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Role of optimal medication given to patients with hypertension and ischemic heart disease prior to an acute coronary syndrome

Călin Pop[1,2], Roberta Florescu[3], Claudia Matei[1], Lavinia Pop[1], Viorel Manea[1], Coralia Cotoraci[2], Liana Mos[2], Antoniu Petris[4]

[1] Department of Cardiology, Emergency County Hospital, Baia Mare - Romania
[2] West University "Vasile Goldis" – Faculty of Medicine, Arad - Romania
[3] Department of Cardiology, Pneumology and Vascular Medicine, RWTH University Hospital, Aachen - Germany
[4] Cardiology Clinic, "St. Spiridon" County Emergency Hospital, University of Medicine and Pharmacy "Grigore T. Popa", Iași - Romania

ABSTRACT

Introduction: Administering optimal cardiovascular medication (OCM) to patients with hypertension (HBP) and ischemic heart disease (IHD) lowers cardiovascular morbidity and mortality.
The main objective of this study was to compare in-hospital cardiac mortality among patients with HBP and/or IHD, treated or untreated with OCM, who developed a first episode of acute coronary syndrome (ACS).
Methods: The study was carried out retrospectively and included patients admitted with a first episode of ACS between 2013 and 2016. The patients were divided into three groups: those with HBP, IHD, and a history of HBP + IHD. Patients were then divided into two subgroups: subgroup A consisted of patients undergoing optimal anti-ischemic and/or antihypertensive therapy, while subgroup B consisted of patients without OCM.
Results: This analysis comprised 1096 patients. Mean age was 64.3 ± 18 years. There were 581 patients in subgroup A – 53%, and 515 patients in subgroup B – 47%. Total cardiac mortality was 9.98%, different depending on the groups and subgroups studied: HBP group total – 7%, subgroup A – 5.1%, significantly lower compared to subgroup B – 9.4% (p = 0.05); IHD group total – 12.2%, subgroup A – 9.07%, significantly lower compared to subgroup B – 15.8% (p = 0.05); HBP + IHD group total – 14.35%, subgroup A – 9.9%, significantly lower compared to subgroup B – 18.8% (p = 0.05).
Conclusions: The lack of OCM in patients with HBP and/or IHD is correlated to a significant increase in in-hospital cardiac mortality among patients who develop a first-episode ACS.

Keywords: Acute coronary syndrome, Cardiac mortality, Hypertension, Ischemic heart disease, Optimal cardiovascular medication

Introduction

The main cause of coronary heart disease (CHD) is atherosclerosis. The administration of an optimal chronic cardiovascular medication (OCM) to patients with symptomatic manifestations of atherosclerosis – hypertension (HBP) and ischemic heart disease (IHD) – lowers cardiovascular morbidity and mortality (1). The Euroaspire IV study showed that ≤50% of CHD patients benefit from cardiovascular prevention and rehabilitation. The study also suggests that blood pressure, blood sugar, and serum cholesterol values are inadequately controlled in most patients being treated by secondary prevention (2). The adherence to cardio-protective treatment is influenced by the economic and cultural characteristics of each country, and Romania is included in the reduced coverage trend observed at the Balkan level (3).

Objectives

The main objective of this study is to compare in-hospital cardiac mortality in patients with a history of HBP and/or IHD, who have experienced a first episode of acute coronary syndrome (ACS), and are being treated with or without OCM, in accordance with the 2016 ESC Prevention and Treatment Guidelines (4). At the same time, the study aims to gather information about the prevalence of OCM in the current medical practice in the north-western area of Romania.

Methods

This study was carried out retrospectively and included patients admitted to the Cardiology Unit of Baia Mare Emergency County Hospital, Romania, with their first episode of

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Corresponding author:
Călin Pop
George Cosbuc Street nr 31
Baia Mare, Romania
medicbm@yahoo.com

ACS, between 2013 and 2016. The hospital provided clinical and invasive cardiology services, with a possibility of interventional treatment for acute myocardial infarction (AMI), for approximately 500,000 inhabitants from the counties of Maramureș and Satu-Mare in north-western Romania. Patients were selected from the hospital database according to their main diagnosis upon admission – ACS. Patients who underwent treatment for myocardial reperfusion (thrombolysis and/or primary angioplasty in acute myocardial infarction – PAAMI) were included in the study, as well as patients who had a conservative treatment. The diagnoses were established based on the ICD–10–AM classification (10th revision, Australian modification) and/or the diagnosis-related group (DRG) system. Personal medical backgrounds were identified as recorded in the electronic database as well as in the patients' observation sheets. Patients were divided into three groups: those with a history of HBP, those with a history of IHD, and those with a history of HBP + IHD, respectively. The HBP group included patients who had been diagnosed with HBP at least 12 months prior to being afflicted with ACS. Patients with a history of IHD were those previously diagnosed with pectoral angina or silent myocardial ischemia, those who had a known coronary anatomy with evident coronary lesions provoking the narrowing of the lumen by ≥50%, or patients with a history of myocardial revascularization. The third patient group comprised subjects with a history of both HBP and IHD, who fulfilled the criteria presented above. The patients included in the analysis were then divided into two subgroups: subgroup A composed of patients who undertook optimal anti-ischemic and/or antihypertensive therapy in accordance with the 2016 ESC prevention and treatment guidelines in effect, while subgroup B consisted of patients without OCM treatment, either through the lack of it or incompleteness (4). A primary problem was to define how long the patients were on OCM or on maximum optimal therapy. Considering the unitary processing of the study data and the retrospective characteristic of the study, the antihypertensive treatment with one or more therapeutic classes up to the moment of being afflicted with ACS was considered as OCM, for the HBP group. The administration of at least one anti-ischemic agent, one antiplatelet agent (AA), and one agent from the class of statins has been considered as OCM for the IHD group. Therefore, this analysis is based on a snapshot of the OCM recommended by the guidelines during presentation, and we cannot comment on how long the patients were taking the medication, at what doses, and the effects on blood pressure or cholesterol levels. The patients' data were processed anonymously, and the project was approved by the ethics committee of the sanitary establishment.

Statistical analysis

The data was presented as a mean (standard deviation [SD]) for the continuous variables and as the number of subjects (%) for the discrete variables. The "N-1" χ^2 test and "t-test" were performed to determine the significant differences ($p \leq 0.05$). The odds ratios (OR), with 95% confidence interval (CI) of in-hospital cardiac mortality, was calculated using regression logistic models. The following factors, possibly explaining high cardiac mortality, were included in the multivariate analysis: age, gender, HBP, history of ICD, smoking, dyslipidemia, diabetes mellitus (DM), ejection fraction (EF), and cardiovascular medication given prior to ACS (angiotensin converting enzyme inhibitors [ACEI], beta-blockers [βB], calcium channel blockers [CCB], antiplatelet agents [AA], diuretics, nitrates, statins, and their combinations). EpiInfo7 and MedCalc Version 17.5.3 (MedCalc Software bvba, Ostend, Belgium) statistics software were used to process the data.

Results

The analysis comprised 1096 patients, of which 624 (57%) were male and 472 (43%) were female. Their mean age was 64.3 ± 18 years; age was higher by seven years for women, as compared to men. In relation to the total number of patients, 581 patients (53%) received OCM (subgroup A), whereas 515 (47%) were inadequately treated (subgroup B).

The three-patient groups comprised 527 patients in the HBP group (273 in subgroup A – 51.80%, 254 in subgroup B – 49.20%), 344 patients in the IHD group (188 in subgroup A – 54.65%, 156 in subgroup B – 45.35%), 225 patients in the HBP + IHD group (120 in subgroup A – 53.4%, 105 in subgroup B – 46.6%). There were no differences related to age, gender, or the received treatment for ACS (conservative or myocardial reperfusion) between the three groups or the subgroups within each group, as shown in Table I. There were no differences present among the various groups in the medical treatment for ACS, because low-weight unfractionated heparins (LWUH), dual antiplatelet therapy (DAPT), βB, ACEI, and high doses of statins were the standard in-hospital treatments.

The prevalence of the main risk factors – smoking, dyslipidemia, DM – was not different in the studied groups, but we noted a significantly higher frequency of cases involving incidents of congestive heart failure (CHF), atrial fibrillation (AFib), and non-fatal strokes (CVA) in the history of subgroup B under the HBP group patients without optimal treatment. In the same subgroup B, but under the IHD group of patients without optimal treatment, we noted a higher frequency of chronic peripheral arterial disease (PAD) of the lower limbs, as shown in Table I.

Regarding the patients who underwent treatment prior to the ACS, we noted a significantly higher rate in the chronic use of ACEI/angiotensin receptor blockers (ARB) and CCB in the group with a history of HBP ($p = 0.0001$). On the other hand, a significantly higher rate in the chronic use of aspirin, βB, and nitrate derivatives was observed in the group with a history of IHD ($p = 0.002$). The statin treatment was similar among the three groups.

The total in-hospital cardiac mortality was 9.98%. In relation to all the patients participating in the study, the in-hospital cardiac mortality in the A subgroups was 8.09%, which was significantly lower than the 12.05% observed in patients from B subgroups ($p = 0.02$) as observed in Figure 1.

The in-hospital cardiac mortality differed depending on the groups studied and the subgroup divisions within the same group. While the HBP group total was 7%, that of subgroup A – 5.1% was significantly lower compared to subgroup B – 9.4% and $p = 0.05$. On the other hand, the IHD group total was 12.2%, wherein subgroup A – 9.07% was

TABLE I - Epidemiologic characteristics of patients with ACS

No. of patients / Variables (%)	Total 1086	HBP A 273	HBP B 254	p	IHD A 188	IHD B 156	p	HBP + IHD A 120	HBP + IHD B 105	p
Age (y)	64.3 ± 18	65.2	63.9	ns	66.1	63.2	ns	64.9	63.5	ns
Gender M	57%	54%	56%	ns	60%	58%	ns	60%	54%	ns
Smoking	48%	45%	47%	ns	51%	52.5%	ns	47.75%	49.25%	ns
Dyslipidemia	46.9%	48%	46.7%	ns	47.2	46.5	ns	46.8	44.2	ns
STEMI	75.1%	72%	74.2%	ns	76.3%	78.1%	ns	74.8%	75.2%	ns
NSTEMI	24.9%	23.1%	25.2%	ns	25.5%	27.3%	ns	24.8%	25.4%	ns
Implant stent/PCI	62.5%	59%	58.5%	ns	66%	67%	ns	61.4%	63.75%	ns
CHF NYHA II-IV	7.5%	6.5%	12%	0.02	6.2%	7.4%	ns	7.6%	8.2%	ns
AFib	6%	5.5%	10.8%	0.02	4.9	5.6	ns	5.9%	7%	ns
COPD	5%	4.5%	4.9%	ns	5.4%	5.1%	ns	4.4%	5.4%	ns
DM	23.8%	25%	24.6%	ns	24%	23.4%	ns	24 %	24. 8%	ns
PAD	6 %	4.2 %	5.5%	ns	5 %	11 %	0.03	5.4%	7.2%	ns
CRF st II-IV	3.8%	4%	5.2%	ns	3%	3.8%	ns	3.6%	4.2%	ns
Non-fatal CVA	4%	4.8%	10.5%	0.01	3 %	3.6%	ns	4.2%	5.8%	ns

ACS = acute coronary syndrome; AFib = atrial fibrillation; CHF = congestive heart failure NYHA class; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CVA = cerebral vascular accident; DM = diabetes mellitus; HBP = hypertension; IHD = ischemic heart disease; ns = nonsignificant; NSTEMI = acute myocardial infarction with non-ST segment elevation; PAD = chronic peripheral arterial disease of the lower limbs; PCI = percutaneous coronary intervention; STEMI = acute myocardial infarction with ST-segment elevation.
A – subgroup with optimal cardiovascular medication therapy.
B – subgroup without optimal cardiovascular medication.

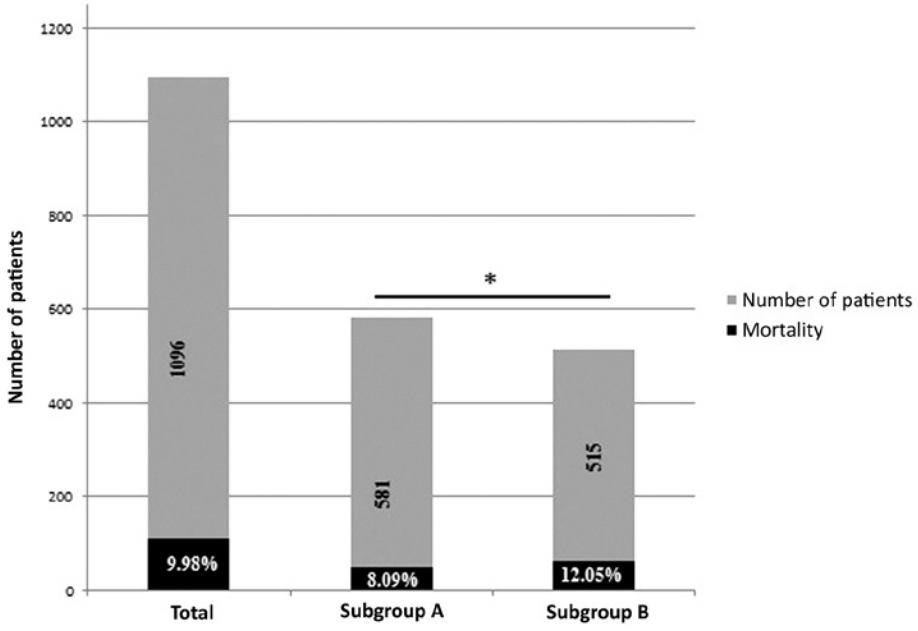

Fig. 1 - Total cardiac mortality in the study group and comparison between the subgroups. Subgroup A – Optimal cardiovascular medication therapy (see text). Subgroup B – Without optimal cardiovascular medication. *p = 0.02.

significantly lower compared to subgroup B –15.8%, with p = 0.05. The HBP + IHD group total was 14.35%, with subgroup A measuring 9.9%, which is significantly lower compared to subgroup B, with 18.8% and p = 0.05. This has been depicted in Figure 2.

Other significant differences in cardiac in-hospital mortality were noted between women and men (12.7% vs. 7.85%, p = 0.007), in patients aged ≤55, as compared to those aged ≥75 (3.93% vs. 15.56%, p = 0.0001), in those with coronary revascularization, as compared to those treated conventionally

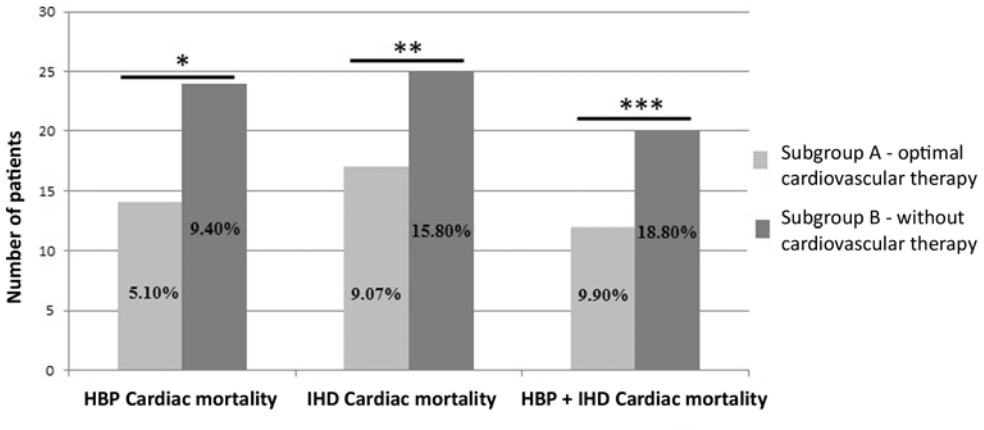

Fig. 2 - Cardiac mortality in the subgroups, in the presence or absence of optimal cardiovascular medication. *p = 0.05; **p = 0.05; ***p = 0.05.

(6.2% vs. 16.3%, p = 0.0001), and in patients with an EF more than 35% (24.3% vs. 7.4%, p = 0.0001). The calculations have been shown in Table II.

The multivariate analysis endeavored to differentiate the effects of in-hospital cardiac mortality according to gender, age, HBP, history of ICD, smoking, dyslipidemia, DM, EF, and different therapeutic classes given prior to ACS (ACEI, ARB, CCB, βB, AA, diuretics, nitrates and statins). Within the multivariate analysis, the death risk was lower for those aged ≤75 (adjusted OR 0.59, 95% CI 0.43-0.85), in men (adjusted OR 0.85, 95% CI 0.75-0.97), in those with an EF ≥35% (adjusted OR 0.64, 95% CI 0.49-0.82), in those with optimal cardiovascular treatment in the A subgroups (adjusted OR 0.76, 95% CI 0.62-0.94) and, in particular, in those who had a combined treatment of ACEI + statin (adjust OR 0.66, 95% CI 0.47-0.91). The latter were older (64 years vs. 59 years, p = 0.02) and had more comorbidities, especially hypercholesterolemia, DM, AFib, and chronic obstructive pulmonary disease (COPD). This discussion has been illustrated in Table III.

Discussion

Our study puts forth obvious arguments that the optimal treatment of patients afflicted with HBP and IHD has an important cardio-protective role and significantly lowers the in-hospital cardiac mortality in those who have experienced a first episode of ACS. The total in-hospital cardiac mortality rate was 9.98%, while that from the A subgroups (optimally treated) was 8.09%, which is significantly lower than the 12.05% noted in patients from B subgroups (without OCM), p = 0.02. The lowest in-hospital cardiac mortality was observed in optimally treated HBP patients (5.1%), followed by those in the IHD group (9.07%), and by those in the combined group HBP + IHD (9.9%). The highest mortality was observed in patients without OCM: HBP – 9.4%, IHD – 15.8%, and the highest measurement of 18.8% in the combined group HBP + IHD. Few studies have aimed to quantify, in real terms, the effect of initial optimal medication on patients with a first episode of ACS. The results are divergent, depending on the methodology and the considered variables. Cuculi et al (5), using data from the AMIS-plus registry (Acute Myocardial Infarction in Switzerland), described the cardio-protective role of administering βB to HBP patients who have developed a first ACS episode. Harjai et al (6) described a similar effect on patients from the PAMI-2 registry (Primary Angioplasty in Myocardial Infarction), whereas Bangalore et al (7), in their observational study REACH (Reduction of Atherothrombosis

TABLE II - Group and subgroups cardiac mortality depending on different variables

Variables (%)	No. of patients	Total group cardiac mortality n = 1096		p	Total cardiac mortality in subgroup A n = 581		p	Total cardiac mortality in subgroup B n = 515		p
Gender Male 624 pts (57%)	Gender Female 472 (43%)	7.85%	12.7%	0.007	3.44%	4.3%	0.44	5.63%	6.79%	0.44
Age ≤55 y 115 (10.5%)	Age ≥75 y 185 (16.9%)	4.5%	15.8%	0.002	0.17%	1.54%	0.01	0.77	3.88%	0.0009
Revascularisation treatment 685 (62.5%)	Conservative treatment 411 (37.5%)	6.2%	16.3%	0.0001	3.2%	5.16%	0.09	4.46%	7.18%	0.06
EF ≤35% 164 (15%)	EF >35% 932 (75%)	24.3%	7.4%	0.0001	4.9%	1.72%	0.0002	7.76%	5.82%	0.21

ACS = acute coronary syndrome; EF = ejection fraction; HBP = hypertension; IHD = ischemic heart disease.
Subgroup A – optimal cardiovascular medication therapy: for the HBP group, antihypertensive treatment with one or more therapeutic classes undergone until attendance for ACS; the administration of at least one anti ischemic agent, of at least one antiaggregant agent and of one agent from the class of statins was considered as optimal cardiovascular medication therapy for the IHD group.
Subgroup B – without optimal cardiovascular medication, either through the lack of it or through its incompleteness.

TABLE III - The effect on cardiac mortality according to different variables in multivariate analysis

Variable	OR – adjusted interval 95% CI
Age ≤75 y	0.59, 95% CI 0.43-0.85
Male	0.85, 95% CI 0.75-0.97
EF ≥35%	0.64, 95% CI 0.49-0.82
Optimal cardiovascular treatment – Subgroup A	0.76, 95% CI 0.62-0.94
Combined treatment ACEI + statin	0.66, 95% CI 0.47-0.91

ACEI = angiotensin converting enzyme inhibitors; CI = confidence interval; EF = ejection fraction; OR = odds ratio.
Subgroup A: optimal cardiovascular medication therapy: for the HBP group, antihypertensive treatment with one or more therapeutic classes undergone until attendance for ACS; the administration of at least one antiischemic agent, of at least one antiaggregant agent and of one agent from the class of statins was considered as optimal cardiovascular medication therapy for the IHD group.

for Continued Health), did not show the lowering of cardiovascular incidents among patients with prior βB treatment. In a retrospective study, the adherence to at least one treatment with cardio-protective attributes from the classes of ACEI, statins, and βB is associated in patients with DM and IHD to a significantly lower cardiovascular mortality of 7.9% versus 11.5%, p = 0.03 (8). The same statins, previously given to patients who later developed an AMI, reduced mortality among patients in comparison to those untreated, and the exclusion of these patients from therapy removes the cardio-protective effect (9). On the other hand, in patients with IHD, who later developed an AMI and had primary angioplasty, the prior, long-term administration of clopidogrel came with no benefit in a prospective study carried out by Bonello et al (10).

The study results show an interesting association showing that patients who develop a first episode of ACS and receive initial OCM have a better short-term prognosis. In-hospital cardiac mortality differences are significantly in favor of the patients who are optimally treated, thus pointing out the cardio-protective effect of cardiovascular medication administered in accordance with the recommendations of the prevention and treatment guidelines for patients with HBP and IHD (4). This may be linked to the use of any class of medication with a clinically and statistically proven cardiovascular benefit, but the study does not bring arguments in favor of one drug or another, except for the combination of ACEI + statin (adjusted OR 0.66, 95% CI 0.47, 0.91). The study also reflects the importance of beginning therapy before the development of ACS, in the case of statin treatment. Data in the PRISM and MIRACL studies show a greatly reduced cardio-protective effect or a delayed start of the vascular protection by 14–30 days, if the administration is carried out at the same time as when the ACS develops (9, 11).

Our study points out that in the north-western area of Romania, 47% of patients with HBP and IHD (subgroup B) do not receive OCM in accordance with current professional guidelines. Two ample studies, SEPHAR and CARDIOZONE, were carried out in Romania, which focused on estimating the prevalence of cardiovascular risk factors, assuming the population in our country present high cardiovascular risk (1). Their results showed a decreased control, even below the European average, of the main cardiovascular risk factors (3, 12). This observation correlates with the reduced application of OCM, as observed in our study. We were glad to note that there was a significantly higher rate of the chronic use of ACEI/ARB and CCB in the HBP group (p = 0.0001) and of aspirin, βB, and nitrate derivatives in the IHD group (p = 0.002). The statin treatment was similar in the three groups. Information regarding the compliance with OCM is beyond the scope of this study, but the cardiologist or GP must permanently monitor and identify the non-adherence to OCM in the presence of uncontrolled BP values or a consistently high total cholesterol and low-density lipoprotein (LDL), because these circumstances represent an aggravating factor for cardiovascular prognosis (3, 8, 12-15). At least on a national level, studies should be carried out based on which would best identify the main reasons behind the modest application of OCM in Romanian patients with HBP and IHD.

Other study results reconfirmed the importance that must be placed on certain characteristics of hypertensive and/or coronary disease among patients who develop ACS, showing a significantly higher cardiac mortality for women, for those aged ≥75 years, as well as those who do not have coronary revascularization.

Study limitations

The principle limitations of this study are derived from its retrospective nature (but in this case, this was the only means of research), as well as from the incomplete nature of compiling data from the IT system and observation sheets of the patients included in the research. An attempt was made to widen the scope of the definition of patients kept under analysis, as well as that of the optimal or suboptimal character of the cardiovascular treatment given in order to cover the variety of situations encountered in the medical practice, but without departing from the spirit and recommendations of the guidelines in effect. Our analysis was based on a snapshot of the OCM recommended by the guidelines at the time of presentation, and we could not comment on how long the patients had been taking the medication, at what doses, or with what effects on blood pressure or cholesterol levels. The lack of complete quantitative and qualitative information as well as the limited number of patients could not lead to the identification of a hierarchy of cardio-protective types of medication. This is a small retrospective observational study and, therefore, it can only report associations between the chronic OCM and the lowering of cardiovascular mortality in acute situations. This would require several prospective registries because conducting randomized clinical trials is unethical.

Conclusions and future perspectives

The study shows that the lack of chronic OCM for patients with HBP and/or IHD is correlated with the significant rise in in-hospital cardiac mortality among those who experience a first ACS episode. This may be linked to the use of any class

of medication with a statistically and clinically proven cardiovascular benefit, with arguments in favor of the systematic administration of the combination of ACEI plus statin. Thus, OCM must be initiated in patients who are yet untreated, and this treatment needs to be continued in patients afflicted with an ongoing cardiovascular disease.

Disclosures

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Conflict of interest: None of the authors has financial interest related to this study to disclose.

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