Risk of obstructive coronary artery disease and major adverse cardiac events in patients with noncoronary atherosclerosis: Insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking (CART) Program

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Background We sought to determine the risk of obstructive coronary artery disease (oCAD) associated with noncoronary atherosclerosis (cerebrovascular disease [CVD] or peripheral arterial disease [PAD]) and major adverse cardiac events following percutaneous coronary intervention (PCI).

Methods Rates of the angiographic end point of oCAD were compared among patients with and without noncoronary atherosclerosis undergoing coronary angiography within the Veterans Health Administration between October 2007 and August 2015. The primary angiographic end point of *oCAD* was defined as left main stenosis ≥50% or any stenosis ≥70% in 1, 2, or 3 vessels. In patients who proceeded to PCI, the rate of the composite clinical end point of death, myocardial infarction, or stroke was compared among those with concomitant noncoronary atherosclerosis (CVD, PAD, or CVD + PAD) versus isolated CAD.

Results Among 233,353 patients undergoing angiography, 9.6% had CVD, 12.4% had PAD, and 6.1% had CVD + PAD. Rates of oCAD were 57.9% for neither CVD nor PAD, 66.4% for CVD, 73.6% for PAD, and 80.9% for CVD + PAD. Compared with patients without noncoronary atherosclerosis, the adjusted risk of oCAD with CVD, PAD, or CVD + PAD was 1.03 (95% CI 1.02-1.04), 1.10 (95% CI 1.09-1.11), and 1.12 (95% CI 1.11-1.13), respectively. In patients who underwent PCI, the adjusted hazard for death, myocardial infarction, or stroke among those with CVD, PAD, or CVD + PAD was 1.36 (95% CI 1.26-1.45), 1.53 (95% CI 1.45-1.62), and 1.72 (95% CI 1.59-1.86), respectively.

Conclusions In patients undergoing coronary angiography, noncoronary atherosclerosis was associated with increased burden of oCAD and adverse events post-PCI. (Am Heart J 2019;213:47-56.)

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Noncoronary atherosclerosis traditionally includes atherosclerotic disease of the cerebral and lower extremity arteries. Although atherosclerosis is a systemic disease, it is unclear the degree to which noncoronary atherosclerosis can predict the presence of obstructive coronary artery disease (oCAD) and subsequent ischemic events. This uncertainty is likely due to a relative dearth of data regarding noncoronary atherosclerosis and its effects on cardiovascular outcomes.[1] There are few contemporary studies assessing the risk of obstructive coronary atherosclerosis in patients with noncoronary atherosclerosis.[2-7] As such, further studies evaluating the natural progression, ischemic outcomes, and current treatment

patterns among patients with noncoronary atherosclerosis are warranted.

The present study aims to evaluate the prevalence of oCAD in a contemporary cohort of patients undergoing coronary angiography grouped according to the presence of noncoronary atherosclerosis. To accomplish this aim, we used data from the Veterans Affairs (VA) Clinical Assessment, Reporting, and Tracking (CART) Program, which collects all catheterization laboratory procedural data across VA catheterization laboratories.[8] Furthermore, we assessed the association between noncoronary atherosclerosis and major adverse cardiac events (MACE) in patients undergoing percutaneous coronary intervention (PCI).

Methods

Study sample

Data for the present study were compiled from the VA CART Program. As previously described, this is a national quality program supporting all VA cardiac catheterization laboratories, where invasive cardiac procedures are performed. Leveraging a software application embedded in the VA electronic health record, a key feature of the CART Program is that it systematically collects all procedural data on catheterization procedures, both diagnostic and interventional, performed at the Veterans Health Administrative (VHA) system.[8] Procedural data elements conform to the standards of the American College of Cardiology's National Cardiovascular Registry (ACC-NCDR).[9] Quality checks on CART data collection are routinely performed to ensure both completeness and accuracy of the collected data.[10] Nonprocedural data are collected from VA administrative encounters (inpatient and outpatient), fee basis (care provided outside the VA system), and pharmacy encounters (prescription and refills). Mortality was ascertained from the VHA Vital Status File, which draws vitality status from the VA Beneficiary Death File, VA Medicare Vital Status File, and the Social Security Administration Death Master File.

The study sample for the present analysis consisted of all patients undergoing index coronary angiography performed in any of the 79 VA cardiac catheterization laboratories between October 1, 2007, and August 31, 2015. A total of 294,521 patients comprised the initial sample. We excluded patients who underwent a non-index catheterization (n = 52,467), those with missing details regarding the extent of CAD (n = 8,015), and those with missing key procedural data (n = 4,596). After applying initial exclusion criteria, 233,353 patients were evaluated for oCAD, of which 54,723 patients underwent PCI. Of this latter cohort, we excluded patients that were missing PCI indication (n = 1,334) and status (n = 955), leaving 52,541 patients evaluated for clinical outcomes. Exclusion criteria were not mutually exclusive (Figure 1).

Variable descriptions

Noncoronary atherosclerosis was defined as cerebrovascular disease (CVD) and/or peripheral arterial disease (PAD). The presence of noncoronary atherosclerotic disease was determined by Current Procedural Terminology and *International Classification of Diseases, Ninth Revision,* procedure and diagnosis codes for CVD and PAD (data supplement). These aforementioned codes were obtained through VA administrative data outside of the CART Program. Categories of noncoronary atherosclerosis were stratified as follows: neither, CVD, PAD, and CVD + PAD. Patients with any degree of coronary artery stenosis at the time of coronary angiography were defined as having CAD. The extent of CAD was classified as nonobstructive or obstructive, with the latter further categorized as 1-vessel, 2-vessel, 3-vessel disease, or left main (LM) obstructive disease. All LM disease patients were grouped together regardless of number of other diseased vessels. CAD was defined as obstructive if there was $\geq$70% stenosis in any coronary artery or $\geq$50% stenosis in the LM coronary artery. Subsequent PCI was limited to procedures within 30 days of index catheterization with procedures documented in CART.

Presentation diagnosis and procedural indication were classified as ST-elevation myocardial infarction (STEMI), non–ST-elevation myocardial infarction (NSTEMI), unstable angina (UA), or other. Procedure status was also grouped as elective, urgent, or emergent/salvage using the NCDR CathPCI registry definitions.[9]

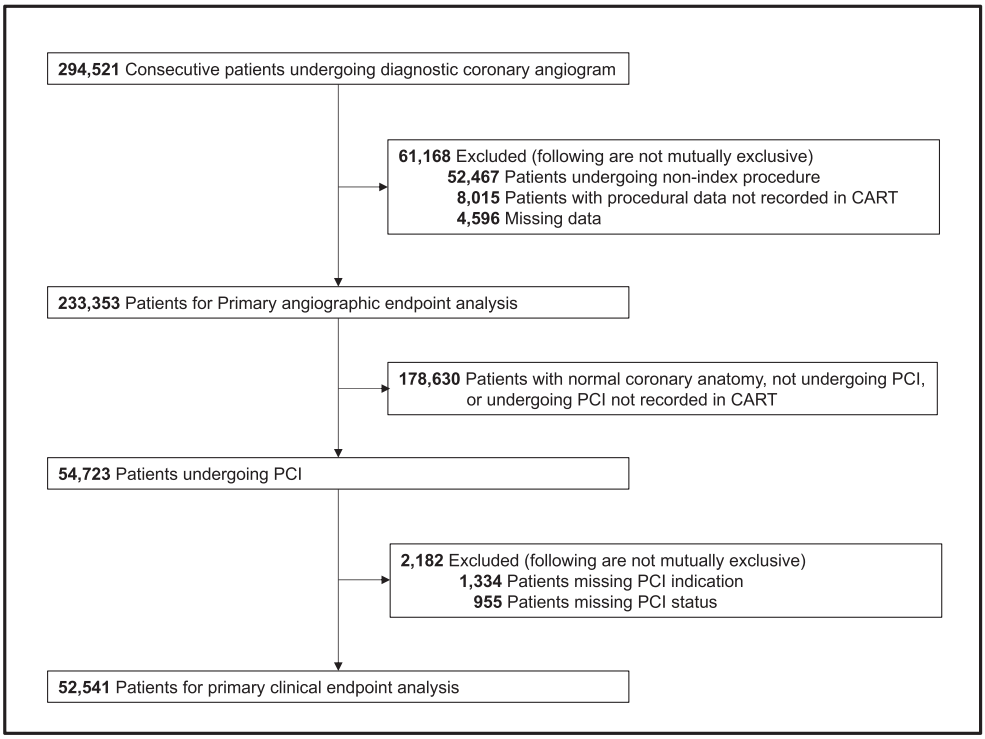
End points

The outcomes of interest consisted of a primary angiographic end point of oCAD and a primary clinical end point of death, MI, or stroke post-PCI through longest available follow-up period (median follow-up 37 months). Key secondary outcomes consisted of the individual components of the primary clinical end point. All were time to event outcomes using a baseline of discharge date from the hospital for PCI and censored as of September 30, 2015, if no event occurred for the patient. Any MI event occurring within 14 days of PCI was excluded due to inability to determine if the etiology was related to the index event. Patients were censored at their date of death for MI or stroke if death occurred prior to the end of the follow up period.

Statistical analyses

After implementing exclusion criteria, the data were reviewed for outliers and missing values. A small proportion of the patients were missing data for body mass index (1.2%) and current smoking status (3.7%). For missing data, values were imputed by simulating random numbers from distributions with patient-specific parameters estimated using models generated from the observed data with no changes in conclusions across multiple imputations. For this reason, only a single imputation was used in the primary analysis.

Figure 1



CONSORT diagram.

To assess the association between noncoronary atherosclerosis and the primary angiographic end point of oCAD, a modified Poisson model was fit using generalized estimating equations.[11,12] The outcome was dichotomized by obstructive versus nonobstructive CAD. Results detailed the relative risk of oCAD for patients with 2 or 3 diseased noncoronary vascular beds relative to patients with single noncoronary bed disease. To evaluate the association between noncoronary atherosclerosis and the extent of oCAD, the base cohort was restricted to patients with CAD. Lastly, to assess the association between noncoronary atherosclerosis and the primary clinical end point of death, MI, or stroke following PCI, the study cohort was restricted to patients undergoing PCI within 30 days of index coronary angiography. Cox proportional-hazards models were then fitted to assess the association between noncoronary atherosclerosis and the primary composite outcome as well as each individual outcome.

All analytic models were adjusted for patient demographics (age, gender, race, ethnicity) and medical history (atrial fibrillation, body mass index, congestive heart failure, diabetes, family history of CAD, hypertension, hyperlipidemia, prior coronary artery bypass graft [CABG], prior MI, prior PCI, and current tobacco use). The Cox proportional-hazards models included adjustments for PCI indication and status. To account for potential clustering patient outcomes within sites, the sandwich variance estimator was used in the generalized estimating equations for the angiographic end point and Cox model for the clinical end point.

Sensitivity analyses were performed to assess the effects of competing risks on the hazard estimates produced by the fitted Cox models for the individual outcomes. These analyses consisted of 3 differing assumptions about the competing risks: MI, stroke, and death. We first fit the proportional hazard models for MI and stroke assuming that patients who died, instead, had an event the day after their date of death. In the second analysis, patients who died were not censored at death but rather given an event the day after the last possible day of follow-up.[13] In the third analysis, the univariate proportional hazard models for MI, stroke, and death were fit such that patients who had one of the alternative competing risk events prior to the event being modeled were instead censored at the time of the prior, alternative event.[14] Additionally, missing data analyses, including results generated from multiple imputations and removal of missing data, produced similar results.

The present study was approved, including waiver of informed consent, by the Colorado Multiple Institutional Review Board. Statistical analyses were performed by the

Table I. Baseline characteristics: diagnostic angiography

	Neither n = 167,627	CVD n = 22,418	PAD n = 29,003	CVD + PAD n = 14,305	*P* value
Demographics					
Age (mean, SD)	63.8 (9.5)	67.2 (9.4)	67.1 (8.7)	69.2 (8.6)	<.001
Sex, male (%)	96.7	97.1	98.4	98.6	<.001
BMI (mean, SD)	30.9 (6.1)	30.1 (6.0)	29.6 (6.1)	28.8 (5.5)	<.001
Medical history (%)					
Atrial fibrillation	12.3	18.7	16.3	19.4	<.001
Heart failure	23.7	33.9	35.4	40.1	<.001
Chronic kidney disease	15.0	25.3	28.5	35.4	<.001
COPD	18.5	24.0	31.1	34.9	<.001
Diabetes mellitus	42.5	51.0	52.5	55.7	<.001
Family history of CAD	16.3	15.9	15.9	16.8	.04
Hypertension	85.3	93.6	93.0	96.5	<.001
Hyperlipidemia	82.5	90.8	90.6	94.8	<.001
Prior CABG	33.1	43.0	45.8	51.6	<.001
Prior MI	14.1	22.3	26.3	33.6	<.001
Prior PCI	24.6	35.9	38.2	45.2	<.001
Current smoker	36.3	34.4	45.4	41.7	<.001
Diagnostic angiography (%)					
Status					<.001
Elective	76.1	72.6	73.8	70.8	
Urgent	20.9	24.8	23.6	26.6	
Emergent/salvage	3.0	2.6	2.6	2.6	
Indication					<.001
STEMI	2.0	1.7	1.5	1.6	
NSTEMI	10.6	13.4	14.3	17.9	
UA	15.6	16.4	15.1	15.4	
Access site					<.001
Femoral	81.0	82.8	78.1	78.2	
Radial	18.1	16.2	19.3	19.0	
Other	0.8	0.9	2.6	2.7	
Coronary findings					<.001
Normal	15.1	9.3	5.6	3.1	
Nonobstructive	26.9	24.4	20.7	16.0	
1	22.8	21.8	22.4	20.1	
2	15.3	17.5	19.8	20.2	
3	13.1	17.2	20.0	23.3	
Any LM	6.8	9.9	11.5	17.3	

P values are provided from analysis of variance and multiple degree of freedom χ^2 tests. *BMI,* Body mass index; *COPD,* chronic obstructive pulmonary disease.

Denver VA CART Analytic Group using R 3.2.5 (R Core Team, 2016) and SAS 9.4 (SAS Institute, Cary, NC).

Results

Diagnostic coronary angiography cohort

Table I details baseline demographics, medical history, and procedural characteristics stratified by noncoronary atherosclerosis: neither, CVD, PAD, and CVD + PAD. Following exclusion criteria, 233,353 veterans undergoing coronary angiography were included in the final study cohort. Among this cohort, 167,627 (71.8%) had neither CVD nor PAD; 22,418 (9.6%) had CVD; 29,003 (12.4%) had PAD; and 14,305 (6.1%) had CVD + PAD. Compared with patients with neither CVD nor PAD, patients with noncoronary atherosclerosis were older and had higher rates of clinical comorbidities including atrial fibrillation, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, hypertension, hyperlipidemia, prior coronary revascularization, prior MI, and active tobacco use. Patients with noncoronary atherosclerosis presented less often with a STEMI but more often with an NSTEMI or UA in relation with patients without noncoronary atherosclerosis.

Risk of obstructive CAD according to presence of noncoronary atherosclerosis

A total of 144,905 (62.1%) patients were found to have the primary angiographic end point of oCAD. Normal coronary arteries or non-oCAD was most prevalent in patients without noncoronary atherosclerosis (Table I). Conversely, the rates of oCAD, including multivessel (≥2) or LM, were highest in patients with noncoronary atherosclerosis (Figure D1, Data Supplement). The unadjusted risk of the primary angiographic end point of oCAD, compared with patients without noncoronary

Table II. Baseline characteristics: percutaneous coronary intervention

	Neither n = 37,272	CVD n = 5122	PAD n = 6676	CVD + PAD n = 3471	*P* value
Demographics					
Age (mean, SD)	64.5 (9.1)	68.1 (9.4)	67.2 (8.7)	69.5 (8.8)	<.001
Sex, male (%)	0.98	0.98	0.99	0.99	.01
BMI (mean, SD)	30.6 (5.8)	30.1 (5.7)	29.5 (5.9)	28.7 (5.3)	<.001
Medical history (%)					
Atrial fibrillation	8.5	14.9	13.0	18.2	<.001
Heart failure	17.3	28.8	31.2	38.8	<.001
Chronic kidney disease	14.4	26.8	28.5	37.4	<.001
COPD	16.9	23.2	30.8	34.9	<.001
Diabetes	43.6	52.7	53.6	57.8	<.001
Family history of CAD	17.5	16.3	16.4	18.2	.02
Hypertension	86.1	94.3	93.6	97.1	<.001
Hyperlipidemia	86.1	92.3	92.0	95.6	<.001
Prior CABG	17.4	27.7	30.2	40.1	<.001
Prior MI	30.3	41.0	44.1	50.0	<.001
Prior PCI	32.0	36.3	41.3	43.2	<.001
Current smoker	36.8	32.7	45.2	39.7	<.001
Procedural characteristics (%)					
Status					<.001
Elective	60.9	60.1	61.3	58.9	
Urgent	30.8	33.4	32.4	34.6	
Emergent/salvage	8.3	6.5	6.3	6.5	
Indication					<.001
STEMI	8.2	6.2	5.7	5.3	
NSTEMI	21.1	24.1	23.7	26.5	
UA	25.6	25.0	25.1	27.4	
Other	45.1	44.8	45.4	40.9	
Access site					<.001
Femoral	83.3	84.9	80.9	80.7	
Radial	16.3	14.8	17.4	17.4	
Other	0.4	0.3	1.6	1.9	
Coronary findings					<.001
Normal	0	0	0	0	
Nonobstructive	3.6	3.5	3.5	2.8	
1	47.8	39.0	35.1	27.4	
2	28.4	28.9	30.8	28.8	
3	15.3	20.2	21.1	25.5	
Any LM	4.8	8.3	9.5	15.5	
Treatment					<.001
1 or more DES	79.0	74.0	73.2	71.0	
BMS	15.9	20.3	20.1	22.2	
POBA	5.1	5.6	6.5	6.7	
Medications (%)					
Discharge					
ACE inhibitor	55.0	53.6	53.1	51.5	.05
Anticoagulant	6.8	12.0	10.1	12.5	<.001
$P2Y_{12}$ inhibitor	95.4	92.6	92.3	89.3	<.001
Statin	83.0	79.7	79.0	76.9	<.001
1 y post-PCI*					
ACE inhibitor	41.8	43.2	40.9	41.2	.22
Anticoagulant	5.3	9.6	7.9	9.6	<.001
$P2Y_{12}$ inhibitor	41.5	42.8	43.4	48.2	<.001
Statin	62.4	63.9	62.8	63.1	.46
2 y post-PCI*					
ACE inhibitor	41.0	41.0	41.2	40.6	.98
Anticoagulant	5.6	9.6	8.4	10.3	<.001
$P2Y_{12}$ inhibitor	28.9	32.5	31.8	39.9	<.001
Statin	61.8	62.1	61.8	63.4	.69

DES, Drug-eluting stent; *BMS*, bare-metal stent; POBA, plain old balloon angioplasty.
*Results restricted to patients with full follow-up and all data calculated for assessing guideline therapies at the time point.

atherosclerosis, was the following: CVD 1.15 (95% CI 1.13-1.17), PAD 1.27 (95% CI 1.25-1.29), and CVD + PAD 1.40 (95% CI 1.37-1.42), *P* values < .001, respectively. This risk persisted after adjustment for covariates: CVD 1.03 (95% CI 1.02-1.04), PAD 1.10 (95% CI 1.09-1.11), and CVD + PAD 1.12 (95% CI 1.11-1.13), *P* values < .001, respectively.

PCI cohort

Following exclusion criteria, 52,541 patients with oCAD underwent PCI that was recorded in CART within 30 days of index diagnostic coronary angiography. Table II depicts baseline demographics, medical history, procedural characteristics, and key medical therapies at discharge stratified by noncoronary atherosclerosis: neither, CVD, PAD, and CVD + PAD. Compared with patients without noncoronary atherosclerosis, patients with CVD and/or PAD were older, had more comorbidities, and had higher rates of active tobacco use. The majority of PCI procedures, approximately 60%, took place in the elective setting. In regard to acute coronary syndromes, patients without noncoronary atherosclerosis presented more often with a STEMI, whereas those with CVD and/or PAD presented more often with an NSTEMI or UA. Most patients were treated with a drug-eluting stent; however, patients with noncoronary atherosclerosis had the highest rates of bare-metal stent implantation.

At the time of discharge for index PCI, patients with noncoronary atherosclerosis were less likely to be prescribed an angiotensin-converting enzyme (ACE) inhibitor (CVD 53.6%, PAD 53.1%, and CVD + PAD 51.5%), oral $P2Y_{12}$ inhibitor (CVD 92.6%, PAD 92.3%, and CVD + PAD 89.3%), or statin therapy (CVD 79.7%, PAD 79%, and CVD + PAD 76.9%) compared with patients without noncoronary atherosclerosis (ACE inhibitor 55%, $P2Y_{12}$ inhibitor 95.4%, and statin 83%). At 1 year post-PCI, the rates of ACE inhibitor (neither 41.8%, CVD 43.2%, PAD 40.9%, and CVD + PAD 41.2%), oral $P2Y_{12}$ inhibitor (neither 41.5%, CVD 42.8%, PAD 43.4%, and CVD + PAD 48.2%), and statin therapy (neither 62.4%, CVD 63.9%, PAD 62.8%, and CVD + PAD 63.1%) use dramatically decreased among all cohorts. Patients with noncoronary atherosclerosis, however, were more likely to be on continued oral $P2Y_{12}$ inhibition and statin therapy. At 2 years post-PCI, the rates of ACE inhibitor and oral $P2Y_{12}$ inhibitor use decreased slightly among all cohorts, whereas rates of statin use remained relatively stable. Patients with noncoronary atherosclerosis continued to be treated with the highest rates of oral $P2Y_{12}$ inhibitors.

Clinical outcomes in PCI cohort by presence of noncoronary atherosclerosis

At 1 year post-PCI, the rate of the primary clinical end point of death, MI, or stroke was highest in patients with substantial noncoronary atherosclerosis: neither (6.5%), CVD (11.9%), PAD (14.3%), and CVD + PAD (19.1%), respectively (Figure 2). After adjustment for differences in baseline characteristics, the hazard for patients with noncoronary atherosclerosis compared with patients without noncoronary atherosclerosis was the following: CVD 1.35 (95% CI 1.26-1.45), PAD 1.53 (95% CI 1.45-1.62), and CVD + PAD 1.72 (95% CI 1.59-1.86), *P* values < .001, respectively. The adjusted hazards for the individual end points of death and MI also paralleled this trend. The adjusted hazard for the individual end point of stroke was the following: PAD 1.45 (95% CI 1.24-1.71), CVD + PAD 1.92 (95% CI 1.56-2.36), and CVD 2.25 (1.82-2.78), *P* values < .001, respectively (Figure 3). The primary and secondary results persisted following sensitivity analyses.

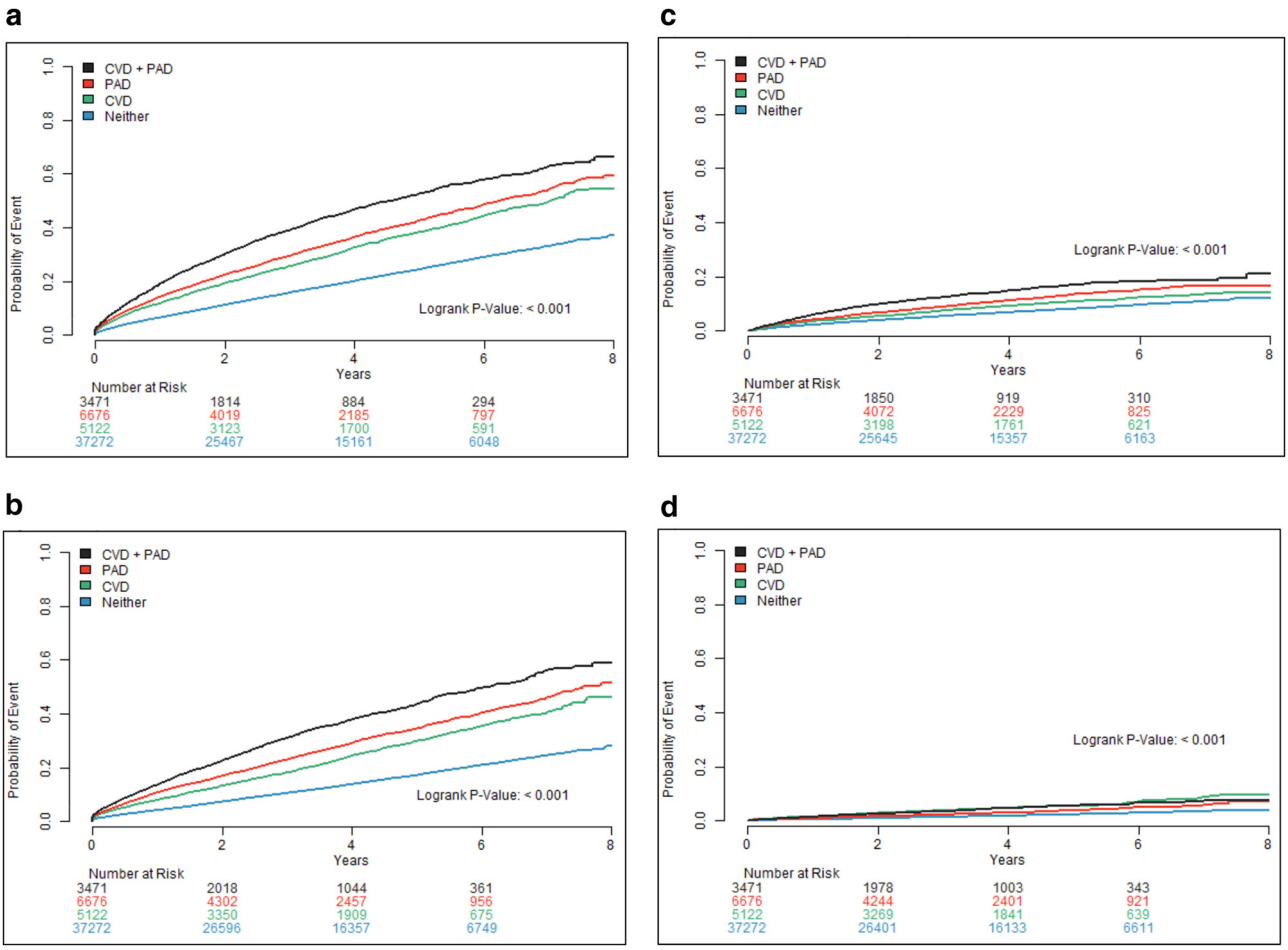
Discussion

Patients with noncoronary atherosclerosis present a clinical challenge. Although their risk of adverse cardiovascular events is high, there are few data on their risk of oCAD and outcomes after PCI. The present study addresses this knowledge gap by leveraging a large contemporary multicenter clinical database of patients undergoing cardiac catheterization and PCI. Key findings from our analysis are the following: (1) the presence of oCAD is common among patients with noncoronary atherosclerosis; (2) the risk of having oCAD increases as the number of diseased noncoronary vascular beds increase; (3) there is also an increased risk of long-term death, MI, or stroke among patients undergoing PCI as the number of diseased noncoronary beds increase.

A key feature of the VA CART Program is that it records both diagnostic coronary anatomy and PCI elements from all catheterization laboratories within the VHA. One of the aims of the current analysis was to evaluate the prevalence of oCAD in the setting of noncoronary atherosclerosis, CVD, and/or PAD. In accordance with published guidelines, obstructive flow-limiting lesions were defined as a ≥70% diameter stenosis in a major epicardial vessel or ≥50% in the LM coronary artery.[15,16] In the present study population, 73% of patients with noncoronary atherosclerosis undergoing coronary angiography were found to have oCAD. Studies have previously described an association between so-called "polyvascular disease" and an increased risk of future ischemic events.[17-22] Our study adds to these findings by quantifying the burden and risk of oCAD according to the presence of CVD and/or PAD. Analysis of outcomes following PCI demonstrates an increased risk for MACE in patients with noncoronary atherosclerosis. The presence of CVD, PAD, or both was associated with a 35%, 53%, and 72% increased risk of death, MI, or stroke, respectively, following PCI.

Prior studies have shown that among both stable and acute coronary syndrome populations, patients with atherosclerosis across multiple vascular beds often experience a treatment deficit in terms of guideline-

Figure 2



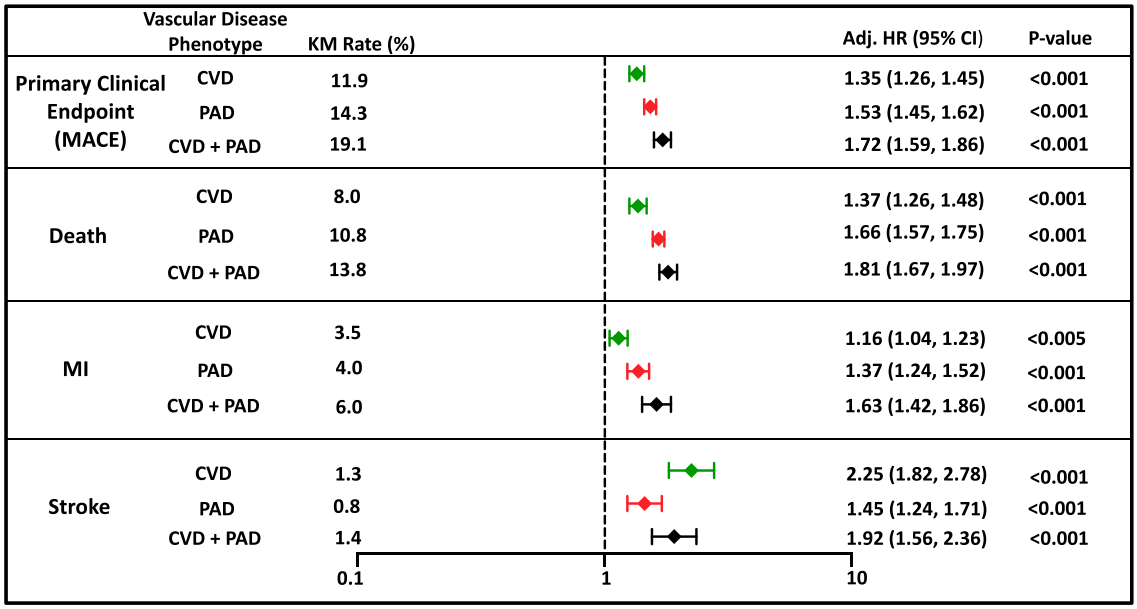
A, Kaplan-Meier curve for primary clinical end point: MACE.Primary clinical end point (MACE) = composite of death, MI, or stroke.**B**, Kaplan-Meier curve for death.**C**, Kaplan-Meier curve for myocardial infarction.**D**, Kaplan-Meier curve for stroke.

recommended medical therapies.[18-20,23-25] Unfortunately, our more contemporary findings indicate that this disparity has not improved. For example, at 30 days post-PCI, patients with CVD + PAD, who are at highest risk for MACE, had the lowest rates of ACE inhibitor (51.5%), $P2Y_{12}$ inhibitor (89.3%), and statin use (76.9%). One possible explanation for lower utilization rates of $P2Y_{12}$ inhibitors among this cohort is a higher frequency of anticoagulant use. As such, concomitant $P2Y_{12}$ inhibitor use may have been tempered due to a higher bleeding risk. An alternative justification for the decreased use of $P2Y_{12}$ inhibitors among patients with noncoronary atherosclerosis is that there was higher use of bare-metal stents, requiring only 30 days of dual antiplatelet therapy post-PCI as opposed to greater durations in the setting of drug-eluting stent implantation.

An important novel aspect of using VA CART Program data is that we were able to evaluate the long-term use of guideline-recommended therapies post-PCI. Our findings indicate that rates of ACE inhibitor, $P2Y_{12}$ inhibitor, and statin use all peaked at 30 days post-PCI and dropped precipitously during the subsequent 2 years.

These data suggest opportunities for increased use of secondary prevention strategies to reduce adverse events over the long term in this high-risk patient cohort. For example, in patients with noncoronary atherosclerosis who undergo PCI, one potential strategy may include the use of prolonged dual antiplatelet therapy (DAPT). The Dual Antiplatelet Therapy study, the largest trial to evaluate the use of prolonged DAPT, found that extending DAPT, aspirin and clopidogrel, for an additional 18 months was associated with a 2% absolute risk

Figure 3



Primary and secondary outcomes according to noncoronary atherosclerosis phenotype* (adjusted**).Primary clinical end point (MACE) = composite of death, MI, or stroke. *HR*, hazard ratio; *KM*, Kaplan-Meier.*Compared with patients with isolated coronary artery disease.**Analytic models adjusted for patient demographics (age, gender, race, ethnicity), medical history (atrial fibrillation, body mass index, congestive heart failure, diabetes, family history of CAD, hypertension, hyperlipidemia, prior CABG, prior MI, prior PCI, and current tobacco use), and clinical characteristics (PCI indication and status).

reduction in MI or MACE.[26] Based on this same study, one of the most widely used and validated prediction models, the DAPT score, was developed to estimate ischemic versus bleeding risk in efforts to guide individualization of prolonged DAPT therapy post-PCI. Although the presence of noncoronary atherosclerosis, specifically CVD or PAD, is not taken into account in calculating a DAPT score, several factors highly prevalent among patients with noncoronary atherosclerosis such as cigarette smoking and diabetes are included.[27] Another potential strategy to mitigate ischemic risk in this high-risk cohort may be to incorporate the use of novel cholesterol-lowering agents such as the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab. In the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk trial, evolocumab was associated with a 3.5% absolute risk reduction in MACE among patients with PAD, of which 40% had a prior PCI.[28] Lastly, a third preventive strategy comes from the recent Cardiovascular Outcomes for People Using Anticoagulation trial, where low-dose rivaroxaban (2.5 mg twice daily) plus low-dose aspirin was found to have a 28% risk reduction in MACE among patients with PAD.[29] The intricacy of implementing low-dose rivaroxaban in the post-PCI setting among patients with noncoronary atherosclerosis will center on maximizing ischemic benefit while reducing bleeding risk. At this time, we advocate completing the minimum recommended post-PCI duration of DAPT as outlined by society guidelines, according to PCI indication, before transitioning to low-dose rivaroxaban.[30] Although both PCSK9 inhibitors and low-dose rivaroxaban have demonstrated considerable potential in minimizing ischemic events in patients with noncoronary atherosclerosis, it is still important to maximize use of longstanding guideline-recommended therapies such as ACE inhibitors and high-intensity statins.

Limitations

There are some limitations of this analysis. First, this is an observational study limited to patients receiving care in the VHA whose procedural data were collected from the VA CART Program. Therefore, the relationships are not necessarily causal. In addition, there may be unmeasured confounders that account for the findings. Second, the diagnoses of CVD and PAD were obtained from CPD and *International Classification of Diseases, Ninth Revision,* codes which were not adjudicated. Similarly, there is the possibility of misclassification bias with respect to the diagnosis of PAD or CVD, particularly in asymptomatic patients. However, such a misclassification would only bias

findings in favor of the null hypothesis. Third, because the data set for the study was from the VHA, it is predominantly male, and our findings may not apply to females or to patients treated outside the VHA.

Conclusions

In a national contemporary cohort of veterans undergoing coronary angiography, the risk of oCAD was greatest in those with noncoronary atherosclerosis. Among veterans undergoing PCI, the risk of long-term death, MI, or stroke increased with the burden of noncoronary atherosclerosis. Lastly, despite being at heightened risk for ischemic events, post-PCI veterans with atherosclerosis across multiple vascular beds were less likely to be treated optimally with guideline-recommended therapies compared with veterans with CAD alone.

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Appendix. Supplementary data

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References

1. Gallino A, Aboyans V, Diehm C, et al. Baumgartner I and European Society of Cardiology Working Group on Peripheral C. Non-coronary atherosclerosis. Eur Heart J 2014;35:1112-9.
2. Doonan AL, Karha J, Carrigan TP, et al. Presence of carotid and peripheral arterial disease in patients with left main disease. Am J Cardiol 2007;100:1087-9.
3. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223-33.
4. Mautner GC, Mautner SL, Roberts WC. Amounts of coronary arterial narrowing by atherosclerotic plaque at necropsy in patients with lower extremity amputation. Am J Cardiol 1992;70:1147-51.
5. Valentine RJ, Grayburn PA, Eichhorn EJ, et al. Coronary artery disease is highly prevalent among patients with premature peripheral vascular disease. J Vasc Surg 1994;19:668-74.
6. Ness J, Aronow WS. Prevalence of coexistence of coronary artery disease, ischemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in an academic hospital-based geriatrics practice. J Am Geriatr Soc 1999;47:1255-6.
7. Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease: morbidity and mortality implications. Circulation 2006;114:688-99.
8. Box TL, McDonell M, Helfrich CD, et al. Strategies from a nationwide health information technology implementation: the VA CART story. J Gen Intern Med 2010;25(Suppl 1):72-6.
9. Brindis RG, Fitzgerald S, Anderson HV, et al. The American College of Cardiology–National Cardiovascular Data Registry (ACC-NCDR):

building a national clinical data repository. J Am Coll Cardiol 2001;37:2240-5.
10. Byrd JB, Vigen R, Plomondon ME, et al. Data quality of an electronic health record tool to support VA cardiac catheterization laboratory quality improvement: the VA Clinical Assessment, Reporting, and Tracking System for Cath Labs (CART) program. Am Heart J 2013;165:434-40.
11. Yelland LN, Salter AB, Ryan P. Performance of the modified Poisson regression approach for estimating relative risks from clustered prospective data. Am J Epidemiol 2011;174:984-92.
12. Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. Stat Methods Med Res 2013;22:661-70.
13. Allison PD. Survival Analysis Using SAS: A Practical Guide 2nd ed;. 2010.
14. Prentice RL, Kalbfleisch JD, Peterson Jr AV, et al. The analysis of failure times in the presence of competing risks. Biometrics 1978;34:541-54.
15. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44-122.
16. Wilson RF, Marcus ML, White CW. Prediction of the physiologic significance of coronary arterial lesions by quantitative lesion geometry in patients with limited coronary artery disease. Circulation 1987;75:723-32.
17. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304:1350-7.
18. Bhatt DL, Peterson ED, Harrington RA, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. Eur Heart J 2009;30:1195-202.
19. Subherwal S, Bhatt DL, Li S, et al. Polyvascular disease and long-term cardiovascular outcomes in older patients with nonST-segment-elevation myocardial infarction. Circ Cardiovasc Qual Outcomes 2012;5:541-9.
20. Suarez C, Zeymer U, Limbourg T, et al. Influence of polyvascular disease on cardiovascular event rates. Insights from the REACH Registry. Vasc Med 2010;15:259-65.
21. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180-9.
22. Verma S, Bhatt DL, Bain SC, et al. Effect of liraglutide on cardiovascular events in patients with type 2 diabetes mellitus and polyvascular disease: results of the LEADER trial. Circulation 2018;137:2179-83.
23. 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;126:1345-54.
24. Gutierrez A, Bhatt DL. Medical management of peripheral artery disease in diabetes mellitus. Eur Heart J 2015;36:1494-5.
25. Brilakis ES, Hernandez AF, Dai D, et al. Quality of care for acute coronary syndrome patients with known atherosclerotic disease: results from the Get With the Guidelines Program. Circulation 2009;120:560-7.
26. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66.
27. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735-49.
28. 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;137:338-50.
29. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018;391:219-29.
30. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2016;134:e123-55.