	<0.001
Hematologic diseases	125	3.8	218	13.6	343	7.1	<0.001
Hypertensive diseases	490	15.1	402	25.0	892	18.4	<0.001
Old AMI	238	7.3	189	11.8	427	8.8	<0.001
Other forms of ischemic heart disease	388	11.9	312	19.4	700	14.4	<0.001
Ill-defined descriptions and complications of heart disease	19	0.6	11	0.7	30	0.6	0.70
Rheumatic heart disease	23	0.7	49	3.1	72	1.5	<0.001
Cardiomyopathies	86	2.6	56	3.5	142	2.9	0.10
Acute endocarditis and myocarditis	2	0.1	1	0.1	3	0.1	>0.99
Other cardiac diseases	64	2.0	56	3.5	120	2.5	<0.01
Conduction disorders and cardiac dysrhythmias	125	3.8	181	11.3	306	6.3	<0.001
Cerebrovascular diseases	176	5.4	235	14.6	411	8.5	<0.001
Vascular diseases	209	6.4	152	9.5	361	7.4	<0.001
COPD	168	5.2	148	6.2	316	6.5	<0.001
Chronic nephropathies	255	7.8	345	21.5	600	12.3	<0.001
Chronic diseases of liver, pancreas and intestine	41	1.3	19	1.2	60	1.2	0.89

Old bypass	80	2.5	64	4.0	144	3.0	<0.01
Old PCI	227	7.0	100	6.2	327	6.7	0.32
Cerebrovascular revascularization	14	0.4	12	0.8	26	0.5	0.21
Other surgery of the heart	27	0.8	7	0.4	34	0.7	0.14
Other surgery of great vessels	86	2.6	37	2.3	123	2.5	0.48
Heart failure	117	3.6	183	11.4	300	6.2	<0.001
Cardiac catheterization	6	0.2	3	0.2	9	0.2	>0.99

Note: To analyze differences in characteristics across age groups we used χ^2 test and Fisher's exact test, where appropriate.
Abbreviations: AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease.

Table 2. Medication adherence (PDC ≥75%) overall and by age group (<80 vs. ≥ 80 years) during the observation follow-up period

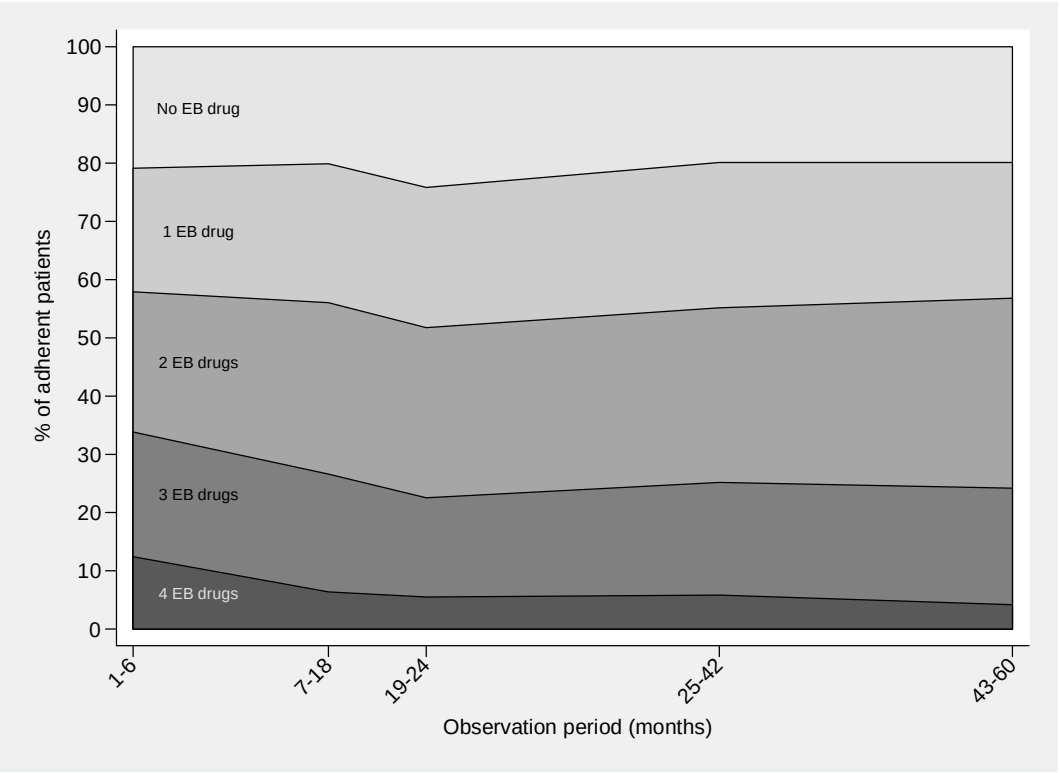
ACEIs/ ARBs	β-blockers	Antiplatelet drugs	Statins	Age <80 yrs		Age ≥80 yrs		All patients	
				n	%	n	%	N	%
Nonadherence to any of the EB drugs				463	14.2	496	30.9	959	19.7
Adherence to 1 EB drug				664	20.4	456	28.4	1120	23.0
✓				*285*	*42.9*	*202*	*44.3*	*487*	*43.5*
	✓			*24*	*3.6*	*15*	*3.3*	*39*	*3.5*
		✓		*264*	*39.8*	*223*	*48.9*	*487*	*43.5*
			✓	*91*	*13.7*	*16*	*3.5*	*107*	*9.6*
Adherence to 2 EB drugs				939	28.9	422	26.3	1361	28.0
✓	✓			*95*	*10.1*	*24*	*5.7*	*119*	*8.7*
✓		✓		*422*	*44.9*	*277*	*65.6*	*699*	*51.4*
✓			✓	*162*	*17.3*	*39*	*9.2*	*201*	*14.8*
	✓	✓		*40*	*4.3*	*23*	*5.5*	*63*	*4.6*
	✓		✓	*8*	*0.9*	*4*	*0.9*	*12*	*0.9*
		✓	✓	*212*	*22.6*	*55*	*13.0*	*267*	*19.6*
Adherence to 3 EB drugs				876	26.9	199	12.4	1075	22.1
✓	✓	✓		*186*	*21.2*	*49*	*24.6*	*235*	*21.9*
✓	✓		✓	*59*	*6.7*	*10*	*5.0*	*69*	*6.4*
✓		✓	✓	*570*	*65.1*	*125*	*62.8*	*695*	*64.7*
	✓	✓	✓	*61*	*7.0*	*15*	*7.5*	*76*	*7.1*
Adherence to 4 EB drugs				312	9.6	34	2.1	346	7.1

Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; EB, evidence-based.

Table 2 shows patients' adherence (as determined by the PDC) to 1, 2, 3, 4 or no evidence-based (EB) drug therapies during the entire observation follow-up period: 19.7% of patients used no EB drug, 23.0% used 1 drug, 28.0% used 2 drugs, 22.1% used 3 drugs, and 7.1% used all of the 4 EB drug therapies. The highest adherence was found for ACEIs/ARBs (58.7%) and antiplatelet agents (59.0%), and the lowest for β-blockers (19.6%) and statins

(36.4%). The most common polytherapies were ACEIs/ARBs plus antiplatelet drugs (14.4%), and ACEIs/ARBs plus antiplatelet drugs plus statins (14.3%). The proportion of adherence to single and combination therapies was significantly lower among patients aged 80 years or more, compared with those aged <80 years (P <0.001). Figure 2 illustrates changes in adherence to EB drugs in the 5-year observation period after AMI. The proportion of patients using a single medication (1 EB drug-group) within the first 6 months of discharge was ≈21% and remained stable over the entire observation period; on the contrary, the proportion of patients treated with 4 EB drugs fell from 12.5% to 4.1%.

Figure 2. Changes in medication adherence over the 5-year observation period



3.1 Mortality

Among the 4861 study patients, 1116 deaths occurred by natural causes (23.0%) during follow-up, yielding an overall incidence rate of 8.2/100 person-years. Cardiovascular causes[k]

[k] ICD-9-CM codes 390–459.

accounted for more than half of all natural causes (n =633), and only 35 deaths by external causes were observed.

Table 3 shows the demographic and clinical characteristics of the cases (i.e., deaths by natural causes) and matched controls. As expected, cases were more likely to have malignant tumors, diabetes, chronic nephropathies, previous AMI and other cardiovascular diseases. Furthermore, cases differed from controls in terms of previous use of drug therapies (except statins), and PCIs were less common among cases than controls. The 2 groups did not differ significantly with respect to SEP.

Table 3. Characteristics of cases and matched controls.

Characteristics	**Cases (n =1116)**		**Controls (n =8921)**		***P* value**
	n	**%**	**n**	**%**	
Socioeconomic position					0.54
High	217	19.4	1774	19.9	
Medium-high	174	15.6	1449	16.2	
Medium	157	14.1	1384	15.5	
Medium-low	222	19.9	1642	18.4	
Low	276	24.7	2074	23.3	
Unknown	70	6.3	598	6.7	
ST segment elevation AMI	365	32.7	3341	37.5	<0.01
Bypass surgery	11	1.0	156	1.8	0.06
PCI	367	32.9	4342	48.7	<0.001
Length of hospital stay					<0.001
<6 days	173	15.7	2237	25.5	
6–9 days	371	33.8	3236	36.8	
>9 days	555	50.5	3311	37.7	
Prior use of drugs					
Antidiabetic drugs	283	25.4	1572	17.6	<0.001
Drugs for cardiac therapy	387	34.7	2455	27.5	<0.001
Drugs for obstructive airway diseases	137	12.3	823	9.2	<0.01
Antihypertensive drugs	924	82.8	7114	79.7	0.02
Statins	282	25.3	2042	22.9	0.67
Antiplatelet drugs	609	54.6	4554	51.1	0.03
Comorbidities					
Malignant tumors	157	14.1	684	7.7	<0.001
Diabetes	195	17.5	763	8.6	<0.001
Disorders of lipoid metabolism	78	7.0	528	5.9	0.16
Obesity	17	1.5	140	1.6	>0.90
Hematologic diseases	191	17.1	817	9.2	<0.001
Hypertensive diseases	353	31.6	1987	22.3	<0.001
Old AMI	187	16.8	885	9.9	<0.001
Other forms of ischemic heart disease	285	25.5	1493	16.7	<0.001
Ill-defined descriptions and complications of heart disease	12	0.9	79	1.1	0.50
Rheumatic heart disease	36	3.2	223	2.5	0.15

Cardiomyopathies	51	4.6	224	2.5	0.10
Acute endocarditis and myocarditis	2	0.2	4	0.04	0.14
Other cardiac diseases	40	3.6	269	3.0	0.31
Conduction disorders and cardiac dysrhythmias	159	14.3	742	8.3	<0.001
Cerebrovascular diseases	180	16.1	977	11.0	<0.001
Vascular diseases	150	13.4	735	8.2	<0.001
COPD	156	14.0	703	7.9	<0.001
Chronic nephropathies	302	27.1	1442	16.2	<0.001
Chronic diseases of liver, pancreas and intestine	22	2.0	88	1.0	<0.01
Old bypass	64	5.7	288	3.2	<0.001
Old PCI	94	8.4	640	7.2	0.13
Cerebrovascular revascularization	4	0.4	61	0.7	0.24
Other surgery of the heart	14	1.3	49	0.6	<0.01
Other surgery of great vessels	51	4.6	195	2.2	<0.001
Heart failure	181	16.2	697	7.8	<0.001
Cardiac catheterization	4	0.4	15	0.2	0.15

Note: To analyze differences in characteristics across age groups we used χ^2 test and Fisher's exact test, where appropriate. We do not report age, sex and duration of follow-up (i.e., matching variables).

3.2 Effect of medication adherence on mortality

Table 4 shows the results of the primary analysis. The unadjusted relationship between medication exposure and mortality exhibited a dose-response gradient; that is, compared with no EB drug-group, rate ratios of death linearly decreased as the number of EB drugs taken increased. After adjusting for significant baseline characteristics, results did not change appreciably: compared with patients with no EB drug therapy after AMI, the risk of mortality was 29% lower among those with 1 EB drug and 87% lower among those treated with all EB drugs.

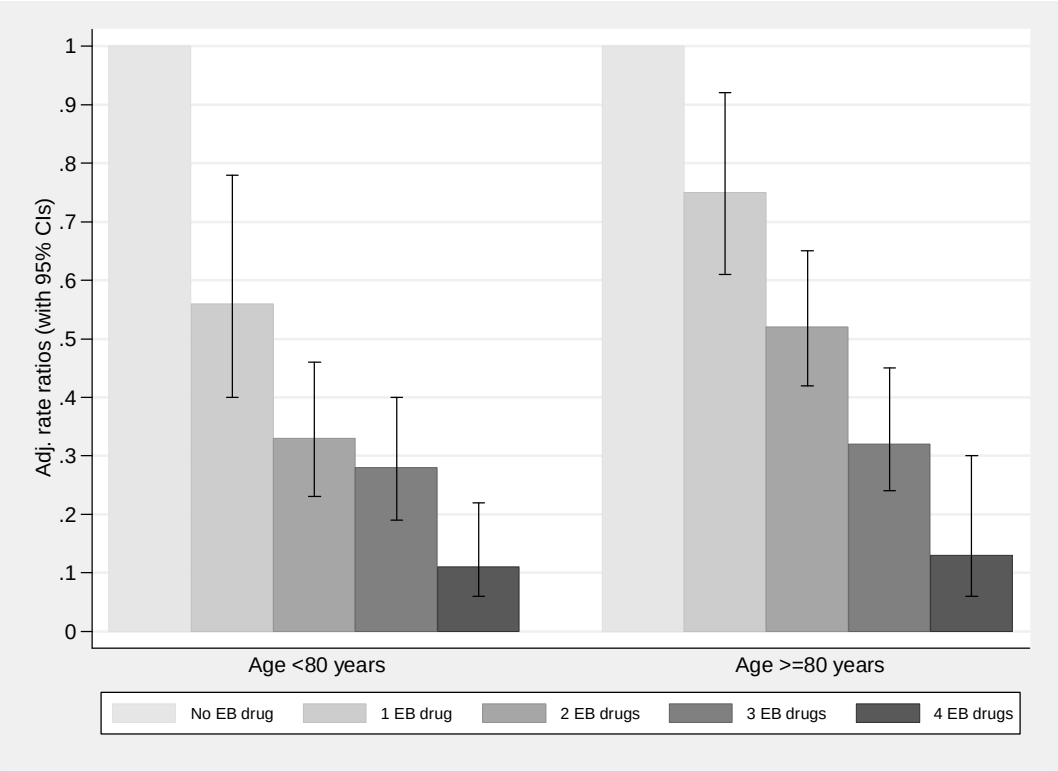
Table 4. Crude and adjusted association of medication adherence (PDC ≥75%) with mortality estimated by conditional logistic regression model.

Drug exposure	**Crude rate ratio**	**95% CI**	***P* value**	**Adjusted* rate ratio**	**95% CI**	***P* value**
No EB drug	1.00		<0.001†	1.00		<0.001†
1 EB drug	0.66	0.56–0.78	<0.001	0.71	0.60–0.84	<0.001
2 EB drugs	0.39	0.32–0.46	<0.001	0.46	0.38–0.55	<0.001
3 EB drugs	0.24	0.19–0.30	<0.001	0.32	0.25–0.41	<0.001
4 EB drugs	0.08	0.05–0.13	<0.001	0.13	0.08–0.21	<0.001

*Adjusted for significant covariates, including age, PCI and bypass at index episode, length of index episode, previous use of antidiabetic drugs, malignant tumors, diabetes, hematologic diseases, old AMI, conduction disorders and cardiac dysrhythmias, vascular diseases, chronic nephropathies, and old bypass.
†Test for linear trend across drug exposure groups.
Abbreviations: CI, confidence interval.

As shown in Figure 3, mortality benefits associated with adherence to single and combination therapies were significant for both patients aged ≥80 years and those aged <80 years, although the effect of single and double therapies (1 and 2 EB drug groups) was more evident among patients of <80 years of age. However, no significant effect modification by age was found.

Figure 3. Adjusted rate ratios of death (with 95% CIs) as a function of medication adherence by age group (<80 vs. ≥ 80 years)



Note: No EB drug is the reference group. Rate ratios of death for <80-year group were adjusted for PCI and bypass at index episode, length of index episode, previous use of drugs for obstructive airway diseases, malignant tumors, diabetes, disorders of lipoid metabolism, COPD, and chronic nephropathies. Rate ratios of death for ≥80-year group were adjusted for age, PCI at index episode, length of index episode, previous use of antidiabetic drugs, malignant tumors, hematologic diseases, old AMI, conduction disorders and cardiac dysrhythmias, chronic nephropathies, chronic diseases of liver, pancreas and intestine, and old bypass surgery.

In a secondary multivariate analysis, we investigated the role of each medication group under study (ACEIs/ARBs, β-blockers, antiplatelet drugs and statins) in reducing mortality. We found a significant overall association between the four medication groups and mortality, although the magnitude of this association was higher for ACEIs/ARBs (adj. rate ratio =0.60; 95% CI =0.52–0.69; *P* <0.001) and statins (adj. rate ratio =0.60; 95% CI =0.50–0.72; *P* <0.001), and lower for β-blockers (adj. rate ratio =0.75; 95% CI =0.61–0.92; *P* <0.01) and antiplatelet drugs (adj. rate ratio =0.73; 95% CI =0.63–0.84; *P* <0.001). As expected, drugs

were more effective in reducing mortality when administered as combination therapies: Table 5 provides the rate ratios of death for the single and combination therapies most commonly observed among cases and matched controls (n >900).

Table 5. Adjusted association of adherence to single and combination therapies (PDC ≥75%) with mortality estimated by conditional logistic regression model

Drug exposure	Adjusted* rate ratio	95% CI	*P* value
No EB drug	1.00		
ACEIs/ARBs only	0.61	0.48–0.77	<0.001
Antiplatelet drugs only	0.80	0.63–0.96	0.02
ACEIs/ARBs plus antiplatelet drugs	0.43	0.35–0.54	<0.001
ACEIs/ARBs plus antiplatelet drugs plus statins	0.27	0.20–0.36	<0.001

*Adjusted for significant covariates, including age, PCI and bypass at index episode, length of index episode, previous use of antidiabetic drugs, malignant tumors, diabetes, hematologic diseases, old AMI, conduction disorders and cardiac dysrhythmias, vascular diseases, chronic nephropathies, and old bypass.
Note: We present rate ratios only for single and combination therapies with adequate sample size (n >900).

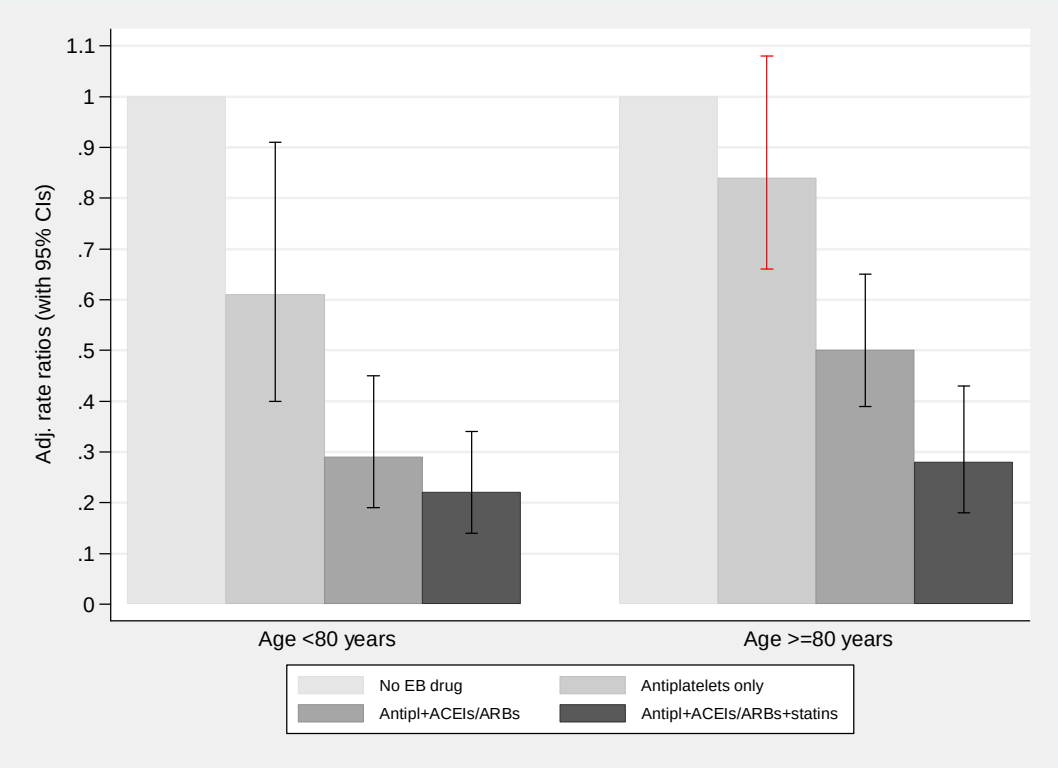
Lastly, because of an interaction term (*P* =0.01) between antiplatelet drug exposure and patient's age, an age-stratified analysis was carried out. In older age the overall effect of antiplatelet therapy on mortality was weaker (<80-year-old: adj. rate ratio = 0.60, 95% CI =0.46–0.77, *P* <0.001; ≥80-year-old: adj. rate ratio = 0.80, 95% CI =0.67–0.95, *P* =0.01) and, as illustrated in Figure 4, single use of antiplatelet drugs was associated with a lower mortality for <80-year patients (adj. rate ratio =0.61; 95% CI =0.40–0.91; *P* =0.02), but not for ≥80-year patients (adj. rate ratio =0.84; 95% CI =0.66–1.08; *P* =0.18).

3.2.1 Sensitivity analyses

To support the external validity of this study, we restricted the analyses to the 3817 incident cases of AMI, more similar to the "standard population" for whom treatment guidelines are tailored. As shown in Table S5 in the Appendix, results did not change appreciably: polytherapies were highly effective in reducing mortality, and a dose-response relationship was found between medication exposure and mortality. ACEIs/ARBs, antiplatelet drugs and statins proved to be effective in reducing mortality, whereas adherence to β-blockers did not achieve statistical significance because of the limited sample size (Table S6 in the Appendix).

Secondly, we lowered the PDC cutoff from 75% to 60% because prescribed daily doses (PDDs) for secondary prevention after AMI are generally lower than DDDs, possibly leading to misclassification bias. As shown in Table S7 and Table S8 in the Appendix, lowering the cutoff led to results consistent with those of the of primary and secondary analyses, although the adjusted relationship between reduced mortality and single medication therapy was no more statistically significant (Table S7).

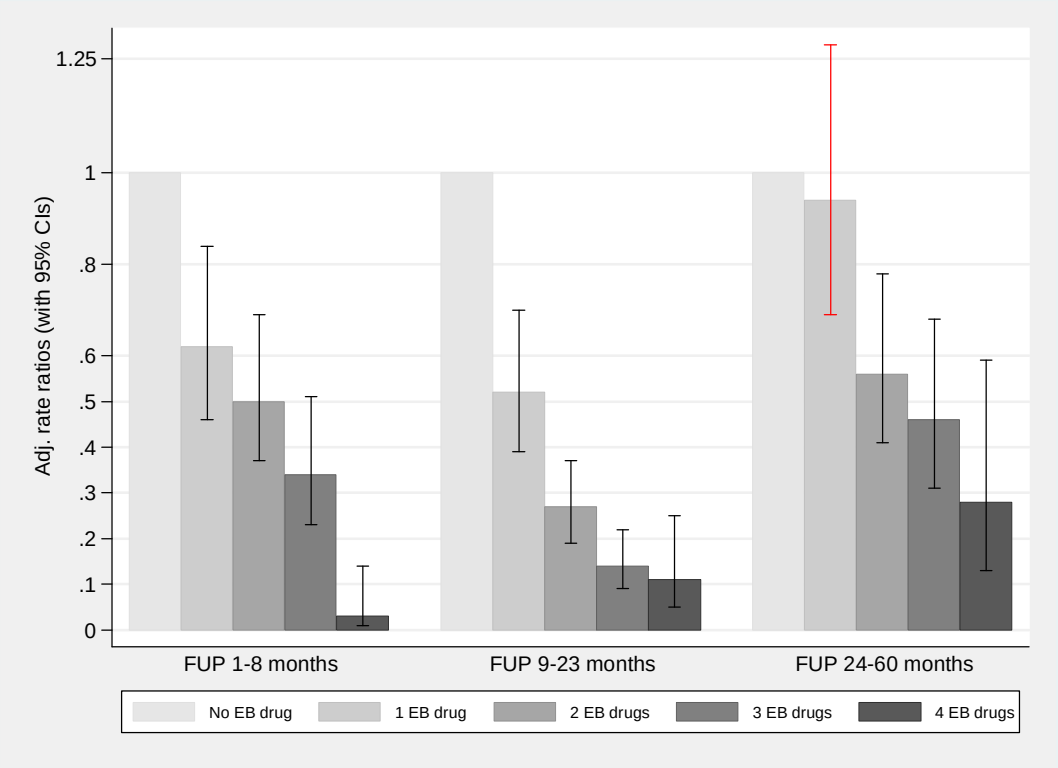
Figure 4. Adjusted rate ratios of death (with 95% CIs) as a function of adherence to antiplatelet medication by age group (<80 vs. ≥80 years)



Note: Rate ratio with red CI is not significantly different from 1 (α =5%). Rate ratios of death for <80-year group were adjusted for PCI and bypass at index episode, length of index episode, previous use of antiplatelet drugs, malignant tumors, diabetes, disorders of lipoid metabolism, COPD, and chronic nephropathies. Rates ratios of death for ≥80-year group were adjusted for age, PCI and bypass at index episode, length of index episode, previous use of antidiabetic drugs, hematologic diseases, old AMI, conduction disorders and cardiac dysrhythmias, vascular diseases, chronic diseases of liver, pancreas and intestine, and old bypass.

After stratification by tertile of observation period (short-term: 1–8 months; medium-term: 9–23 months; long-term: 24–60 months), the protective effect of polytherapy on mortality was confirmed, although it was more evident in the short-term period (Figure 5). On the contrary, we found a significant interaction between use of single therapies and time since index date (P =0.03); specifically, single therapy proved to be associated with short- and medium-term mortality, but not with long-term mortality (Figure 5).

Figure 5. Adjusted rate ratios of death (with 95% CIs) in short-, medium- and long-term observation period, as a function of medication adherence



Note: cut-off points were based on a tertile split. Rate ratio with red CI is not significantly different from 1 (α =5%). Rate ratios were adjusted for age, PCI and bypass at index episode, length of index episode, previous use of antidiabetic drugs, malignant tumors, diabetes, hematologic diseases, old AMI, conduction disorders and cardiac dysrhythmias, vascular diseases, chronic nephropathies, and old bypass.
Abbreviations: FUP, follow-up.

4 DISCUSSION

In this population-based study, we found that EB pharmacotherapy is effective in reducing mortality following AMI. Specifically, we observed a dose-type response gradient of mortality reduction with increasing number of EB drugs taken. Other observational studies of the impact of combination therapies on post-AMI long-term mortality had similar results,[10-12,19] but did not investigate whether the magnitude of this relationship differed as a function of patients' age. To this aim, we stratified analyses by age group and found that mortality benefits associated with EB polytherapies were significant for both patients aged ≥80 years and those aged <80 years, even after 2 years of follow-up. This result suggests that the beneficial effect of combined use of the 4 EB drug therapies—as recommended by guidelines[1,20]—is evident also in nontrial older populations. However, prior studies have shown that medication nonadherence among older people is common,[4,9,21] and our findings further support that very few octogenarians and older patients were adherent to the 4 EB drug therapies (2.1%). These data imply that quality improvement efforts should be made to include medication adherence as a key component of secondary prevention care in addition to prescription of indicated medications.[4] These efforts include taking into consideration other medications the patient must take, scheduling when doses are to be taken, providing individualized medication education, helping the patient select a reminder cue, and ensuring regular follow-up with clinical pharmacists.[22,23]

Meta-analyses of randomized clinical trials of secondary prevention found that β-blocker use was associated with a 23% relative risk reduction in all-cause mortality, while the magnitude of relative mortality risk reductions ascribable to ACEIs/ARBs and statins was mildly lower (13% and 21%, respectively).[1] On the contrary, our study demonstrated modest superiority of ACEIs/ARBs and statins over β-blockers. Indeed, the evidence of benefits associated with β-blocker use is mostly from trials predating the advent of modern reperfusion therapy,[24] and some authors have argued that the incremental survival benefits associated with β-blockers in the era of early revascularization might be less pronounced than those observed for other

EB medications, especially among lower risk AMI populations with preserved left ventricular function.[25]

An interesting finding of the present study is the differential effect of antiplatelet therapy on mortality by age group. Specifically, we found a 40% risk reduction in mortality among elderly and adults, and a 20% risk reduction among octogenarians and older patients. We know from the Global Registry of Acute Coronary Events (GRACE) and the Thrombolysis in Myocardial Infarction (TIMI) Study Group that older patients are at higher risk of bleeding episodes.[26,27] Not only does bleeding result in an immediate threat, but it is also associated with increased coronary artery disease mortality and reinfarction, both in the short and the long term.[28] Thus, it is reasonable to infer that the risk-benefit ratio associated with antiplatelet therapy is less favorable for very old subjects than for elderly and adults. Our finding suggests that the management of secondary prevention after AMI in older patients should balance the risk of recurrent acute coronary syndrome episodes and the risk of bleeding. Such a strategy includes assessing the individual risk of bleeding, selecting the antiplatelet agent that is best for the patient, using the correct dose of medications, recognizing the early signs of bleeding and using gastroprotective agents to minimize upper gastrointestinal bleeding. [28]

4.1 Strengths and limitations

This study has some noteworthy strengths. First, both exposure and covariate definitions were time dependent because we used a risk set sampling that attributes the same length of observation to case and matched controls and ensures an equal time window to measure exposure; in this way we prevented time-related bias, which may produce illusory results in favor of the treatments under study.[29,30] Second, drug exposure was prospectively collected, removing the possibility of recall bias.[31] Third, we did several sensitivity analyses which, overall, produced results consistent with those of the primary and secondary analyses.

This study has also several limitations. First, we were unable to track relevant clinical information (e.g., body mass index and severity of AMI). Although our analyses were

adjusted for many factors including SEP, comorbid conditions, and concomitant and preexisting use of EB therapies, it is possible that the lack of more detailed clinical data leaves room for residual confounding. In sensitivity analysis, we tried to address this limitation by restricting the study population to cases with no history of AMI and coronary disease—that is, a subgroup of "clinically homogeneous" patients. Of note, results did not change appreciably and the trend of mortality reduction with increasing number of EB drugs was still evident.

Second, we had no information on lifestyle behaviors (e.g., smoking, diet, and physical activity); nonetheless, available evidence has shown that adherence-related mortality benefits associated with evidence-based medication are mediated by drug effects more than by generic health adherer behavioral attributes.[32]

Third, we used pharmacy data on filled prescriptions to estimate adherence, but had no information on actual medication consumption. Furthermore, DDDs may have caused an underestimation of adherence, because they are generally higher than PDDs for secondary prevention after AMI. However, when we lowered the cutoff of adherence from 75% to 60% results remained stable.

Lastly, our study is based on post-AMI patients resident in the Local Health Authority of Bologna, the capital of Emilia-Romagna region in Italy. Nevertheless, our study is comprehensive, consisting of all patients in one of the largest Local Health Authorities of Italy, and there is no reason to deem that our findings would not be generalizable to other jurisdictions that have similar drug reimbursement policies to that of Italy.

4.2 Conclusions

This population-based study indicates that the beneficial effect of EB polytherapy on long-term mortality following AMI is evident also in nontrial older populations. Given that adherence to combination therapies has been shown to be largely suboptimal, the

implementation of strategies and initiatives to increase the use of post-AMI secondary preventive medications in old patients is crucial.

APPENDIX

Table S1. ICD-9-CM codes for identification of AMI cases: primary diagnosis of AMI (410.x1) or secondary diagnosis of AMI (410.x1) associated with one of the following conditions as primary diagnosis

ICD-9-CM code	Condition
411	Other acute and sub-acute forms of ischemic heart disease
413	Angina pectoris
414	Other forms of chronic ischemic heart disease
423.0	Hemopericardium
426	Conduction disorders
427	Cardiac dysrhythmias
428	Heart failure
429.5	Rupture of chordae tendineae
429.6	Rupture of papillary muscle
429.71	Acquired cardiac septal defect
429.79	Certain sequelae of myocardial infarction not elsewhere classified other
429.81	Other disorders of papillary muscle
518.4	Acute edema of lung unspecified
518.81	Acute respiratory failure
780.01	Coma
780.2	Syncope and collapse
785.51	Cardiogenic shock
799.1	Respiratory arrest
997.02	Iatrogenic cerebrovascular infarction or hemorrhage
998.2	Accidental puncture or laceration during a procedure

Abbreviations: ICD-9-CM, International Classification of Diseases (Clinical Modification, 9th revision); AMI, acute myocardial infarction.

Table S2. Therapeutic indications, side effects and main warnings for post-AMI secondary prevention medications

ACEIs
Therapeutic indications: Essential hypertension, acute coronary syndrome with ST segment elevation, chronic heart failure, diabetic nephropathy.
Side effects: The most common side effect is dry cough due to increased levels of bradykinin.
Main warnings: In some patients, administration of ACEIs can cause fast arterial pressure-relieving, especially when they also take diuretics. Do not prescribe to patients allergic to ACEIs; to be avoided during pregnancy.

ARBs
Therapeutic indications: Hypertension, heart failure, diabetic nephropathy.
Side effects: No important side effect is related to ARBs use; sometimes hypotension can occur.
Main warnings: To be avoided during pregnancy and breastfeeding; pay attention if the patient has a diagnosis of renal artery stenosis.
Note: *Weak evidence of carcinogenic effects and low efficacy in comparison with ACEIs put this class as a second choice in recent local recommendations.*

β-blockers

Therapeutic indications: Angina pectoris, heart attack, arrhythmia, chronic heart failure, hypertension.
Side effects: Bronchoconstriction, bradycardia, hypoglycemia, fatigue, cold hands and feet, sleep disturbance and nightmares.
Main warnings: To be avoided if the patient has a history of asthma; pay attention to patients with a diagnosis of diabetes.

Antiplatelet drugs
Therapeutic indications: AMI, prevention of angina, myocardial infarction and claudicatio, after bypass implantation and angioplasty or stenting of coronary artery.
Side effects: Aspirin can cause dyspepsia and peptic ulcer disease. When additional risk factors are present, gastroprotective therapy can be associated.
Main warnings: If gastric disorders occur, give clopidogrel instead of aspirin.

Statins
Therapeutic indications: Secondary prevention of myocardial infarction and ictus, severe dyslipidemia.
Side effects: Skeletal muscles disorders (myalgia, myositis, myopathy), increased levels of hepatic enzymes, insomnia, rashes.
Main warnings: Pay attention if patients have a history of hepatic disease or abnormal use of alcohol.

Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Table S3. ICD-9-CM codes for identification of comorbid conditions

Condition	ICD-9-CM codes	
	AMI episode	Hospital admissions in the previous 2 years
Malignant tumors	140.0–208.9, V10	140.0–208.9, V10
Diabetes		250.0–250.9
Disorders of lipoid metabolism		272
Obesity	278.0	278.0
Hematologic diseases	280–285, 288, 289	280–285, 288, 289
Hypertensive diseases		401–405
Old AMI	412	410, 412
Other forms of ischemic heart disease		411, 413, 414
Ill-defined descriptions and complications of heart disease		429
Rheumatic heart disease	393–398	391, 393–398
Cardiomyopathies	425	425
Acute endocarditis and myocarditis		421, 422
Other cardiac diseases	745, V15.1, V42.2, V43.2, V43.3, V45.0	745, V15.1, V42.2, V43.2, V43.3, V45.0
Conduction disorders and cardiac dysrhythmias		426, 427
Cerebrovascular diseases	433, 437, 438	430–432, 433, 434, 436, 437, 438
Vascular diseases	440–448 (except 441.1, 441.3, 441.5, 441.6, 444), 557.1	440–448, 557

COPD		491–492, 494, 496
Chronic nephropathies	582–583, 585–588	582–583, 585–588
Chronic diseases of liver, pancreas and intestine	571–572, 577.1–577.9, 555, 556	571–572, 577.1–577.9, 555, 556
Old bypass surgery	V45.81	V45.81, 36.1
Old PCI	V45.82	V45.82, 36.0, 00.66
Cerebrovascular revascularization		00.61, 00.62, 38.01, 38.02 38.11, 38.12, 38.31, 38.32
Other surgery of the heart		35, 37.0, 37.1, 37.3, 37.4, 37.5, 37.6, 37.9
Other surgery of great vessels		38–39.5 (except 38.01, 38.02, 38.5, 38.11, 38.12, 38.31, 38.32, 38.93)
Heart failure		428
Cardiac catheterization	38.93	

Abbreviations: COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention.

Table S4. Medication use over 12 months before AMI

Medication	**ATC codes**
Antidiabetic drugs	A10
Drugs for cardiac therapy	C01
Drugs for obstructive airway diseases	R03
Antihypertensive drugs	C02 (antihypertensive drugs), C03 (diuretics), C07 (β-blockers), C08 (calcium channel blockers), C09 (ACEIs/ARBs)
Statins	C10AA
Antiplatelet drugs	B01AC

Table S5. Crude and adjusted association of medication adherence (PDC ≥75%) with mortality estimated by conditional logistic regression model (only incident cases of AMI)

Drug exposure	**Crude rate ratio**	**95% CI**	***P* value**	**Adjusted* rate ratio**	**95% CI**	***P* value**
No EB drug	1.00		<0.001†	1.00		<0.001†
1 EB drug	0.66	0.54–0.81	<0.001	0.70	0.57–0.87	<0.01
2 EB drugs	0.38	0.31–0.48	<0.001	0.45	0.36–0.56	<0.001
3 EB drugs	0.24	0.18–0.31	<0.001	0.31	0.23–0.42	<0.001
4 EB drugs	0.09	0.05–0.16	<0.001	0.13	0.07–0.24	<0.001

*Adjusted for significant covariates, including age, ST segment elevation, PCI and bypass at index episode, length of index episode, previous use of antidiabetic drugs, malignant tumors, diabetes, chronic nephropathies, and heart failure.
†Test for linear trend across drug exposure groups.
Note: We excluded patients hospitalized for AMI, other cardiac disease, PCI, bypass or surgery of the heart and great vessels before index admission (n =1044).
Abbreviations: CI, confidence interval.

Table S6. Adjusted association of medication adherence to the 4 medication groups (PDC ≥75%) with mortality (only incident cases of AMI)

Drug exposure	Adjusted* rate ratio	95% CI	*P* value
ACEIs/ARBs			
Nonadherence	1.00		
Adherence	0.57	0.48–0.69	<0.001
β-blockers			
Nonadherence	1.00		
Adherence	0.88	0.68–1.13	0.32
Antiplatelet drugs			
Nonadherence	1.00		
Adherence	0.70	0.59–0.84	<0.001
Statins			
Nonadherence	1.00		
Adherence	0.60	0.47–0.75	<0.001

*Adjusted for significant covariates, including age, ST segment elevation, PCI and bypass at index episode, length of index episode, previous use of antidiabetic drugs, malignant tumors, diabetes, chronic nephropathies, and heart failure.
Note: We excluded patients hospitalized for AMI, other cardiac disease, PCI, bypass or surgery of the heart and great vessels before index admission (n =1044).

Table S7. Crude and adjusted association of medication adherence (PDC ≥60%) with mortality estimated by conditional logistic regression model

Drug exposure	Crude rate ratio	95% CI	*P* value	Adjusted* rate ratio	95% CI	*P* value
No EB drug	1.00		<0.001†	1.00		<0.001†
1 EB drug	0.77	0.63–0.93	<0.01	0.85	0.70–1.04	0.13
2 EB drugs	0.53	0.44–0.64	<0.001	0.61	0.50–0.74	<0.001
3 EB drugs	0.25	0.20–0.30	<0.001	0.32	0.26–0.40	<0.001
4 EB drugs	0.14	0.10–0.18	<0.001	0.21	0.15–0.28	<0.001

*Adjusted for significant covariates, including age, PCI and bypass at index admission, length of index episode, previous use of antidiabetic drugs, malignant tumors, diabetes, hematologic diseases, old AMI, conduction disorders and cardiac dysrhythmias, vascular diseases, chronic nephropathies, and old bypass.
†Test for linear trend across drug exposure groups.

Table S8. Adjusted association of medication adherence to the 4 medication groups (PDC ≥60%) with mortality (only incident cases of AMI)

Drug exposure	Adjusted* rate ratio	95% CI	*P* value
ACEIs/ARBs			
Nonadherence	1.00		
Adherence	0.57	0.50–0.66	<0.001
β-blockers			
Nonadherence	1.00		
Adherence	0.65	0.55–0.77	<0.001
Antiplatelet drugs			
Nonadherence	1.00		
Adherence	0.80	0.69–0.94	<0.01

Statins			
Nonadherence	1.00		
Adherence	0.69	0.58–0.81	<0.001

*Adjusted for significant covariates, including age, PCI and bypass at index admission, length of index episode, previous use of antidiabetic drugs, malignant tumors, diabetes, hematologic diseases, old AMI, conduction disorders and cardiac dysrhythmias, vascular diseases, chronic nephropathies, and old bypass.

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