Effect of comorbidity on coronary reperfusion strategy and long-term mortality after acute myocardial infarction

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Background Chronic comorbidity is a prognostic determinant in ST-segment elevation myocardial infarction (STEMI). This study was aimed at determining to what extent this effect is independent or derives from adoption of different therapeutic strategies.

Methods Seven hundred forty patients with STEMI hospitalized within 12 hours of symptom onset were enrolled in a population-based registry, in a health district comprising 1 teaching hospital with and 5 district hospitals without percutaneous coronary intervention (PCI) facilities. Three categories of increasing chronic comorbidity score (CS-1, n = 259; CS-2, n = 235; CS-3, n = 246) were identified from age-adjusted associations of comorbidities with 1-year survival.

Results Higher CS was associated with lower direct admission or transferal rates to hospital with PCI. Coronary reperfusion therapy (PCI in 91.5% of 470 cases) was adopted less frequently ($P < .001$) in CS-3 (41.9%) than CS-2 (69.4%) or CS-1 (78.8%). Compared with conservative therapy (n = 270), reperfusion therapy reduced 1-year mortality in the whole series not significantly ($P = .816$) in CS-1 but significantly in CS-2 ($P = .012$) and CS-3 ($P = .001$). This trend persisted after adjusting for age, Killip class, and acute myocardial infarction location (hazard ratio [HR] = 0.63 [95% CI 0.14-2.80], HR = 0.62 [95% CI 0.31-1.25], and HR = 0.47 [95% CI 0.26-0.86] in CS-1, CS-2, and CS-3, respectively). By hypothesizing an extension of coronary reperfusion therapy utilization rate in CS-2 and CS-3 to that in CS-1, from 21 (crude analysis) to 20 (adjusted analysis) deaths were classified as potentially avoidable.

Conclusion Increased mortality in patients with chronic comorbidity and STEMI derives, at least in part, from underutilization of coronary reperfusion therapy, and might be reduced with a more aggressive therapeutic approach. (Am Heart J 2006;151:1094-1100.)

Compared to conservative therapy, coronary reperfusion with early thrombolysis during acute myocardial infarction (MI) improves several clinically valuable outcomes and has therefore been included for several years[1] as a class I recommendation in treatment guidelines of ST-segment elevation MI (STEMI). Guidelines also indicate that primary percutaneous coronary intervention (PCI), when performed rapidly in high-volume centers, is to be preferred over thrombolysis.[1] Evidence suggests that in selected populations, such as older patients[2,3] and those with previous coronary artery bypass grafting (CABG) or cardiogenic shock, PCI may produce better results than thrombolysis.[4] Nevertheless, even in well-developed health care systems, many eligible patients do not receive either thrombolysis or PCI,[5] particularly when they are older[6] or when they present with previous MI, chronic hearth failure, or other comorbidities.[7,8] Scoring systems proposed for risk stratification have revealed that chronic comorbidity independently predicts adverse long-term outcomes after MI.[9] Based on these premises, scoring systems for standardized assessment of comorbidity should enable

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identification of patients at high risk of both coronary reperfusion treatment underutilization and unfavorable long-term prognosis.

The Florence Acute Myocardial Infarction (AMI-Florence) registry is a population-based, prospective observational study carried out in Florence (Italy), where primary PCI is the most widely used coronary reperfusion treatment of MI.[10] In a previous analysis of this registry,[10] several preexisting comorbid conditions were independent negative predictors of coronary reperfusion therapy utilization, but we did not analyze the specific advantage of coronary reperfusion across subgroups with different burdens of comorbidities. The present analysis was aimed at evaluating the impact of different levels of chronic comorbidity on utilization of coronary reperfusion therapy and prognosis in patients with STEMI admitted to hospital within 12 hours of symptom onset.

Methods

Patient population

The design of the AMI-Florence registry has been detailed elsewhere.[10] Briefly, the Florence health district (about 800 000 inhabitants) comprises 5 community hospitals and 1 teaching hospital, the latter implementing high-volume programs for primary PCI (fully operative 24 h/d, 7 d/wk). All residents in the Florence area arriving alive to the emergency department of 1 of the 6 hospitals between March 2000 and February 2001 with a suspected STEMI were prospectively screened for eligibility and enrolled (N = 920)[10] in the study if, in accordance with the 1999 American College of Cardiology/American Heart Association guidelines,[1] MI was confirmed by ST-segment elevation ≥0.1 mV in ≥2 adjacent leads or new onset left bundle-branch block and typical chest pain for >30 minutes or total CPK increased to >2 times the upper normal limit within 72 hours. The present analysis is based on 740 of the 920 patients hospitalized within 12 hours of symptom onset.

Data collection

Standardized information was collected on demographics, medical history (with particular attention to MI, angina, CABG, sustained cardiac arrhythmias, or chronic heart failure; peripheral artery disease; stroke; depression; diabetes; chronic renal failure [creatinine >1.5 mg/dL]; chronic obstructive pulmonary disease; and active [<5 years] cancer), clinical and electrocardiographic features of MI, time delay to hospital admission, inhospital treatment, and outcome. To obtain a really population-based study, enrolling all incident MI cases in the area, the completeness of enrollment was checked through the regional hospital discharge system. One-year life status was assessed by consulting patients' municipalities of residence.

Comorbidity score

A chronic comorbidity score (CS) was developed from medical history through the following steps: (1) the association of each chronic comorbid condition with 1-year probability of death was assessed in age-adjusted Cox proportional hazard models, where β coefficients and standard error (SE) indicate, respectively, the strength and the precision of the association (e^{β} represents an estimate of the hazard ratio [HR]); (2) the β coefficient/SE ratio (also called Wald test),[11] which by definition is directly proportional to the strength of the association and inversely proportional to its variability, was taken to represent a disease-specific score assessing the impact of comorbidities on 1-year prognosis. The Wald test, commonly used to determine the significance of β coefficients, is a Z test, transforming the original distribution into one where the mean and SD become 0 and 1, respectively. This standardization allows for comparing the relative weight of variables with different distributions; (3) a summary CS was calculated for each patient by summing his/her disease-specific scores. The resulting CS tertiles were taken to identify 3 categories (from CS-1 to CS-3) of patients with increasing burden of chronic comorbidity.

Statistical analysis

Categorical and continuous variables were compared with 2-tailed χ^2 and Student t test, respectively. $P < .05$ was considered statistically significant. The indication to primary PCI or thrombolysis was left to attending physicians. However, because in the study area thrombolysis was used in a minority of cases,[10] for the purpose of the present analysis, PCI and thrombolysis were grouped into a single "coronary reperfusion therapy" variable. Survival analyses were carried out for the whole series and within each CS category, determining survival curves with the Kaplan-Meier method and analyzing differences with the log-rank test. Cox models were calculated to assess the effect of treatment and of demographic and clinical variables on 1-year survival. To this purpose, HRs and 95% CIs were calculated for each covariate, while adjusting for all the other covariates. The proportional assumption central to the Cox model was examined by inspecting log-cumulative hazard curves for nonparallelism. Analyses were carried out using STATA statistical package 6.0 (Stata Corporation, College Station, TX, 1999).

Potentially avoidable deaths

In general, deaths are classified as "avoidable" when they might be prevented by promoting lifestyle modification and early detecting and blocking the progression of a certain disease.[12] We defined the potentially avoidable death fraction as the proportion of deaths that might have been avoided by increasing utilization of coronary reperfusion to the highest possible level. Because an intervention is rarely applicable to the totality of a population, we hypothesized that the highest frequency of coronary reperfusion recorded in any of the 3 CS categories would represent the maximal frequency applicable in the real clinical world. Based on this hypothesis, we determined the potential effect of increasing utilization of coronary reperfusion therapy to the same level in the other CS categories. Following these assumptions and maintaining the therapy-specific mortality observed in each CS category unchanged, we first calculated a crude number of potentially avoidable deaths within each category. Adjusting the mortality reduction associated with coronary reperfusion for the other significant predictors of 1-year mortality from Cox models, the potentially avoidable death fraction for each CS category was calculated from the following formula:

Table I. Age-adjusted bivariate association of chronic comorbid conditions with 1-year mortality in 740 patients with STEMI

Condition	Patients with condition, n (%)	Cox analysis, β (SE)	Disease-specific score, (β/SE)
Chronic heart failure	60 (8.1)	.928 (.214)	4.336
Cancer, onset ≤5 y	19 (2.6)	1.025 (.347)	2.954
Stroke	59 (8.0)	.670 (.231)	2.900
Peripheral artery disease	91 (12.3)	.610 (.214)	2.850
Angina, onset >1 m	146 (19.7)	.508 (.200)	2.540
Diabetes	165 (22.3)	.389 (.196)	1.985
CABG	12 (1.6)	1.008 (.511)	1.973
Depression	33 (4.5)	.559 (.329)	1.699
Previous MI	117 (15.8)	.353 (.208)	1.697
Cardiac arrhythmias	116 (15.7)	.313 (.203)	1.542
COPD	75 (10.1)	.306 (.239)	1.280
Renal failure*	62 (8.4)	.305 (.247)	1.235
Angina, onset ≤1 m	132 (17.8)	.218 (.263)	0.829
Cancer, onset >5 y	35 (4.7)	.094 (.367)	0.256

COPD, Chronic obstructive pulmonary disease.
* Serum creatinine >1.5 mg/dL.

Table II. Baseline clinical characteristics and outcome, by chronic CS category

	Comorbidity score categories			
Variable	**CS-1 (n = 259)**	**CS-2 (n = 235)**	**CS-3 (n = 246)**	***P***
Sex, males	176 (68.0)	172 (73.2)	169 (68.7)	.398
Age, mean (SD)	64.2 (13.5)	69.7 (12.2)	74.8 (10.7)	.001
Killip class				
1	223 (86.1)	174 (74.0)	139 (56.5)	
2-3	27 (10.4)	49 (20.9)	86 (35.0)	.000
4	9 (3.5)	12 (5.1)	21 (8.5)	
ECG MI type				
Q wave, any location	229 (88.4)	202 (86.0)	173 (70.3)	.000
Non–Q wave	30 (11.6)	33 (14.0)	73 (29.7)	
Delay, median (min)*	130	135	120	.408
Admission to hospital with PCI	141 (54.4)	116 (49.4)	91 (37.0)	.000
Transferal for PCI treatment†	74 (62.7)	64 (53.8)	47 (30.3)	.000
Treatment				
Conservative	55 (21.2)	72 (30.6)	143 (58.1)	.000
Reperfusion‡	204 (78.8)	163 (69.4)	103 (41.9)	
Mortality				
Inhospital	11 (4.3)	19 (8.1)	37 (15.0)	.000
1-y	16 (6.2)	40 (17.0)	72 (29.3)	.000

Values are presented as number (%) unless otherwise noted. *ECG*, Electrocardiogram.
* Time delay between symptom onset and hospital admission.
† Percentage calculated on those first admitted to hospital without PCI facilities.
‡ Coronary reperfusion with primary PCI or thrombolysis.

potentially avoidable death fraction

$$= [(P - pi)(1 - HRi)]/[1 - pi(1 - HRi)],$$

where P = highest proportion of reperfused patients in any of 3 CS categories; pi = proportion of patients actually reperfused in one of the other two CS categories; HRi = hazard ratio from Cox models in the corresponding CS category. An adjusted number of avoidable deaths was then calculated for each CS category by multiplying the actual number of deaths observed in each category subgroup by the corresponding potentially avoidable death fraction (Table IV).

Results

Overall, 198 patients had no comorbidity, whereas 542 had at least one chronic comorbidity. Of these, 184 had a cardiac, 135 a noncardiac, and 223 at least one cardiac and one noncardiac comorbidity. The prevalence of comorbidity increased from 48% at age <55 years to 83% at age >74 years ($P < .001$).

The prevalence of each comorbidity and results from age-adjusted bivariate Cox analyses testing the association of comorbidities with 1-year prognosis, which were

Table III. Multivariate Cox analysis of variables associated with 1-year risk of death in the whole series and within each chronic CS category

		Comorbidity score categories		
	Whole series (n = 740) HR (95% CI)	**CS-1 (n = 259) HR (95% CI)**	**CS-2 (n = 235) HR (95% CI)**	**CS-3 (n = 246) HR (95% CI)**
Age (continuous)	1.05 (1.03-1.07)	1.09 (1.04-1.15)	1.07 (1.03-1.11)	1.02 (0.99-1.05)
Killip class				
1	1	1	1	1
2-3	2.86 (1.90-4.31)	4.09 (1.33-12.61)	2.90 (1.43-5.88)	2.45 (1.42-4.22)
4	5.33 (3.12-9.09)	9.00 (2.21-36.61)	8.15 (3.22-20.63)	3.85 (1.85-8.02)
ECG MI type				
Q wave, any location	1	1	1	1
Non–Q wave	0.70 (0.45-1.10)	0.27 (0.02-3.38)	0.88 (0.33-2.30)	0.68 (0.40-1.15)
Treatment type				
Conservative	1	1	1	1
Reperfusion*	0.60 (0.40-0.92)	0.63 (0.14-2.80)	0.62 (0.31-1.25)	0.47 (0.26-0.86)
CS category				
1	1	–	–	–
2	1.87 (1.04-3.38)	–	–	–
3	2.12 (1.18-3.82)	–	–	–

* Coronary reperfusion with primary PCI or thrombolysis.

Table IV. Crude and adjusted numbers of potentially avoidable deaths in chronic CS categories 2 and 3, in the hypothesis of utilization of coronary reperfusion therapy with the same frequency observed in CS-1 category

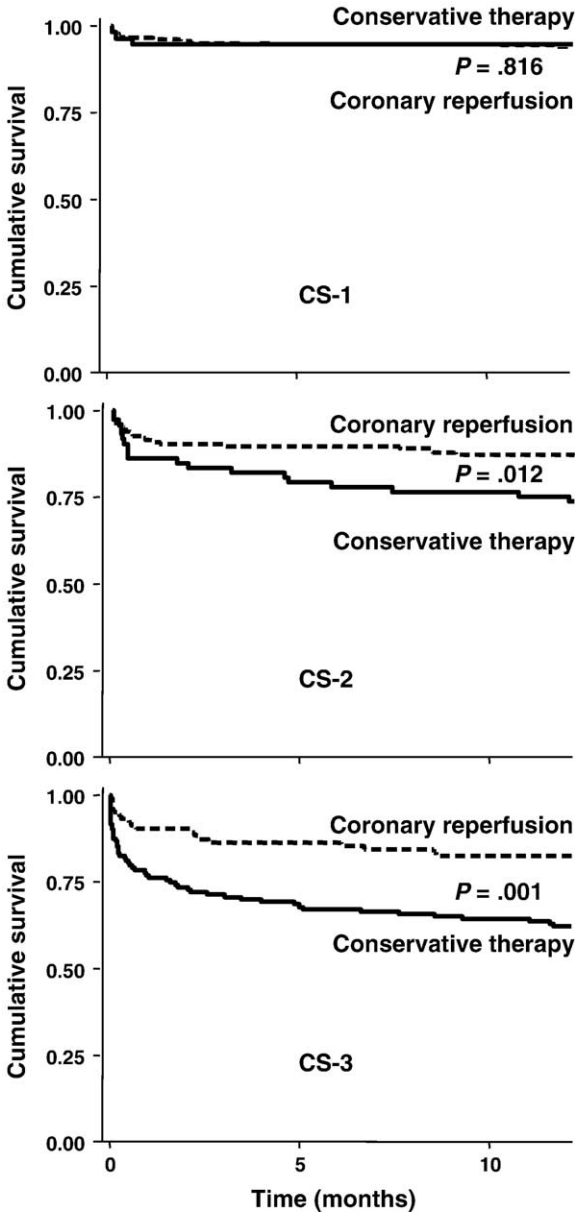
		Observed				Hypothetical				Avoidable deaths	
		Adopted therapy		1-y mortality		Adopted therapy		1-y mortality		Crude	
CS category	**Treatment**	**n1**	**p1**	**n2**	**p2**	**n3**	**p3**	**n4**	**p4**	**N4-n2**	**Adjusted***
1	Reperfusion†	204	0.788	13	6.4	204	0.788	13	6.4		
	Conservative	55	0.212	3	5.5	55	0.212	3	5.5		
	Total	259	1.000	16	6.2	259	1.000	16	6.2	0	0
2	Reperfusion†	163	0.694	21	12.9	185	0.788	24	12.9		
	Conservative	72	0.306	19	26.4	50	0.212	13	26.4		
	Total	235	1.000	40	17.0	235	1.000	37	15.8	−3	−2
3	Reperfusion†	103	0.419	18	17.5	194	0.788	34	17.5		
	Conservative	143	0.581	54	37.8	52	0.212	20	37.8		
	Total	246	1.000	72	29.3	246	1.000	54	21.8	−18	−18

n1, p1, n3, p3: Actual and expected numbers (n) and proportions (p) of patients receiving coronary reperfusion or conservative therapy; n2, p2, n4, p4: actual and expected numbers (n) and proportions (p) of patients dying within 1-year follow-up.
* Based on calculation of potentially avoidable death fraction (see Methods).
† Coronary reperfusion with PCI or thrombolysis.

used to calculate individual disease-specific scores, are reported in Table I. Based on the CS score tertiles distribution, 259 (35.0%) patients were in CS-1, 235 (32.0%) in CS-2, and 246 (33.0%) in CS-3 category. The mean number of chronic comorbidities per patient increased significantly across the 3 categories, from 0.24 in CS-1 to 1.28 and 3.09 in CS-2 and CS-3, respectively ($P < .001$).

Baseline demographic and clinical characteristics and inhospital and long-term mortality by CS category are reported in Table II. The sex distribution was similar across CS categories, whereas age, prevalence of Killip class >1, and non–Q-wave MI increased progressively with increasing CS category. The median time delay between onset of symptoms and hospital admission (129 minutes, interquartile range 85-214 minutes) was similar across CS categories. Conversely, the proportions of direct admission to the hospital with PCI facilities, transferal from community hospitals to the hospital with PCI facilities, and coronary reperfusion therapy were significantly reduced with increasing CS category. Within each CS category, PCI was the prevailing

Figure 1



Cumulative survival (Kaplan-Meier) by chronic comorbidity score (CCS) category and type of treatment from AMI (time 0) to 12-month follow-up.

modality of coronary reperfusion (overall, 91.4% of cases, range 88.3%-93.2%). Overall, we recorded 67 inhospital and 61 further deaths within the 1-year follow-up. In accordance with analysis design, compared with those in CS-1 category, patients in CS-2 and CS-3 categories had a 2.7 and a 4.7 times greater 1-year all-cause mortality. The cumulative incidence of major complications potentially related to treatment with either thrombolysis or PCI (eg, bleeding requiring blood transfusion, stroke, acute renal failure, vascular damage requiring surgery) did not differ across CS categories. Unadjusted cumulative survival curves stratified by CS category and type of treatment (coronary reperfusion vs conservative therapy) are shown in Figure 1. In general, coronary reperfusion was associated with a better prognosis than conservative therapy; this difference being progressively more marked with increasing CS category. In a multivariate Cox regression analysis for the whole series, CS category retained its association with 1-year mortality (P for trend = .018, with CS entered as a continuous variable) after adjusting for age, Killip class, MI location, and type of therapy (Table III). Compared with conservative treatment, coronary reperfusion therapy significantly reduced the 1-year risk of death by 40% in the whole series. Three further multivariate Cox regression analyses (Table III) showed that although it was significant only in CS-3 category, a reduction in 1-year mortality associated with coronary reperfusion therapy was evident within each category, being greater in CS-3 (−53%) than in CS-2 (−38%) or CS-1 (−37%) category.

As previously stated, potentially avoidable deaths were calculated by hypothesizing an increase in coronary reperfusion rate in CS-2 and CS-3 categories from their actual values (69.4% and 41.9%, respectively) (Table II) to that observed in CS-1 category (78.8%), while keeping constant the therapy-specific mortality observed in each category. In a crude calculation based on such hypothesis, 3 and 18 deaths resulted to be avoidable in CS-2 and CS-3 categories, respectively (Table IV). This would have reduced 1-year mortality in these two categories from 17.0% to 15.8% and from 29.3% to 21.8%, respectively, and, in the whole series, from 17.3% to 14.5% (overall, a 16.4% relative reduction in mortality). Similar results were achieved when the mortality reduction associated with coronary reperfusion was adjusted for the other significant predictors of 1-year mortality in Cox analyses. Following this method, the potentially avoidable deaths were 2 and 18 in CS-2 and CS-3 categories, respectively (Table IV), corresponding to a 15.6% relative reduction in 1-year mortality in the whole series.

Discussion

The most rapid and complete coronary reperfusion is the desirable therapeutic goal to be achieved in acute MI.[1] At least in selected subgroups in whom thrombolysis is known to be less effective or relatively contraindicated,[4] primary PCI may produce better results and extends the benefit of coronary reperfusion to nearly all cases of STEMI.[13] Whereas underutilization of thrombolysis in older patients with AMI may be justified, at least in part, by an age-associated increase in the

contraindications to lytic agents, absolute contraindications to primary PCI are seldom encountered in the real clinical world. Furthermore, it has been reported that compared with thrombolysis, primary PCI is associated not only with higher coronary patency rates and improved outcomes,[2] but also with reduced complications, even at older ages.[3] Therefore, we would have expected that in the Florence area, where PCI is largely the most preferred coronary reperfusion therapy in STEMI,[10] this therapeutic strategy would be adopted following age- and comorbidity-independent patterns.

In contrast with such expectations but in accordance with recent reports from other countries,[6] a previous analysis of the AMI-Florence registry found that an advanced age was an independent negative predictor of utilization of coronary reperfusion.[14] The present analysis showed that the proportion of patients receiving coronary reperfusion therapy was progressively reduced with increasing chronic comorbidity, from 78.8% in CS-1 to 41.9% in CS-3 category. These findings suggest that attending physicians systematically favored the adoption of the most aggressive, but potentially most life-saving, treatment in less severely ill patients, despite the fact that the average time delay between symptom onset and hospital admission was similar across CS categories. Such an attitude was indirectly confirmed by the reduced proportion of patients in CS-2 and CS-3 categories who, after having being admitted to community hospitals without PCI facilities, were transferred to the teaching hospital for possible primary PCI. These observations in patients with STEMI are in keeping with the recent report from the CRUSADE Quality Improvement Initiative, which demonstrated a substantial underutilization of early invasive management in patients with non–ST-segment elevation acute coronary syndromes and associated comorbidities.[15]

This behavior appears somewhat paradoxical after we observed that mortality reduction associated with coronary reperfusion was larger in those patients in higher CS categories, who more often had been denied the potential benefits of that therapeutic approach. Indeed, Cox regression analyses stratified by CS category and adjusted for potential confounders confirmed the results of crude analysis: patients in CS-1 and CS-2 categories exhibited smaller (−37 and −38%, respectively) and nonsignificant reduction in 1-year mortality associated with coronary reperfusion than those in CS-3 category (−53%). Interestingly, neither a higher proportion of non–Q-wave MI nor older age, which in any case should not be taken as a limitation to primary PCI,[2,3,16] could fully account for the reduced utilization of coronary reperfusion in CS-2 and CS-3, as compared with CS-1 category. In the hypothesis that underutilization of PCI in patients with greater comorbidity was due to concerns on post–contrast medium renal failure, we have reanalyzed our data with exclusion of the 62 (13 CS-2 and 49 CS-3) patients with a history of chronic renal failure. With this exclusion, PCI utilization was only modestly increased (from 69.4% to 70.3% and from 41.9% to 46.2% in CS-2 and CS-3 categories, respectively), whereas compared with conservative treatment, reperfusion-associated reduction in 1-year mortality was substantially unchanged (HR 0.65 and HR 0.42 in CS-2 and CS-3 categories, respectively).

Based on these results, we calculated the numbers of potentially avoidable deaths by hypothesizing an extension of the utilization rate of coronary reperfusion in CS-2 and CS-3 categories from their actual values of 69.4% and 41.9% to the 78.8% utilization rate observed in CS-1 category, while keeping constant the therapy-specific 1-year mortality in each category. With this method, from 20 (adjusted analysis) to 21 (crude analysis) deaths were classified as potentially avoidable, corresponding to an overall reduction in 1-year mortality ranging from 15.6% to 16.4%. These results are in keeping with previous analyses of randomized controlled trials of thrombolysis. For example, it has been reported that although in the GISSI-1 trial the thrombolysis-associated reduction in mortality was not significant above age 70 years, the number of life saved per 1000 patients treated was much larger in older than in middle-aged patients.[17] This reinforces the view that the systematic underutilization of coronary reperfusion therapy at older ages[5-7,18] unfairly limits the opportunity of achieving the best treatment that is offered to older patients. The same consideration holds true for patients with comorbidities, particularly in the light of the fact that with the advent of primary PCI, which has fewer contraindications than thrombolysis, almost all patients with STEMI are presently eligible to coronary reperfusion therapy.[5,7]

Our conclusions are potentially biased by the fact that estimates of avoidable deaths were not obtained within a randomized trial and were based on a relatively limited sample size, including <150 deaths in 3 CS categories. On the other hand, the strength of the present analysis of our observational registry consists of having reported on the consequences of different therapeutic strategies as they are adopted in the real clinical world. In this perspective, we believe that the present analysis highlighted to what extent long-term mortality after STEMI is affected by therapeutic choices in the acute phase that are linked to the presence of comorbid conditions. Analysis also confirmed the need for enriching the training of medical specialists to target frail, often old, individuals presenting with acute coronary syndromes and a relevant burden of chronic comorbidity.[19] This targeting process might help in extending to the largest possible number of patients the benefits of the best possible treatment, a goal at least as important as the research of new technologies, aimed at further improving individual patient's outcomes.

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Appendix A

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