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Chronic aspirin and statin therapy in patients with impaired renal function and acute coronary syndromes: results from the IN-ACS Outcome Registry

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Abstract

Background: The cardioprotective role that statin and aspirin has appears to be reduced in patients with chronic kidney disease (CKD). This analysis aims to evaluate the impact of statin and aspirin on the outcome of patients with CKD and acute coronary syndrome (ACS).

Methods: All patients who were enrolled in the IN-ACS Outcome registry, diagnosed with CKD, were included in our analysis. We divided patients into four groups, according to previous chronic therapy: neither aspirin nor statin therapy (Group 1), aspirin only therapy (Group 2), statin only therapy (Group 3) and aspirin plus statin therapy (Group 4).

Results: Of the 5483 patients enrolled that had data on glomerular filtration rate available, 1484 had CKD: These segregated into 589 patients in Group 1, 477 in Group 2, 89 in Group 3 and 329 in Group 4. Despite having a higher baseline risk profile, groups 3 and 4, as compared to the other two groups, exhibited a significantly lower in-hospital mortality (1% in Group 3, 2% in Group 4; but 8% in Group 1 and 7% in Group 2, $p = 0.0007$); while at 30 days it remained so, as it was 1% in Group 3, 4% in Group 4 (and 10% in Group 1 and 10% in Group 2 $p = 0.0002$); and at 1 year it was 11% in Group 3 and 13% in Group 4 (compared to 20% in Group 1 and 23% in Group 2, $p = 0.0012$).

Conclusions: In a large cohort of patients with CKD and ACS, chronic treatment with statin or the combination of aspirin and statin is associated with short-term and long-term better outcomes for in-hospital mortality, as compared to those receiving no therapy or aspirin therapy alone.

Keywords

Aspirin, statin, glomerular filtration rate, kidney disease, acute coronary syndrome, heart attack risk, mortality, preventive therapy

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Introduction

Chronic use of aspirin and statin may reduce the risk of subsequent myocardial infarction (MI) and improve outcome in patients with documented ischaemic heart disease[1,2] (IHD) or in patients at high risk of a first cardiovascular event.[3,4] Moreover, previous aspirin and statin therapy may interfere with the clinical presentation of acute myocardial infarction, with a higher incidence of Non-ST-Elevation MI (NSTEMI) as compared to ST-Elevation MI (STEMI).[5,6] However, in patients with impaired renal function, which is a

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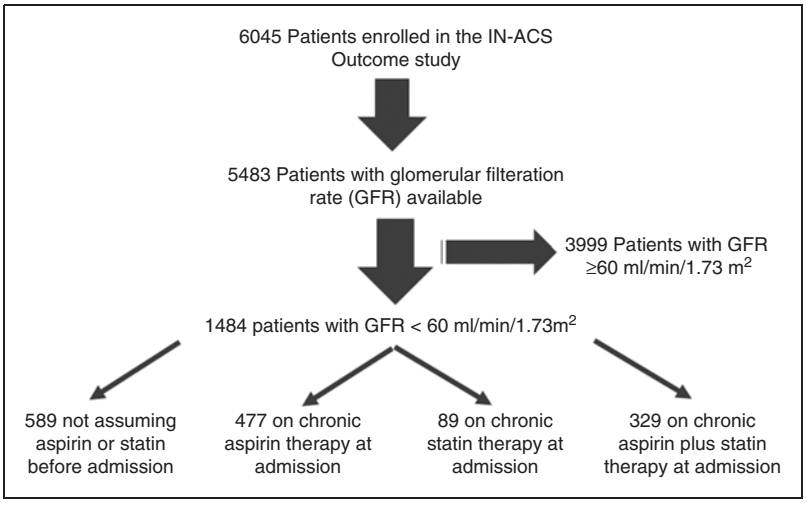

Figure 1. Flow chart for patient enrolment. Of the 6045 patients with ACS included in the IN-ACS Outcome Study, 1484 patients showed impaired renal function. According to their previous history of statin or aspirin therapy, these patients were divided in four groups: no aspirin nor statin therapy (Group 1), aspirin therapy (Group 2), statin therapy (Group 3), and aspirin plus statin therapy (Group 4).
ACS: Acute coronary syndrome.

condition associated with higher prevalence of traditional risk factors for atherosclerosis[7] and with impaired prognosis after acute MI,[8] the cardioprotective role of aspirin and antiplatelet therapy appears to become reduced.[9,10] The results of some trials of statin therapy in patients with impaired renal function[11–14] show conflicting results, plus a meta-analysis of randomized controlled trials in patients with impaired renal function treated with statin failed to show a treatment benefit to all-cause mortality.[15]

The current limitation to the understanding of the efficacy and safety of aspirin and statin therapy in patients with impaired renal function is directly due to the exclusion of patients with impaired renal function in many randomized studies.[16] The aim of this study was to assess the effects of previous chronic aspirin and statin use on the outcomes of patients having impaired renal function, with respect to hospital admission for acute coronary syndrome (ACS). To address this issue, the population of the IN-ACS Outcome Study was evaluated.

Methods

The IN-ACS Outcome Study is an Italian observational, multicentre (38 centres) study designed to assess epidemiology, management and outcome of patients with ACS (STEMI and non-ST-elavtion acute coronary syndromes (NSTEACS)).[17] The enrolling interval time was between December 2005 and February 2007, with a 12-month enrolment period for each centre.

The patient characteristics, in-hospital diagnostic and therapeutic procedures, and prescriptions at discharge were collected using a web-based Case Record Form (CRF) and stored in a central database. Patient management was based on clinical decisions by the individual's physician. Clinical follow-up data at the 30-day time point and the 1-year point were collected by the local team and entered in the central database.

Of the 6045 patients with ACS (either myocardial infarction without ST elevation (NSTEMI) or acute coronary syndrome without ST elevation (NSTEACS)) enrolled in the IN-ACS Outcome Study, 5483 patients had data on glomerular filtration available and, among these, 1484 patients that showed an impaired renal function at admission were chosen to be included in our study. Renal function was evaluated using the Modification of Diet in Renal Disease equation,[18] which incorporates age, race, sex and creatinine levels. We considered that individuals with impaired renal function had glomerular filtration rate values $<60\,\mathrm{ml/min/1.73\,m^2}$.

According to chronic statin or aspirin therapy before the index ACS, these patients were divided in 4 Groups: Group 1, no aspirin nor statin therapy ($n=589$ patients); Group 2, aspirin therapy ($n=477$ patients); Group 3, statin therapy ($n=89$ patients); and Group 4, aspirin plus statin therapy ($n=329$ patients, Figure 1).

A diagnosis of STEMI was defined as chest pain associated with an electrocardiographic ST-elevation of 1 mm or more, in two or more contiguous leads, or a new left bundle-branch block within 48 hours after the onset of chest pain.

A diagnosis of NSTEACS was defined as chest pain within 48 hours, associated with an electrocardiographic ST-segment depression or T-wave inversion, or transient (<20 minutes) ST elevations with (NSTEMI) or without (unstable angina) increases in the troponin or creatine kinase-myocardial band isoenzyme (CK-MB) levels.

Exclusion criteria were conditions where the ACS that occurred was secondary to other reasons (such as anaemia, trauma or non-cardiac surgery), the patient's enrolment in other centres for the same study, and the inability to obtain a signed informed consent.

Signed informed consent was obtained from all patients at enrolment.

In each participating centre, the local Institutional Ethical Board approved the study.

Endpoint

The primary end-points of this sub-study were the 30-day and 1-year all-cause mortality.

The two secondary end-points included: (a) all-cause mortality or re-infarction at 30-days and (b) 1-year and a global net clinical end-point of death, reinfarction, stroke, new cardiac revascularization and major bleeding at the 30-day and 1-year time points.

Definitions of the events

MI was defined according to the revised criteria proposed by the joint European and American Task Force.[19]

Re-hospitalization for STEMI was defined as re-hospitalization due to persistent chest pain, associated with persistent ST elevation of >1 mm in at least two contiguous peripheral leads or >2 mm in at least two contiguous precordial leads, and an increase of CK-MB and/or troponins.

Re-hospitalization for NSTEMI was defined as re-hospitalization due to chest pain lasting at least 5 minutes in the last 24 hours, associated with typical electrocardiogram (ECG) changes and an increase of CK-MB and/or troponins.

Stroke was defined as a neurological disability lasting more than 24 hours.

Bleeding was defined as major when it was intracranial, retroperitoneal, intraocular, or with any haemoglobin level reduction of greater than 5 g/dl (a haematocrit reduction >15%).

Statistical analyses

Continuous variables were reported as mean and standard deviation; and compared by ANOVA if normally distributed, or Kruskal-Wallis test, if not. Categorical variables were reported as frequencies and percentages; they were compared by Pearson's chi-square test. Plots of the Kaplan-Meier estimates of the survival curves of the four therapeutic groups were presented along with the results of the log-rank test. Multivariable analysis was performed with the aim of identifying independent predictors of all-cause mortality at 1-year follow-up. A Cox model was used when considering variables of clinical interest; if more than two categories were present, dummy variables were introduced to define a reference group (RG). Also, we inserted the following in the model: age ≥75 years, gender, diabetes, history of hypertension, history of coronary artery disease, heart rhythm (atrial fibrillation/flutter, sinus rhythm, other rhythm), history of heart failure, history of cerebrovascular or peripheral artery disease, chronic pulmonary disease, systolic blood pressure ≤100, glomerular filtration rate <30 ml/min/1.73 m^2, ejection fraction <40% and previous chronic therapy (nor aspirin nor statin, aspirin, statin, aspirin plus statin). Age, glomerular filtration rate, ejection fraction and systolic blood pressure were entered in the model using the clinical cut-off. Results were expressed as Hazard Ratio (HR) with 95% Confidence Interval (CI). For all tests, a value of 2-tailed $p \leq 0.05$ was considered statistically significant. SAS software (version 9.2) was used for all statistical analysis.

Results

The clinical characteristics of the four groups of patients are presented in Table 1. Patients who were pre-treated with aspirin and/or statin (Group 2, 3 and 4) had more cardiovascular risk factors than patients who were not pre-treated, except for active smoking habits that were more frequent in Group 1. Moreover, the pre-treated patients more frequently had a history of previous cardiac revascularization. During hospitalization, patients in Group 3 (those pre-treated with statin alone) were more frequently revascularized, compared to the three other groups that did not show significant differences among them (Table 1).

In-hospital and long-term mortality

In-hospital mortality was significantly lower in patients taking chronic statin therapy, as compared to patients without therapy or patients taking only aspirin (8% in Group 1, 7% in Group 2, 1% in Group 3, and 2% in Group 4; $p = 0.0007$, Table 2). The lower mortality for Group 3 and Group 4 was also observed at both the 30-day follow-up ($p = 0.0002$) and 1-year follow-up ($p = 0.001$, Table 2 and Figure 2).

At multivariable analysis, previous statin therapy alone or in combination with aspirin were both

associated with lower 1-year mortality (HR 0.44, 95% CI 0.23-0.85, $p = 0.015$ for Group 3; H R 0.57, 95% CI 0.39-0.82, $p = 0.005$ for Group 4, respectively). The other independent predictors of 1-year mortality were: female sex, gender, age ≥75 years, previous heart failure, atrial fibrillation at admission, other rhythm at admission, history of cerebro-vascular or peripheral artery disease and systolic blood pressure ≤100 mmHg at admission, ejection fraction <40% and glomerular filtration rate <30 ml/min/1.73 m^2 (Table 3).

Secondary end-points

There were no significant differences in the rate of in-hospital re-infarction, stroke or major bleeding among the four groups (Table 2). At the 30-day follow-up, there was a significantly lower incidence of the combined end-points of death and reinfarction in Group 3 and Group 4, compared to Group 1 and Group 2 ($p = 0.001$, Table 2). There were no significant differences for the combined net clinical end-point among the four groups ($p = 0.08$, Table 2).

At the 1-year follow-up, Group 3 showed the lowest rate of the combined end-points of death and reinfarction, while Group 2 had the highest rate ($p = 0.003$, Table 2). Moreover, the combined net clinical end-point was lowest in Group 3 and highest in Group 2 ($p = 0.02$, Table 2).

Impact of chronic aspirin and statin use on the presentation of myocardial infarction

Irrespective of their history of coronary artery disease, patients on chronic aspirin and/or statin therapy were less likely to have STEMI and more frequently had a

Table 1. Clinical characteristics of the four study groups

	No aspirin/statin ($n = 589$)	Aspirin alone ($n = 477$)	Statin alone ($n = 89$)	Aspirin + statin ($n = 329$)	p
Age[a]	76 ± 11	78 ± 9	73 ± 10	74 ± 9	<0.0001
Male gender	301 (51)	257 (54)	45 (51)	187 (57)	0.37
Smoking habit (1392 patients)[c]	113 (20)	34 (8)	12 (14)	38 (12)	<0.0001
Dyslipidaemia (1324 patients)[c]	167 (34)	165 (39)	68 (78)	241 (75)	<0.0001
Diabetes mellitus	168 (29)	184 (39)	38 (43)	140 (43)	<0.0001
Hypertension (1467 patients)[c]	438 (76)	395 (83)	80 (90)	282 (86)	<0.0001
Family history of IHD (1290 patients)[c]	83 (16)	67 (17)	15 (19)	64 (22)	0.15
Previous angina (1467 patients)[c]	71 (12)	129 (27)	29 (33)	145 (44)	<0.0001
Previous MI (1459 patients)[c]	70 (12)	171 (37)	23 (26)	185 (57)	<0.0001
Previous PCI	17 (3)	67 (14)	15 (17)	126 (38)	<0.0001
Previous CABG	14 (2)	51 (11)	10 (11)	68 (21)	<0.0001
Previous myocardial revascularization	25 (4)	109 (23)	23 (26)	163 (50)	<0.0001
Previous HF	32 (5)	50 (10)	12 (13)	40 (12)	0.0009
Previous stroke/TIA	42 (7)	77 (16)	9 (10)	40 (12)	<0.0001
History of vascular disease (1438 patients)[c]	102 (18)	187 (40)	30 (34)	121 (38)	<0.0001
Peripheral vascular disease (1425 patients)	70 (12)	137 (30)	24 (28)	104 (33)	<0.0001
Dialysis patient (1413 patients)[c]	9 (2)	12 (3)	2 (2)	5 (2)	0.64
Glomerular filtration rate (ml/min/1.73 m^2)[b]	48 [38–55]	45 [35–53]	47 [38–56]	45 [36–53]	0.01
EF (%)	46 ± 11	46 ± 12	45 ± 11	46 ± 11	0.82
COPD (1452 patients)[c]	77 (13)	73 (16)	11 (12)	39 (12)	0.54
STEMI at admission	261 (44)	122 (26)	24 (27)	59 (18)	<0.0001
NSTEACS at admission	328 (56)	355 (74)	65 (73)	270 (82)	<0.0001
Heart rate at admission[a]	83 ± 24	83 ± 21	81 ± 20	81 ± 21	0.38
Systolic BP at admission	136 ± 32	144 ± 31	134 ± 27	139 ± 30	<0.0001
Coronary revascularization	298 (51)	218 (46)	57 (64)	157 (48)	0.01

Results are expressed as absolute number with percentage in brackets; [a]Mean ± standard deviation; [b]Median with interquartile range; [c]Percentages were evaluated on patients with data available, reported in brackets for each variable; BP: blood pressure; CABG: coronary artery by-pass; COPD: chronic obstructive pulmonary disease; EF: Ejection fraction; HF: heart failure; IHD: ischaemic heart disease; MI: myocardial infarction; NSTEACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; TIA: transient ischaemic attack.

NSTEMI, compared to patients not taking these drugs (Table 1). Moreover, the group of patients receiving the combination therapy had the lowest incidence of STEMI, compared to patients taking only one drug (Table 1).

Discussion

In the patients with impaired renal function and ACS who enrolled in the IN-ACS Outcome multicentre study, previous use of chronic statin therapy was associated with a significantly lower mortality, as compared to patients not taking statin therapy. In contrast, the cardioprotective role of previous chronic aspirin therapy, in terms of a reduction of 1-year all-cause mortality, was observed only when used in combination with statin therapy and was not documented in patients treated with aspirin alone.

Patients with chronic renal failure have an increased cardiovascular risk[7] and their outcome after an ACS is worse, when compared to patients with normal renal function.[8] Despite this increased risk, patients with chronic kidney disease are generally less treated[20] and often excluded from large randomized trials.[16] In these patients, the cardioprotective role of preventive therapy appears to be reduced. In the DOPPS study,[9] which enrolled 28,320 patients with severe renal failure, chronic aspirin therapy was not associated with a reduction in the rate of death nor MI. Moreover, in a recent large meta-analysis,[10] the benefit of anti-platelet therapy among persons with chronic kidney disease seemed uncertain. Also, the role of statin in patients with renal failure is currently questionable. In the 4 D Study[11] and in the AURORA trial,[13] neither atorvastatin nor rosuvastatin had any statistically significant effects on cardiovascular death outcomes in patients with severe renal failure; however, recently the SHARP study[14,21] showed a significant reduction in major atherosclerotic events in a wide range of patients with chronic kidney disease who were treated with the combination of simvastatin and ezetimibe. In this study, we observed that a group of patients with

Table 2. Primary and secondary end-points

	No aspirin/statin ($n=589$)	Aspirin alone ($n=477$)	Statin alone ($n=89$)	Aspirin + statin ($n=329$)	p	p^b
Death						
In hospital	48 (8)	35 (7)	1 (1)	8 (2)	0.0007	0.0001
30 days	59 (10)	46 (10)	1 (1)	12 (4)	0.0002	<0.0001
1 year	120 (20)	108 (23)	10 (11)	43 (13)	0.001	0.0002
Re-infarction						
In hospital	10 (2)	11 (2)	1 (1)	7 (2)	0.83	0.89
30 days	11 (2)	17 (4)	1 (1)	11 (3)	0.23	0.93
1 year	23 (4)	40 (8)	3 (3)	29 (9)	0.007	0.26
Death + Reinfarction						
30 days	67 (11)	59 (12)	2 (2)	20 (6)	0.0012	0.0002
1 year	137 (23)	135 (28)	13 (15)	62 (19)	0.003	0.002
Stroke						
In hospital	5 (1)	7 (1)	0 (0)	4 (1)	0.57	0.99
30 days	7 (1)	9 (2)	0 (0)	5 (2)	0.52	0.84
1 year	11 (2)	17 (4)	2 (2)	8 (2)	0.37	0.94
Major bleeding						
In hospital	7 (1)	8 (2)	0 (0)	2 (1)	0.38	0.22
30 days	7 (1)	10 (2)	0 (0)	3 (1)	0.28	0.29
1 year	9 (2)	12 (3)	1 (1)	4 (1)	0.47	0.42
Net clinical outcome[a]						
30 days	122 (21)	95 (20)	9 (10)	56 (17)	0.08	0.04
1 year	210 (36)	196 (41)	24 (27)	107 (33)	0.02	0.02

Results are expressed as absolute number and percent in brackets; [a]Death, reinfarction, stroke, new cardiac revascularization and major bleeding
[b]p-value for Group 1 (no aspirin/statin) and Group 2 (aspirin alone), compared to Group 3 (statin alone) and Group 4 (statin + aspirin).

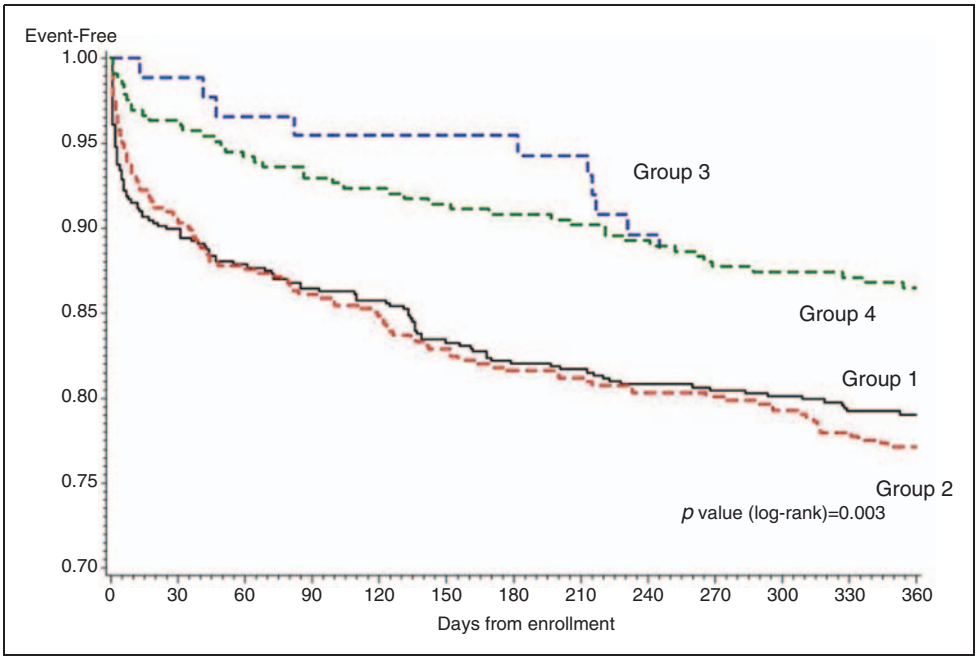

Figure 2. Kaplan-Meier curves in the four groups of patients, for the primary end-point (all causes of death).

Table 3. Multivariable analysis: Independent predictors of all causes of death at 1-year follow-up

	HR	95% CI	*p*
All causes of death at 1-year follow-up			
Chronic statin therapy	0.44	0.23–0.85	0.015
Chronic aspirin and statin therapy	0.57	0.39–0.84	0.005
Female sex	1.39	1.09–1.79	0.009
Age ≥75 years old	2.34	1.72–3.17	<0.0001
Previous heart failure	1.47	1.05–2.06	0.03
Atrial fibrillation at admission	1.45	1.05–1.99	0.02
Other rhythm at admission	1.82	1.15–2.89	0.01
SBP ≤100 mmHg at admission	2.46	1.81–3.35	<0.0001
Ejection fraction <40%	2.24	1.73–2.91	<0.0001
GFR <30 ml/min/1.73 m^2	2.58	1.98–3.34	<0.0001
History of vascular disease	1.32	1.02–1.71	0.036

CI: confidence interval; GFR: glomerular filtration rate; HR: hazard ratio; SBP: systolic blood pressure.

different degrees of renal failure exhibited a significant reduction in mortality among patients with ACS that had been pre-treated with statin therapy. In particular, despite a higher baseline risk profile, these patients appeared to show better survival and a better net clinical outcome, even including stroke and major bleeding. This effect was not observed in those patients who at baseline had taken only aspirin therapy, confirming that aspirin alone is perhaps not enough for patients with impaired renal function to prevent cardiovascular events.

Different reasons explaining the lack of effect of aspirin therapy in our patients might be: first of all, the group on aspirin therapy had a higher prevalence of cardiovascular risk factors, with an increased rate of prior myocardial revascularization and myocardial infarction, although these characteristics were also observed in the two groups assuming statin therapy; alternatively, the development of an acute coronary syndrome in patients with a background of routine antiplatelet therapy may mean the patients are more refractory or hyporesponsive to these agents. Indeed, previous studies show a higher incidence of aspirin resistance in patients with impaired renal function.[22,23] In this group of patients, the combination therapy of statin and aspirin might be of particular advantage, due to the potentially synergistic effect of these therapies,[24,25] as documented by the lower 1-year all-cause mortality we observed in our study. Finally, another possible explanation might be due to the adherence to aspirin therapy: In our study, prior aspirin therapy was self-reported by patients, so we have no information about the reality of patient compliance.

In a previous study[20] we showed that in patients with impaired renal function, chronic aspirin and statin therapy may interfere with the clinical presentation of acute MI, creating a high rate of NSTEMI and a reduced rate of STEMI. In this larger and multicentre study, we

confirmed that in patients with chronic kidney disease, the pre-treatment with aspirin and statin may reduce the incidence of STEMI. This shift in the presentation of acute MI is important, because it is associated with clinical and therapeutical consequences. Indeed, when diagnosing NSTEMI, we assume that, in many instances, a thrombus incompletely or intermittently has occluded a coronary artery, causing non-transmural or short-lasting transmural myocardial ischaemia. These patients will not benefit from thrombolysis and do not need emergent revascularization, but rather require stabilizing pharmacological treatment.[26,27] In contrast, in STEMI a thrombus completely and permanently occludes a coronary artery, causing transmural myocardial ischaemia, so the thrombus will benefit from an acute percutaneous coronary intervention or thrombolysis.[28,29] Therefore, in observing a shift in the incidence of STEMI to NSTEMI, fewer patients will require emergent percutaneous coronary interventions, which may be postponed for 48–72 hours, accommodating hospitals without on-site invasive facilities.

Study limitations

Our study has some limitations. First of all, despite a prospective collection of data in 38 centres, the chronic therapy given in the study was not randomized, so consequently there is some bias in the comparability of patients that could not be excluded due to the retrospective nature of the study, so these data should be confirmed in larger randomized trials. Moreover, the four groups of patients included a mix of patients who assumed chronic therapy for either primary or secondary prevention of cardiovascular events, yet the estimation of effects considering primary and secondary prevention therapy was not performed, due to the low number of patients. Finally, another limitation is the inclusion of patients with different degrees of impaired renal function, with a low number of patients on dialysis, so consequently we cannot extend our results to these patients.

Conclusions

In this large population of patients with impaired renal function presenting with ACS, statin therapy alone or in combination with aspirin therapy before the index ACS is associated with a better outcome at the 1-year follow-up time point. Large randomized studies in patients with impaired renal function should be performed, to address the possible synergistic effect of combined therapy with aspirin and statin in the sub-group of ACS patients having chronic renal failure.

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Conflict of interest

None declared.

References

1. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *NEJM* 1996; 335: 1001–1009.
2. ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; 2: 349–360.
3. Raju N, Sobieraj-Teague M, Hirsh J, et al. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *Am J Med* 2011; 124: 621–629.
4. The LIPID study group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *NEJM* 1998; 339: 1349–1357.
5. Spencer FA, Santopinto JJ, Gore JM, et al. Impact of aspirin on presentation and hospital outcomes in patients with acute coronary syndromes. *Am J Cardiol* 2002; 90: 1056–1061.
6. Spencer FA, Allegrone J, Goldberg J, et al. Association of statin therapy with outcomes of acute coronary syndromes: The GRACE study. *Ann Intern Med* 2004; 140: 857–866.
7. National Kidney Foundation. Kidney disease outcome quality initiative. Clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39: S1–S266.
8. Anavekar NS, McMurray JJV, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *NEJM* 2004; 351: 1285–1295.
9. Ethier J, Bragg-Gresham JL, Piera L, et al. Aspirin prescription and outcomes in hemodialysis patients: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2007; 50: 602–611.
10. Palmer SC, Di Micco L, Razavian M, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease. *Ann Intern Med* 2012; 156: 445–459.
11. Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *NEJM* 2005; 353: 238–248.
12. Holdaas H, Fellström B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: A multicentre, randomised, placebo-controlled trial. *Lancet* 2003; 361: 2024–2031.

13. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *NEJM* 2009; 360: 1395–1407.
14. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease: A randomised placebo-controlled trial. *Lancet* 2011; 377: 2181–2192.
15. Strippoli GFM, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: Meta-analysis and meta-regression of randomized controlled trials. *BMJ* 2008; 336: 645–651.
16. Charytan D and Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int* 2006; 70: 2021–2030.
17. Rizzello V, Lucci D, Maggioni AP, et al. Clinical epidemiology, management and outcome of acute coronary syndromes in the Italian network on acute coronary syndromes (IN-ACS Outcome Study). *Acute Card Care* 2012; 14: 71–80.
18. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann Intern Med* 1999; 130: 461–470.
19. Thygesen K, Alpert JS and White HD. Universal definition of myocardial infarction. *Circulation* 2007; 116: 2634–2653.
20. Sciahbasi A, Arcieri R, Quarto M, et al. Impact of chronic aspirin and statin therapy on presentation of patients with acute myocardial infarction and impaired renal function. *Prev Cardiol* 2010; 13: 18–22.
21. Berthold HK, Krone W, Erdmann E, et al. Lipid lowering in patients with chronic kidney disease: a SHARP turn in the wrong direction? *Eur J Cardiovasc Prev Rehabil* 2011; 18: 858–861.
22. Tanrikulu AM, Ozben B, Koc M, et al. Aspirin resistance in chronic renal failure. *J Nephrol* 2011; 24: 636–646.
23. Krasopoulos G, Brister SJ, Beattie WS, et al. Aspirin "resistance" and risk of cardiovascular morbidity: Systematic review and meta-analysis. *BMJ* 2008; 336: 195–198.
24. Hennekens CH, Sacks FM, Tonkin A, et al. Additive benefits of pravastatin and aspirin to decrease risks of cardiovascular disease. *Arch Intern Med* 2004; 164: 40–44.
25. Chapman MJ. From pathophysiology to targeted therapy for atherothrombosis: A role for the combination of statin and aspirin in secondary prevention. *Pharmacol Ther* 2007; 113: 184–196.
26. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007; 28: 1598–1660.
27. Gibler WB, Cannon CP, Blomkalns AL, et al. Practical implementation of the guidelines for unstable angina/Non-ST-elevation myocardial infarction in the emergency department. *Circulation* 2005; 111: 2699–2710.
28. Van de Werf F, Ardissino D, Betriu A, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2003; 24: 28–66.
29. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association's Task Force on Practice Guidelines. *Circulation* 2004; 110: e82–e293.