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Number of drugs used in secondary cardiovascular prevention and late survival in the population of Valencia Community, Spain☆,☆☆

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ABSTRACT

Background: Drug treatment for secondary prevention of cardiovascular disease is recommended by guidelines, but it is not always followed in real life. This study wanted to assess the size of this gap and its impact on mortality in subjects after a cardiovascular event (MACE).

Methods: Patients with any of MACE in the period from January 1st 2011 to December 31st 2013, and more than one year of follow-up were selected from population of the Valencian Community. Drugs for secondary prevention were antiplatelets, renin-angiotensin system blockers and statins. Assessment of treatment was performed one year after the initial event. Mortality risk was assessed using Cox by the number of drug classes (G0 no medication, G1 one, G2 two and G3 three drugs) adjusted by confounders.

Results: A total of 92,436 patients (62% men, mean age 72 years) of whom 60.5% presented with stroke, 30.6% with myocardial infarction and 8.9% with revascularization were included. Among them, 4.1% were G0, 20.2% G1, 32.9% G2 and 42.7% G3. A progressive decrease in mortality was observed in G1 (HR 0.83, CI 95% 0.73–0.95), G2 (HR 0.70, CI 95% 0.60–0.82) and G3 (HR 0.61, CI95% 0.51–0.74) vs. G0. In diabetic subgroup, significant reduction of risk was observed in the G2 (0.79, CI 95% 0.63–0.98) and G3 (0.72, CI9 5% 0.56–0.95), but not in G1 (0.97, CI 95% 0.80–1.17).

Conclusion: A gap between guidelines and reality in the use of cardiovascular protecting drugs one year after the initial event still exists and it is largely related with all-cause late mortality.

1. Introduction

In the last years, although a healthier lifestyle, the increasing abandon of smoking habit and a better use of interventional techniques and of available drugs have contributed to an important improvement of cardiovascular morbidity and long-term survival, mostly in developed countries, the burden of cardiovascular diseases is still very important [1–6]. Consequently, secondary prevention of major events continues to be currently key in the clinical management of cardiovascular disease [7].

Clinical trials have shown that at least three different drug classes, namely, antiplatelets, RAS-b and lipid-lowering statins, significantly decrease the long-term morbidity and mortality in secondary cardiovascular prevention [1,8]. Besides, the reduction in the event rate by means of a combined administration of those three drug classes can be superior to each of them separately [9]. The use of these drugs in clinical practice, however, is far from optimal [1,2,8]. Survival rates in clinical practice still fall behind those achieved in randomized clinical trials, and the considerable lack of adherence to the chronic prescribed medications [2,10–18] has been identified as an opportunity for improvement [19–22].

The present study aims to assess the use of pharmacological secondary prevention of cardiovascular events and its relationship with the incidence of all-cause late mortality (beyond first year from the initial event) in a real-life setting of a Mediterranean population in Eastern Spain.

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2. Methods

2.1. Study design

This is a retrospective study designed to assess the real-life of secondary cardiovascular prevention and their impact on mortality in a population-based cohort from the Electronic Health Recording (EHR) system of the Valencian Community in Eastern Spain, that contains the medical records of over 92% of Valencia's population. Patients were followed up after suffering their first cardiovascular event and grouped according to different pharmacological strategies, ranging from none to the currently recommended three-drug regimen (antiplatelet, statin and RAS-b).

2.2. Sample selection and treatment grouping

Subjects had to be registered in the EHR system (Abucasis database), with at least 18 years at the time of the registered event, namely a hospital admittance due to stroke, myocardial infarction (MI) or coronary revascularization (REV) in the period from January 1st 2011 to December 31st 2013. The primary endpoint of the study was the time incidence of all-cause late mortality as recorded in the EHR system, during the period between January 1st 2012 and December 31st 2014 with a minimal follow-up of one year for every patient.

Patients were characterized by their initial event (stroke, MI and REV) and the intensity of the secondary prevention treatment that were receiving one year after the initial event as follows:

- Group 0 (G0): patients who after one year of the initial event were not taken any of the following treatments: antiplatelet, RAS-b or statin.
- Group 1 (G1): patients who after one year of the initial event were taken only one out of the three drug classes listed above.
- Group 2 (G2): patients who after one year of the initial event were taken only two out of the three drug classes listed above.
- Group 3 (G3): patients who after one year of the initial event were taken the three types of drugs classes

Treatments were drawn from the drug-specific EHR database GAIA in which all prescriptions were recorded. If during three consecutive months the patient did not collect the prescribed medication, then the treatment was removed. Treatment assessment was performed after one year of the initial event. Patients assigned to one group remained in that group, although they might have received another treatment regimen later and they were analyzed as for intent-of-treatment. We also performed a sensitivity analysis in the sub-sample of diabetic participants.

Data recorded included sociodemographic variables (gender, age, body mass index, lifestyle), medical history and cardiovascular risk factors: 1) Diabetes: defined as a medical diagnosis or antidiabetic drugs/insulin treatment or fasting blood glucose >200 mg/dL and HbA1c >7%, at the moment of the inclusion in the study; 2) Hypertension: defined by physician's diagnosis, elevation of systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg or treatment with antihypertensive drugs at the time of inclusion. 3) Hyperlipidemia; hypercholesterolemia, defined by medical diagnosis, treatment with lipid-lowering drugs or blood total cholesterol >250 mg/dL; hypertriglyceridemia, defined as medical diagnosis, treatment with specific drugs (fibrates or niacin or omega-3) or blood triglyceride level >300 mg/dL; or mixed dyslipidemia, defined as a medical diagnosis or combination of the above, at the time of inclusion. Pharmacological treatments were described according to the following therapeutic groups: antiplatelets, RAS-b and statins, Subjects that had not enough data for the analyses of the study objectives in their registries were disregarded.

2.3. Statistical analysis

Descriptive results of the demographic characteristics were expressed as the mean ± SD for continuous variables, or number (n) and percentage (%) for categorical variables. To compare groups of patients, parametric tests (t-student or ANOVA) or non-parametric tests (Mann-Whitney or Kruskal-Wallis) were used, according to the characteristics of variables and the number of groups to be compared. For qualitative variables the chi-square test was used.

Survival time using Cox proportional hazards models for drug group (G0, G1, G2, G3), were adjusted by age (continuous), gender (male, female), systolic blood pressure (continuous), LDL-cholesterol (continuous), HDL-cholesterol (continuous), diabetes (yes, no) (Model 1). We further adjusted for hypertension (yes, no) (Model 2) and for dyslipidemia (yes, no) (Model 3). These analyses were repeated for the diabetic sub-sample.

For statistical analysis we used the survey package in R software (version 3.0.3; R Development Core Team 2014) for the statistical analysis. The level of significance was 0.05.

3. Results

3.1. Study patients

We identified 174,654 subjects with a first major adverse cardiovascular event (MACE) from 1 January 2011 onwards. We removed 3182 (1.9%) subjects who died during the first year after the initial event and another 3822 (2.2%) subjects whose first event was death. Thirty-five (0.02%) additional subjects had their first and second event the same day and were also excluded. Another 2869 (1.6%) subjects with their treatment assessment done before one year after the initial event were removed. Finally, we had to exclude another 72,310 (41.4%) subjects due to any missing value in the variables of interest. Age, sex distribution and initial events in those no selected are in Supplementary Table 1.

A total of 92,436 subjects were finally included in the analysis with a total of 157,241 person-year. The inclusion event was stroke in 55,937 (60.5%), MI in 28,311 (30.6%), and REV in 8188 (8.9%). The general characteristics of the study population are shown in Table 1. There were 55,402 (60%) men, the mean age was 72 years, 74,743 (80.9%) had hypertension, 38,752 (42.9%) diabetes and 4685 (5%) were active smokers at the time of the inclusion event.

3.2. Drugs used for cardiovascular protection

In the drug assessment among the subjects included in the study after one year of the first event, 3803 (4.1%) were not taking any cardiovascular preventive drug (G0), 18,714 (20.2%) only one drug (G1), 30,440 (32.9%) two drugs (G2) and 39,479 (42.7%) the three recommended classes of drugs (G3) as it has been summarized in Table 1. The distribution of drug intake by each of the initial events is in Supplementary Table 2. Overall the drug treatment was better in younger subjects (use of three drugs in 53% of subjects <72 years old) and in those after MI and revascularization as compared with those after stroke.

Overall, 68,782 (74.4%) were taken antiplatelets, 61,689 (66.7%) statins and 68,653 (74.2%) RAS-b. Among the factors related with the use of medication, the risk of taking no drugs or only one was increased in males (RR 1.26, CI 95% 1.24–1.64) and in those with a previous stroke (RR 1.71, CI 95% 1.68–1.74).

Diabetic subjects were more adherent to treatment (RR 1.27, CI 95% 1.24–1.64). In this subpopulation a total of 38,752 subjects were finally included in the analysis with a total of 65,878 persons-year. None of the three considered cardiovascular preventive drug classes were taken by 1630 (4.2%) subjects (G0) one year after their initial cardiovascular event, 6478 (16.7%) only one drug (G1), 12,667 (41.6%) two drugs (G2) and 17,977 (46.4%) the three classes of drugs (G3). A previous stroke (RR 1.61, CI 95% 1.54–1.67) and active smoking (RR 1.18, CI 95% 1.03–1.30) were factors related with a low adherence.

3.3. All-cause late mortality

In the total study population during the accumulated observation period of 1.7 ± 1.5 years, 4664 (5.0%) out of 92,436 subjects died with an incidence of 11,5 per 1000 patients/year. The distribution among the groups by the intensity of drug prevention and their general characteristics are shown in Supplementary Table 3. The number of patients that died among the subjects with stroke was 2963 (5.2% and incidence 11.8/1000/year) while it was 1387 (4.9% and incidence 11.9/1000/year) among the subjects with a previous MI and 314 (3,8% and incidence 8.5/1000/year) after a REV procedure.

In the diabetic subgroup, out of a total of 38,752 subjects, 2511 (6.5%, incidence 14,9/1000/year) died. The number of patients that died among the subjects with a stroke was 1513 (6,7% and incidence 15,3/1000/year) while the mortality among the subjects with a MI was 791 (6.7%, incidence 16.1/1000/year) and 207 (4.7% and incidence 10.6/1000/year) after a revascularization procedure.

3.4. Impact of cardiovascular protection treatment on mortality

Regarding the total population, the results of the Cox-proportional hazard ratios of mortality in each group of drug intensity prevention (G0, G1, G2 and G3) and the survival curves are shown in Table 2

Table 1
Participants' demographic and clinical characteristic of subjects grouped by the number of cardiovascular preventive drugs.

Group	Group 0 N = 3803	Group 1 N = 18,714	Group 2 N = 30,440	Group 3 N = 39,479
Inclusion event				
MI (n)/(%)	424 (11.2)	2511 (13.4)	6848 (22.5)	18,528 (46.9)
Stroke (n)/(%)	3131 (82.3)	15,280 (81.7)	21,378 (70.2)	16,148 (40.9)
Revascularization (n)/(%)	248 (6.5)	923 (4.9)	2214 (7.3)	4803 (12.2)
Age of inclusion event (y)/(sd)	74.9 (13.4)	74.3 (12.5)	73.3 (11.3)	69.9 (11.4)
Men (n)/(%)	1924 (50.6)	9571 (51.1)	17,242 (56.6)	26,665 (67.5)
BMI (kg/m2)/(sd)	28.40 (5.3)	28.67 (4.9)	29.05 (4.8)	29.48 (4.6)
SBP (mmHg)/(sd)	130.8 (19.0)	133.2 (19.6)	134.4 (19.5)	134.3 (19.6)
DBP (mmHg)/(sd)	73.4 (11.5)	74.6 (11.5)	74.6 (11.4)	74.5 (11.4)
Hypertension (n)/(%)	930 (24.5)	10,912 (58.3)	23,477 (77.1)	39,424 (99.1)
Fasting glucose (mg/dl)/(sd)	111 (43.7)	107 (36.9)	112 (38.5)	115 (38.67)
HbA1c (%)	6.5 (1.4)	6.4 (1.3)	6.5 (1.3)	6.6 (1.3)
Diabetes (n)/(%)	1630 (42.9)	6478 (34.6)	12,667 (41.6)	17,977 (46.4)
Total cholesterol (mg/dl)/(sd)	183 (39.3)	184 (39.1)	175 (39.6)	162 (37.6)
HDL-cholesterol (mg/dl)/(sd)	50 (14.7)	51 (14.8)	49 (14.0)	46 (12.8)
LDL-cholesterol (mg/dl)/(sd)	109 (31.5)	110 (31.7)	101 (32.4)	90 (30.0)
Triglycerides (mg/dl)/(sd)	122 (58.3)	124 (58.3)	128 (59.8)	131 (60.8)
eGFR (mil/min/1.73 m2)/(sd)	76.2 (29.6)	74.2 (26.0)	72.6 (25.4)	74.0 (24.2)
Current smokers (n)/(%)	150 (19.7)	810 (19.5)	1468 (19.6)	2301 (21.9)

() The percentage or standard deviation in each group of cardiovascular prevention drugs used is shown in brackets.

(upper panel) and in Fig. 1A, respectively. Using the mortality of subjects in G0 as the reference, there was a significant and progressive reduction in the HR across the G1, G2 and G3. Mortality was consistently reduced around 15–20%, 30% and 40% respectively, depending on the model used. This effect was similar in patients with stroke and with MI but not for revascularization (Table 2).

In the diabetic subgroup, the same survival analysis models were done. The results are provided in Table 2 (bottom panel) and the survival curves in Fig. 1B. Using the mortality in G0 subjects as the reference, there also was a significant and progressive reduction in the HR of the different models but only across the G2 (around 20–30%) and G3 (30–40%). An average non-significant reduction of 5% was found in G1. As in general population, the more drug classes were taken, the more intense the risk reduction on late mortality in diabetics. Likewise, the effect was similar in patients with stroke and with MI but not for revascularization, Table 3.

3.5. Impact of cardiovascular protection for each kind of drug on mortality

Overall, 68,782 (74.4%) were taken antiplatelets, 61,689 (66.7%) statins and 68,653 (74.2%) RAS-b with a percentage of mortality of 3834 (4.81%), 3277 (4.44%) and 3407 (4.94%), respectively. Adjusted by age, sex, diabetes and for each kind of treatment, the mortality HR was in those receiving antiplatelets 0,90 (0,83–0,97), statins 0.89 (0,82–0,96) and RAS-b 1,03 (0,96–1,11). The comparison of high potency statins, rosuvastatin and atorvastatin 80 mg, with the low potency ones denotes better reduction of mortality in subjects after MI or REV, HR 0.75 (0,65–0,85) and 0.76 (0,58–1,00), respectively.

4. Discussion

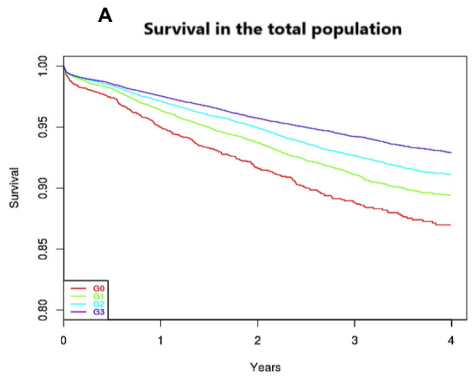
Although guidelines recommend therapies to reduce MACE in patients after a stroke, MI or those with atherosclerotic disease, a wide gap between the recommendations and the reality exists. In the present study, a large gap in adherence was observed, with only 43% patients having the full pack of drugs for secondary prevention one year after having a stroke, MI or coronary REV. The lack of adherence impacted all-cause late mortality, with a steady increment in the protection according to the number of drug classes taken for cardiovascular protection. The risk of low adherence was higher in those after a stroke that after a coronary heart disease event, MI or REV. The impact was observed in the total population of the study and in the subgroup of diabetics although it differed slightly when the initial event was a stroke or a MI/REV.

The present data of adherence to drugs for secondary prevention agree with other previously reported. A meta-analysis of data on 376,162 patients from 20 studies assessing adherence in people who have had an MI showed that adherence across all studies was 66% [23]. After 6 months of follow up in patients hospitalized for MI or with atherosclerotic disease, only 43% were fully adherent to ACEi or statins [24]. A Spanish cohort study included 7462 patients with acute coronary syndrome; after 9 months following hospital discharge, the proportion of patients having enough treatment to cover 75% of the follow-up period was 69.9% of patients taking antiplatelets, 43.3% taking beta-blockers, 45.4% taking angiotensin antagonists, and 58.8% taking statins [2].

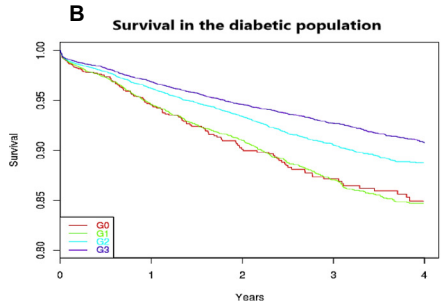
The fact that low adherence to prescribed treatment is an important barrier to achieving optimal treatment targets has been a matter of concern, although few publications have analyzed this association. A recent study including 4015 post-MI patients and 12,976 patients with atherosclerosis showed that the fully adherent group had a significantly lower rate of MACE than the nonadherent (18.9% vs. 26.3%; HR: 0.73; $p = 0.0004$) and partially adherent (18.9% vs. 24.7%; HR: 0.81; $p = 0.02$)

Table 2
Cox proportional hazard models of mortality risk in the total population and in the diabetic subgroup, according to the intensity of pharmacological prevention.

Drug group	Subjects	Deaths	Percent	HR (CI 95%) Model 1	HR (CI 95%) Model 2	HR (CI 95%) Model 3
All subjects						
	92,436	**4664**	5.0%			
G0	3803	313	8.2%	Ref.	Ref.	Ref.
G1	18,714	1203	6.4%	0.84 (0.75, 0.96)	0.81 (0.71, 0.93)	0.83 (0.73, 0.95)
G2	30,440	1604	5.3%	0.71 (0.63, 0.80)	0.67 (0.58, 0.77)	0.70 (0.60, 0.82)
G3	39,479	1544	3.9%	0.61 (0.54, 0.70)	0.57 (0.49, 0.66)	0.61 (0.51, 0.74)
Diabetic subjects						
	38,752	**2511**	6.5%			
G0	1630	154	9.4%	Ref.	Ref.	Ref.
G1	6478	592	9.1%	0.96 (0.80, 1.15)	0.93 (0.77, 1.12)	0.97 (0.80, 1.17)
G2	12,667	848	6.7%	0.75 (0.63, 0.89)	0.71 (0.59, 0.86)	0.79 (0.63, 0.98)
G3	17,977	917	5.1%	0.66 (0.55, 0.79)	0.62 (0.50, 0.76)	0.72 (0.56, 0.95)



Group 0				
3803	2276	1557	977	435
Group 1				
18714	11362	7954	5120	1415
Group 2				
30440	18218	12843	8324	2151
Group 3				
39479	22006	15392	9993	3868



Group 0					
1630	952	642	423		218
Group 1					
6478	3851	2675	1712		915
Group 2					
12667	7525	7483	3318		1847
Group 3					
17977	10081	10047	4505		2502

Fig. 1. Survival curves for the all-cause late mortality in the overall population (1A) and in the diabetic population (1B) according to the intensity of the pharmacological prevention for model 3. G0: patients who after one year of the initial event were not receiving any of the following treatments: antiplatelets, RAS-b or statin. G1: patients who after one year of the initial event were receiving only one out of the drugs listed above. G2: patients who after one year of the initial event were receiving only two out the drugs listed above. G3: patients who after one year of the initial event were receiving the three types of drugs.

groups at 2 years [24]. And, the fully adherent group had reduced per-patient costs for MI hospitalizations of $369 and $440 compared with the partially adherent and nonadherent groups, respectively. Another study in Germany included 1003 patients after an acute coronary syndrome event in a 12-month structured program (without control group) managed in a special setting by office-based cardiologists [25]. Treatment rates of recommended medications remained very high at 12 months, comparable to rates at hospital discharge, and a total of 798 patients (79.6%) were still participating in the program. 1-year mortality was 7.6%, which was considered low compared to other registries.

A different study included 4655 survivors of MI and showed that the highest risk of mortality was observed in patients adherent to none of the medications (antiplatelets, statins, and RAS-b) compared with adherents to all medications, with a 38% increase in risk of mortality (HR, 1.38; 95% CI, 1.06–1.80) [26]. The same authors concluded in a different work that outpatient adherence to recommended therapy in patients with MI was suboptimal and was related to health services utilization [27]. Yet, another group showed that improved adherence to statins was associated with a lower risk of stroke, particularly of ischemic stroke [28].

To our knowledge the present study is the first at a population level, based on real world practice from the EHR of the Valencian Community, analysing the relationship between the lack of adherence to the three preventive cardiovascular drug classes and mortality in subjects after a MACE. Given the advances in information systems and the increase in the electronic health recording, it is now possible to develop combined research and surveillance programs that encompass a large number of subjects [29]. This study reflects the view that EHR-based studies from general practice are the most representative setting for evaluating burden of disease associated to health conditions such as renal dysfunction.

Patients taking the three classes of drugs (G3) had a 39% (CI 95% 30–46%) reduction in mortality rates compared to those who did not take any cardiovascular preventive drugs (G0). The protective effect of the treatment was evident for each drug status independently, for instance, patients taking only one drug (G1), had a 26% (CI 95% 4–25%) reduction in late mortality rates compared to those who did not take any cardiovascular preventive drugs (G0). For patients with diabetes, the results were quite similar, except for patient taking only one drug (G1), where there was no statistical significance in the reduction of mortality rates.

Regarding causes of nonadherence, it is generally recognized that this is determined by the interplay of socioeconomic, medication-related, condition-related, health system-related, patient-related factors and medical inertia [30]. Few studies have explored associations between cognitive impairment and medication adherence post-stroke, with substantial heterogeneity in studies, but in a recent metanalysis no evidence was found [31]. Younger age, depression, and a complex drug treatment plan were associated with lower medication adherence for secondary prevention following acute MI [19]. A recent metanalysis including 35 studies, randomizing 925,171 participants concluded that intensification of patient care interventions improves short- and long-term medication adherence to lipid-lowering medication [32]. A strategy to reduce poor adherence is the use of a fixed-dose combination or polypill, including key medications to reduce cardiovascular risk, as a once-daily dose pill [33]. In the FOCUS project, the polypill group showed improved adherence compared with the group receiving separate medications after 9 months of follow-up: 50.8% versus 41% ($p = 0.019$; intention-to-treat population) and 65.7% versus 55.7% ($p = 0.012$; per protocol population) [19].

5. Limitations

Our study should be contemplated in its strengths and weaknesses. Real world data coming from EHR provide useful information regarding effectiveness in a real-world setting of heterogeneous populations and interventions in contrast with randomized clinical trials that let us estimate efficacy in such a highly-controlled experimental setting of homogeneous populations that external validity can result threatened.

Limitations are the lack of information about the cause of mortality and the fact that assessment of adherence was done one year after the initial event with the assumption that that was the treatment of the subject during the study period as in an intention-to-treat analysis. The mortality adjustment was only done considering certain main risk factors (age, gender, blood pressure, lipid profile and presence of diabetes) but other well-known prognostic variables such as the left ventricular ejection fraction or the NYHA functional class could not be included.

6. Conclusion

In conclusion, disregarding recommendation about drug secondary prevention is associated with in a huge impact in mortality. Whether the cause is a lack of patient compliance or physician lack of prescription, the consequence is the same, a higher risk of late death due to an avoidable factor. Every effort should be made to improve late survival

Table 3
Cox proportional hazard models of mortality risk in the population by initial event and in non-diabetic and diabetic subgroup, according to the intensity of pharmacological prevention.

	Subjects	Deaths	Percent	HR (CI 95%) Model1	HR (CI 95%) Model2	HR (CI 95%) Model3
No-diabetics						
STROKE						
Group 0	3131	251	8.02	Ref.	Ref.	Ref.
Group 1	15,280	966	6.32	0.87 (0.76,1)	0.81 (0.71,0.93)	0.83 (0.73,0.95)
Group 2	21,378	1061	4.96	0.69 (0.6,0.79)	0.67 (0.58,0.77)	0.7 (0.6,0.82)
Group 3	16,148	685	4.24	0.61 (0.52,0.7)	0.57 (0.49,0.66)	0.61 (0.51,0.74)
MI						
Group 0	424	48	11.32	Ref.	Ref.	Ref.
Group 1	2511	179	7.13	0.64 (0.46,0.88)	0.68 (0.49,0.95)	0.67 (0.48,0.94)
Group 2	6848	438	6.4	0.61 (0.45,0.83)	0.69 (0.5,0.95)	0.66 (0.46,0.95)
Group 3	18,528	723	3.9	0.52 (0.38,0.69)	0.60 (0.43,0.85)	0.56 (0.37,0.86)
Revascularization						
Group 0	248	14	5.65	Ref.	Ref.	Ref.
Group 1	923	58	6.28	1.07 (0.59,1.93)	1.15 (0.63,2.09)	1.3 (0.71,2.39)
Group 2	2214	105	4.74	0.76 (0.43,1.34)	0.87 (0.47,1.61)	1.28 (0.64,2.58)
Group 3	4803	136	2.83	0.46 (0.26,0.8)	0.55 (0.28,1.07)	1.05 (0.44,2.51)
Diabetics						
STROKE						
Group 0	1267	116	9.16	Ref.	Ref.	Ref.
Group 1	4942	450	9.11	1.01 (0.82,1.23)	0.95 (0.77,1.18)	1 (0.8,1.24)
Group 2	8521	539	6.33	0.74 (0.61,0.91)	0.68 (0.54,0.85)	0.77 (0.59,0.99)
Group 3	7780	408	5.24	0.67 (0.54,0.83)	0.59 (0.46,0.76)	0.72 (0.52,0.99)
MI						
Group 0	188	28	14.89	Ref.	Ref.	Ref.
Group 1	986	103	10.45	0.65 (0.43,0.99)	0.71 (0.46,1.09)	0.71 (0.46,1.11)
Group 2	2936	240	8.17	0.54 (0.36,0.8)	0.62 (0.4,0.95)	0.63 (0.38,1.02)
Group 3	7687	420	5.46	0.47 (0.32,0.69)	0.55 (0.35,0.87)	0.57 (0.32,0.99)
Revascularization						
Group 0	175	10	5.71	Ref.	Ref.	Ref.
Group 1	550	39	7.09	1.09 (0.54,2.21)	1.09 (0.53,2.23)	1.25 (0.6,2.6)
Group 2	1210	69	5.7	0.88 (0.45,1.73)	0.85 (0.4,1.79)	1.26 (0.54,2.93)
Group 3	2510	89	3.55	0.54 (0.28,1.05)	0.51 (0.23,1.13)	1.00 (0.35,2.82)

after a major MACE event by increasing the current adequate treatment rates.

Declaration of Competing Interest

The other authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.05.071.

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