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Authors

Schulman-Marcus, Joshua
Hartaigh, Bríain Ó
Giambrone, Ashley E
et al.

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Effects of Cardiac Medications for Patients With Obstructive Coronary Artery Disease by Coronary Computed Tomographic Angiography: Results from the Multicenter CONFIRM Registry

Joshua Schulman-Marcus, MD[a], **Bríain ó Hartaigh, PhD**[b], **Ashley E Giambrone, PhD**[c], **Heidi Gransar, MS**[d], **Valentina Valenti, MD**[b], **Daniel S. Berman, MD**[d], **Matthew J. Budoff, MD**[e], **Stephan Achenbach, MD**[f], **Mouaz Al-Mallah, MD**[g], **Daniele Andreini, MD**[h], **Filippo Cademartiri, MD, PhD**[i], **Tracy Q. Callister, MD**[j], **Hyuk-Jae Chang, MD**[k], **Kavitha Chinnaiyan, MD**[l], **Benjamin J. W. Chow, MD**[m], **Ricardo Cury, MD**[n], **Augustin Delago, MD**[o], **Martin Hadamitzky, MD**[p], **Joerg Hausleiter, MD**[q], **Gudrun Feuchtner, MD**[r], **Yong-Jin Kim, MD**[s], **Philipp A. Kaufmann, MD**[t], **Jonathon Leipsic, MD**[u], **Fay Y. Lin, MD**[a], **Erica Maffei, MD**[v], **Gianluca Pontone, MD**[h], **Gilbert Raff, MD**[l], **Leslee J. Shaw, PhD**[w], **Todd C. Villines, MD**[x], **Allison Dunning, MS**[y], and **James K Min, MD**[b]

[a] Department of Medicine, The NewYork-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY [b] Department of Radiology, The NewYork-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY [c] Department of Healthcare Policy and Research, Weill Cornell Medical College, New York, NY [d] Department of Imaging and Division of Cardiology, Department of Medicine, Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA [e] Department of Medicine, Harbor UCLA Medical Center, Los Angeles, California [f] Department of Medicine, University of Erlangen, Erlangen, Germany [g] Department of Medicine, Wayne State University, Henry Ford Hospital, Detroit, Michigan [h] Department of Clinical Sciences and Community Health, University of Milan, Centro Cardiologico Monzino, IRCCS Milan, Italy [i] Cardio Vascular Imaging Unit, Giovanni XXIII Hospital, Monastier, Italy and Department of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands [j] Tennessee Heart and Vascular Institute, Hendersonville, Tennessee, USA [k] Division of Cardiology, Severance Cardiovascular Hospital, Seoul, South Korea [l] William Beaumont Hospital, Royal Oaks, Michigan [m] Department of Medicine and Radiology, University of Ottawa Heart Institute, Ontario, Canada [n] Baptist Cardiac and Vascular Institute, Miami, FL, USA [o] Capitol Cardiology Associates, Albany, New York, USA [p] Division of Cardiology, DeutschesHerzzentrumMünchen, Munich, Germany [q] Medizinische Klinik I der Ludwig-Maximilians-Universität München, Munich, Germany [r] Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria [s] Department of Medicine and Radiology, Seoul National University Hospital, Seoul, South Korea [t] Department of

Address for correspondence: James K. Min, MD, FACC, FSCCT, 413 East 69th Street, Suite 108, Dalio Institute of Cardiovascular Imaging, Weill Cornell Medical College and the NewYork-Presbyterian Hospital, New York, NY 10021, Phone: 646-962-6268, jkm2001@med.cornell.edu.

Nuclear Cardiology, Cardiovascular Center, University Hospital Zurich, Zurich, Switzerland [u] Department of Medical Imaging and Division of Cardiology, St. Paul's Hospital, University of British Columbia, Vancouver, BC [v] Cardio Vascular Imaging Unit, Giovanni XXIII Hospital, Monastier, Italy [w] Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA [x] Department of Medicine, Walter Reed National Medical Center, Bethesda, MD, USA [y] Duke Clinical Research Institute, Durham, NC, USA

Abstract

Objective—This study sought to determine the correlation between baseline cardiac medications and cardiovascular outcomes in patients with obstructive coronary artery disease (CAD) diagnosed by coronary computed tomographic angiography (CCTA).

Methods—1637 patients (mean age 64.8 ± 10.2 years, 69.6% male) with obstructive CAD from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry were followed over the course of three years. Obstructive CAD was defined as a >50% stenosis in an epicardial vessel. Medications analyzed included statins, aspirin, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). Using Cox proportional-hazards models, we calculated the hazard ratio (HR) with 95% confidence intervals (95% CIs) for incident major adverse cardiovascular events (MACE), defined as death, acute coronary syndrome, or myocardial infarction.

Results—At the time of CCTA, 59%, 54%, 40%, and 46% of patients were using statins, aspirin, beta-blockers, and ACE inhibitors or ARBs, respectively. Statins were associated with a 43% (95% CI = 0.38-0.87, p=0.008) lower adjusted risk of MACE. Following adjustment, aspirin, beta-blockers, ACE inhibitors and ARBs did not attenuate the risk of MACE. When restricted to patients with multivessel obstructive CAD, only statins were associated with lower risk of MACE.

Conclusion—In patients with obstructive CAD by CCTA, the baseline use of statins was associated with improved clinical outcomes. Other cardiac medications—including aspirin, beta-blockers, ACE inhibitors, and ARBs—were not associated with reduced risk of MACE.

Keywords

Coronary Artery Disease; Coronary computed tomographic angiography; major adverse cardiac events; medication therapy; statins

INTRODUCTION

Coronary computed tomographic angiography (CCTA) is a noninvasive imaging modality that permits accurate detection and exclusion of obstructive coronary artery disease (CAD), although the ideal medical management of patients with CCTA-identified obstructive CAD remains unclear. For patients without prior known myocardial infarction or coronary revascularization, current guidelines advocate the use of statins as a first-line therapy.[1–3] Whether intensification of medical therapy with medications such as beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) is associated with improved cardiovascular outcomes is unknown.[2] In the present

prospective multi-site international study, we examined the association between clinical outcomes and baseline cardiac medications for patients with newly identified obstructive CAD by CCTA.

METHODS

Study population

The CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry is a global, multicenter, observational registry comprising clinical, procedural, and follow-up data for 27,125 patients undergoing CCTA for clinically indicated reasons. Details concerning the CONFIRM registry's design and rationale have been published previously.[4,5] Briefly, inclusion criteria for this analysis were patients referred for suspected CAD who were subsequently identified as having at least obstructive coronary stenosis, as defined by a >50% luminal stenosis (n=2,807). Patients were excluded from this study if they had a prior diagnosis of MI or prior coronary revascularization. Medication data were not collected at all CONFIRM sites, and patients with incomplete medication data were excluded (n=1,170). Each study site received institutional review board approval for all registry procedures, including follow-up methodologies.

Clinical data collection

Standardized data collection methods were employed at participating study sites.[4,5] Data were systematically collected for each consecutive patient, while applying consistent definitions for suspected cardiac symptoms, risk factors, and angiographic CAD extent and severity. Patient information was gathered for traditional cardiac risk factors including hypertension, diabetes, dyslipidemia, current smoking, and a family history of premature CAD. Patients who were treated for hypertension, diabetes, or dyslipidemia, or who otherwise had a prior diagnosis for these conditions were categorized as having that risk factor. Family history of premature CAD was defined as a primary relative with a diagnosis early in life (i.e., mother <65 years of age or father <55 years of age). Chest pain was defined and categorized by the interviewing physician as non-anginal, atypical angina, or typical angina pectoris.

CCTA Performance and Interpretation

Standardized protocols for image acquisition, as defined by the Society of Cardiovascular Computed Tomography, were employed at all participating sites. Specific details of CCTA procedures have been defined in detail elsewhere.[4] Each site applied the standard anatomic segmental analysis for image interpretation. All segments were coded for the presence and severity of coronary stenosis and were scored as normal (0% luminal stenosis), mild-moderate (1% to 49% luminal stenosis), or obstructive (>50% luminal stenosis). Stenoses were judged on a per-patient and per-vessel basis, with the latter based upon stenosis in the left main (LM) artery, the left anterior descending (LAD) artery, the left circumflex (LCx) artery and the right coronary artery (RCA).

Study outcome

Patients were followed prospectively over the course of 3 years. The primary outcome measure was major adverse cardiovascular events (MACE), which included a combination of death from any cause, acute coronary syndrome (ACS), and non-fatal MI that occurred during the initial 3 years following CCTA. An ACS was defined as a hospitalization with the occurrence of unstable anginal symptoms with electrocardiographic changes. Acute MI was further ascertained using biomarker quantification during patients' hospital stay. Ascertainment and adjudication of events in CONFIRM have previously been described.[4] All-cause mortality was adjudicated by trained study personnel or by querying of national medical databases. Cause of death was not collected in CONFIRM. Other outcomes were ascertained by direct interview or telephone contact using a standard script or through review of medical records.

Statistical methods

Categorical variables are presented as counts and proportions. Continuous variables are presented as means ± SD. Variables were compared using the chi-squared test for categorical variables and by Student's unpaired t-test for normally distributed variables, or by Wilcoxon's non-parametric test for non-normally distributed variables. Time-to-event analyses for the study endpoint were calculated using univariable Cox proportional-hazards models reporting hazard ratios (HR) with 95% confidence intervals (95% CIs). Given considerable medication heterogeneity, a medication was considered present if the patient was taking the medication regardless of concurrent therapies. Multivariable Cox proportional hazards models were also constructed with variables based on clinical judgment and prior CONFIRM analyses.[5,6]. Variables included baseline demographics, cardiac risk factors, individual medications, number of vessels with obstructive disease, and coronary revascularization. In multivariable analyses, all variables were adjusted for simultaneously. This approach controlled for the effect of baseline differences in the comparator cohorts as well as the impact of non-randomized treatment allocation on survival. A two-tailed p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (www.sas.com, Cary, NC).

RESULTS

Clinical characteristics of the study population (n=1637) and patients with incomplete medication data (n=1170) are listed in Table 1. Overall, the study population had a higher burden of risk factors but similar severity of obstructive CAD. In the study population, slightly more than half (59%) of the patients were taking statins, 54% aspirin, 40% beta-blockers, and 46% ACE inhibitors/ARBs. Approximately two thirds (61%) of patients had chest pain symptoms. By CCTA, 60% of patients were diagnosed with 1-vessel CAD, 23% with 2-vessel CAD, and the remainder with 3-vessel or LM disease. Many of the study patients were on multiple medications (Table 2). Overall, 116 (7.1%) of the patients experienced the study outcome (43 nonfatal acute coronary syndromes, 7 fatal acute coronary syndromes, 66 other deaths).

Univariable and Multivariable Clinical Predictors of Major Adverse Cardiac Event Risk

As shown in Table 3, the unadjusted risk of MACE was associated with older age, hypertension, and increasing severity of CAD. In multivariable analysis, only age and increasing severity of CAD remained strong independent predictors of MACE.

Univariable and Multivariable Medication Predictors of Major Adverse Cardiac Event Risk

Aspirin was associated with a reduced unadjusted risk of MACE, whereas the associations between statin, beta-blocker and ACE inhibitor use and MACE were not significant (Figure 1). Yet, in multivariable analyses, statins were predictive of lowering the risk of MACE, while aspirin, beta-blockers, and ACE inhibitors were not (Table 3). Similar results were found when the analyses were restricted to patients with increased extent and severity of CAD (Table 4). The relationship between statins and MACE did not differ materially (HR 0.43, 95% CI = 0.25-0.75, p=0.003) after omitting patients with subsequent coronary revascularization. In a further sensitivity check, only statins remained associated with decreased MACE (HR 0.56, 95% CI 0.35-0.88, p=0.01) in the cohort inclusive of patients with incomplete medication data.

Analysis of Differing Medication Regimens

In exploratory analyses, no medication combination was associated with additional improvements in survival compared to statins alone. Similarly, when compared to the use of statins alone, the use of all four classes of medication was not associated was significant additional improvement in survival (Figure 2).

DISCUSSION

In this large, global, multicenter registry of patients with obstructive CAD diagnosed by CCTA, baseline statin use was consistently associated with a reduction in the risk of MACE across 3 years of follow-up. Other cardiac medications (aspirin, beta blockers, ACE inhibitors and ARBs) were not significantly associated with reduced MACE. These findings suggest that patients with obstructive CAD diagnosed by CCTA derive the largest benefit from a medication regimen that includes statins.

Prior studies of statins for both primary and secondary prevention in patients with established CAD have reported considerable improvements in adverse outcomes.[7–9] A large meta-analysis of statin therapy in patients at low vascular risk demonstrated a 20% risk reduction in vascular events for each 1.0mmol/L (40mg/dL) decrement in LDL. Statins were associated with reductions in major coronary events, cardiac revascularization, stroke, cardiac mortality and all-cause mortality even in patients at low vascular risk.[7] In secondary prevention patients (most of whom had prior MI or revascularization), statin use was associated with even greater declines in all-cause mortality and major vascular events.[9] To date, few studies have examined the precise benefit of statins in patients with obstructive CAD diagnosed by CCTA. One recent retrospective study of patients with atypical chest pain who were found to have non-obstructive CAD by CCTA failed to observe a significant clinical improvement in patients subsequently initiated on statins.[10] However, this study used a propensity score matching approach and was retrospective.

Conversely, the current analysis was restricted to patients with obstructive CAD diagnosed by CCTA, which is a cohort at higher risk of adverse events.[5] Our present findings suggest that such patients may derive greater absolute benefit from early and aggressive statin initiation than patients with lesser amounts of atherosclerosis. This notion is additive to the prior literature in that until recently, many patients with suspected CAD in statin trials did not have direct visualization of their coronary anatomy. Further studies regarding the interplay of anatomic CAD, ischemia, and statins in patients with CAD but without prior MI thus appear warranted. In the meanwhile, our findings lend further support to current recommendations that patients with obstructive CAD by CCTA should be treated with statins similar to other patients with chronic stable ischemic heart disease [1,2].

Previous meta-analyses exploring the effects of aspirin in secondary prevention have reported a beneficial reduction in the risk of fatal and non-fatal events.[11,12] Conversely, the role of aspirin in primary prevention is much less clear, even in high-risk groups such as diabetics, largely because of increased bleeding rates.[12–14] In this study, while the use of aspirin was associated with a decline in the risk of MACE, the relationship marginally attenuated to non-significance after adjusting for numerous covariates. Had there been a longer duration of follow-up with sufficient sample size, it is feasible this trend may have reached statistical significance. In this light, future studies regarding the use of aspirin in patients with obstructive CAD as diagnosed by CCTA are needed.

Of the other cardiac medications examined in this study, neither beta-blockers nor ACE inhibitors were related to the risk of MACE. While beta blockers improve symptoms of stable angina, no studies to date have demonstrated improved MACE outcomes from beta blocker use in patients with stable CAD without prior MI. In such patients, beta blockers are therefore indicated only for symptomatic relief under current guidelines. [2,3] Among patients with stable CAD and preserved left ventricular function, ACE inhibitors have been associated with a small reduction in mortality, MI, and revascularization.[15–17] Guidelines therefore state that ACE inhibitors/ARBs may be considered a useful adjunct in patients with stable CAD and other vascular risk factors.[2,3] Additional research is clearly warranted to determine the benefits, if any, of these medication classes among patients with obstructive CAD as diagnosed by CCTA.

Several limitations need to be emphasized. The patients involved in this study reflected only a small sample of the overall patients enrolled in the CONFIRM registry. Hence, the number of clinical endpoints was relatively small. The CONFIRM registry did not collect cause of death, and as such, not all deaths may be cardiovascular or related to the CCTA findings. Furthermore, other relevant outcomes such as stroke were not ascertained in CONFIRM. For myocardial infarction, there is a possible limitation of events being adjudicated by phone or medical review. Still, it should be noted that this is the largest prospective registry of consecutively enrolled CCTA patients for whom outcome data are available. During the data collection phase of this study, medication dosage, name and prior duration of therapy were not collected, nor was information regarding any subsequent change in medication, risk factor modification, or lifestyle changes following the results of patients' CCTA. Further studies should clarify the effect of CCTA on subsequent medication management. The present study had insufficient data concerning left ventricular function or history of

congestive heart failure, which may limit the interpretation of the findings regarding the impact of beta-blockers and ACE inhibitors.

Growing numbers of patients are frequently diagnosed with obstructive CAD by novel imaging modalities such as CCTA. We have previously reported that these patients are at increased risk of mortality and adverse cardiovascular outcomes.[5,18] However, there are few data guiding the management of such patients. Many contemporary patients may not have met eligibility criteria for older secondary prevention trials, yet it is unclear whether they should be considered similar to primary prevention cohorts with cardiovascular risk factors alone. The current study suggests a beneficial association between early statin initiation and reduced clinical events in patients with obstructive CAD diagnosed by CCTA. The baseline use of other cardiac medications including aspirin, beta blockers, ACE inhibitors or ARBs were not associated with reductions in MACE risk, but these findings may be limited owing to insufficient data regarding medication changes subsequent to the CCTA. While further research is clearly needed to guide the treatment of patients with obstructive CAD diagnosed by CCTA, at the minimum, our findings support efforts to increase the use of statins in such patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CCTA	Coronary computed tomographic angiography
CAD	coronary artery disease
CONFIRM	COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry
LM	Left Main
LAD	left anterior descending
LcX	left circumflex
RCA	right coronary artery
MACE	major adverse cardiac events
ACS	Acute coronary syndrome
HR	hazard ratio

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Highlights

- We analyzed medication use of patients with obstructive CAD diagnosed by CCTA
- Statins were significantly associated with lower risk of MACE
- Secondary prevention medications were not associated with reduced risk of MACE
- Findings were similar in patients with multivessel CAD

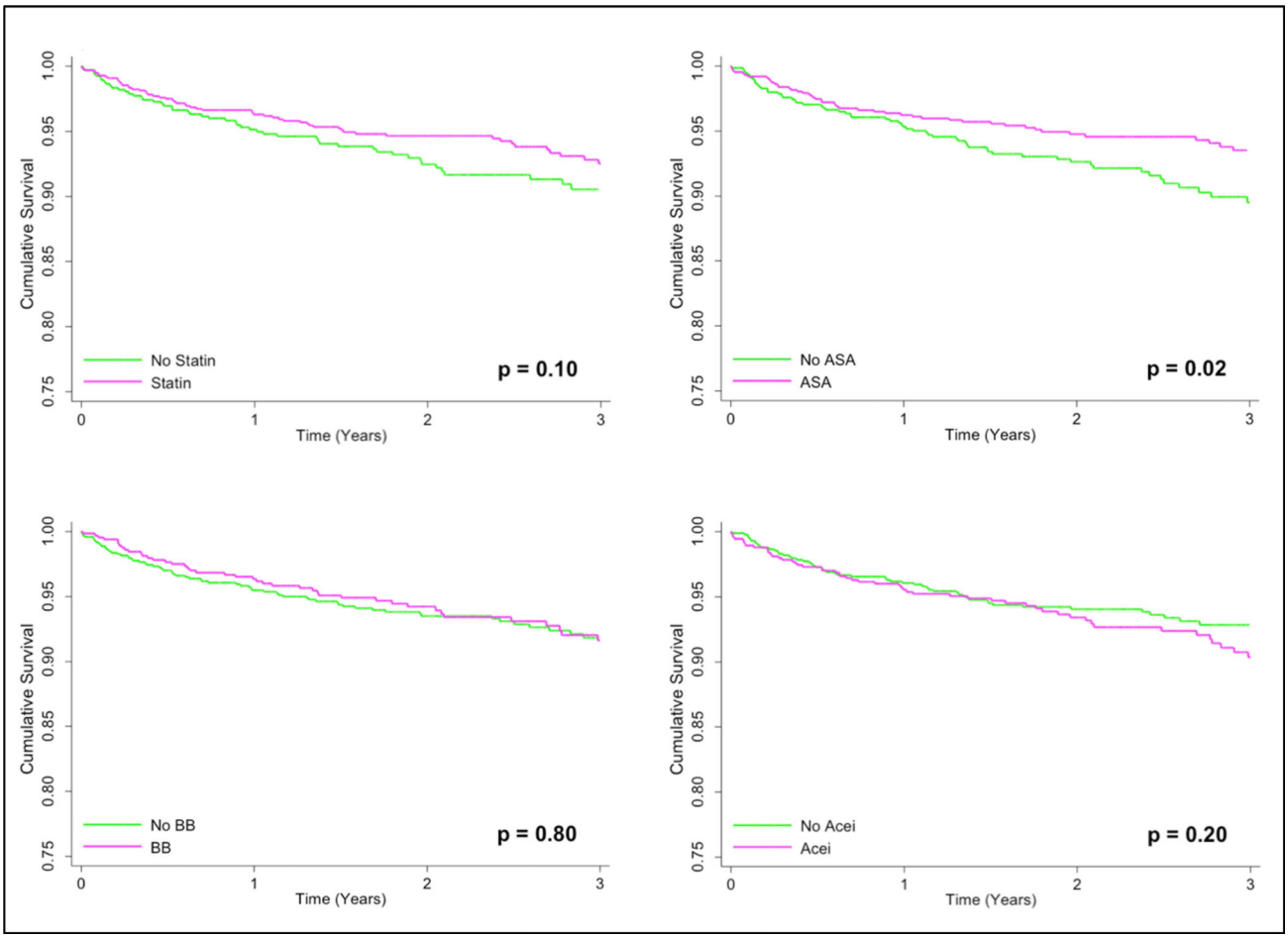

Figure 1. Unadjusted 3-Year Survival by the Use of Selected Medications Survival curves for statins, aspirin, beta-blockers, ACE inhibitors/ARBs

Presence of medication may also include other medications

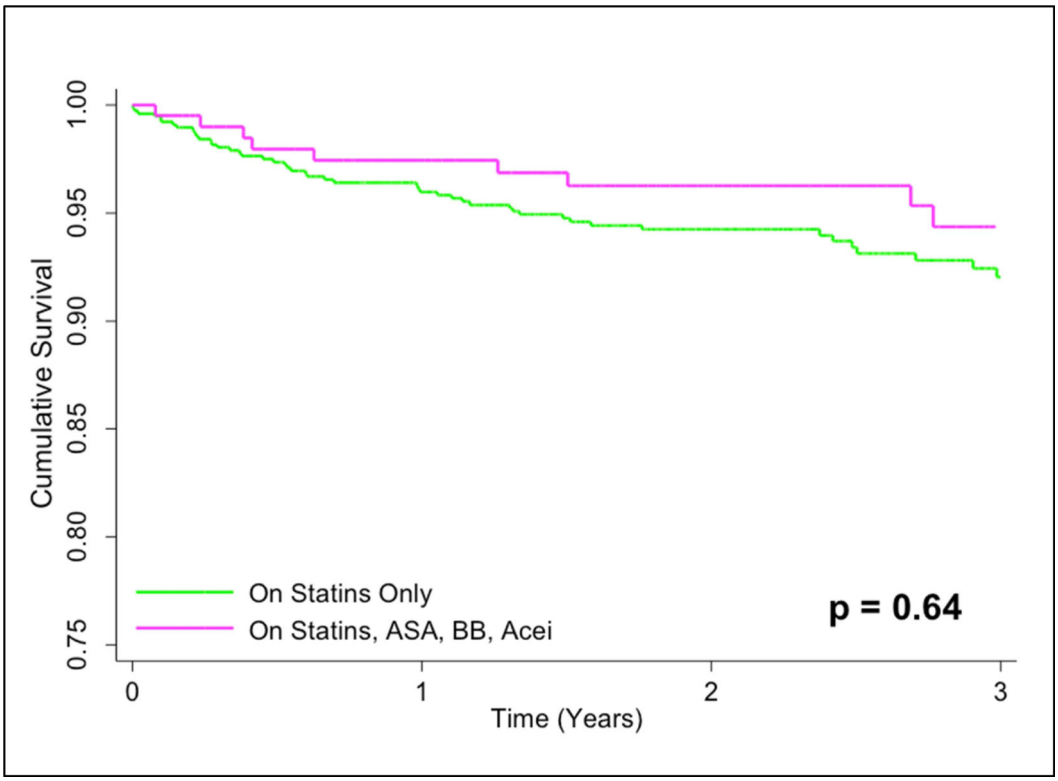

Figure 2.
Unadjusted Survival by Primary versus Secondary Medication Regimen

Table 1

Study demographics

	Complete Med Data (n=1637)	Incomplete Med Data (n=1170)	p-value
Age, mean ± SD	64.8±10.2	61.7 ± 10.5	<0.001
Male, n (%)	1139 (69.6)	762 (65.2)	0.014
Cardiovascular risk factors, n (%)			
Current smoker	388 (23.8)	196 (16.9)	<0.001
Diabetes	390 (23.9)	234 (20.2)	0.02
Family history of premature CAD	552 (33.8)	1019 (37.1)	<0.001
Hyperlipidemia	1142 (70.1)	754 (65.3)	0.007
Hypertension	1064 (65.2)	709 (62.0)	0.08
Chest Pain, n (%)			<0.001
Typical	327 (20.7)	158 (14.1)	
Atypical	502 (31.8)	395 (35.3)	
Non-cardiac	138 (8.8)	110 (9.8)	
Asymptomatic	610 (38.7)	457 (40.8)	
Dyspnea, n (%)	250 (16.6)	425 (46.1)	<0.001
Medication, n (%)			
Statins	970 (59.3)	na	
Aspirin	883 (53.9)	na	
Beta-blockers	651 (39.8)	na	
ACE inhibitors/ARBs	747 (45.6)	na	
Other*	559 (34.2)	na	
CAD Severity, n (%)			0.74
1-vessel	987 (60.3)	702 (60.1)	
2-vessel	382 (23.3)	285 (24.4)	
3-vessel	268 (16.4)	182 (15.6)	
Any coronary revascularization	403 (24.6)	368 (31.5)	<0.001
Early coronary revascularization (<90 days)	278 (17.0)	295 (25.2)	<0.001

* Includes nitrates, calcium channel blockers, and non-statin lipid lowering medications

Table 2

Baseline Characteristics Stratified by Medication

	Statin (n=970)	Aspirin (n=833)	Beta Blocker (n=651)	Ace Inhibitor/ARB (n=747)
Age, mean ± SD	64.9 ± 9.5	64.4 ± 10.1	65.1 ± 9.9	65.2 ± 9.7
Male, n (%)	677 (69.8)	610 (69.1)	424 (65.1)	503 (67.3)
Cardiovascular risk factors, n (%)				
Current smoker	228 (23.6)	167 (19.0)	130 (20.2)	150 (20.2)
Diabetes	259 (26.8)	242 (27.6)	176 (27.3)	215 (29.0)
Family history of premature CAD	351 (36.3)	246 (27.9)	176 (27.1)	224 (30.1)
Hyperlipidemia	837 (86.7)	627 (71.5)	462 (71.4)	503 (67.9)
Hypertension	644 (66.6)	567 (64.7)	458 (70.9)	555 (74.6)
Chest Pain, n (%)				
Typical	354 (38.2)	347 (41.3)	251 (40.7)	310 (43.0)
Atypical	281 (30.3)	265 (31.6)	197 (31.9)	232 (32.2)
Non-cardiac	81 (8.7)	35 (4.2)	38 (6.2)	44 (6.1)
Asymptomatic	212 (22.8)	192 (23.0)	131 (21.2)	135 (18.7)
Dyspnea, n (%)	132 (14.7)	112 (14.0)	90 (15.3)	118 (18.0)
Medication, n (%)				
Statin	970 (100)	586 (66.4)	427 (65.6)	460 (61.6)
ASA	586 (60.4)	883 (100)	489 (75.1)	490 (65.6)
Beta blocker	427 (44.0)	489 (55.4)	651 (100)	399 (53.4)
ACEi/ARB	460 (47.4)	490 (55.5)	399 (61.3)	747 (100)
Other	372 (38.4)	444 (50.3)	303 (46.5)	293 (39.2)
CAD Severity, n (%)				
1-vessel	547 (56.4)	544 (61.6)	382 (58.7)	460 (61.6)
2-vessel	241 (24.9)	206 (23.3)	171 (26.3)	176 (23.6)
3-vessel	182 (18.8)	133 (15.1)	98 (15.1)	111 (14.9)
Any coronary revascularization	291 (30.0)	192 (21.7)	166 (25.5)	206 (27.6)
Early coronary revascularization (<90 days)	181 (18.7)	109 (12.3)	108 (16.6)	144 (19.2)

Table 3

Clinical characteristics associated with MACE for patients with obstructive CAD

	Univariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
Age	1.06 (1.04-1.08)	<0.001	1.06 (1.04-1.08)	<0.001
Male	1.00 (0.67-1.49)	1.00	1.15 (0.76-1.74)	0.51
Diabetes	1.12 (0.74-1.69)	0.60	1.12 (0.74-1.70)	0.59
Family history of premature CAD	1.26 (0.86-1.84)	0.23	1.24 (0.83-1.83)	0.29
Hyperlipidemia	1.06 (0.71-1.59)	0.78	1.46 (0.92-2.30)	0.11
Hypertension	1.93 (1.25-2.96)	0.003	1.50 (0.96-2.34)	0.07
Current smoker	1.40 (0.94-2.08)	0.10	1.45 (0.96-2.19)	0.08
Medication				
Statins	0.74 (0.51-1.06)	0.10	0.57 (0.38-0.87)	0.008
Aspirin	0.65 (0.45-0.93)	0.02	0.74 (0.49-1.12)	0.16
Beta-blockers	0.95 (0.66-1.38)	0.80	1.05 (0.70-1.59)	0.80
ACE inhibitors	1.27 (0.88-1.83)	0.20	1.38 (0.91-2.08)	0.13
CAD Severity				
1-vessel	1.00 (Reference)			
2-vessel	2.04 (1.33-3.14)	0.001	1.86 (1.20-2.88)	0.006
3-vessel/left main	2.52 (1.61-3.95)	<0.001	1.97 (1.23-3.16)	0.005
Early coronary revascularization(<90days)	1.97 (1.31-2.95)	0.001	1.64 (1.08-2.48)	0.02

*Multivariable HR adjusted for age, sex, clinical risk factors, medication, CAD severity, and early coronary revascularization. CAD indicates coronary artery disease; HR, hazard ratio; CI, confidence interval.

Table 4

Clinical Characteristics Associated with MACE for Patients with More Extensive CAD

	2v/3v/LM CAD (n=650)		3v/LM CAD (n=268)	
Variable	**Multivariable HR (95% CI)**	**p-value**	**Multivariable HR (95% CI)**	**p-value**
Age	1.03 (1.00-1.06)	0.03	1.05 (1.01-1.10)	0.03
Male	0.91 (0.52-1.58)	0.74	0.81 (0.36-1.83)	0.61
Diabetes	1.46 (0.86-2.48)	0.16	2.20 (1.04-4.64)	0.04
Family history of premature CAD	1.46 (0.88-2.44)	0.14	1.82 (0.84-3.91)	0.13
Hyperlipidemia	1.35 (0.73-2.49)	0.34	2.40 (0.85-6.77)	0.10
Hypertension	1.17 (0.66-2.08)	0.60	0.61 (0.26-1.42)	0.25
Current smoker	1.16 (0.68-2.00)	0.58	1.37 (0.61-3.09)	0.45
Medications				
Statins	0.44 (0.25-0.77)	0.004	0.30 (0.12-0.74)	0.009
Aspirin	0.74 (0.42-1.28)	0.28	0.83 (0.35-1.93)	0.66
Beta-blockers	1.05 (0.60-1.82)	0.87	0.50 (0.20-1.25)	0.14
ACE inhibitors	1.56 (0.89-2.74)	0.12	1.48 (0.58-3.79)	0.41
Early coronary revascularization(<90days)	1.56 (0.92-2.64)	0.10	1.87 (0.88-3.96)	0.11

*Multivariable HR adjusted for age, sex, clinical risk factors, medications, CAD severity, and early coronary revascularization. 2v indicates two vessel, 3v three vessel, LM left main, CAD coronary artery disease; HR, hazard ratio; CI, confidence interval.