GUIDELINE-DIRECTED STATIN THERAPY IN PATIENTS WITH NEW OR WORSENING SYMPTOMS OF PERIPHERAL ARTERY DISEASE

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GUIDELINE-DIRECTED STATIN THERAPY IN PATIENTS WITH NEW OR WORSENING SYMPTOMS OF PERIPHERAL ARTERY DISEASE

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University of Missouri-Kansas City, 2018

ABSTRACT

Objective: The ACC/AHA cholesterol guidelines recommend patients with peripheral artery disease (PAD) be treated with a moderate to high-intensity statin. The extent to which PAD patients with new or worsening claudication symptoms are offered guideline statin therapy is unknown.

Methods: In the PORTRAIT registry, patterns of statin therapy were assessed in 1144 patients at 16 PAD specialty clinics (between June 2011-December 2015) before and after an evaluation for new or worsening claudication symptoms. It was documented whether patients had been previously treated with a guideline-directed statin as well as switched from non-guideline to guideline statin therapy. Patient factors predicting intensification to guideline statin were examined. Site and provider-level variation in guideline statin intensification were summarized by calculating median odds ratios.

Results: Among 1144 patients, 810 (70.8%) were initially on guideline therapy compared with 334 (29.2%) that were not. In the latter, 103 (30.8%) were prescribed guideline therapy after evaluation. Patients with typical symptoms displayed greater odds of intensification to guideline statin (OR 3.75; 95% CI: 1.22-11.53) while older patients had lower odds (OR 0.60/decade; 95% CI: 0.40-0.87). Variability in guideline statin intensification was observed

across sites (Adjusted Median Odds Ratio = 3.63; 95% CI 1.88-5.42, ($p < 0.05$)) but not providers (Adjusted Median Odds Ratio = 1.90; 95% CI 1.00-2.55, ($p > 0.05$)).

Conclusions: In conclusion**,** most patients evaluated at a PAD specialty clinic for new or worsening claudication symptoms arrived on a guideline-directed statin. Only 31% originally off guideline therapy were intensified to a guideline statin. These findings highlight an important opportunity to optimize medical therapy for patients with PAD.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine have examined a thesis "Guideline-Directed Statin Therapy in Patients with New or Worsening Symptoms of Peripheral Artery Disease," presented by Yevgeniy Khariton, candidate for Master of Science Degree and certify that in their opinion it is worthy of acceptance.

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CHAPTER 1

INTRODUCTION

Peripheral artery disease (PAD) – a progressive atherosclerotic obstruction of lower extremity arteries – affects 8 to 12 million Americans[1,2] and increases in incidence after the fourth decade of life,[3] with nearly 1 in 5 elderly patients reporting symptoms. Clinically significant PAD is often diagnosed by healthcare providers based upon patient-reported signs and symptoms, that range from no symptoms to intermittent claudication (exertional "cramping pain") with typical or atypical features to chronic limb ischemia ("rest pain").[4] Patient symptoms associated with each category are described in Table I, as originally defined by Rose et al., where typical versus atypical intermittent claudication is often distinguished by duration of pain and relationship with exertion.[5]

Table I. Definitions of Typical/Atypical Claudication and Critical Limb Ischemia

	Patient Symptoms
No Symptoms	• Absence of extremity pain at rest or exertion
Typical Claudication	• Pain begins only on exertion • Pain involves the lower extremity • Pain causes the patient to reduce walking • Pain resolves within 10 minutes of rest
Atypical Claudication	• Pain sometimes begins at rest and/or on exertion • Pain involves the lower extremity • Pain does not resolve within 10 minutes of rest • Pain does not cause the patient to reduce walking

Critical Limb Ischemia	• Pain at rest • Non-healing wound on the lower extremity • Gangrene of the lower extremity

This distinction between PAD symptom phenotypes is important, as prior studies have shown a direct relationship between PAD symptom burden and cardiovascular outcomes.[2,6]

Moreoever, clinical diagnosis of PAD is confirmed using the ankle-brachial index (ABI), a non-invasive test that measures the ratio of the highest ankle systolic pressure to the highest brachial systolic pressure. Currently, the ABI remains the gold-standard for PAD diagnosis and is routinely used in the clinical setting (Figure 1).[3,7-9]

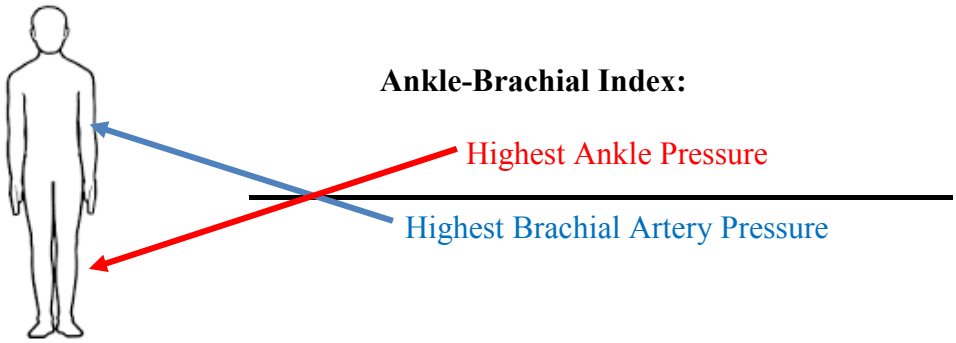


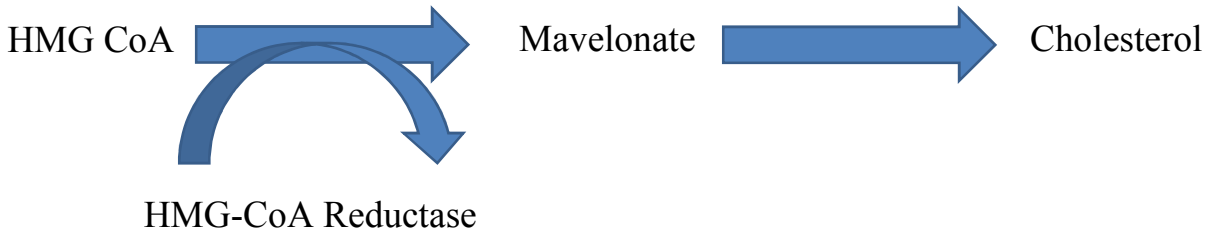
Figure 1. Measurement of Ankle-Brachial Index

Ankle-Brachial Index is calculated by dividing the highest left or right ankle systolic pressure by the highest brachial artery systolic pressure.

Importantly, with higher numbers of asymptomatic (versus symptomatic) PAD patients, rates of under- and delayed diagnosis are high.[10] This poses significant implications for patient care as, PAD is associated with significant premature cardiovascular morbidity (e.g. lower-limb amputation) and mortality that persists after accounting for other cardiovascular disease risk factors irrespective of symptom burden. This is principally explained by a significant co-incidence of PAD with coronary and cerebrovascular disease and, accordingly, a substantial overlap in both modifiable (e.g. tobacco use, diabetes mellitus, hypertension) and non-modifiable (e.g. age, gender) risk factors.[11] Overall, with an increasingly aging and comorbid population, the incidence and prevalence of PAD is expected to increase while requiring significant healthcare resources.[12]

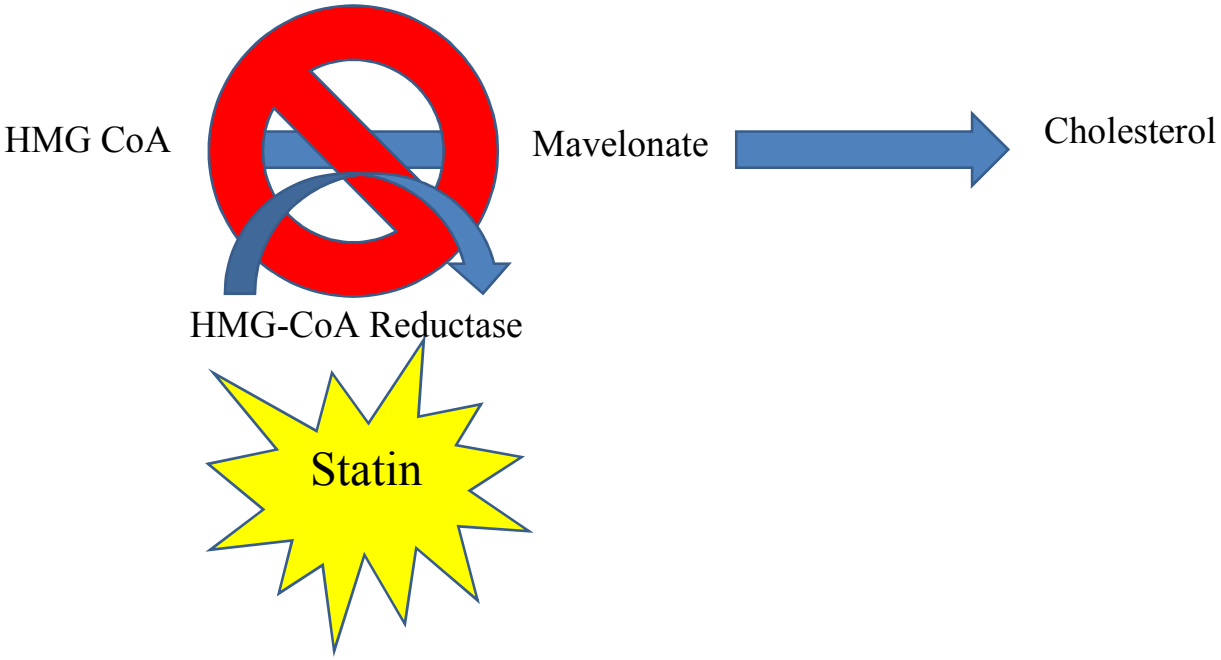
The primary goals in treating patients with PAD are symptom relief and cardiovascular risk management, which are addressed using percutaneous (or surgical) revascularization techniques and medical (e.g. aspirin, statin) and lifestyle therapies (e.g. structured exercise program, smoking cessation), respectively.[3] Currently, among guideline-directed medical therapies, moderate-high intensity doses of HMG-CoA inhibitors ("statins") [13] (Figure 2) are considered a cornerstone for cardiovascular disease prevention in PAD and have been commonly prescribed since the early 21st century. Statins' pleiotropic ability to (1) reduce cholesterol biosynthesis by inhibition of the enzyme HMG-CoA Reductase and (2) exert anti-inflammatory activity within the vasculature underscores their unique role in PAD risk management.

A. Without Statin



Mechanism of Action of HMG-CoA Reductase

B. With Statin



Mechanism of Action of HMG-CoA Inhibitors ("Statins")

Figure 2. Mechanism of Action of HMG-CoA Inhibitors ("Statins")

Moreover, statins' ability to prevent cardiovascular death underscores their importance in PAD,[14-19] where there is an increased risk for adverse cardiovascular events (i.e. myocardial infarction, stroke)[20] exceeding that observed in coronary artery disease or cerebrovascular disease alone.[21]

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines were developed as an update to prior clinical practice guidelines. These, newer guidelines represented a paradigm shift from a "treat to low-density lipoprotein cholesterol (LDL-C)" to "treat to risk" approach focused on reducing atherosclerotic cardiovascular disease risk (ASCVD) in patients with *clinical* ASCVD (prior myocardial infarction, coronary or other arterial revascularization, and atherosclerotic peripheral artery disease). Accordingly, the expert panelists recommended moderate to high-intensity statins as a Class 1A recommendation for all adult patients with PAD.[13] Despite these recommendations, the 2016 ACC/AHA Lower Extremity PAD Guidelines did not discriminate between low and moderate-high potency statin therapy and recommended treatment with *any* statin for all PAD patients (Class IA Recommendation). Moreoever, apart from statin under-dosing, statins are known to be under-prescribed in clinical practice,[22,23] particularly in PAD patients compared to other high-risk groups. Evidence of their suboptimal use is evident in cross-sectional,[14,15] procedural,[24] and administrative[23] databases. Accordingly, a unique opportunity to assess whether clinicians capitalize on key cardiovascular prevention strategies is at the time a patient with PAD presents to a specialty care clinic for further evaluation of new or worsening PAD symptoms. To date, however, little is known about optimization of guideline-directed statin therapy in patients with new or worsening PAD symptoms.

A multicenter, observational registry known as PORTRAIT (Patient Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories; Figures 3-6), which recruited patients from PAD specialty clinics in the United States, Netherlands, and Australia, was retrospectively accessed to examine rates of intensification to guideline statin therapy (transitioning from no statin *or* low-intensity statin to moderate *or* high-intensity statin therapy) following PAD evaluation for new or worsening PAD symptoms. The aims of the project were to: (1) determine physician compliance with the 2013 ACC/AHA cholesterol guidelines for statin treatment intensification, (2) determine predictors of intensification to guideline therapy in the PAD population, and (3) examine site variability in guideline statin intensification at the time of initial encounter with a PAD specialist. It was hypothesized that there would be high, overall, physician adherence to guideline-directed statin therapy and that rates of guideline intensification would be lower in diabetics and older patients. Finally, it was believed there would be significant site-level variability in statin intensification across the registry. Describing the adoption of the ACC/AHA 2013 cholesterol guidelines in patients actively being evaluated at a PAD specialty clinic represents an important opportunity to identify subgroups that are currently not receiving optimal care and identify target areas to improve the quality of PAD care.

CHAPTER 2

METHODS

Study Design

PORTRAIT (Patient Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories) is an international, prospective observational registry of patients referred to a specialty provider with a new diagnosis or exacerbation of PAD. Its study design has been previously described.[25] In brief, consecutive patients with objective evidence of symptomatic PAD were enrolled at 16 specialty PAD clinics between June 2011 and December 2015 across the United States, Netherlands, and Australia (Figures 3-6). All patients had a resting ankle-brachial index (ABI), calculated by dividing the highest ankle pressure (left or right) by the highest average brachial pressure (left or right) (Figure 1), of ≤ 0.90 or a significant drop in post-exercise ankle pressure of ≥ 20 mmHg. Patients with non-compressible ankle-brachial indices (ABI ≥ 1.30), lower-limb revascularization in the 12 months prior to the PAD visit, an active episode of critical limb ischemia, inability to speak English, Spanish, or Dutch (depending on enrollment site), and inability to provide written informed consent (e.g. hearing impairment, prisoner, and unable to provide written informed consent) were excluded (Table II). Symptomatic PAD – typical and atypical – was defined using the San Diego intermittent claudication questionnaire, which describes the presence, location, and character of symptoms in each affected leg.[26]

Table II. Original Patient Inclusion and Exclusion Criteria for PORTRAIT

• Age ≥ 18 years • New-onset or recent exacerbation of exertional leg symptoms, regardless of whether symptoms are typical or atypical (buttock, thigh, hip or calf pain, numbness or discomfort inhibiting the patient's ability to walk distances) • Ankle-brachial index = resting ankle-brachial index assessment ≤0.90 or drop in post-exercise ankle pressure ≥20mmHg	• Non-compressible ankle-brachial index (ABI ≥1.30) • Patient had a lower-limb revascularization procedure in the ipsilateral leg where the patient is currently having symptoms in the past year (atherectomy, endarterectomy, bypass surgery, angioplasty) • Patient presents with a current episode of critical limb ischemia (ischemic rest pain, ulceration or gangrene) (Fontaine III, IV, or Rutherford grade IV-VI) • Non-English speaking or non-Spanish speaking for US sites; Non-Dutch speaking for Dutch sites; Non-English speaking for Australian sites • Hearing impairment • Currently a prisoner • Patient previously enrolled in PORTRAIT study • Unable to provide written informed consent

Patients were enrolled at the PAD specialty clinic (general cardiology, interventional cardiology, interventional radiology, vascular medicine, or vascular surgery) before a treatment plan was established. A baseline interview was conducted by trained personnel to obtain information about patients' quality of life, symptoms and functioning, and socio-economic background. Clinical information (medical history, PAD history, and medications)

was abstracted from patients' medical records using standardized case record forms. PORTRAIT investigators obtained IRB approval from all participating centers that recruited patients. Informed consent was obtained from all participants. PORTRAIT received Saint Luke's IRB approval under 'Exempt Status' for all projects.

Trained data abstractors gathered information from the medical records about whether or not patients were on a statin as well as statin dosing information before and no later than one month after their PAD evaluation (Figure 3). Information on statin dose before and after PAD evaluation was collected from the 'medications' section of the Clinical Information Form. The categorization of statin intensity (low, moderate, high) is outlined in Table III. Being on guideline-directed statin therapy, as per the 2013 ACC/AHA cholesterol guidelines, was defined as being on a moderate to high-intensity statin.[13] Those patients without documentation of a statin prescription or prescribed a low-intensity statin were classified as not being on guideline-directed therapy. Non-guideline to guideline statin therapy was defined as transitioning from no statin *or* low-intensity statin to moderate *or* high-intensity statin therapy.

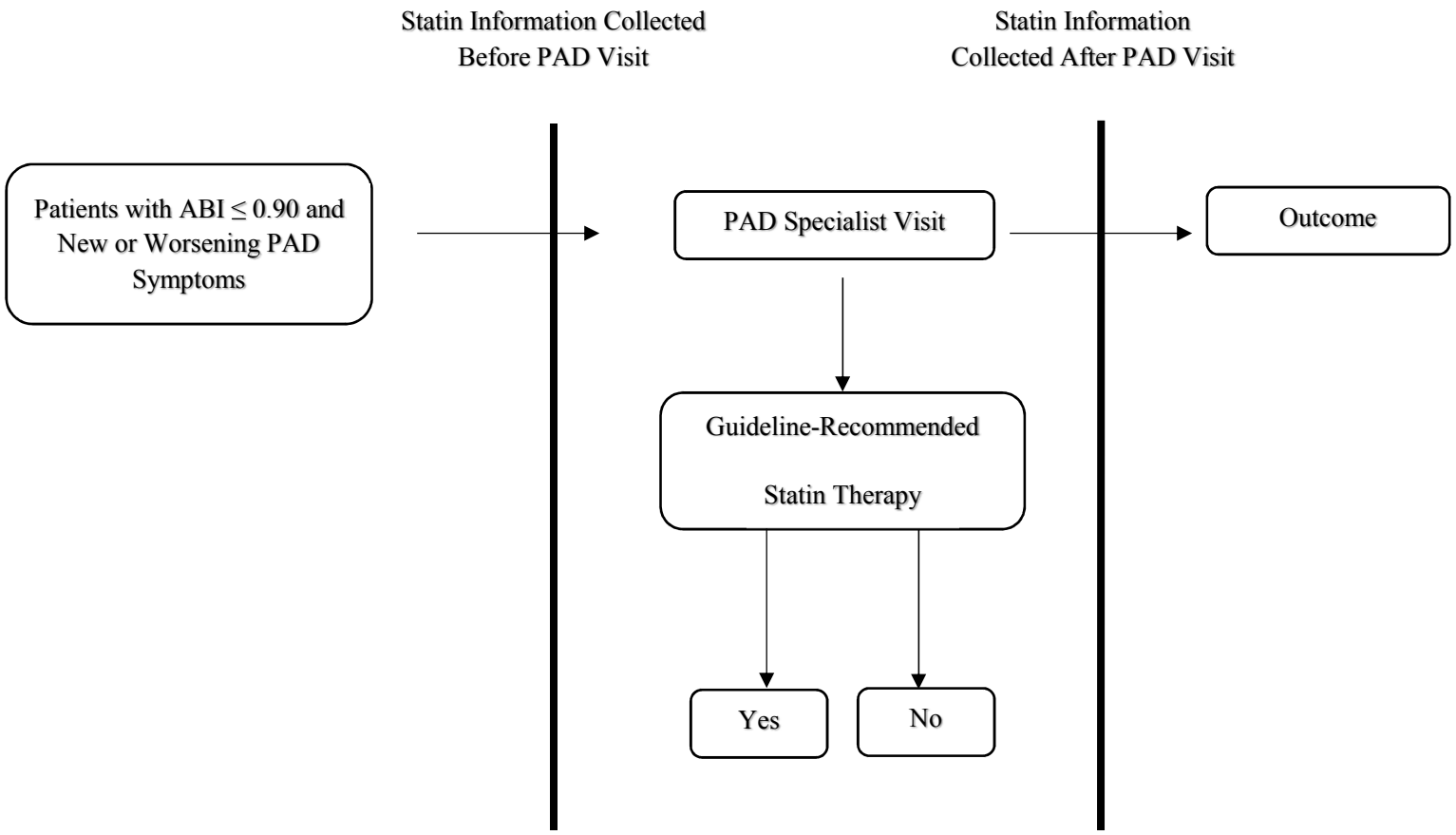


Figure 3**.** Statin Intensity Data Collection Timeline

Timeline of data collection of statin information in PORTRAIT.

Table III. Statin Potency Definitions a Low, Moderate, and High-Intensity Statin per the ACC/AHA 2013 Cholesterol Guidelines

LOW	MODERATE	HIGH
Fluvastatin 20-40 mg	**--**	**--**
Lovastatin 20 mg	**Lovastatin 40 mg**	**--**
Simvastatin 10 mg	**Simvastatin 20-40 mg**	**--**
Pravastatin 10-20 mg	**Pravastatin 40-80 m**	**--**
--	**Rosuvastatin 5-10 mg**	**Rosuvastatin 20-40 mg**
--	**Atorvastatin 40-80 mg**	**Atorvastatin 40-80 mg**

Moderate and high potency statins were defined as guideline-directed therapy for patients with PAD

Patients with statin-related contraindications to treatment, including those with prior adverse symptoms (i.e. myalgia) or end-organ injury were prospectively identified from the

medical records if contraindications were described before or during the PAD evaluation. Patients were excluded from the denominator if such contraindications were documented.

Measures

Information about patients' baseline PAD-specific health status was collected using the Peripheral Artery Questionnaire (PAQ). The PAQ is a disease-specific, sensitive, and validated health status measure that quantifies the following patient domains: physical function, symptoms, symptom stability, social limitation, treatment satisfaction, and quality of life. A total of 20 items are included in this multi-dimensional health assessment, with one item identifying the symptomatic extremity and the remaining 19 comprised of variable Likert response scales. A standardized scoring algorithm was used to calculate a Health Status Summary Score (range of 0-100, with higher scores indicating better health status). This Summary score was calculated by combining all scales except the Treatment Satisfaction and Symptom Stability Scales.[27] Original validation studies of the PAQ concluded the 7 domains of the instrument to be internally reliable (Cronbach alpha = 0.80-0.94), with there being adequate test-retest reliability (0.6 to 2.3-point mean change; $p > 0.05$ for all domains) and substantial sensitivity to change following extremity revascularization (13.7 to 41.9-point mean change; $p < 0.05$ for all domains). Finally, construct validity was establishing by comparing the PAQ with other measures of patient health status (walking exercise time, walking impairment questionnaire, and Short Form-36 score).[27,28]

Statistical Analysis

Demographic and patient characteristics of those who were and were not on guideline-directed statin treatment before and after the PAD evaluation were described using Student's

t-tests for continuous variables and nonparametric (Chi-square) tests for categorical variables. Rates of guideline statin intensification were calculated.

Next, a hierarchical multivariable logistic regression model with a random effect for site – and with a binary outcome for guideline statin intensification (yes versus no) after initial PAD specialty clinic visit – was constructed to identify predictors of intensification among only those patients not on guideline statin treatment before their visit. Per the number of patients that were transitioned from non-guideline to guideline statin therapy, the model was limited to nine patient predictors based upon prior literature [29,30] and clinical relevance: age, sex, race (Caucasian versus non-Caucasian), high school educational level or greater, presentation with typical claudication symptoms, history of depression, history of coronary artery disease (composite outcome of percutaneous coronary intervention, coronary artery bypass grafting, or myocardial infarction), patient health status as assessed by the Peripheral Artery Questionnaire (PAQ) summary score, and country of enrollment. Out of 16 participating sites, one was excluded from the model as all patients (n = 3) were already on guideline-directed statin therapy prior to the PAD visit. To verify whether rates of non-guideline to guideline statin therapy differed before versus after the release of the guideline statement in December 2013, a sensitivity analysis was performed comparing the proportion of patients intensified to guideline statin therapy before and after December 1, 2013.

A median odds ratio (MOR) was calculated to quantify provider and site-level variability in guideline statin intensification among patients not on guideline statin treatment before their PAD specialty clinic encounter. A MOR estimates the average relative difference in two patients with the same patient and site-level covariates undergoing guideline statin intensification when treated at two random sites or by two random providers.[31] These were

calculated as smoothed rates, adjusting for the volume of patient sites enrolled.[32] Both unadjusted and adjusted rates were calculated. Both site and provider were treated as random effects through a 3-level adjusted logistic regression model (patient-provider-site). The adjusted model included the same covariates as described for the logistic regression model.

The percentage of missing data for baseline covariates was small (less than 1%), with only two data fields having missing information (symptom presentation and education level). Accordingly, no data imputation methods were used. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Inc., Cary, NC) and R Version 3.3.2 software. Forrest plots were generated using Prism 7, Copyright 2018 Graphpad Software, Inc. Two-sided P-values less than 0.05 were considered statistically significant. The author of this thesis had full access to all the data in the analysis, performed all statistical analyses, and takes responsibility for its integrity and the data analysis.

CHAPTER 3

RESULTS

A total of 1275 patients were enrolled in the PORTRAIT registry. The analytical cohort of this study consisted of 1144 patients, after having excluded patients with missing statin information (e.g. dose) as well as both patient and medical-specific reasons for statin intolerance (Figure 7).

Guideline-Directed Statin Treatment Before and After PAD Evaluation

Of 1144 patients with a new diagnosis or exacerbation of PAD, 810 (70.8%) were on guideline-directed statin treatment before their initial PAD evaluation. Patients who were on guideline therapy were more likely to have completed high school and to be of non-white race. They were also more likely to have a history of dyslipidemia, tobacco abuse, hypertension, diabetes, chronic kidney disease, myocardial infarction, heart failure, and stroke (Table IV).

After the initial evaluation, 910 (79.5%) patients were on guideline-directed statin therapy as opposed to 234 patients receiving low-intensity (5.2%) or no statin therapy (15.3%). Patients receiving guideline-directed statin therapy were more likely to have a history of dyslipidemia and myocardial infarction. While there was significant variability as to the treatment provider and site of patients originally presenting on guideline therapy, these differences were attenuated after initial evaluation. All other comorbidities and functional assessments were similar between groups (Table IV). Differences in the proportion of patients prescribed non-guideline and guideline statin therapy before and after PAD evaluation are presented in Figures 8-10. Notably, 98.1% of patients originally prescribed low-intensity statin therapy remained off guideline therapy and only 31.3% originally off statin therapy underwent guideline statin intensification following the PAD visit.

Patient Correlates of Statin Intensification

A total of 334/1144 (29.1%) patients were eligible to be newly prescribed guideline statin therapy, as they either had not been on a statin before (n=281) or were receiving a low-intensity statin (n=53). Patients with typical (versus atypical) symptoms were more likely to newly receive guideline statin therapy following PAD evaluation [OR 3.74, 95% CI 1.23; 11.41] while older patients had lower odds of guideline statin intensification [OR 0.60, 95% CI 0.41; 0.88] (Figure 11).

Sensitivity Analysis Comparing Statin Intensification Before and After Guideline Publication

Intensification rates were 45.9% (78 out of 170) before the release of 2013 ACC/AHA guidelines, whereas intensification rates only reached 15.2% (25 out of 164) following the publication of the guidelines (P-test for trend <.001).

Site and Provider Variability for Statin Intensification

For the 15 enrolling sites with documentation of non-guideline to guideline statin therapy, rates ranged from 4% in the lowest performing site to 74% in the highest performing site (Figure 12). At the provider level, performance rates ranged from 4% to 77% (Figure 13). An unadjusted median odds ratio [MOR] was calculated for site variability (MOR 3.16 [95% CI 2.07; 4.26, p = 0.001]) and provider variability (MOR 2.05 [95% CI 1.41; 2.62, p = 0.04]) indicating that, for patients with similar covariates presenting to one site vs. another site (or one provider vs. another), there was a two- to three-fold odds of being newly prescribed a guideline statin. In the fully adjusted model for country and patient-level factors, site variability remained significant (MOR 3.63 [95% CI 1.88; 5.42, p < 0.05]) while provider variability became non-significant (MOR 1.90 [95% CI 1.00; 2.55, p > 0.05]).

CHAPTER 4

DISCUSSION

While 7 out of 10 patients presenting to a specialty clinic for PAD evaluation were already on guideline-directed statin therapy, only a third of those not on guideline therapy were appropriately treated at the time of their visit. Patients who were older were less likely to be transitioned from non-guideline to guideline statin therapy, while individuals with typical symptoms were more likely to experience appropriate titration. Finally, there was substantial and unexplained site and provider-level variability in non-guideline to guideline prescription rates where as few as 4% and as many as 74% of patients had appropriate statin titration across individual PORTRAIT sites. Site variability remained significant, even after adjusting for country and patient-level factors. These findings highlight the importance of systematic efforts to monitor and titrate the intensity of statin therapy for patients with PAD.

These findings represent a relatively unique observation in a referral population comprised of PAD patients. First, data was presented on statin prescription and intensification prospectively collected in a multinational PAD cohort focusing on patients with new or worsening PAD symptoms only, which allowed for review of active prescription behavior across PAD specialty care providers. Prior evidence had primarily been from retrospective and administrative studies where statins had been shown to be markedly underused in mixed cohorts of patients with PAD.[22,23,33] Statin prescription was noted in only 62% of the patient cohort studied in REACH,[34] and Berger et al. documented the persistent underuse of statins in PAD patients treated at multispecialty outpatient clinics.[35] Finally, an analysis examining the adoption of the 2013 ACC/AHA cholesterol guidelines described an underwhelming trend of moderate and high-intensity statin use in a heterogeneous cohort of patients with clinical

atherosclerotic cardiovascular disease – a 62.7% prescription rate before guideline publication compared with 67.0% rate after publication – signifying only a modest improvement.[36] Collectively, while these prior studies have historically emphasized an overall underuse of statins in patients with PAD, these data may reflect the practice of physicians who were not explicitly considering how best to manage patients with PAD. This contemporary data offers insight into the current management of PAD patients – as they present with new or worsening symptoms to a PAD specialty clinic – and, while highlighting overall high rates of treatment with guideline statin therapy, also describe missed opportunities for prescribing guideline statin therapy.

At the patient level, differences in clinical and socio-demographic characteristics before and after specialist evaluation were similar. In line with prior work, participants with a history of cardiovascular disease and risk factors were more likely to be appropriately treated with statin therapy. [37,38] Among those eligible to newly receive guideline statin therapy, patients who were older were less likely to be appropriately treated, and those with typical symptoms were more likely. While providers may display more caution when considering prescribing a moderate to high intensity statin in the elderly,[39] recent evidence suggests that patients $\geq$ 75 years with clinical atherosclerotic cardiovascular disease are more likely to experience a survival benefit from guideline-directed statin therapy compared with lower-intensity statin treatment.[40] Furthermore, all of the patients enrolled in PORTRAIT had confirmed PAD as verified by their ankle-brachial index, and by definition share an increased cardiovascular risk,[41] regardless of the nature of the symptomatology of their PAD. Accordingly, there was no clinical plausibility to preferentially offering guideline-directed statin therapy to patients reporting typical (as opposed to atypical) symptoms.

When describing variability in guideline statin intensification rates there was dramatic variability across sites, even after adjusting for country and patient-level factors, that was largely unexplained. Prior work suggests that there are many reasons healthcare providers may miss the opportunity to appropriately intensify statin therapy[23,42] : lack of clinician familiarity with the 2013 ACC/AHA guidelines[43], clinician disagreement with guideline recommendations [44], and medical and patient-centered contraindications to statin eligibility.[36] In the case of PAD, where multiple disciplines can be treating the disease, there may be an unclear understanding about who should be responsible for titrating statin therapy for patients with PAD. Importantly, these results showed that, even after taking into consideration patient-specific and medical contraindications to statin therapy, there remained significant variability across sites.

The sensitivity analyses comparing guideline statin intensification rates before and after the release of the 2013 ACC/AHA guidelines did not reflect an uptake of the guidelines following the publication, as intensification rates were actually lower following the release, further questioning provider familiarity and confidence in implementing the guidelines.[45,46]

Future work should further document additional barriers as they relate to guideline adoption in the context of PAD management. From a quality of care perspective, efforts should look into applying system-based quality initiatives (e.g. EMR alert systems) and programs that provide feedback on physicians' performance regarding guideline-based medications as examples of strategies to optimize cardiovascular risk management in PAD. The findings demonstrated there to be only significant site-level variability in patterns of statin intensification, upholding the contemporary belief that an organizational practice culture that supports efforts to improve PAD care may be one of the most important factors influencing

the quality of health care delivered and an important predictor of statin intensification.[47] However, currently, there are limited strategies to identify other key determinants of hospital-level outcomes, and much of this variability in performance needs to be further explored.[48-50]

Finally, additional studies are needed to clarify the association between statin intensity and patient outcomes (e.g major acute limb events, patient-reported health status),[2,51] as most studies have only reported on outcomes differences by statin use (yes versus no).[16-18] However, in a recent observational analysis of US Veterans, investigators found that patients treated with high-intensity statin therapy had lower odds of experiencing lower limb amputation and all-cause mortality.[2] These results parallel original findings from the Heart Protection Study (HPS), which assessed the effects of Simvastatin 40 mg versus placebo on both major and peripheral vascular events in the United Kingdom.[52] Finally, Foley et al. described lower rates of major cardiovascular events in patients treated with higher (versus low-moderate) intensity statin therapy. Importantly, in regard to patient-centered outcomes, the association between statin intensity and patient-reported health status has not been well-described.

These results must be interpreted in the context of the following potential limitations. First, while PORTRAIT is a prospective observational registry, there is potential for residual confounding. Therefore, there may be other reasons, besides those that were captured in the registry, that might help explain the findings: quality programs that centers had in place, physician and patient attitudes, and beliefs about statin intake. Second, even though patients were recruited from two non-US countries – the Netherlands and Australia – with different health care systems and policies, it was verified that their national guidelines[53] (Dr. John Beltrame, MD, personal communication, 2017) are consistent with the ACC/AHA guidelines as it concerns prescribing statin therapy in this high-risk population. Third, the majority of

centers that were recruiting patients for this study were selected based upon prior collaboration with the coordinating center and may not necessarily be representative for other PAD specialty clinics. Fourth, PORTRAIT enrollment occurred between 2011-2015 while the ACC/AHA guidelines were published in 2013. This may explain a potentially slower uptake of the latest guidelines.[54] These findings are relevant given prior recommendations of using statins to primarily target pre-specified low-density lipoprotein cholesterol concentrations instead of using statins more widely as a strategy to curb global cardiovascular risk.[54] Finally, given the small sample size of patients eligible for the guideline statin intensification model (n = 334), it is possible that the model was under-powered to detect statistical significance in several of the chosen covariates.

To conclude, this analysis of real world data from the PORTRAIT study found that, while most patients who were referred to a specialty PAD provider were on an appropriate intensity statin, the majority of patients presenting off guideline-directed statin therapy remain undertreated. This suggests that a substantial proportion of providers miss a significant opportunity to appropriately initiate or titrate statin therapy upon initial patient evaluation. Older patients were at increased risk of missing out on appropriate statin therapy while patients presenting with typical claudication symptoms were at lower risk, thereby highlighting significant treatment gaps in care. There was site-level treatment variation, reflecting marked discrepancies in how health institutions address cardiovascular risk in the PAD population.

Table III. Peripheral Artery Questionnaire (PAQ) Assessment

PORTRAIT *Registry*

Patient -centered Outcomes Related to TREatment practices in peripheral Arterial disease: an Investigating Trajectories

2. The following questions refer to blockages in the arteries of your body, particularly your legs, and how that might affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you (PAQ)

2.1 Blockages in the arteries, often referred to as peripheral vascular disease, affect different people in different ways. Some feel cramping or aching while others feel fatigue. Which leg (or buttock) causes you the most severe discomfort, fatigue, pain, aching, or cramps? [Choose one]

☐ The right leg (buttock)	☐ The left leg (buttock)	☐ Both are the same	☐ Neither

2.2 Please review the list below and indicate how much limitation you have due to your peripheral vascular disease (discomfort, fatigue, pain, aching, or cramps) in your calves (or buttocks) over the past 4 weeks.

Place an X in one box on each line

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
Walking around your home	☐	☐	☐	☐	☐	☐
Walking 1-2 blocks on level ground	☐	☐	☐	☐	☐	☐
Activity	**Extremely limited**	**Quite a bit limited**	**Moderately limited**	**Slightly limited**	**Not at all limited**	**Limited for other reasons or did not do the activity**
Walking 1-2 blocks up a hill	☐	☐	☐	☐	☐	☐
Walking 3-4 blocks on level ground	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐
Vigorous work or exercise	☐	☐	☐	☐	☐	☐

2.3 Compared with 4 weeks ago, have your symptoms of peripheral vascular disease (discomfort, fatigue, pain, aching, or cramps) in your calves (or buttocks) changed?

My symptoms have become...

☐ Much worse	☐ Slightly worse	☐ Not changed	☐ Slightly better	☐ Much better	☐ I've had no symptoms over the last 4 weeks

2.4 Over the past 4 weeks, how many times did you have discomfort, fatigue, pain, aching, or cramps in your calves (or buttocks)?

☐ All of the time	☐ Several times per day	☐ At least once a day	☐ 3 or more times per week but not every day	☐ 1-2 times per week	☐ Less than once a week	☐ Never over the past 4 weeks

2.5 Over the past 4 weeks, how much has discomfort, fatigue, pain, aching or cramps in your calves (or buttocks) bothered you?

☐ Extremely bothersome	☐ Moderately bothersome	☐ Somewhat bothersome	☐ Slightly bothersome	☐ Not at all bothersome	☐ I have had no leg discomfort

2.6 Over the past 4 weeks, how often have you been awakened with pain, aching, or cramps in your legs or feet?

☐ Every night	☐ 3 or more times per week but not every night	☐ 1-2 times per week	☐ Less than once a week	☐ Never over the past 4 weeks

2.7 How satisfied are you that everything possible is being done to treat your peripheral vascular disease?

☐ Not satisfied at all	☐ Mostly dissatisfied	☐ Somewhat satisfied	☐ Mostly satisfied	☐ Completely satisfied

2/2/15 PORTRAIT Study Baseline Interview Interviewer Initials __ __ __ Patient ID: __ __ -__ __ __ __ 2

2.8 How satisfied are you with the explanations your doctor has given you about your peripheral vascular disease?

☐ Not satisfied at all	☐ Mostly dissatisfied	☐ Somewhat satisfied	☐ Mostly satisfied	☐ Completely satisfied

2.9 Overall, how satisfied are you with the current treatment of your peripheral vascular disease?

☐ Not satisfied at all	☐ Mostly dissatisfied	☐ Somewhat satisfied	☐ Mostly satisfied	☐ Completely satisfied

2.10 Over the past 4 weeks, how much has your peripheral vascular disease limited your enjoyment of life?

☐ It has extremely limited my enjoyment of life	☐ It has limited my enjoyment of life quite a bit	☐ It has moderately limited my enjoyment of life	☐ It has slightly limited my enjoyment of life	☐ It has not limited my enjoyment of life at all

2.11 If you had to spend the rest of your life with your peripheral vascular disease the way it is right now, how would you feel about this?

☐ Not satisfied at all	☐ Mostly dissatisfied	☐ Somewhat satisfied	☐ Mostly satisfied	☐ Completely satisfied

2.12 Over the past 4 weeks, how often have you felt discouraged or down in the dumps because of your peripheral vascular disease?

☐ I felt that way all of the time	☐ I felt that way most of the time	☐ I occasionally felt that way	☐ I rarely felt that way	☐ I never felt that way

2.13 How much does your peripheral vascular disease affect your lifestyle? Please indicate how your discomfort, fatigue, pain, aching or cramps in your calves (or buttocks) may have limited your participation in the following activities over the past 4 weeks?

Choose a description for each activity/line

Activity	Severely limited	Limited quite a bit	Moderately limited	Slightly limited	Did not limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐

Table IV. Baseline Patient Characteristics

	Guideline-Directed Therapy Before Visit			Guideline-Directed Therapy After Visit		
	Yes 810 (%)	**No 334 (%)**	**P-Value**	**Yes 910 (%)**	**No 234 (%)**	**P-Value**
Male	515 (63.6%)	213 (63.8%)	0.95	579 (63.6%)	149 (63.7%)	0.99
Age	67.8 ± 9.2	67.2 ± 9.7	0.31	67.4 ± 9.3	68.6 ± 9.7	0.09
White	395 (48.7%)	218 (65.3%)	< 0.001	481 (52.9%)	132 (56.4%)	0.33
Insurance	587 (72.5%)	274 (82.0%)	< 0.001	680 (74.7%)	181 (77.4%)	0.41
≥ HS Education	590 (73.6%)	198 (59.8%)	< 0.001	631 (70.1%)	157 (67.4%)	0.42
Never Smoker	81 (10.0%)	33 (9.9%)	< 0.001	84 (9.3%)	30 (12.8%)	0.05
ABI	0.7 ± 0.2	0.7 ± 0.2	0.27	0.7 ± 0.2	0.7 ± 0.2	0.83
Typical Symptoms	646 (85.9%)	260 (85.0%)	0.693	724 (86.6%)	182 (82.0%)	0.08
Rutherford Category						
Mild	170 (21.3%)	73 (23.4%)	0.259	199 (22.2%)	44 (19.2%)	0.31
Moderate	411 (51.4%)	152 (46.3%)		452 (50.3%)	111 (48.5%)	
Severe	218 (27.3%)	103 (31.4%)		247 (27.5%)	74 (32.3%)	
Pain-Free Walking Distance (meters)	138.2 ±123.1	104.2 ± 149.5	0.04	126.2 ± 129.6	116.5 ± 161.8	0.67
History of PVI	108 (13.3%)	16 (4.8%)	< 0.001	112 (12.3%)	12 (5.1%)	0.001

	Guideline-Directed Therapy Before Visit			Guideline-Directed Therapy After Visit		
	Yes 810 (%)	**No 334 (%)**	**P-Value**	**Yes 910 (%)**	**No 234 (%)**	**P-Value**
History of CHF	96 (11.9%)	27 (8.1%)	0.06	98 (10.8%)	25 (10.7%)	0.97
History of DLD	734 (90.6%)	203 (60.8%)	< 0.001	791 (86.9%)	146 (62.4%)	< 0.001
History of HTN	678 (83.7%)	244 (73.1%)	< 0.001	741 (81.4%)	181 (77.4%)	0.16
History of TIA/CVA	110 (13.6%)	26 (7.8%)	0.005	114 (12.5%)	22 (9.4%)	0.19
History of MI	191 (23.6%)	35 (10.5%)	< 0.001	192 (21.1%)	34 (14.5%)	0.02
History of PCI	216 (26.7%	42 (12.6%)	< 0.001	218 (24.0%)	40 (17.1%)	0.03
History of CABG	192 (23.7%)	41 (12.3%)	< 0.001	196 (21.5%)	37 (15.8%)	0.05
History of CKD	106 (13.1%)	23 (6.9%)	0.002	108 (11.9%)	21 (9.0%)	0.21
History of Depression	107 (13.2%)	39 (11.7%)	0.48	112 (12.3%)	34 (14.5%)	0.36
History of DM	310 (38.3%)	84 (25.1%)	< 0.001	323 (35.5%)	71 (30.3%)	0.14
Iliac Disease	161 (42.7%)	94 (49.5%)	0.13	205 (45%)	50 (45.0%)	0.99
Femoral Disease	266 (70.6%)	133 (70.0%)	0.89	315 (69.1%)	84 (75.7%)	0.17
Distal Disease	43 (11.4%)	19 (10.0%)	0.61	50 (11.0%)	12 (10.8%)	0.96
PAQ Summary Score	48.9 ± 22.2	48.0 ± 21.4	0.49	49.4 ± 21.9	45.6 ± 22.1	0.02

	Guideline-Directed Therapy Before Visit			Guideline-Directed Therapy After Visit		
	Yes 810 (%)	**No 334 (%)**	**P-Value**	**Yes 910 (%)**	**No 234 (%)**	**P-Value**
LDL Collected within 12 Months Prior to Screening	519 (64%)	208 (62%)	< 0.001	596 (65%)	131 (56%)	< 0.001
LDL-C Score	86.6 ± 34.0	120.6 ± 40.1	<0.001	93.4 ± 38.9	96.3 ± 39.0	<0.001
Site Characteristics						
Non-Academic	80 (13.9%)	11 (6.5%)	0.03	81 (13.5%)	10 (6.8%)	0.07
Specialty			< 0.001			0.09
Int. Cardiology	387 (47.8%)	99 (29.6%)		401 (44.1%)	85 (36.3%)	
Cardiology	95 (11.7%)	45 (13.5%)		102 (11.2%)	38 (16.2%)	
Vascular Surgery	252 (31.1%)	174 (52.1%)		328 (36.0%)	98 (41.9%)	
Country			<0.001			0.24
United States	579 (71.5%)	170 (50.9%)		600 (65.9%)	149 (63.7%)	
Netherlands	182 (22.5%)	130 (38.9%)		250 (27.5%)	62 (26.5%)	

	Guideline-Directed Therapy Before Visit			Guideline-Directed Therapy After Visit		
	Yes 810 (%)	**No 334 (%)**	**P-Value**	**Yes 910 (%)**	**No 234 (%)**	**P-Value**
Australia	49 (6.0%)	34 (10.2%)		60 (6.6%)	23 (9.8%)	

Results are expressed as n (%) or mean ± standard deviation. Abbreviations: HS (high school); CABG (coronary artery bypass graft surgery); CKD (chronic kidney disease); DM (diabetes mellitus); Int. Cardiology (interventional cardiology); LDL-C (low density lipoprotein cholesterol); MI (myocardial infarction); PCI (percutaneous intervention); PAQ (peripheral artery questionnaire); PHQ-8 (personal health questionnaire depression scale).
Table IV. Overview of Patients (%) by Statin Intensity Categories (No statin; Low; Moderate; High Intensity) Before and After the Initial PAD Visit (N = 1144)

1. St. Luke's Mid-America Heart Institute, Kansas City, MO (David Safley, MD)
2. Truman Medical Center, Kansas City, MO (Mark Friedell, MD)
3. Ochsner St. Anna General Hospital, New Orleans, LA (Christopher White, MD)
4. Duke University Medical Center, Durham, NC (Manesh Patel, MD)
5. St. Joseph Mercy, Ann Arbor, MI (Herbert Aronow, MD)
6. Cleveland Clinic, Cleveland, OH (Medhi Shishehbor, MD)
7. Miriam Hospital, Providence, RI (Peter Soukas, MD)
8. Rhode Island HS, Providence, RI (Dawn Abbott, MD)
9. Yale New Haven Hospital, New Haven, CT (Carlos Mena, MD)
10. Bridgeport Hospital, Bridgeport, CT (Ed Tuohy, MD)

Figure 4. Site Map of the 10 PORTRAIT Enrollment Sites in the United States of America

1. St. Elisabeth Hospital, Tillburg (Patrick Vriens, MD, PhD)
2. Twee Steden Hospital, Tillburg (Marnix De Fijter, MD, PhD)
3. Zorgsaam Terneuzen (Alex Derom, MD)
4. Albert Schweitzer Hospital, Dordrecht (Rudolf Tutein-Nolthenius, MD, PhD)
5. St. Antonius Hospital, Nieuwegein (Jean-Paul de Vries, MD, PhD)

Figure 5. Site Map of the 5 PORTRAIT Enrollment Sites in The Netherlands

1. Queen Elisabeth Hospital, Adelaide (John Beltrame, MD, PhD; Rob Fitridge, MBBS MS FRACS)

Figure 6. Map of the 1 PORTRAIT Enrollment Site in Australia

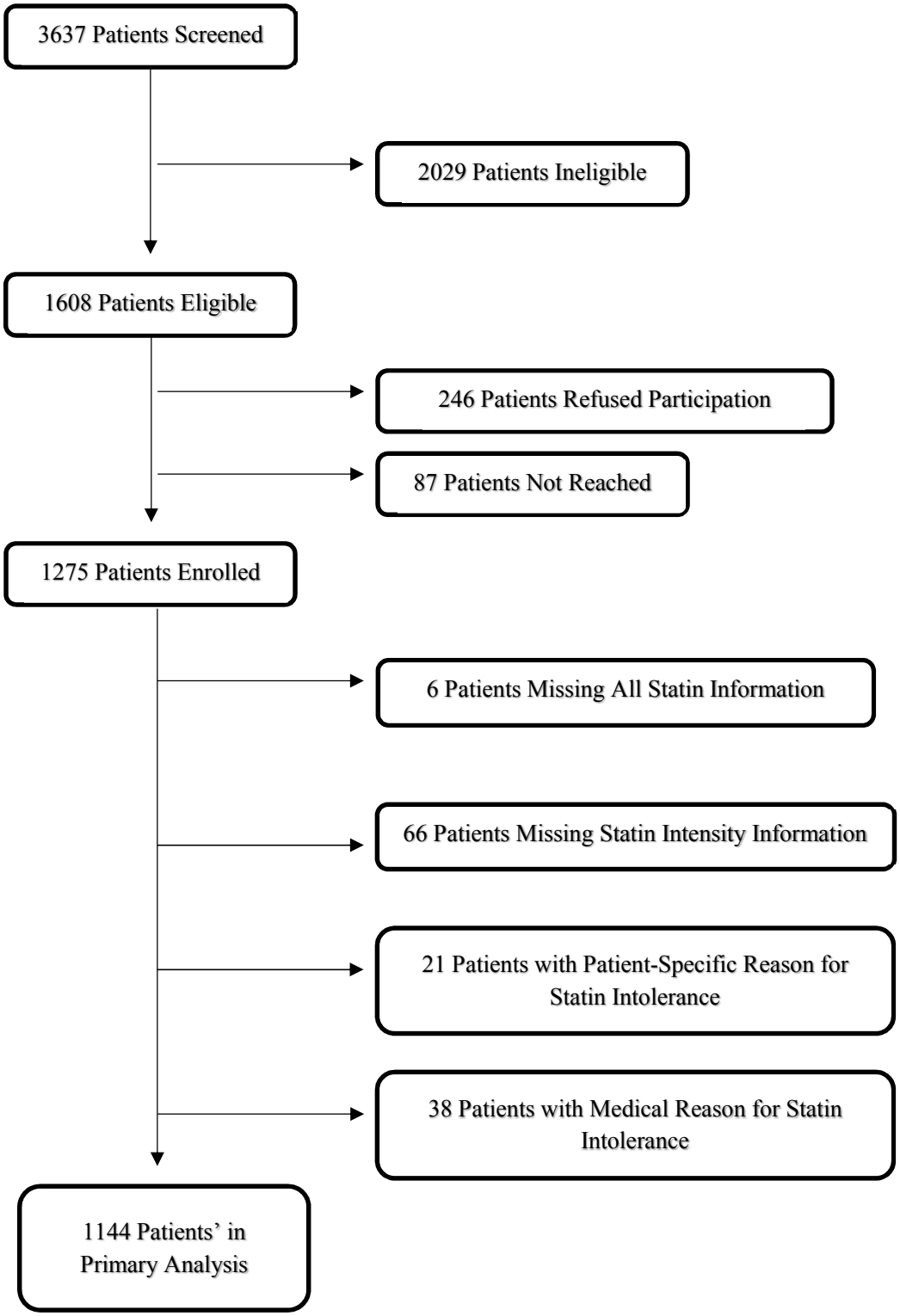
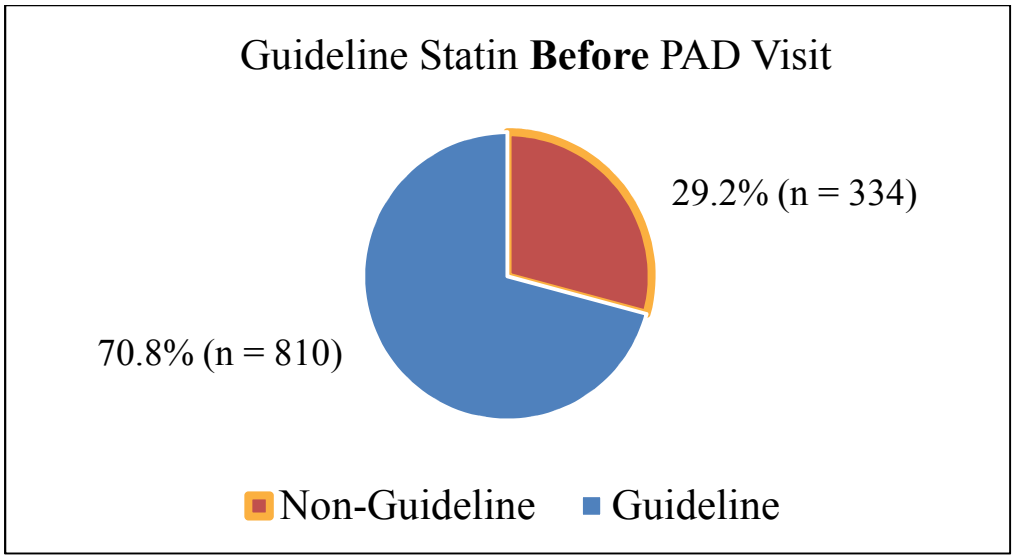


Figure 7. Patient Flowchart (N = 1144)



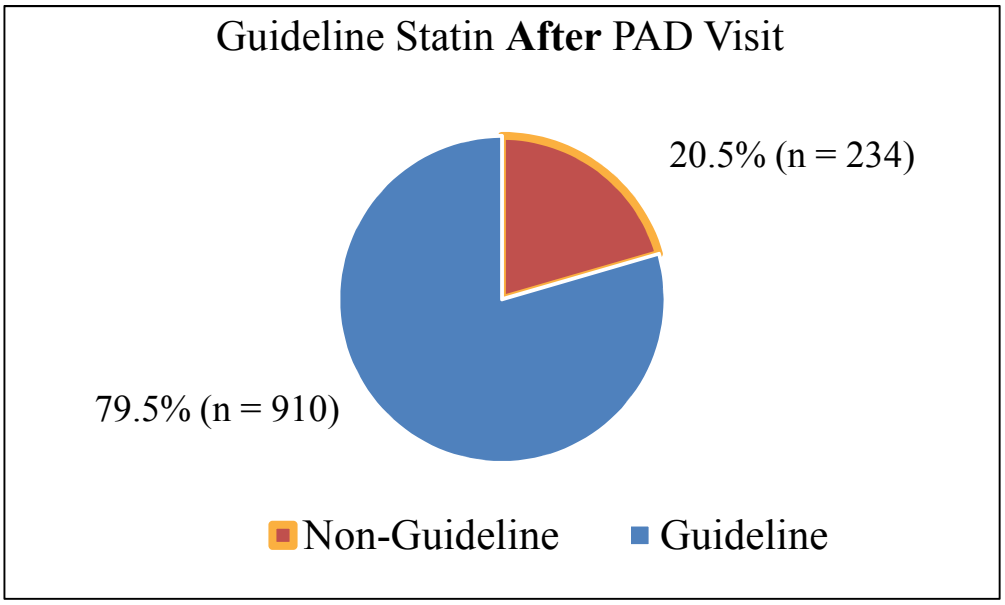


Figure 8. Overview of Patients (%) by Statin Categories (Non-Guideline; Guideline) Before and After Initial PAD Visit (N = 1144)

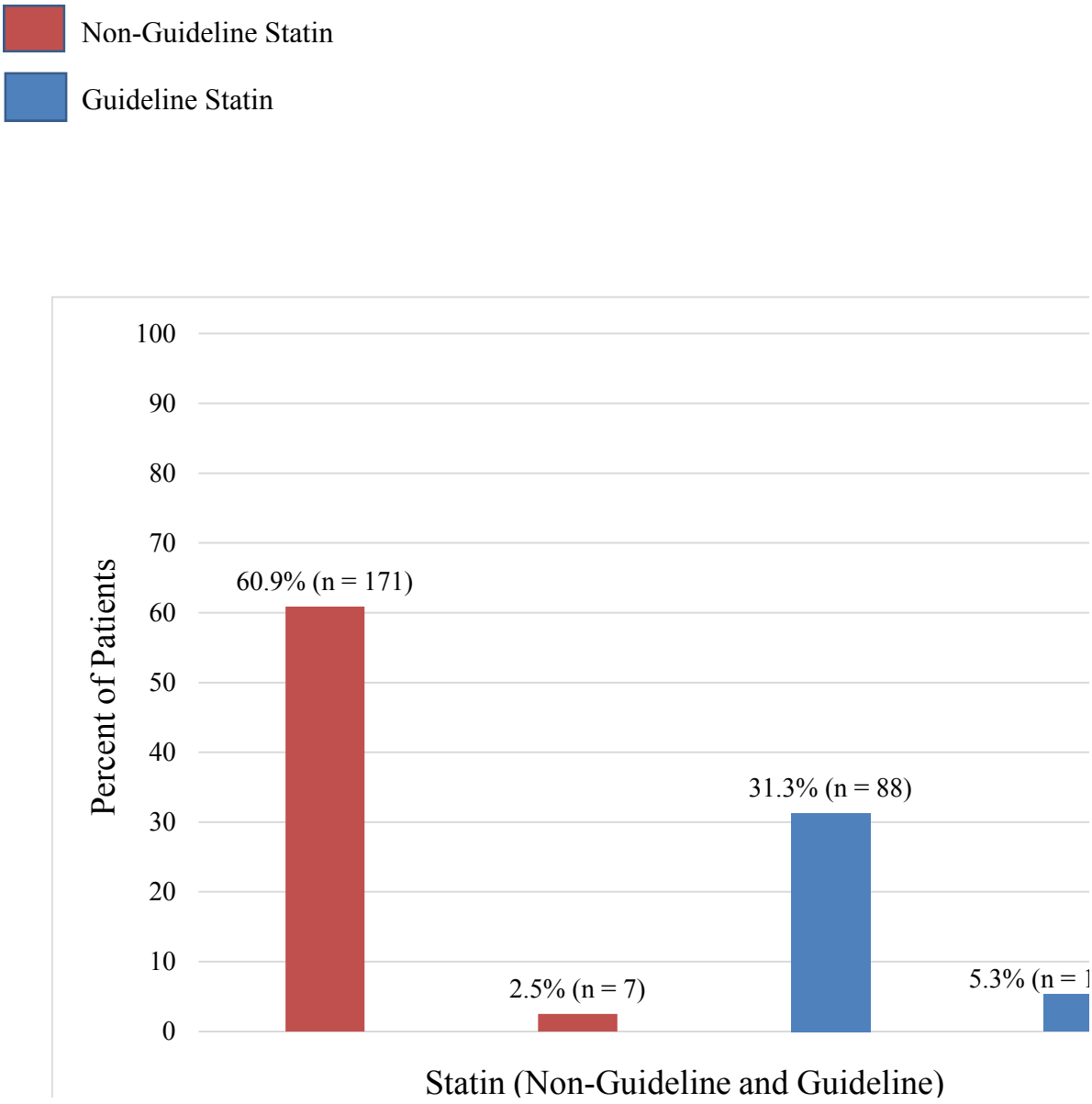


Figure 9. Intensification to Guideline Statin Therapy in Patients Off a Statin Prior to the Visit (N =281)

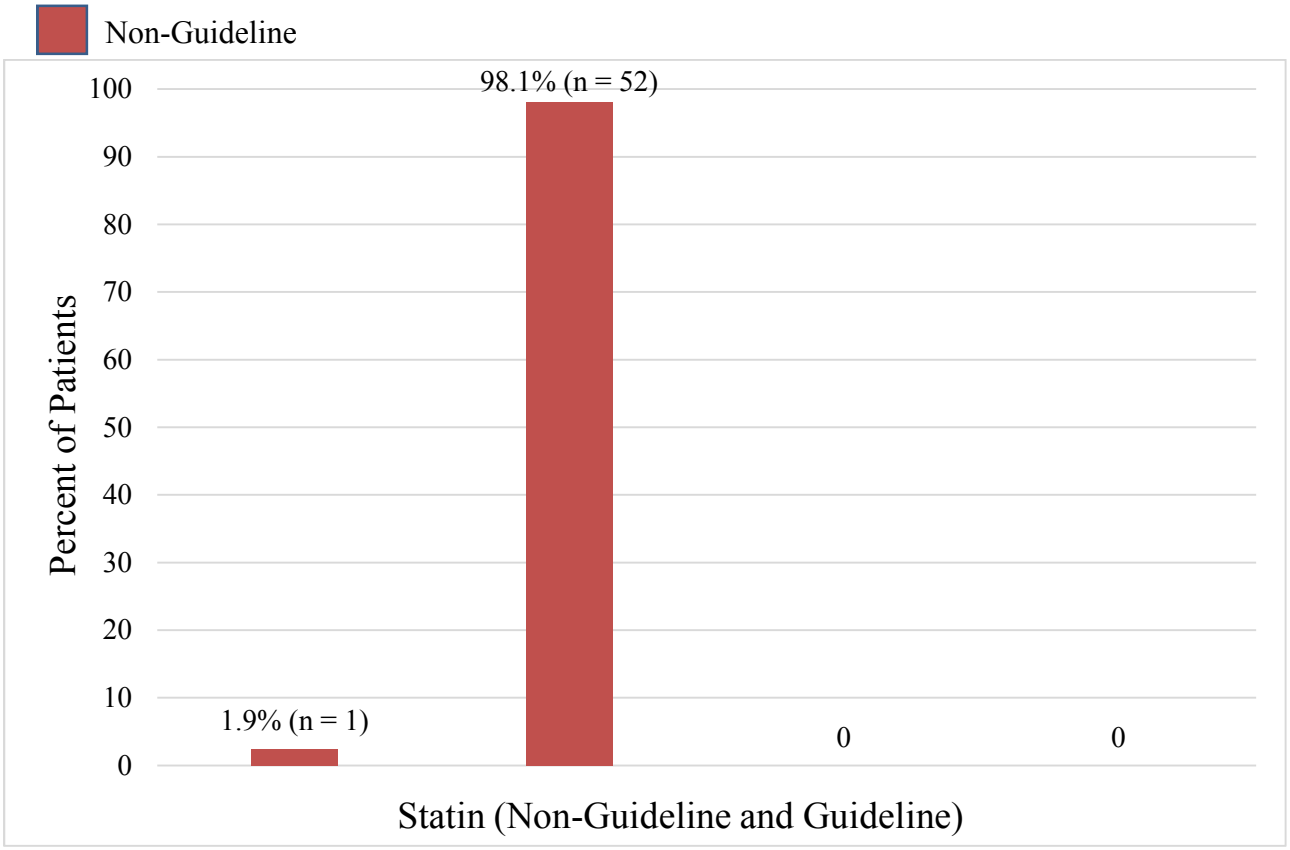


Figure 10. Intensification to Guideline Statin Therapy in Patients on Low-Intensity Statin Prior to the Visit (N = 53)

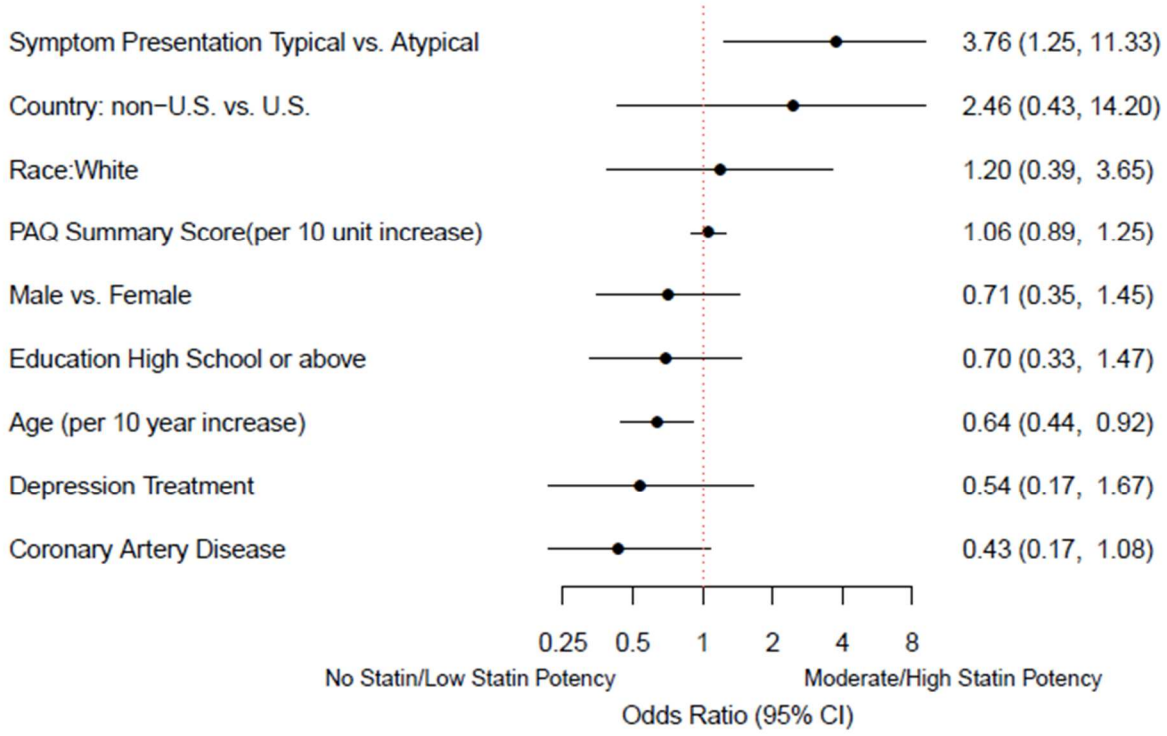


Figure 11. Patient Predictors of Intensification to Guideline Statin Therapy After Initial Visit (N = 334

Estimates are Presented as Odds Ratio with Corresponding 95% Confidence Intervals.
Abbreviations: PAQ: Peripheral Artery Questionnaire.

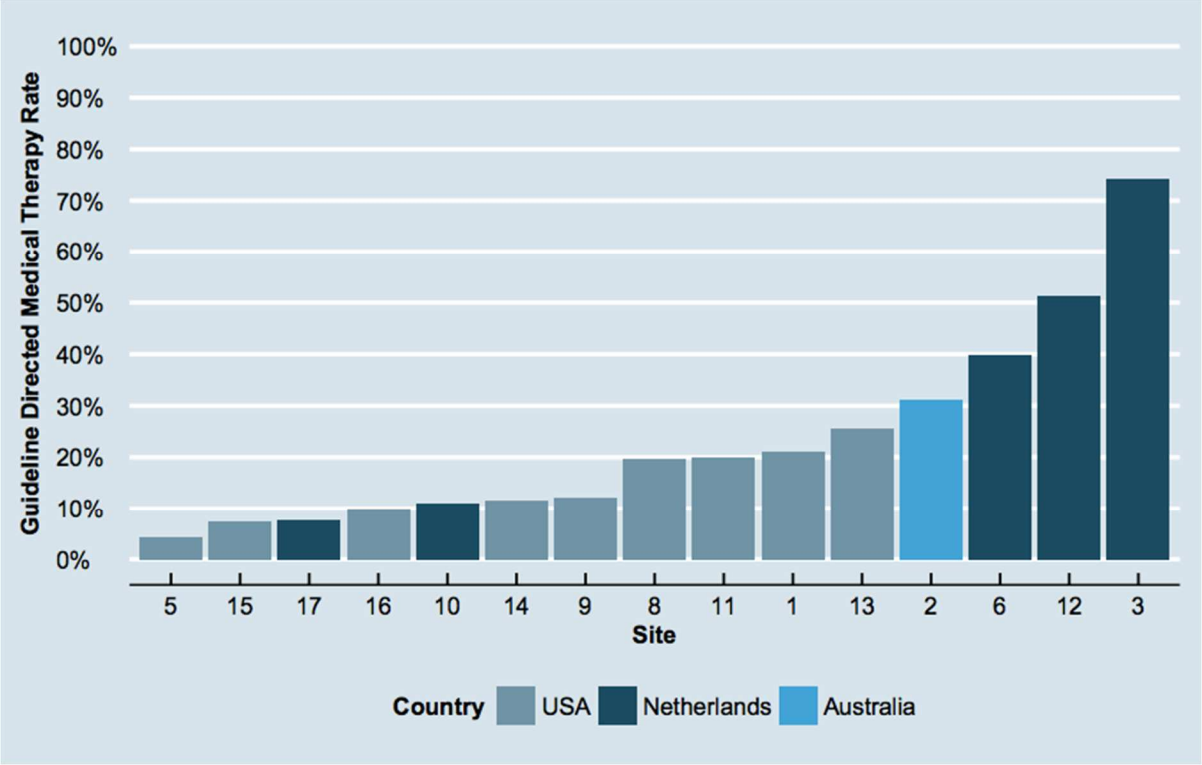


Figure 12**.** Heterogeneity of Intensification to Guideline Statin Therapy Across PORTRAIT Sites (N = 334)

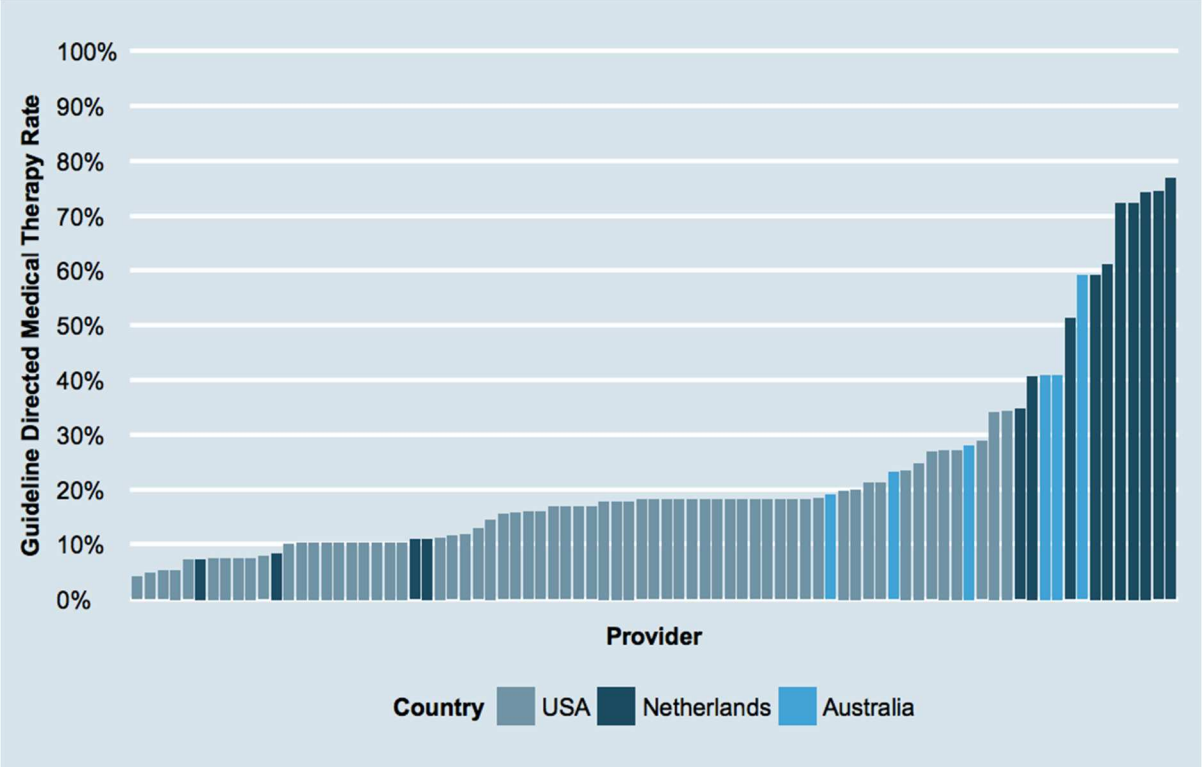


Figure 13. Heterogeneity of Intensification to Guideline Statin Therapy Across PORTRAIT Providers (N = 334)

SAS SYNTAX

Baseline Characteristics:

```
proc freq data = statin15;
 tables HxCHF*priorstatinlevel7 sex*priorstatinlevel7 RaceWhite*priorstatinlevel7 Insurance*priorstatinlevel7
 HxPVI*priorstatinlevel7 Hxdyslip*priorstatinlevel7 HxHTN*priorstatinlevel7 HxHTN*priorstatinlevel7
 HxHTN*priorstatinlevel7 HxCVATIA*priorstatinlevel7 HxMI*priorstatinlevel7
 HxPCI*priorstatinlevel7 HxCABG*priorstatinlevel7 HxCKD*priorstatinlevel7 HxDeprtrt*priorstatinlevel7
 HxDM*priorstatinlevel7 femoraldisease*priorstatinlevel7 iliacdisease*priorstatinlevel7 distaldisease*priorstatinlevel7
 Functionruth*priorstatinlevel7 providerspec*priorstatinlevel7 Acadaff*priorstatinlevel7 country*priorstatinlevel7; run;
```

```
proc freq data = statin15;
 tables educhs_b*priorstatinlevel7 spectypatyp*priorstatinlevel7/missing chisq;
 run;
```

```
proc ttest data = statin15;
 class priorstatinlevel7;
 var age PAQSumm_b ABIvalue PFWD_b;
 run;
```

```
proc freq data = statin15;
 tables HxCHF*therapycat_c sex*therapycat_c RaceWhite*therapycat_c Insurance*therapycat_c
 HxPVI*therapycat_c Hxdyslip*therapycat_c HxHTN*therapycat_c HxHTN*therapycat_c
 HxHTN*therapycat_c HxCVATIA*therapycat_c HxMI*therapycat_c
 HxPCI*therapycat_c HxCABG*therapycat_c HxCKD*therapycat_c HxDeprtrt*therapycat_c
 HxDM*therapycat_c femoraldisease*therapycat_c iliacdisease*therapycat_c distaldisease*therapycat_c
 Functionruth*therapycat_c providerspec*therapycat_c Acadaff*therapycat_c country*therapycat_c;
 run;
```

```
proc freq data = statin15;
 tables educhs_b*therapycat_c spectypatyp*therapycat_c/missing chisq;
 run;
```

```
proc ttest data = statin15;
 class therapycat_c;
 var age PAQSumm_b ABIvalue PFWD_b;
 run;
```

```
proc freq data = statin15;
 table priorstatinlevel7 therapycat_c; run;
```

```
proc freq data = work.statin11;
 tables therapycat;
 run;
```

Hierarchical Multivariable Logistic Regression:

```
proc glimmix data = model2 initglm;
 class sex RaceWhite_B educhs_b SpecTypAtyp HxCAD HxDeprtrt siteID providerid country_bin;
 model therapycat_cm = age sex RaceWhite_B educhs_b SpecTypAtyp HxCAD HxDeprtrt PAQSumm_B country_bin/dist =
 binomial link = logit solutions;
 random intercept/subject = siteID;
 random intercept/subject = providerid(siteid);
 nloptions tech=newrap;
 estimate 'Age (per 10 year increase)' age 10/exp cl;
  estimate 'Male vs. Female' sex 1 -1/exp cl;
  estimate 'Race:White' RaceWhite_B -1 1/exp cl;
  estimate 'Education High School or above' educhs_b -1 1/exp cl;
  estimate 'Symptom Presentation Typical vs. Atypical' SpecTypAtyp 1 -1/ exp cl;
  estimate 'Coronary Artery Disease' HxCAD -1 1/exp cl;
  estimate 'Depression Treatment' HxDeprTrt -1 1/exp cl;
  estimate 'PAQ Summary Score(per 10 unit increase)' PAQSumm_B 10/exp cl;
  estimate 'Country: non-U.S. vs. U.S.' country_bin 1 -1/exp cl;
 RUN;
```

```
proc glimmix data= model1  initglm;
 class siteid providerid;
 model therapycat_cm = /dist=binomial link=logit solutions;
 random intercept/subject=siteid;
 random intercept/subject=providerid(siteid);
 run;
```

Sensitivity Analysis:

```
data model3; set model2;
 if enrollDt >= "01DEC2013"d then Group1 = 1;
 else Group1 = 0;
 run;

proc freq data = model3;
 tables group1*therapycat_cm group1*priorstatinlevel1/chisq;
 run;
```

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VITA

Yevgeniy Khariton was born June 30, 1989 in Beltse, Moldova. After his family immigrated to the United States in 1993, he underwent primary and secondary education within the public-school system (Parkway North High School) in Saint Louis, Missouri. After having been accepted to the University of Missouri-Kansas City BA/MD Medical School program, he successfully earned both his bachelors and medical degree in 2013. Upon graduating medical school, he attended Washington University in Saint Louis for Internal Medicine Residency training while beginning early coursework towards a Masters in Medical Education (MEHP) degree through Johns Hopkins University (online degree program).

Following completion of his residency training, he was accepted to Mid-America Heart Institute/University of Missouri Kansas City for a combined Cardiovascular Research Outcomes and Clinical Cardiology Fellowship training program while working towards a master's degree in Bioinformatics with an emphasis in Clinical Research from the department of Biomedical Health and Informatics, University of Missouri Kansas City School of Medicine. Upon completion of his degree, Yevgeniy Khariton plans to practice heart failure/transplant cardiology, in an academic setting, while being involved with graduate medical education as well as cardiovascular outcomes research with a focus on health-related quality of life and process of care measures in heart failure.

Yevgeniy Khariton is a member of the Alpha Omega Alpha Society (AOA), America Heart Association (AHA), Heart Failure Society of America (HFSA), and American College of Cardiology (ACC).