


Renin-Angiotensin-Aldosterone System Inhibitors, Statins, and Beta-Blockers in Diabetic Patients With Critical Limb Ischemia and Foot Lesions

Journal of Cardiovascular
Pharmacology and Therapeutics
2022, Vol. 27: 1-8
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10742484221101980
journals.sagepub.com/home/cpt


Paolo Cimaglia, MD¹, Davide Bernucci, MD², Laura Sofia Cardelli, MD², Anna Carone, MD¹, Giuseppe Scavone, MD¹, Marco Manfrini, PhD¹, Stefano Censi, MD¹, Simone Calvi, MD¹, Roberto Ferrari, MD, PhD^{1,2}, Gianluca Campo, MD^{1,2}, and Luca Dalla Paola, MD¹

Abstract

Medical therapy for secondary prevention is known to be under-used in patients with peripheral artery disease (PAD). Few data are available on the subgroup with critical limb ischemia (CLI). Prescription of cardiovascular preventive therapies was recorded at discharge in a large, prospective cohort of patients admitted for treatment of CLI and foot lesions, stratified for coronary artery disease (CAD) diagnosis. All patients were followed up for at least 1 year. The primary endpoint was major adverse cardiovascular events (MACE). 618 patients were observed for a median follow-up of 981 days. Renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, beta-blockers, and antithrombotic drugs were prescribed in 52%, 80%, 51%, and 99% of patients, respectively. However, only 43% of patients received optimal medical therapy (OMT), defined as the combination of RAAS inhibitor plus statin plus at least one antithrombotic drug. It was observed that the prescription of OMT was not affected by the presence of a CAD diagnosis. On the other hand, it was noticed that the renal function affected the prescription of OMT. OMT was independently associated with MACE (HR 0.688, 95%CI 0.475-0.995, $P = .047$) and, after propensity matching, also with all-cause mortality (HR 0.626, 95%CI 0.409-0.958, $P = .031$). Beta-blockers prescription was not associated with any outcome. In conclusion, patients with critical limb ischemia are under-treated with cardiovascular preventive therapies, irrespective of a CAD diagnosis. This has consequences on their prognosis.

Keywords

peripheral artery disease, diabetic foot, secondary prevention, statin, RAAS inhibitor

Introduction

Today, the WHO estimates that diabetes is the seventh leading cause of death in the world. Diabetic patients with the most advanced stage of peripheral artery disease (PAD), namely critical limb ischemia (CLI), have the worst prognosis.¹ As many as 50% of them die from cardiovascular (CV) causes within 5 years, a rate 5 times higher than that of diabetic patients without CLI.² This is likely due to the high prevalence of coronary artery disease (CAD), which, in turn, is associated with major adverse CV events.³ Thus, secondary prevention through lifestyle changes and aggressive medical therapy is mandatory for these patients.⁴ Guideline-directed secondary prevention has shown beneficial in diabetic patients with or without CAD.⁵ However, diabetic patients with PAD are undertreated compared to those with CAD,⁶⁻⁸ and there are little data for those with CLI.⁹ The reason for undertreating

these extremely high-risk patients is unknown and seems unjustified.

We have analyzed the prescription of optimal medical therapy (OMT) and its relationship with adverse events in a prospective cohort of diabetic patients with CLI and foot lesions, undergoing invasive procedures.

¹ Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy

² Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara, Cona, Italy

Manuscript submitted: August 17, 2021; **accepted:** April 30, 2022.

Corresponding Author:

Paolo Cimaglia, Maria Cecilia Hospital, GVM Care & Research, Via Corriera I, 48033 Cotignola (RA), Italy.
Email: pcimaglia@gvmnet.it



Methods and Materials

Clinical and procedural data from all patients admitted to the Diabetic Foot Unit of the Maria Cecilia Hospital (Cotignola, Italy) are recorded in a dedicated database, verified for accuracy against the clinical charts. The analysis is based on current clinical practice; therefore, the regulatory authorities required an ordinary written informed consent to procedures and data collection, which was obtained from all patients. The protocol of the study is in accordance with the Declaration of Helsinki.

Study Population

The inclusion criteria were: (i) age greater than 18 years; (ii) diagnosis of diabetes mellitus; (iii) diagnosis of critical limb ischemia (CLI) with foot lesions (consistent with Rutherford classes 5 or 6). The exclusion criteria were non-atherosclerotic disease (e.g., arteritis, embolic disease), acute limb-threatening ischemia, trauma, known hypercoagulable state, or any acute cardiac disease such as acute coronary syndrome, acute heart failure or unstable arrhythmias.

Definitions

Diabetes and CLI were defined according to the Standards of Medical Care in Diabetes criteria¹⁰ and the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II),² respectively. CLI was defined as the presence of chronic rest pain and/or non-healing ulcers or gangrene secondary to arterial occlusive disease. Artery disease was proven through transcutaneous oxygen tension (lower than 30 mm Hg) and imaging (ultrasound examination and/or angiography). A multidisciplinary “foot team” including a foot surgeon, an interventional cardiologist, a clinical cardiologist, a vascular surgeon, and a diabetologist was responsible for the diagnosis and management of critical limb ischemia.

History of coronary artery disease (CAD) was defined as any documentation of myocardial infarction, coronary revascularization and/or positive imaging test. An independent team reviewed the cardiovascular medical history of each patient. The medical therapy prescribed at discharge was recorded. Driven by the presence of atrial fibrillation and by the revascularization procedures, antithrombotic drugs, including antiplatelet and anticoagulant agents, were prescribed virtually to all patients and are not the focus of the present investigation. Our attention is directed to the other secondary prevention drugs such as renin-angiotensin-aldosterone system (RAAS) inhibitors, statins and beta-blockers. According to European guidelines, optimal medical therapy (OMT) was defined as the combination of a RAAS inhibitor (either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) and a statin.¹¹ Atorvastatin 40 or 80 mg and rosuvastatin 10 to 40 mg were considered as high-potency statins. When the study was conducted, target LDL for patients with atherosclerotic CV disease was lower than 70 mg/dl.

Laboratory Assessment

Blood samples were collected at admission for all patients, and analyses regarding blood count, renal function, metabolic and inflammatory profile were performed with standardized methods. The Friedewald and the Cockcroft-Gault formula were used to calculate the LDL cholesterol and the estimated glomerular filtration rate (eGFR), respectively.

Follow-Up

After discharge, patients underwent outpatient visits every 2 weeks until clinical stabilization of the surgical site. Afterward, they were visited every 2 months. During the visits, patients were examined and assessed for compliance with medical therapy and the occurrence of adverse events. Additional exams and tests were performed at the physician’s discretion. All patients were followed for at least 1 year. Median follow-up was 981 [557-1325] days, with 267 (43%) patients reaching the 2-year time point.

Outcomes

The primary endpoint was the patient-oriented major cardiovascular events (MACE, defined as the composite of all-cause death, myocardial infarction, and stroke).¹² The secondary outcomes were all-cause mortality and major amputation (defined as any amputation above the ankle). Source documents of adverse events were reviewed by blinded reviewers from another institute (University Hospital of Ferrara) for the final adjudication.

Statistical Analysis

Continuous variables are presented as mean \pm standard deviation or median [interquartile range] and categorical variables as counts and proportions (%). For continuous variables, the differences between groups were compared using the one-way analysis of variance and the Kruskal-Wallis test for parametric and non-parametric data, respectively.

A propensity score matching approach was followed to obtain 2 comparable groups of subjects to evaluate the average treatment effect (ATE). Covariates balancing was performed by nearest neighbor one-to-one matching without replacement. The method used to estimate the distance measure was the logistic regression, and the caliper distance equals 0.2. The median, mean, and maximum quartile differences were calculated together with the standardized difference to compare the mean of continuous and binary variables between treatment groups to check the balance between matched subjects. A standard difference greater than 0.1 has been taken to indicate a significant difference in the mean or prevalence of a covariate between treatment groups.

Survival was estimated in the 2 groups of OMT for each outcome of interest from the Kaplan-Meier curves, which were compared using the log-rank test. To adjust for confounders, Cox proportional hazards regression modeling

strategy was employed to analyze the effect of predictors on MACE, all-cause mortality, and major amputation, following the disjunctive cause criterion. Briefly, each predictor was tested in univariable Cox regression model against each outcome of interest to find causal associations. Moreover, each predictor was tested for association toward exposure (OMT) by univariable logistic regression, verifying the linear relationship assumptions between predictors and the log odds of response. Covariates that are causes of the exposure or the outcome (or are causes of both) were employed to adjust for the full Cox regression multivariable model. To obtain the reduced model, a variable selection was carried out by backward elimination of the least significant predictor employing the AIC stopping rule. Proportionality hazards assumption was verified for each model. Fitted models were plotted as predicted survival proportion at any given point in time for the 2 risk groups, and results are reported as hazard ratios with associated 95% confidence intervals (CIs). The analysis was performed with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between June 2015 and December 2017, 723 diabetic patients were admitted in our unit for treatment of CLI and foot lesions, and net of patients with exclusion criteria, 618 were enrolled. All patients underwent lower limb angiography, and 597 (97%) received percutaneous transluminal angioplasty (PTA). Furthermore, 549 (89%) patients underwent concomitant diabetic foot surgery. The patients with established CAD diagnosis were 270 (43.7%). Table 1 shows the characteristics of the population.

Medical Therapy

Data on medical therapy at discharge are shown in Table 2. In detail, 614 (99.4%) patients received at least one antithrombotic drug, with 112 (18.2%) receiving anticoagulants. The main indication for anticoagulants prescription was atrial fibrillation (96, 85.7% of the cases). Statins were prescribed in 80% of patients. Overall, 139 (22.5%) received high-potency statins. 52% of the population was treated with renin-angiotensin-aldosterone system (RAAS) inhibitors. According to our definition, optimal medical therapy (OMT) was provided to 266 (43.0%) patients, while 281 (45.5%) patients took only one of the two drugs and 71 (11.5%) none. The presence of CAD did not affect the prescription of RAAS inhibitors and statins (at any dose), alone or in combination. On the contrary, anticoagulants, beta-blockers, and high-potency statins were less frequently prescribed in patients without CAD diagnosis. The patients diagnosed with CAD were more likely to be on target LDL cholesterol than those without CAD diagnosis (49.3% vs 35.1%, $P < .001$).

Factors Associated With OMT Prescription

The variables associated with the prescription of OMT are shown in Figure 1. Patients with high BMI, hypertension, dyslipidemia or high HbA1c had a higher probability of receiving OMT, while patients with atrial fibrillation or severe kidney disease had a lower chance of receiving it. The characteristics of the 2 groups are reported in Table 1, while complete logistic regression data are reported in the supplemental material (Table S1).

Major Adverse Cardiovascular Events

During the follow-up, 179 (29%) patients experienced a major cardiovascular event (MACE). In detail, 155 (25%) patients died, 33 (5.3%) had a myocardial infarction and 4 (0.6%) a cerebrovascular accident. The rate of MACE in patients with and without established CAD diagnosis was 33.5% and 26.3% respectively (difference 7.2%, 95%CI -0.5 to 14.9 , $P = .065$). At univariable analysis, a diagnosis of CAD was associated with MACE (HR 1.376, 95%CI 1.020-1.855, $P = .037$), but not at the multivariable analysis.

Patients on OMT had a lower risk of MACE, even after adjusting for the confounders (HR 0.688, 95%CI 0.475-0.995, $P = .047$) (Table 3, Figure 2). The interaction between OMT and CAD was not significant ($P = .779$).

All-Cause Mortality and Major Amputation

OMT was inversely associated with the risk of all-cause mortality at univariable analysis (HR 0.612, 95%CI 0.438-0.854, $P = .004$), but not after adjusting for confounders (HR 0.729, 95%CI 0.491-1.083, $P = .118$) (Table S2). Notably, CAD status was not associated with mortality ($P = .130$).

During follow-up, 59 (9.6%) patients underwent major amputation. OMT was not associated with the occurrence of major amputation ($P = .117$) (Figure 2).

Propensity Matching Analysis

A matched cohort of 506 subject was obtained with a 1:1 ratio between patients with and without optimal medical therapy (OMT) after balancing for eGFR, hemoglobin A1c and atrial fibrillation which were clinically relevant variables strongly associated to the outcomes (Table S3). The rate of MACE in patients with and without established CAD diagnosis was 29.7% and 22.9%, respectively (difference 6.8%, 95%CI -1.4 to 15.1 , $P = .102$).

In the matched cohort, OMT was confirmed independently associated with the risk of MACE (HR 0.671, 95%CI 0.452-0.997, $P = .048$; Table S4) and not associated with the risk of major amputation ($P = .366$). Regarding MACE, the interaction between OMT and CAD was not significant ($P = .954$).

Differently from the whole population, in the matched cohort OMT was independently associated with mortality (HR 0.626, 95%CI 0.409-0.958, $P = .031$; Table S5).

Table 1. Characteristics of the Study Population.

	Entire study population (n = 618)	No OMT (n = 352)	OMT (n = 266)	P
Age, years	73 [65-80]	74 [65-80]	72.00 [65-80]	.293
Male sex, no. (%)	445 (72.0)	254 (72.2)	191 (71.8)	.928
BMI, kg/m ²	26.4 [23.9-30.3]	26.0 [23.3-29.4]	27.3 [24.7-30.8]	<.001
Medical history, no. (%)				
Hypertension	544 (88.0)	294 (83.5)	250 (94.0)	<.001
Dyslipidemia	473 (76.5)	249 (70.7)	224 (84.2)	<.001
Type 1 diabetes	23 (3.7)	15 (4.3)	8 (3.0)	.521
Current smokers	57 (9.3)	31 (8.9)	26 (9.8)	.779
CAD	270 (43.7)	148 (42.0)	122 (45.9)	.368
Prior PCI/CABG	217 (35.6)	114 (32.9)	103 (39.0)	.125
Chronic heart failure	78 (13.3)	53 (15.8)	25 (10.0)	.049
Atrial fibrillation	160 (26.1)	103 (29.3)	57 (21.7)	.033
Carotid artery disease	87 (14.7)	47 (13.9)	40 (15.7)	.559
Previous stroke	70 (11.4)	41 (11.7)	29 (11.0)	.799
CKD	342 (55.3)	213 (60.5)	129 (48.5)	.004
ESRD on dialysis	64 (10.4)	56 (16.0)	8 (3.0)	<.001
COPD	62 (10.1)	41 (11.7)	21 (7.9)	.138
Laboratory data				
Hemoglobin, g/dl	11.80 [10.50-13.10]	11.75 [10.50-13.00]	11.90 [10.70-13.10]	.521
White blood cells, 10 ³ /μL	8.9 [7.1-11.0]	8.9 [7.1-10.9]	8.9 [7.3-11.1]	.516
Platelets, 10 ³ /μL	260 [203-329]	261 [207-332]	251 [197-323]	.653
eGFR, ml/min	56.4 [37.6-79.7]	51.2 [30.7-75.7]	61.5 [46.8-83.8]	<.001
eGFR > 30 ml/min, no. (%)	514 (83.4)	266 (76.0)	248 (93.2)	<.001
Cholesterol, mg/dl	144.0 [120.0-173.8]	145.0 [122.0-174.0]	141.0 [116.0-172.0]	.206
HDL, mg/dl	39.0 [31.0-49.0]	39.0 [30.0-49.0]	39.0 [31.0-50.0]	.441
Triglycerides, mg/dl	119.0 [93.0-163.0]	119.0 [93.0-161.0]	119.00 [93.0-165.0]	.723
LDL, mg/dl	77.4 [56.1-102.2]	78.8 [60.0-102.0]	72.2 [52.8-99.6]	.020
Hemoglobin A1c, mmol/mol	56.0 [46.0-68.0]	53.0 [45.0-65.0]	59.0 [49.0-72.0]	<.001
CRP, mg/dl	1.10 [0.40-4.70]	1.30 [0.40-4.62]	1.00 [0.40-4.78]	.339
Albumin, g/dl	3.58 [3.14-3.88]	3.54 [3.12-3.86]	3.65 [3.20-3.89]	.134
PAD status, no. (%)				
Previous PTA	257 (41.9)	151 (43.4)	106 (39.8)	.409
Previous amputation	211 (34.2)	127 (36.2)	84 (31.6)	.265
ATK artery disease	362 (59.8)	207 (59.7)	155 (60.1)	.933
BTK artery disease	572 (93.0)	331 (94.3)	241 (91.3)	.154
Rutherford category				.653
5	492 (79.6)	278 (79.0)	214 (80.5)	
6	126 (20.4)	74 (21.0)	52 (19.5)	
Osteomyelitis	258 (44.8)	139 (42.6)	119 (47.6)	.238

Abbreviations: ATK/BTK, above/below the knee; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OMT, optimal medical therapy; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PTA, percutaneous transluminal angioplasty.

Beta-Blockers

At univariable analysis, beta-blockers were not associated with any of the explored outcomes, neither in the overall population nor when the 2 CAD groups were examined separately.

High-Potency Statins

Among patients on OMT, 189 (71%) were on low-potency statin and 77 (29%) on high-potency statin. At univariable analysis, statin potency was not related to any of the explored outcomes.

Discussion

The main message of our analysis is that diabetic patients complicated by CLI and foot lesions, even when cared for in a modern and high-volume center are not receiving optimal preventive medication for atherosclerosis progression and MACE reduction.

We believe that this study, even if it has highlighted the flaws in our own work, is relevant and of the utmost importance in understanding that the avoidance of prescribing OMT is a common and dangerous behavior that needs to be changed. In fact, in our cohort, patients with CLI who received guideline-recommended preventive therapy with

Table 2. Medical Therapy at Discharge.

	Entire study population (n = 618)	Established CAD diagnosis (n = 270)	No CAD diagnosis (n = 348)	P
Oral anticoagulants	112 (18.2)	61 (22.7)	51 (14.7)	.01
Aspirin	563 (91.2)	248 (92.2)	315 (90.5)	.57
Clopidogrel	576 (93.4)	253 (94.1)	323 (92.8)	.63
At least one antithrombotic drug	614 (99.4)	270 (100)	344 (98.9)	.14
RAAS inhibitors	320 (51.9)	140 (52.0)	180 (51.7)	1.00
Beta-blockers	316 (51.2)	176 (65.4)	140 (40.2)	<.01
Statins	493 (79.8)	224 (83.0)	269 (77.3)	.08
Low-potency	354 (57.3)	138 (51.1)	216 (62.1)	<.01
High-potency	139 (22.5)	86 (31.9)	53 (15.2)	<.01
OMT	263 (42.5)	120 (44.4)	143 (41.1)	.40
Ezetimibe	37 (6.0)	19 (7.0)	18 (5.2)	.42
Insulin therapy	467 (75.9)	214 (79.9)	253 (72.9)	.06
Insulin units (IU/die)	32 [16-50]	32 [18-50]	32 [12-50]	.60
Oral antidiabetic drugs	160 (26.0)	57 (21.2)	103 (29.7)	.02

Abbreviations: CAD, coronary artery disease; OMT, optimal medical therapy; RAAS, renin-angiotensin-aldosterone system.

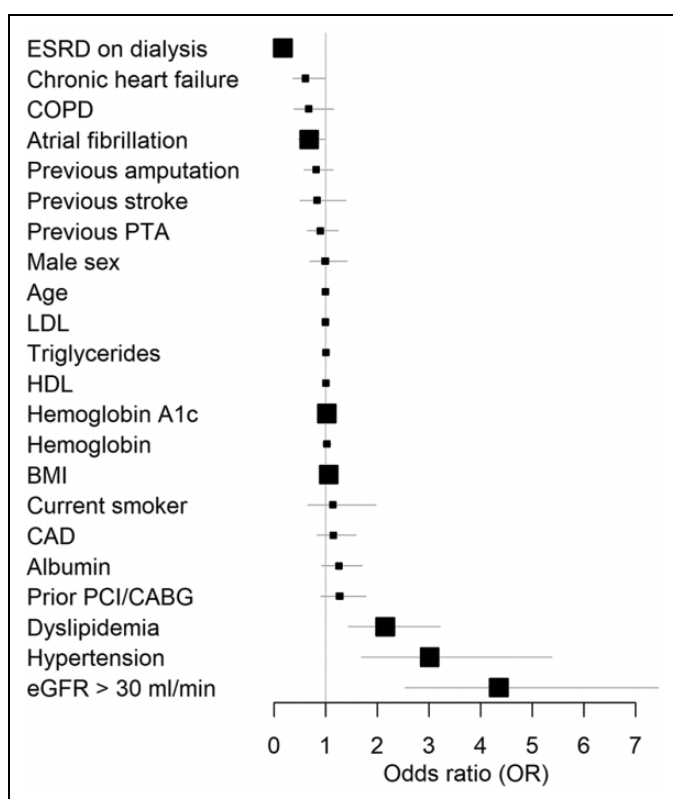


Figure 1. Optimal medical therapy prescription. Forest plot of baseline variables and their association with optimal medical therapy prescription. Large square boxes represent P values $<.05$.

renin-angiotensin-aldosterone system (RAAS) inhibitors, statins and antithrombotic drugs experienced less MACE and death. There are several reasons that might explain this widespread attitude. At a glance, we believe it is a question of erroneous perception, where the peripheral problem becomes the most important to solve, outweighing the more general and systemic problem of the progression of atherosclerosis in

districts other than the peripheral arteries, such as the coronary or cerebral arteries. In contrast, the optimized preventive therapy is effective, relatively well tolerated, and readily available at low cost (today all preventive drugs for cardiovascular system are generic). Therefore, the tendency to not prescribing it to diabetic with CLI patients should be reduced, as they are the ones who would benefit the most from OMT.

That PAD patients are generally undertreated is well known.⁶⁻⁸ As of today, there are few previous works that has concentrated on patients with CLI, who are at the worst stage of PAD and who would, theoretically, be the ones benefitting from OMT. Unlike previous studies on PAD,¹³ in our cohort, CAD diagnosis did not influence the prescription of OMT. This is not surprising as patients with PAD have the same risk of MACE as those with CAD and equally benefit from preventive medical treatment.¹

Instead, the prescription of OMT was affected by the renal function of the patient. This is mainly related to the use of RAAS inhibitors which were prescribed only in 52% of the patients. Likely, this is because RAAS inhibitors may negatively affect glomerular filtration rate (GFR) and enhance the risk of hyperkalemia and hypotension. On the other hand, RAAS inhibitors have shown to slow down the progression of diabetic nephropathy and of coronary atherosclerosis and reduce the risk of MACE in patients with CVD. In fact, European guidelines recommend RAAS inhibitors as first choice antihypertensive drug in patients with peripheral artery disease and diabetes, particularly when CKD is associated.¹¹ Furthermore, RAAS inhibitors are recommended in patients with CAD and diabetes, regardless of hypertension, to reduce major cardiovascular events, and such effect has been observed also in PAD patients.¹⁴ Considering the high prevalence of hypertension (88%), CKD (55%) and CAD (44%) in our cohort of patients with diabetes and PAD, virtually all patients were supposed to receive RAAS inhibitors. The GFR value below which inhibitors of RAAS start to damage rather than benefit the patient is still debated. However, even considering a

Table 3. Univariate and Multivariable Cox Regression for the Prediction of MACE.

	HR	Univariate analysis 95%CI	P	HR	Multivariable analysis 95%CI	P
Prior stroke	2.074	1.397-3.080	<.001	1.989	1.282-3.087	.002
Atrial fibrillation	1.996	1.458-2.731	<.001	1.742	1.227-2.473	.002
White blood cells	1.162	1.067-1.266	<.001	1.136	1.034-1.247	.008
Hemoglobin	0.684	0.541-0.863	.002	0.743	0.568-0.973	.031
Insulin units	0.726	0.581-0.907	.005	0.711	0.560-0.904	.005
OMT	0.590	0.429-0.811	.001	0.688	0.475-0.995	.047
eGFR	0.475	0.375-0.602	<.001	0.649	0.500-0.842	.001
BMI	0.745	0.603-0.921	.007			
Hemoglobin A1c	0.760	0.615-0.939	.011			
CRP	1.145	1.034-1.267	.009			
Albumin	0.770	0.624-0.950	.015			
CAD	1.376	1.020-1.855	.037			
COPD	2.058	1.344-3.152	<.001			
Age	0.969	0.782-1.202	.777			
Male sex	1.258	0.888-1.781	.196			
Chronic heart failure	2.168	1.487-3.162	<.001			
Carotid artery disease	1.441	0.969-2.142	.071			
HDL	0.848	0.700-1.028	.093			
LDL	1.075	0.888-1.300	.458			
Hypertension	1.116	0.699-1.780	.646			
Dyslipidemia	0.740	0.537-1.020	.066			

Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OMT, optimal medical therapy.

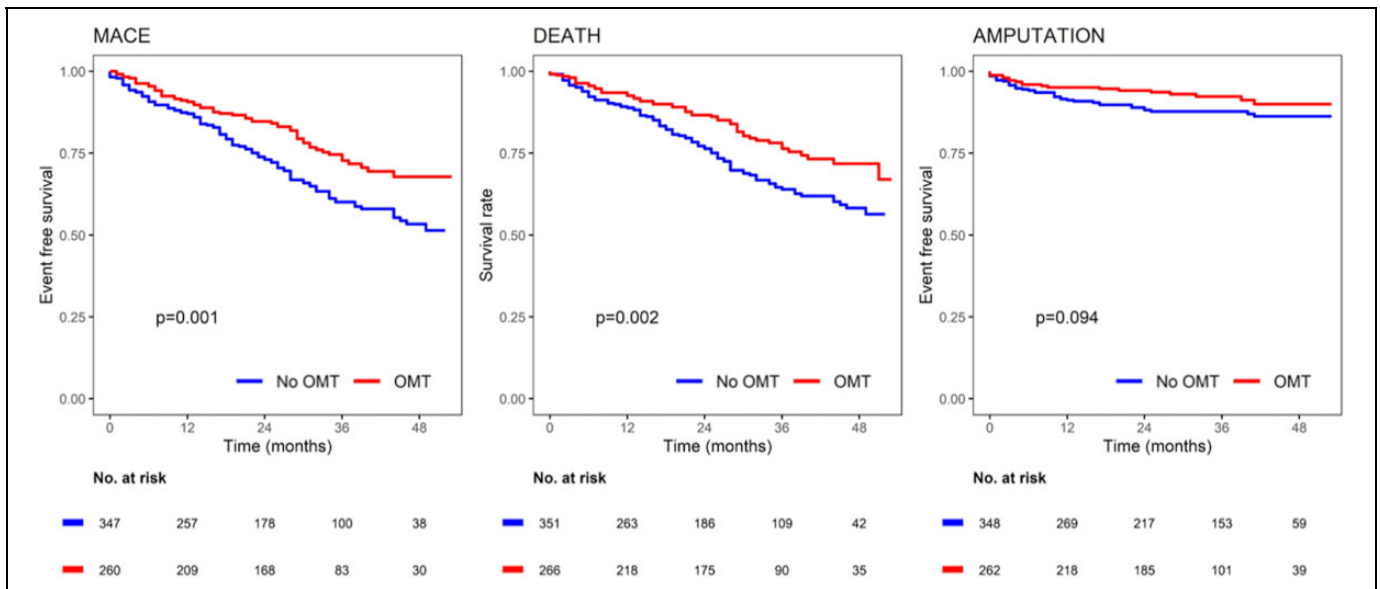


Figure 2. Outcomes occurrence according to OMT prescription. Kaplan-Meier curves for MACE, mortality and major amputation. Log-rank test P values were reported in the graphs.

conservative threshold of 30 ml/min, RAAS inhibitors in our cohort were still underused. 83% of patients had GFR > 30 ml/min, and only 52% received such therapy. Interestingly, RAAS inhibitors were prescribed less in patients without hypertension, suggesting that they are perceived as anti-hypertensive rather than anti-atherosclerotic. Again, this seems to be a problem of erroneous perception as the beneficial effect of RAAS

inhibitors on MACE is independent of blood pressure reduction and it is related to their effect at endothelial level, reducing apoptosis and improving endothelial regeneration, thus maintaining endothelial continuity and reducing the progression of atherosclerosis.¹⁵

In our cohort, lipid-lowering drugs were prescribed more than RAAS inhibitors: only 2 out of 10 patients did not receive

statin therapy, likely because of its side effects. This is probably due to a clear indication of guidelines to strongly reduce LDL cholesterol in patients with atherosclerotic CVD (including PAD), with statins as the first choice drug.¹¹ In the last 10 years, statin prescription in PAD patients has slightly increased without, however, reaching optimal rates.^{16,17} According to the latest guidelines, PAD patients are considered at very high CV risk and need to reach an LDL target lower than 55 mg/dl through aggressive lipid-lowering therapy.¹⁸ A recent meta-analysis in patients affected by CLI showed that, besides MACE, statins also decreased the risk for major adverse limb events.¹⁹

CAD diagnosis did not affect the prescription of statin in our population but influenced its potency. Patients with established CAD were more likely to receive high-potency statins, although it did not affect the outcomes. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were not available at the time of our analysis. These drugs may be useful, particularly in subgroups at very-high risk such as patients with CAD and CLI.²⁰

In our cohort, beta-blockers were highly prescribed in patients with CAD diagnosis, mainly for the high incidence of atrial fibrillation. As expected, the prophylactic use of beta-blockers was not related to an improvement of the outcome, irrespective of CAD status. A beneficial effect is expected in patients with heart failure and reduced ejection fraction (EF), which was not available in our dataset. However, the prevalence of heart failure in our patients was low.

Finally, age may be a reason for not prescribing preventive therapies as physicians may be doubtful on their utility.²¹ Accordingly, about a quarter of our population was over 80 years and 9% was over 85 years.

Study Limitations

We are aware that our study may have several limitations. First, in the last few years, novel opportunities for risk reduction in diabetic and CAD patients have emerged (e.g., ticagrelor, low-dose rivaroxaban, proprotein convertase subtilisin/kexin type 9 inhibitors, sodium-glucose cotransporter-2). Thus, the OMT definition used was adequate only for the time of the survey but needs to be updated in future more contemporary studies. Second, the low number of events of the secondary outcomes may affect the power of the analysis (especially for major amputation). Third, lifestyle behavior and antidiabetic drugs were not included in OMT definition. Finally, this is a single-center study, although of high volume.

Conclusion

We think that this study can be viewed as advice to rectify what we consider to be an ineffective but easily improvable attitude. In fact, diabetic patients with critical limb ischemia and foot lesions tend to be undertreated despite the high risk of major CV events. Our analysis suggests that when treating PAD patients with CLI, optimal medical therapy with RAAS

inhibitors, statins and antithrombotic may reduce MACE and mortality.

Author Contributions

Conceptualization: PC, GC, and LDP; methodology: DB, AC, GS, and SCE; formal analysis: PC, MM, and SCa; data curation: DB, LSC, and AC; writing—original draft preparation: PC, GS, and SCE; writing—review and editing: RF, GC, and LDP.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: RF has received research grants and personal fees from Novartis and Servier, personal fees from Merck Serono, Boehringer Ingelheim, Sunpharma, Lupin, Doc Generici, Pfizer, and Spa Prodotti Antibiotici. He is a director of Art Research and Science S.r.l (A.R.S.1).

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Supplemental Material

Supplemental material for this article is available online.

References

1. Agnelli G, Belch JJF, Baumgartner I, Giovas P, Hoffmann U. Morbidity and mortality associated with atherosclerotic peripheral artery disease: a systematic review. *Atherosclerosis*. 2020; 293:94-100. doi:10.1016/j.atherosclerosis.2019.09.012
2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg*. 2007;45(1): S5-S67. doi:10.1016/j.jvs.2006.12.037
3. Le Feuvre C, Jacqueminet S, Barthelemy O. Myocardial ischemia: a silent epidemic in type 2 diabetes patients. *Future Cardiol*. 2011;7(2):183-190. doi:10.2217/fca.10.127
4. Armstrong EJ, Chen DC, Westin GG, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. *J Am Heart Assoc*. 2014;3(2):e000697. doi:10.1161/JAHA.113.000697
5. Eldor R, Raz I. American Diabetes Association indications for statins in diabetes: is there evidence? *Diabetes Care*. 2009; 32(suppl 2):S384-S391. doi:10.2337/dc09-s345
6. Subherwal S, Patel MR, Kober L, et al. Missed opportunities: despite improvement in use of cardioprotective medications among patients with lower-extremity peripheral artery disease, underuse remains. *Circulation*. 2012;126(11):1345-1354. doi:10.1161/CIRCULATIONAHA.112.108787
7. Colantonio LD, Hubbard D, Monda KL, et al. Atherosclerotic risk and statin use among patients with peripheral artery disease. *J Am Coll Cardiol*. 2020;76(3):251-264. doi:10.1016/j.jacc.2020.05.048
8. Berger JS, Ladapo JA. Underuse of prevention and lifestyle counseling in patients with peripheral artery disease. *J Am Coll Cardiol*. 2017;69(18):2293-2300. doi:10.1016/j.jacc.2017.02.064

9. Conte MS, Bandyk DF, Clowes AW, Moneta GL, Namini H, Seely L. Risk factors, medical therapies and perioperative events in limb salvage surgery: observations from the PREVENT III multicenter trial. *J Vasc Surg.* 2005;42(3):456-464. doi:10.1016/j.jvs.2005.05.001
10. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2018. Diabetes Care.* 2018;41(suppl 1). doi:10.2337/dc18-S002
11. Visseren FL, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* 2021;42(34):3227-3337. doi:10.1093/EURHEARTJ/EHAB484
12. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. *Circulation.* 2018;137(24):2635-2650. doi:10.1161/CIRCULATIONAHA.117.029289
13. Montminy ML, Gauvin V, Turcotte S, Milot A, Douville Y, Bairati I. Factors influencing the prescription of cardiovascular preventive therapies in patients with peripheral arterial disease. *PLoS One.* 2016;11(2):e0148069. doi:10.1371/journal.pone.0148069
14. Östergren J, Sleight P, Dagenais G, et al. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J.* 2004;25(1):17-24. doi:10.1016/J.EHJ.2003.10.033
15. Ferrari R, Fox K. Insight into the mode of action of ACE inhibition in coronary artery disease: the ultimate “EUROPA” story. *Drugs.* 2009;69(3):265-277. doi:10.2165/00003495-200969030-00003
16. Reynolds K, Mues KE, Harrison TN, et al. Trends in statin utilization among adults with severe peripheral artery disease including critical limb ischemia in an integrated healthcare delivery system. *Vasc Med.* 2020;25(1):3-12. doi:10.1177/1358863X19871100
17. Anderson JL, Knowlton KU, May HT, et al. Temporal changes in statin prescription and intensity at discharge and impact on outcomes in patients with newly diagnosed atherosclerotic cardiovascular disease—real-world experience within a large integrated health care system: the IMPRES study. *J Clin Lipidol.* 2018;12(4):1008-1018.e1. doi:10.1016/j.jacl.2018.03.084
18. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455
19. Kokkinidis DG, Arfaras-Melainis A, Giannopoulos S, et al. Statin therapy for reduction of cardiovascular and limb-related events in critical limb ischemia: a systematic review and meta-analysis. *Vasc Med.* 2020;25(2):106-117. doi:10.1177/1358863X19894055
20. Bonaca MP, Nault P, Giugliano RP, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the Fourier trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk). *Circulation.* 2018;137(4):338-350. doi:10.1161/CIRCULATIONAHA.117.032235
21. Gulliford M, Ravindrarajah R, Hamada S, Jackson S, Charlton J. Inception and deprescribing of statins in people aged over 80 years: cohort study. *Age Ageing.* 2017;46(6):1001-1005. doi:10.1093/ageing/afx100