Accepted Manuscript

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PII: S0735-1097(17)41522-1

DOI: 10.1016/j.jacc.2017.11.007

Reference: JAC 24431

To appear in: *Journal of the American College of Cardiology*

Received Date: 31 October 2017

Accepted Date: 7 November 2017

Please cite this article as: Singh A, Collins BL, Gupta A, Fatima A, Qamar A, Biery D, Baez J, Cawley M, Klein J, Hainer J, Plutzky J, Cannon CP, Nasir K, Di Carli MF, Bhatt DL, Blankstein R, Cardiovascular Risk and Statin Eligibility of Young Adults After an Myocardial Infarction: Partners YOUNG-MI Registry, *Journal of the American College of Cardiology* (2017), doi: 10.1016/j.jacc.2017.11.007.

Cardiovascular Risk and Statin Eligibility of Young Adults After an Myocardial Infarction: Partners YOUNG-MI Registry

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Running title: Statin Eligibility of Young Adults After an MI

Disclosures: *Dr. Bhatt* discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott); Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda. *Dr. Blankstein* discloses the following relationships - Advisory Board: Amgen, Inc. Research Support: Amgen, Inc. Gilead Sciences, Inc. Dr. Ankur Gupta is supported by NIH grant number 5T32HL094301. *Dr. Qamar* is supported by NIH grant number T32HL007604. Other authors report no relevant disclosures.

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Abstract

Background Despite significant progress in primary prevention, the rate of MI has not declined in young adults.

Objectives We aimed to evaluate statin eligibility based on the 2013 American College of Cardiology / American Heart Association (ACC/AHA) guidelines for treatment of blood cholesterol and 2016 United States Preventive Services Task Force (USPSTF) recommendations for statin use in primary prevention in a cohort of adults who experienced a first-time myocardial infarction (MI) at a young age.

Methods: The YOUNG-MI registry is a retrospective cohort study from two large academic centers which includes patients who experienced an MI at 50 years of age or younger. Diagnosis of Type 1-MI was adjudicated by study physicians. Pooled cohort risk equations (PCE) were used to estimate atherosclerotic cardiovascular disease (ASCVD) risk score based on data available prior to MI or at the time of presentation.

Results: Of 1685 patients meeting inclusion criteria, 210 (12.5%) were on statin therapy prior to MI and were excluded. Among the remaining 1475 individuals, the median age was 45 years, there were 294 (20%) women, and 846 (57%) had STEMI. At least one cardiovascular risk factor was present in 1225 (83%) patients. The median 10-year ASCVD risk score of the cohort was 4.8% (interquartile range: 2.8, 8.0). Only 724 (49%) and 430 (29%) would have met criteria for statin eligibility per the 2013 ACC/AHA guidelines and 2016 USPSTF recommendations, respectively. This finding was even more pronounced in women, in whom 184 (63%) were not eligible for statins by either guideline, compared with 549 (46%) of men ($p<0.001$).

Conclusions The vast majority of adults who present with an MI at a young age would not have met current guideline-based treatment thresholds for statin therapy prior to their MI. These findings highlight the need for better risk assessment tools among young adults.

Keywords: young adults, myocardial infarction, prevention, risk, statin

Condensed Abstract: This study evaluated how current guidelines classified the eligibility for primary prevention statins when applied to a large cohort of patients who experienced a first MI before or at 50 years, as would have been determined prior to their MI. Among 1475 patients, the majority (n=1068;72%) had an ASCVD score <7.5%. Only 724 (49%) and 430 (29%) met criteria for statin eligibility (statin considered or statin recommended) per the 2013 ACC/AHA guidelines and 2016 USPSTF recommendations, respectively. Our findings suggest that current guidelines may fail to identify at-risk young individuals, and better risk assessment tools are needed for this population.

Abbreviations

ACC – American College of Cardiology
AHA – American Heart Association
ASCVD – Atherosclerotic Cardiovascular Disease
CAD – Coronary Artery Disease
HDL – High Density Lipoprotein
LDL – Low Density Lipoprotein
MI – Myocardial Infarction
NCEP – National Cholesterol Education Panel
PCE – Pooled Cohort Equations
STEMI – ST-segment Elevation Myocardial Infarction
USPSTF – United States Preventive Services Task Force

Introduction

Significant progress in prevention of coronary artery disease (CAD) has led to a decrease in the incidence of myocardial infarction (MI) (1). However, recent reports highlight that the reduction in the rate of MI has not extended to young adults, and young women in particular, continue to have worse cardiovascular outcomes than men (2,3).

Identifying individuals who are at risk for cardiovascular events is paramount, as such individuals can be targeted for more aggressive primary prevention efforts.(4) Nevertheless, predicting risk in young adults is challenging, and most risk calculators fail to identify susceptible young adults as high risk. For instance, a prior study applied the National Cholesterol Education Program (NCEP) III guidelines (5) to a group of young adults with MI and reported that only 25% would have been eligible for statin therapy prior to their MI (6).

However, risk prediction has evolved considerably, and the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for cholesterol lowering (7) and 2016 United States Preventive Services Task Force (USPSTF) recommendations for primary prevention statin use (8) have significantly expanded the number of individuals who are candidates for statin therapy (9).

The under-estimation of cardiovascular risk among young individuals, and the subsequent lost opportunity to prevent events is concerning, given the disparity in reducing the rate of MI this population (3). Therefore, we sought to determine how contemporary guidelines perform in identifying the need for statin therapy, among a cohort of men and women who experienced a first-time MI at a young age. In addition, within this cohort we evaluated the prevalence of major cardiovascular risk factors, to determine their utility in enhancing the identification of at-risk young individuals.

Methods

Study Population

The design of the YOUNG-MI registry has been previously described (10). In brief, this is a retrospective cohort study from two large academic medical centers (Brigham and Women's Hospital and Massachusetts General Hospital) which included patients who experienced an MI at or before 50 years of age between 2000 and 2016. All records were adjudicated by a team of study physicians, as previously described (10), using the Third Universal definition of MI.(11) For the present analysis, only patients with Type 1 MI were included. Individuals with known CAD (defined as prior MI or revascularization) were excluded. Individuals were also excluded if they had missing values for lipid profiles or systolic blood pressure, which are necessary components for the Pooled Cohort Equations (PCE) for estimation of cardiovascular risk and hence determination of statin eligibility (12). **Online Figure 1** provides a consort diagram of the study population.

Risk Factors

Presence of cardiovascular risk factors was ascertained by a detailed review of electronic medical records during or before the index admission. For each risk factor, we also determined whether it was known prior to admission or diagnosed during hospitalization. Diabetes was defined as fasting plasma glucose >126 mg/dL or hemoglobin A1c ≥6.5% or diagnosis/treatment for diabetes. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or diagnosis/treatment of hypertension. Dyslipidemia was defined as total cholesterol ≥240 mg/dL, serum triglycerides ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women, or diagnosis/treatment of dyslipidemia. Obesity was defined as a body mass index ≥ 30 kg/m^2 or a diagnosis of obesity. Smoking was defined as

current (tobacco products used within the last month), former, or never. Family history of premature CAD was defined as fatal MI, non-fatal MI or coronary revascularization occurring before 55 years of age for first-degree male family members and before 65 years of age for first-degree female family members, and was captured by a thorough review of the electronic medical records which included all clinic notes prior to admission, admission history and physical, discharge summaries and follow-up visit notes.

Assessment of Cardiovascular Risk

In order to determine whether each individual would qualify for statin therapy prior to their MI, we calculated the atherosclerotic cardiovascular disease (ASCVD) risk score based on data available prior to MI or at time of presentation using the PCE. For individuals younger than 40 years of age at presentation, an age of 40 was assigned, as PCE are only applicable to individuals aged 40 to 79 years. For those with a triglyceride level of > 400 mg/dL, the method described by Martin et al. was used to estimate low-density lipoprotein (LDL) cholesterol, as this method has been shown to be more accurate compared with the Friedewald equation in such scenarios.(13) Risk factors that were diagnosed during the index hospitalization for MI were not used for calculating the risk scores, as the intent of our study was to evaluate how many patients would have met criteria for statin therapy *prior* to presentation.

In addition to the ASCVD 10-year risk, we also estimated the lifetime cardiovascular risk based on the burden of traditional risk factors (14). The criteria used to define each risk category is provided in **Online Table 1.** The cohort was also divided into low lifetime risk group (lifetime risk <39%) and high lifetime risk group (lifetime risk ≥39%), based on prior studies (15).

Statin Eligibility

The 2013 ACC/AHA guidelines (7) and the 2016 USPSTF recommendations (8) were used to assess statin eligibility. Individuals were considered to be statin eligible if guidelines indicated statins are recommended or statins are considered. Although, our goal was to evaluate contemporary statin guidelines, we also assessed statin eligibility according to the older NCEP III guidelines (5). Specific criteria that were followed for each guideline are detailed in **Online Table 2**.

Data management

Study related data for all patients who meet inclusion criteria were stored on our customized secure electronic adjudication system and REDCap. REDCap is an encrypted, secure, Health Insurance Portability and Accountability Act compliant web platform for electronic data capture and serves as an intuitive interface to enter data with real time validation (16). The YOUNG-MI registry has been approved by the Institutional Review Board at Partners HealthCare.

Statistical analysis

Categorical variables are reported as frequencies and proportions, and compared with Chi squared or Fisher's exact test, as appropriate. Continuous variables are reported as means or medians and compared with t-tests or Mann-Whitney U test, as appropriate.

In order to determine how the ASCVD risk score or the 2013 ACC/AHA guidelines can be enhanced to identify more individuals prior to their MI, we reclassified all statin ineligible individuals with LDL cholesterol ≥ 160 mg/dL or family history of premature cardiovascular disease to statin considered, as these criteria were offered by the guidelines as additional factors which may influence ASCVD risk (7).

Because most patients did not have any available data on lipid values prior to their MI, and since lipid levels can decrease at the time of MI, we performed two separate sensitivity analyses to determine the potential impact of using lipid values obtained at the time of MI. First, we performed a sensitivity analysis which only included patients who had available cholesterol measurements prior to their MI. Second, we performed a separate sensitivity analysis where we increased the total cholesterol level of all patients who did not have prior cholesterol values by 12%. This was based on the observed decreased in total cholesterol in our cohort among patients who had measurements of total cholesterol prior to their MI and upon admission. Because blood pressure during hospitalization for MI can be labile, we also performed a sensitivity analysis which only included patients who had available blood pressure measurements prior to their MI. A two-sided p-value of <0.05 was considered significant. All analyses were performed using Stata Version 14.2 (StataCorp, College Station, TX).

Results

Baseline characteristics

The cohort consisted of 1685 patients who met inclusion criteria, of whom 210 (12.5%) were on statin therapy prior to MI. These patients were excluded from all subsequent analyses. The remaining cohort consisted of 1475 individuals with a median age of 45 years, of whom 294 (20%) were women and 1060 (72%) were white. There were 255 patients (17.3%) under the age of 40 at the time of the MI (range 19-39 years). Other baseline characteristics are provided in **Table 1**.

Prevalence and Awareness of Risk Factors

When examining the prevalence of risk factors, 1225 (83%) patients had at least one of the following: diabetes, dyslipidemia, hypertension, or smoking. Dyslipidemia was the most

common risk factor, which was present in 818 (55%) patients, followed by smoking in 772 (52%) and hypertension in 649 (44%). **Figure 1** shows the distribution of the most common risk factors within our cohort, stratified by the proportion of patients who are recommended, considered, or not recommended statins by the 2013 ACC/AHA guideline.

Among the patients with dyslipidemia, 163/818 (20%) had no prior history of this condition and were first diagnosed during the index hospitalization for MI. Similarly, diabetes and hypertension were first diagnosed in 55/246 (22%) and 61/649 (9%) of patients, respectively. When considering the three major cardiovascular risk factors proposed by the USPSTF – namely, diabetes, dyslipidemia and hypertension, 226 (21%) out of 1069 patients were unaware of having at least one of these risk factors.

Cardiovascular Risk & Statin Eligibility

The median ASCVD risk score of the population was 4.8% (IQR 2.8-8%), with 1068 (72%) having an ASCVD risk score of <7.5%. When considering the lifetime cardiovascular risk of the population, 1184 (80.3%) were at high risk **(Figure 2)**. **Online Figure 2** provides detailed risk factor burden and lifetime risk estimates stratified by sex.

When applying the 2013 ACC/AHA guideline, only 455 (31%) would have met criteria for initiation of statin therapy prior to their MI, an additional 269 (18%) would have met criteria for consideration of statin therapy, and the remaining 751 (51%) would not have been eligible for primary prevention statin therapy **(Central Illustration)**.

When applying the 2016 USPSTF recommendations, only 269 (18%) would have met criteria for initiating statin therapy, an additional 161 (11%) would have met criteria for consideration of statin therapy, and the remaining 1045 (71%) would not have been eligible for statin therapy **(Central Illustration).**

When applying both the 2013 ACC/AHA and the 2016 USPTF recommendations to our entire study population, only 742 (50%) patients would have been categorized as statin eligible– i.e., categorized as statin recommended or statin considered by either guideline -- prior to their MI. Furthermore, 23% (52/226) and 43% (98/226) of patients with at least three of the following risk factors - diabetes, hypertension, dyslipidemia and smoking - would not have been eligible for statin therapy according to the 2013 ACC/AHA guidelines and 2016 USPSTF recommendations, respectively **(Figure 3).**

The number of patients in which the variables required for calculating the ASCVD risk score, were available pre-presentation, are provided in **Online Table 3.** When we increased the total cholesterol of all patients without prior lipid values, we observed a similar proportion eligible for statin therapy **(56% by 2013 ACC/AHA and 34% by 2016 USPSTF, Online Table 4)**. When we limited our analyses to patients who had available cholesterol levels prior to their MI, we observed that a greater proportion of these patients were eligible for statins compared with the overall study population **(63% vs. 48% by 2013 ACC/AHA; Online Table 5).** This was driven by the fact that this group had more risk factors, including a higher prevalence of diabetes and hypertension, than those who did not have lipid values obtained prior to their MI **(Online Table 6).** When we limited our analysis to patients who had available blood pressure measurements prior to MI, there was no significant difference in statin eligibility (**Online Table 7).**

We also evaluated the NCEP III guidelines, according to which 347 (23%) would have met criteria for initiating statin therapy, 160 (11%) would have met criteria for consideration of statin therapy, and the remaining 968 (66%) would not have been eligible for statin therapy.

(Online Table 8). Figure 4 depicts the proportion of statin eligibility and the overlap between the three guidelines.

Sex Differences

When considering the prevalence of risk factors by sex, there were significant differences. When compared with men, women had a lower prevalence of hyperlipidemia (30% vs. 59%; p<0.001), lower total cholesterol, LDL cholesterol and triglycerides, but higher HDL cholesterol. Women also had a higher prevalence of obesity (37% vs. 28%; p=0.003) and a trend towards a higher prevalence of smoking (57% vs. 51%; p=0.068). The median ASCVD risk score was significantly lower in women (3.2 vs. 5.2; p<0.001) and 244 (83%) women had an ASCVD score of <7.5% compared to 824 (70%) men (p<0.001, **Table 2**).

When applying the 2013 ACC/AHA guidelines, over 64% of women would not have been eligible for statin therapy compared with 49% of men (p<0.001) **(Figure 5).** When applying the USPSTF recommendations, 82% of women would not have been eligible compared with 68% of men (p=0.002). Overall, only 37% of women would have been eligible for statin therapy by either the 2013 ACC/AHA or USPSTF guidelines compared with 54% of men (p<0.001, **Table 2**).

Enhancement of Statin Eligibility

We estimated the effect of modifying the risk prediction and incorporating additional risk factors to increase statin eligibility and these are provided in the Online Appendix and **Online Figure 3.**

Discussion

To the best of our knowledge, this study is the first to apply the 2013 ACC/AHA cholesterol guidelines and 2016 USPSTF primary prevention recommendations for statin therapy

to a large cohort of adults who experienced an MI at a young age, and one of the largest to look at distributions of risk factors prior to MI among adults under the age of 50. We found that despite the expanded use of statins advocated by these recommendations (9,17), current guidelines did not identify most young adults who experienced a MI to be eligible for statins at the time of or prior to their event. In our study, 51% of subjects would not have been eligible for statin therapy prior to their MI if the 2013 ACC/AHA guidelines were implemented and 71% would not have been eligible by the 2016 USPTF recommendations. Our findings were more striking in women, where only 36% and 18% were determined to be eligible by the 2013 ACC/AHA guidelines and 2016 USPSTF recommendations, respectively. It is notable that the underestimation of risk in this cohort exists despite the high prevalence of traditional cardiovascular risk factors (with 4 out of every 5 patients having at least one major cardiovascular risk factor). Furthermore, in calculating the ASCVD risk score we conservatively increased the minimum age to 40, and reclassified all patients in the statin considered category (i.e., ASCVD risk score of 5-7.5%) as statin eligible, as has been suggested by others as a method for improving the applicability of these criteria to young adults. (18).

Risk prediction in young adults

In 2002, Akosah et al. (6) evaluated the statin eligibility of 222 "young adults" (men ≤ 55 and women ≤ 65 years) hospitalized for MI using the NCEP III guidelines that were used at that time and found that 82% of women and 59% of men did not meet thresholds for pharmacotherapy prior to their MI, despite a high prevalence of cardiovascular risk factors, particularly among women. The authors concluded that there is a need for better risk prediction in young adults. While various guidelines have subsequently been developed, no studies have been performed applying the various proposed criteria to young adults. When applied to other

populations, the ASCVD risk calculator based on the PCE has been shown to overestimate risk (15,19,20); however, our findings suggest that this risk score, which is highly dependent on age(15,16), also has the potential to underestimate risk in younger individuals. While the 2016 USPSTF recommendations and 2001 NCEP III guidelines each identify a small proportion of individuals that was not eligible by 2013 ACC/AHA guidelines, even when considering patients who may be eligible by any of the 3 guidelines, a significant proportion of at-risk population would not have been categorized as statin eligible **(Figure 4).**

Opportunities for enhancing risk prediction

In the current era of generic statins which are generally well tolerated, several mechanisms have been suggested for better identification of more at-risk individuals. For instance, Navar-Boggan et al. (18) suggested that decreasing the treatment threshold to include the statin considered group (i.e., ASCVD risk score of 5-7.5%) would improve the sensitivity of identifying individuals who ultimately experienced cardiovascular events. In our cohort, this increased statin eligibility by 18% for the ACC/AHA guideline. In addition to performing these measures, we also evaluated how including other risk factors proposed by the 2013 ACC/AHA statin guidelines may further enhance risk prediction. Specifically, we found that reclassifying all patients with LDL cholesterol >160 mg/dL and a family history of premature CAD as statin eligible, would increase the proportion of treated patients from 49% to 66%. However, any criteria that would identify more at-risk individuals, would lead to a higher proportion of treated patients across the population who would not necessarily experience events. Thus, while our findings suggest that incorporating the above risk factors in making decisions regarding the role of statins in young individuals may be important, future investigations should further elucidate

the population-level impact of such approaches aimed at expanding the number of individuals treated.

Any effort to expand the number of treated young individuals should also incorporate the following considerations: (i) While no randomized studies have assessed the role of statins for primary prevention among young adults, Mendelian randomization studies suggest that a longer exposure to low LDL cholesterol may provide long term benefits; (21) (ii) while the overall risk of most young patients is low, younger individuals represent the largest proportion of the population who are at risk; (24) (iii) patients who experience an MI at a younger age suffer a larger economic impact as their lifetime earnings and societal contributions are affected to a greater extent. Ultimately, in the absence of randomized data, (23) and given the need to balance the risks and benefits of treatment, together with patients' disutility from being on statin therapy, there is an important need to incorporate shared decision making between patients and physicians (26).

In addition to the aforementioned efforts in identifying at-risk patients, our study also reinforces the need for more primordial prevention (25-27). In fact, greater than 80% of the patients who had an MI at a young age had at least one modifiable risk factor, with dyslipidemia, smoking, and hypertension being the most prevalent. USPSTF has established guidelines for screening for traditional cardiovascular risk factors in adults, and current recommendations include: screening for hypertension annually in patients aged 40 years and above, and every 3-5 years in patients 18 to 40 years of age(30); screening overweight or obese adults age 40 to 70 years for diabetes (31); and providing pharmacotherapy or behavioral interventions to adults for smoking cessation.(32) The USPSTF recommends screening for dyslipidemia every 5 years in patients aged 40 and above, but recommends neither for nor against screening patients aged 21-

39 years, citing lack of evidence in this age group.(8) The 2013 ACC/AHA cholesterol guidelines have expanded the number of individuals eligible for statin therapy, and accordingly recent data suggests that there has been a gradual but sustained increase in statin use for primary preventions (33).

Sex Differences in Statin Eligibility

Women had significantly lower statin eligibility compared with men, even though there were no significant differences in age or the burden of risk factors between men and women. While the more pronounced underestimation of risk in women in our cohort cannot be explained by differences in age or risk factors alone, it is noteworthy that the PCE has been shown to overestimate risk in women (28). Further research is required to better identify risk and prevent cardiovascular disease in women, particularly as women have worse outcomes post-MI compared with similarly aged men (29).

Limitations

Our study is retrospective in nature and thus subject to limitations regarding uniformity of data collection. However, our retrospective cohort design is ideal for studying less frequent conditions, such as MI in young individuals. In addition, we performed a manual review of all admission notes rather than rely on billing or other coded information in order to, both adjudicate the presence of MI, as well as determine the prevalence of various risk factors. While our findings reinforce the need for better identification of risk among young individuals, a limitation of our study is that we only evaluated individuals who experienced an MI, without considering the overall at-risk population for this age group. As a result, we were not able to determine the prevalence of various risk factors across the population of at-risk patients who did not experience a myocardial infarction, as has previously been done by other population based cohorts. (36) In

the future, use of machine learning algorithms, may facilitate other study designs, such as retrospective case-control studies, which may provide further information in this regard.

Lipid levels maybe falsely lowered at the time of MI, however one of the largest studies examining this did not find a clinically meaningful change. (31) Nevertheless, we analyzed the change in total cholesterol for patients who had available measurements before their MI and during the index admission. In these patients, the total cholesterol decreased by 12%. Consequently, we performed a sensitivity analysis by increasing the total cholesterol of all patients who did not have prior cholesterol values by 12%, and our findings remained robust, suggesting that any potential changes in lipid values peri-MI did not have a significant impact on our findings.

Guidelines recommend considering factors such as high-sensitivity C-reactive protein, coronary artery calcium and ankle brachial pressure index, but results from such testing were not available for our cohort. Finally, our risk estimates may be too conservative, as we increased the age of some of the patients by more than 10 years, and it is likely that we would have observed an even higher proportion of patients who were not statin eligible if we used actual age in calculating the ASCVD risk score from PCE. However, the PCE are derived from and thereby applicable only to those who are 40 -79 years of age (12).

Despite the fact that this study was conducted across two large academic medical centers, our results remain generalizable to other settings, as our study examines baseline risk level and is not related to the treatment received. While there may be geographical differences in some cardiovascular risk factors, these are unlikely to influence our main results, as our population had a high prevalence of underlying risk factors, and it was their younger age, rather than failure to capture these risk factors, that contributed to them being classified as statin ineligible. Our study

population was mostly white, and we recognize that certain groups such as South Asians may have a higher predisposition to develop premature CAD and risk scores may further underestimate risk (38-40), however we did not have sufficient power to analyze sub-groups based on race/ethnicity.

Conclusions

The vast majority of adults who present with an MI at a young age would not have met current guideline-based treatment thresholds for statin therapy prior to their MI. These findings highlight the need for developing better risk assessment tools among young adults.

Clinical perspectives

Clinical Competencies: Providers need to be cautious when applying statin recommendations endorsed by guidelines to young individuals under the age of 50, as a low ASCVD risk score maybe falsely reassuring in certain clinical scenarios, and consequently lead to under-treatment. We recommend that in addition to calculating the ASCVD risk score, clinicians consider incorporating additional risk markers – such as premature family history of CAD, or clustering of traditional and novel risk factors – when having risk-benefit discussions with young adults in the context of shared decision making.

Translational Outlook: Re-calibration of risk scores or development of novel risk scores to more accurately estimate cardiovascular risk in young adults is needed.

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Figure Legends

Central Illustration: Guideline-based Statin Eligibility of Young Adults Prior to MI. Contemporary statin guidelines were applied to 1,475 young adults not on statins prior to myocardial infarction. The right panel displays the stepwise implementation of the 2013 American College of Cardiology/American Heart Association cholesterol guidelines. The left panel displays the stepwise implementation of the 2016 United States Preventive Services Task Force statin recommendations. The cohort is stratified by statin eligibility according to specified guideline criteria into three groups—statin recommended (green), statin considered (gray) and statin not recommended (red). The risk factors considered by USPSTF guidelines include diabetes, hypertension, dyslipidemia and smoking. LDL – Low density lipoprotein, ASCVD – atherosclerotic cardiovascular disease, CV – cardiovascular, ACC / AHA – American College of Cardiology / American Heart Association, USPSTF – United States Preventive Services Task Force.

Figure 1: Prevalence of cardiovascular risk factors stratified by statin eligibility. Distribution of the most common risk factors within our cohort, stratified by the proportion of patients who are recommended (green), considered (gray), or not recommended (red) statins by the 2013 American College of Cardiology / American Heart Association guidelines.

Figure 2: Lifetime cardiovascular risk. Proportion of patients with high lifetime cardiovascular risk (≥39%) among young adults with MI.

Figure 3: Burden of risk factors and statin ineligibility. Proportion of patients not eligible for statin therapy stratified by cumulative burden of cardiovascular risk factors by 2013 ACC / AHA (orange) and 2016 USPSTF recommendations (blue). * Cardiovascular risk factors considered include diabetes, hypertension, dyslipidemia and smoking. ACC / AHA – American College of

Cardiology / American Heart Association, USPSTF – United States Preventive Services Task Force.

Figure 4: Statin Eligibility of Young Adults Prior to MI by Various Guidelines. The square box represents the total population (n=1475) of patients who experienced a myocardial infarction at a young age. The colored circles represent the proportion of statin eligible (statins considered / statin recommended) individuals. The size is directly proportional to magnitude of statin eligibility, with the 2013 2013 ACC / AHA guidelines represented by the red circle, 2016 USPSTF recommendations represented by the green circle and NCEP III guidelines represented by the golden circle. Overlap between circles represents individuals that were eligible by multiple respective guidelines. AHA – American College of Cardiology/American Heart Association, USPSTF – United States Preventive Services Task Force, NCEP – National Cholesterol Education Panel.

Figure 5: Sex differences in statin eligibility. Classification of statin eligibility by the 2013 ACC/AHA guidelines (orange) and 2016 USPSTF recommendations (blue) for women (right panel) and men (left panel). ACC/AHA – American College of Cardiology / American Heart Association, USPSTF – United States Preventive Services Task Force.

Table 1: Baseline Characteristics

Factor	**N=1475**
Age at time of MI, median (IQR)	45 (41,48)
Female	294 (19.9%)
White	1060 (71.9%)
ST Elevation Myocardial Infarction	846 (57.4%)
Diabetes	246 (16.7%)
Hypertension	649 (44 %)
Dyslipidemia	818 (55.5%)
Current Smoking	772 (52.3%)
Former Smoker	196(13.2%)
Premature CAD in 1st degree relative	424 (28.7%)
Obesity	437 (29.6%)
Total cholesterol mg/dL, mean (SD)	191.3 (55.9)
HDL cholesterol mg/dL, mean (SD)	37 (10.6)
LDL cholesterol mg/dL, mean (SD)	118.4 (45.9)
Triglycerides mg/dL, median (IQR)	145 (101,217)
ASCVD score, median (IQR)	4.8 (2.8, 8.0)
ASCVD Risk Category	
<5 %	770 (52.2%)
5-7.5 %	298 (20.2%)
7.5-20 %	365 (24.7%)
>20 %	42 (2.8%)
Recommended / Considered for statin therapy by 2013 ACC/AHA	724 (49.1%)
Recommended / Considered for statin therapy by 2016 USPSTF	430 (29.2%)
Recommended / Considered for statin therapy by either guideline	742 (50.3%)
Recommended / Considered for statin therapy by NCEP III	507 (34.4%)

Numbers represent N (% of total), unless otherwise stated

MI – myocardial infarction, CAD – coronary artery disease, HDL – High density lipoprotein, LDL – Low density lipoprotein, ASCVD – atherosclerotic cardiovascular disease

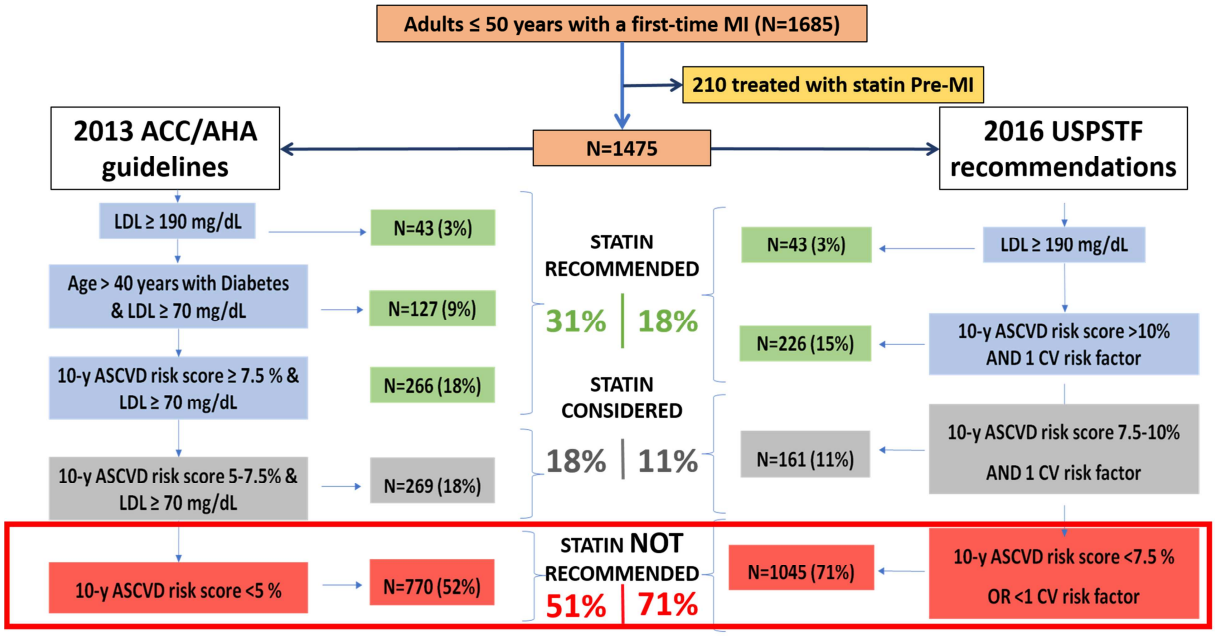
Table 2: Sex differences

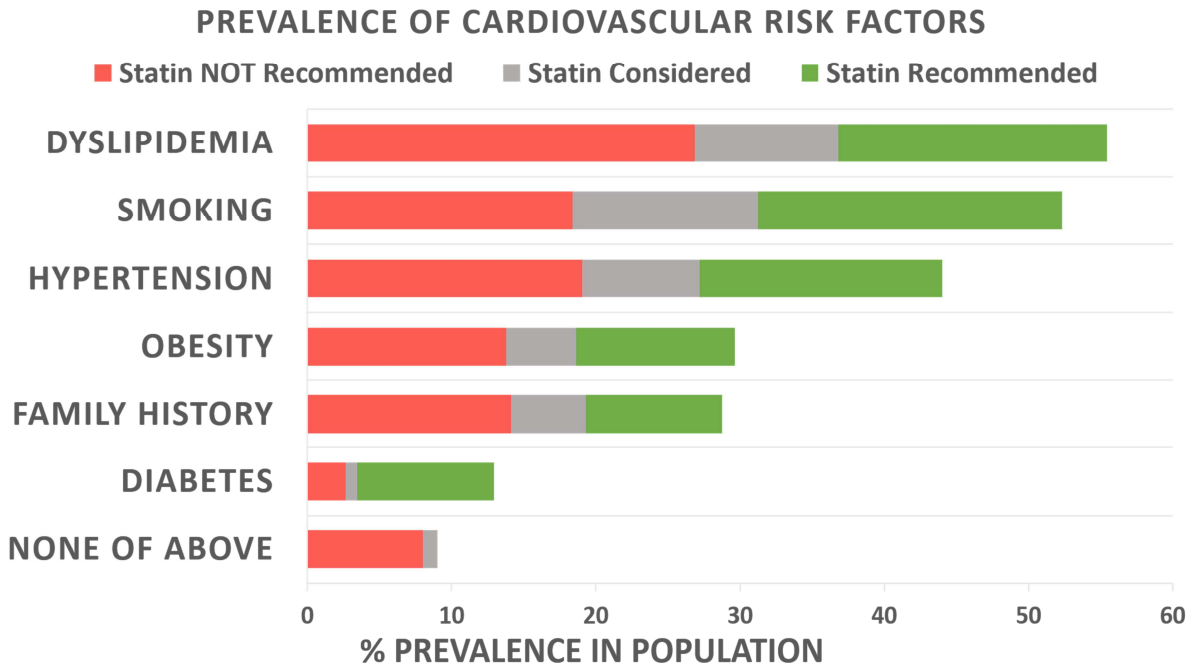
Factor	Male (n=1181, 80%)	Female (n=294, 20%)	p-value
Age at time of MI, median (IQR)	45 (41, 48)	46 (42,48)	0.24
White	856 (72.5%)	204 (69.4%)	0.31
Diabetes	190 (16.1%)	56 (19%)	0.22
Hypertension	517 (43.8%)	132 (44.9%)	0.74
Hyperlipidemia	702 (59.4%)	116 (39.5%)	<0.001
Current Smoking	604 (51.1%)	168 (57.1%)	0.068
Former Smoker	167 (28.9%)	29 (23%)	0.19
Premature CAD in 1st degree relative	334 (28.3%)	90 (30.6%)	0.43
Obesity	329 (27.9%)	108 (36.7%)	0.003
Total cholesterol mg/dL, mean (SD)	193.1 (57)	184.1 (50.9)	0.014
HDL cholesterol mg/dL, mean (SD)	36.1 (9.5)	40.9 (13.8)	<0.001
LDL cholesterol mg/dL, mean (SD)	119.8 (45.9)	112.8 (45.6)	0.02
Triglycerides mg/dL, median (IQR)	153 (104, 230)	122 (86,177)	<0.001
ASCVD score, median (IQR)	5.2 (3.2, 8.5)	3.2 (1.2, 6.0)	<0.001
ASCVD Risk Group			
<5 %	571 (48.3%)	199 (67.7%)	<0.001
5-7.5 %	253 (21.4%)	45 (15.3%)	
7.5-20 %	326 (27.6%)	39 (13.3%)	
>20 %	31 (2.6%)	11 (3.7%)	
Recommended / Considered for statin therapy by 2013 ACC/AHA	603 (51.1%)	102 (34.7%)	<0.001
Recommended / Considered for statin therapy by 2016 USPSTF	377 (31.9%)	53 (18%)	<0.001
Recommended / Considered for statin therapy by either guideline	632 (53.5%)	110 (37.4%)	<0.001
Recommended / Considered for statin therapy by NCEP III guidelines	378 (32%)	129 (43.9%)	<0.001

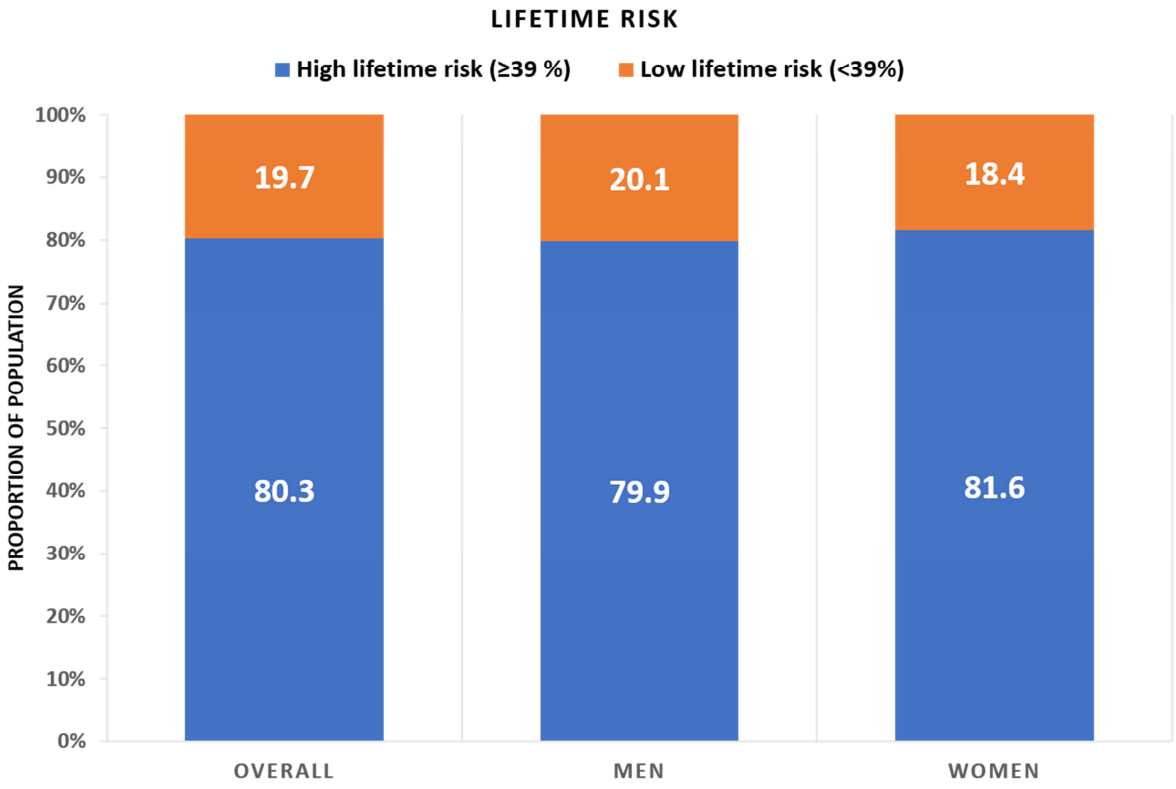
Numbers represent N (% of total), unless otherwise stated. MI – myocardial infarction, CAD – coronary artery disease, HDL – High density lipoprotein , LDL – Low density lipoprotein, ASCVD – atherosclerotic cardiovascular disease

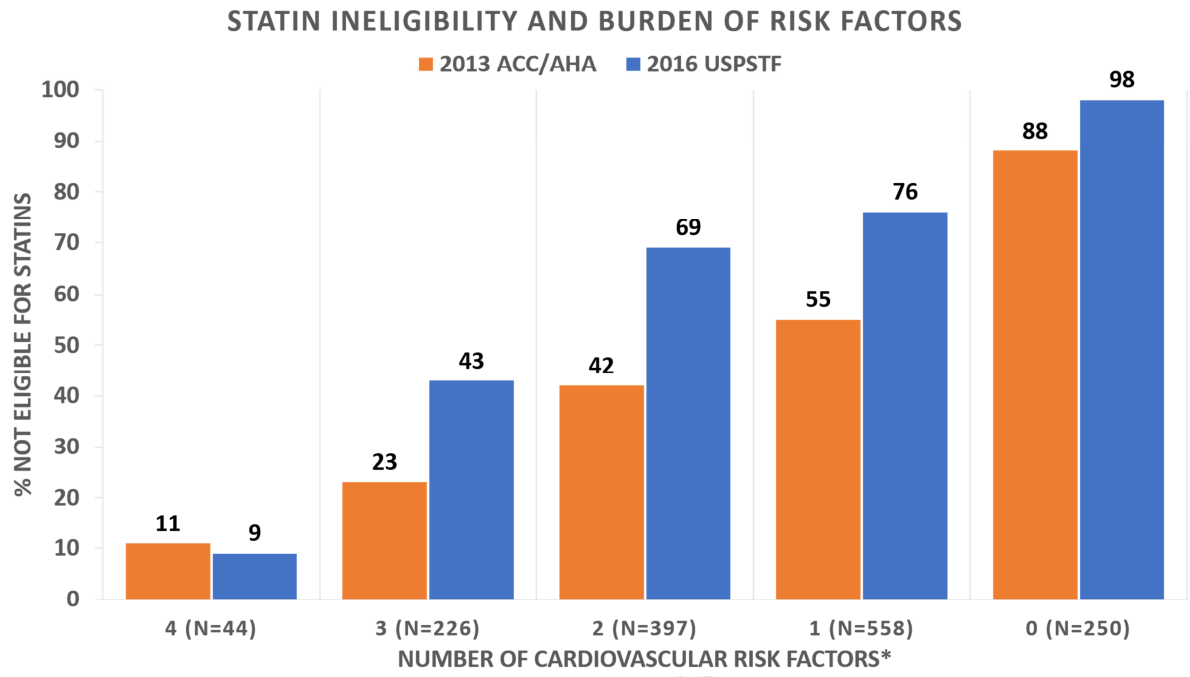
Central Illustration

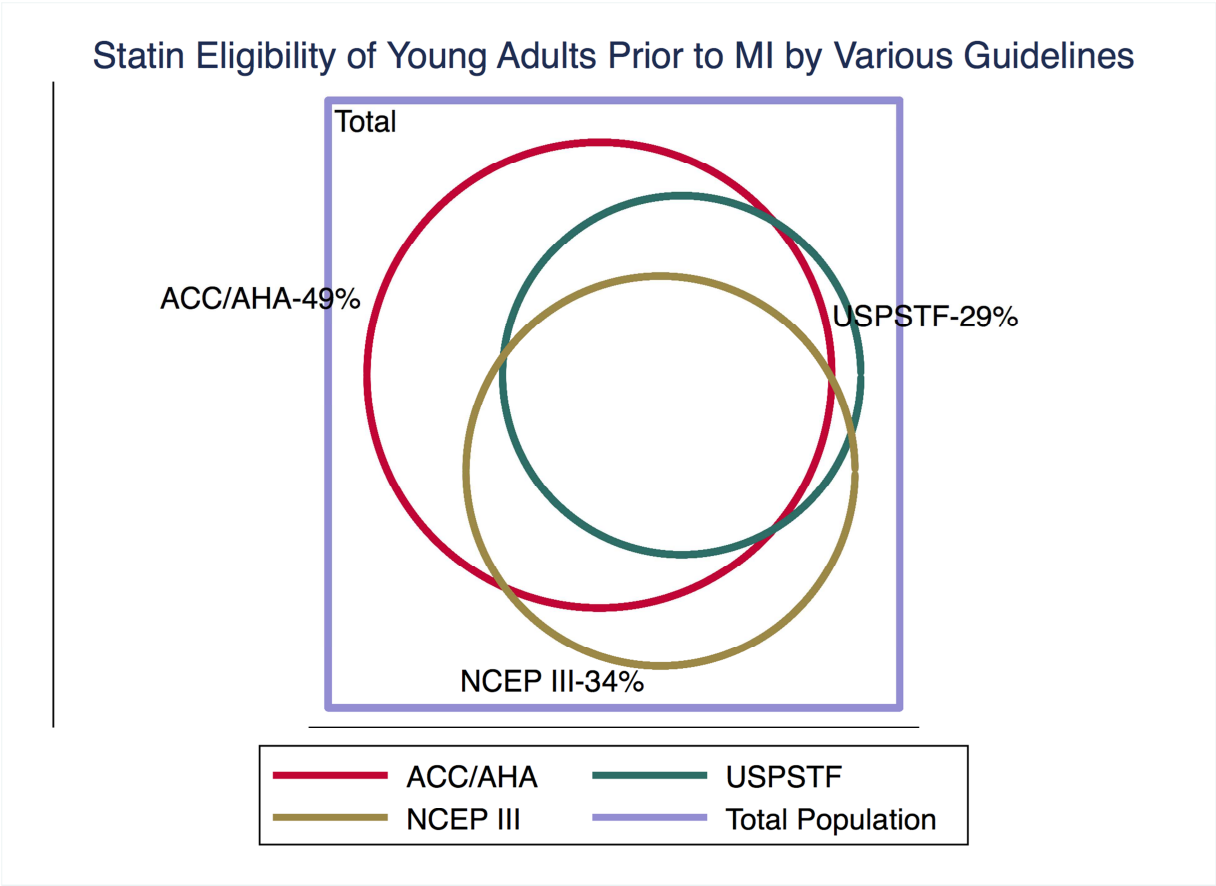
How many young adults would meet guideline criteria for statins prior to MI?

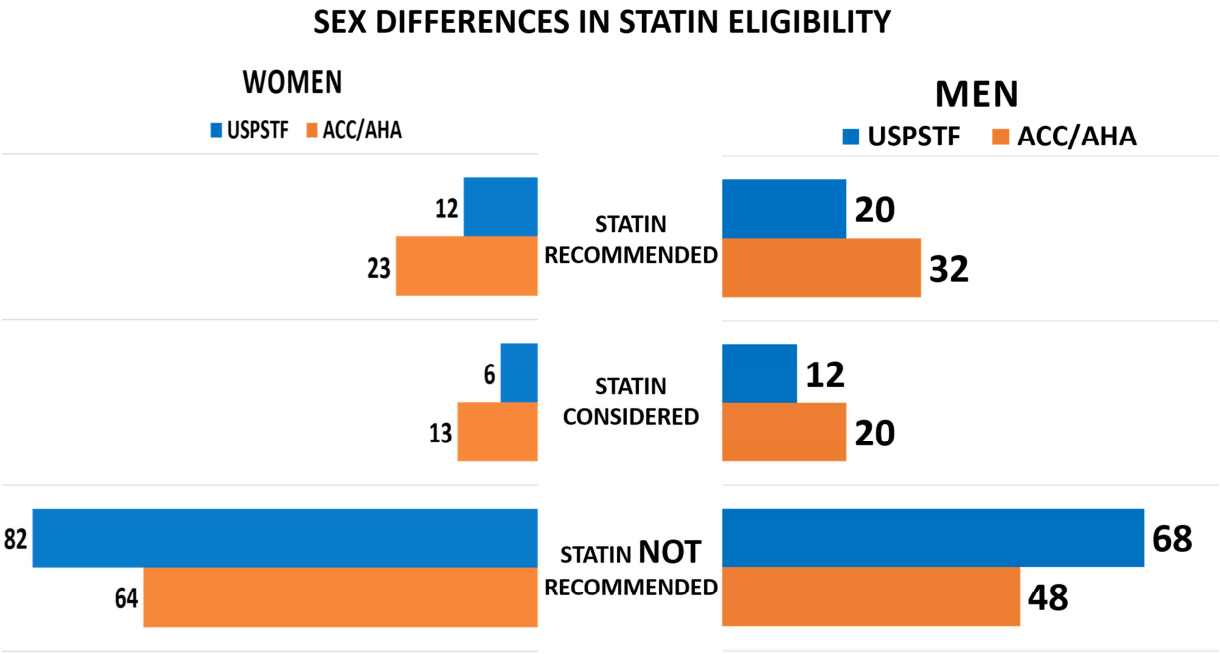












Cardiovascular Risk and Statin Eligibility of Young Adults Who Experience a Myocardial Infarction: From the Partners YOUNG-MI Registry

Supplementary material

Table of contents:

1. Definitions

Online Table 1 – Criteria for lifetime risk categories

Risk Category	Definition
All optimal risk factors	Defined as total cholesterol <180 mg/dL, blood pressure <120/<80 mm Hg, nonsmoker, and nondiabetic.
≥1 Not optimal risk factor	Defined as total cholesterol 180 to 199 mg/dL, systolic blood pressure 120 to 139 mm Hg, diastolic blood pressure 80 to 89 mm Hg, nonsmoker, and nondiabetic.
≥1 Elevated risk factor	Defined as total cholesterol 200 to 239 mg/dL, systolic blood pressure 140 to 159 mm Hg, diastolic blood pressure 90 to 99 mm Hg, nonsmoker, and nondiabetic.
1 Major risk factor	Defined as total cholesterol ≥240 mg/dL, systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥100 mm Hg, smoker, or diabetic.
≥2 Major risk factors	2 or more criteria in major risk factor category.

Based on Lloyd-Jones, Donald M., et al. "Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age." *Circulation* 113.6 (2006): 791-798.

Online Table 2 - Specific criteria followed for each guideline

Criteria used for 2013 ACC / AHA guidelines
1. Statins were classified as **recommended** if any of the following hierarchical criteria were present: a. LDL cholesterol ≥ 190 mg/dL b. Diabetes with age 40 years or more and LDL cholesterol ≥ 70 mg/dL **c.** ASCVD risk score ≥ 7.5% and LDL cholesterol ≥ 70 mg/dL
2. Statins were classified as **considered** if ASCVD risk score was between 5 - 7.5% and LDL cholesterol ≥ 70 mg/dL
3. Statins were classified as **not recommended** if none of the above criteria were met.
Criteria used for 2016 USPSTF recommendations
1. Statins were classified as **recommended** if any of the following hierarchical criteria were present: a. LDL cholesterol ≥ 190 mg/dL b. ASCVD risk score ≥ 10% and 1 cardiovascular risk factor ***** was present
2. Statins were classified as **considered** if ASCVD risk score was between 7.5% - 10% and 1 cardiovascular risk factor was present
3. Statins were classified as **not recommended** if none of the above criteria were met.
Criteria used for NCEP III guidelines
1. Statins were classified as **recommended** if any of the following hierarchical criteria were present: a. Diabetes with LDL cholesterol ≥ 100 mg/dL b. Framingham risk score (FRS) > 20% with LDL cholesterol ≥ 100 mg/dL c. 2+ risk factors**ǂ** with FRS 10-20% with LDL cholesterol ≥ 130 mg/dL d. 2+ risk factors with FRS <10% with LDL cholesterol ≥ 160 mg/dL e. 0-1 risk factor with LDL cholesterol ≥ 190 mg/dL
2. Statins were classified as **considered** if any of the following criteria were present: a. Diabetes with LDL cholesterol < 100 mg/dL b. Framingham risk score (FRS) > 20% with LDL cholesterol < 100 mg/dL c. 2+ risk factors with FRS 10-20% with LDL cholesterol 100-129 mg/dL d. 0-1 risk factor with LDL cholesterol 160-189 mg/dL
3. Statins were classified as **not recommended** if none of the above criteria were met.

*****Cardiovascular risk factors considered by the USPSTF recommendations include hypertension, dyslipidemia, diabetes and smoking. **ǂ** risk factors considered by the NCEP III guidelines include cigarette smoking, hypertension or on antihypertensive medication, HDL cholesterol <40 mg/dL, family history of premature cardiovascular disease and age ≥45 in men. HDL ≥ 60 mg/dL is considered as a negative risk factor.

2.Sensitivity analyses

Online Table 3

Variables in ASCVD score: Age, Sex, Race, SBP, Treatment for HTN, Total cholesterol, HDL cholesterol, Smoking, Diabetes

Variable	Number in which available prior to MI
Systolic Blood Pressure	269 (18.2%)
Total cholesterol \ HDL cholesterol	242 (16.4%)
Diabetes	191 / 246 (77.6%)

Not applicable for other variables.

Online Table 4 - Adjusting total cholesterol

Total cholesterol was increased by 12% for patients that did not have lipid values available prior to MI.

Criteria	2013 ACC/AHA	2016 USPSTF
Statin Not Recommended	655 (44%)	971 (66%)
Statin Considered	300 (20%)	163 (11%)
Statin Recommended	520 (36%)	341 (23%)

Online Table 5 – Analysis limited to patients who had available data on cholesterol values prior to MI (N=242)

Criteria	2013 ACC/AHA	2016 USPSTF
Statin Not Recommended	89 (37%)	155 (64%)
Statin Considered	56 (23%)	16 (7%)
Statin Recommended	97 (40%)	71 (29%)

Online Table 6 – Characteristics of patients with cholesterol data available prior to MI

Risk Factor	Pre- MI lipids available (N=242)	Pre – MI lipids not available (N=1233)	p-value
Age at time of MI, mean (SD)	44.0 (5.0)	43.9 (5.2)	0.82
Caucasian	164 (67.8%)	896 (72.7%)	0.12
Female	63 (26.0%)	231 (18.7%)	0.009
Diabetes	57 (23.6%)	189 (15.3%)	0.002
Hypertension	126 (52.1%)	523 (42.4%)	0.006
Dyslipidemia	138 (57.0%)	680 (55.2%)	0.59

Current Smoking	103 (42.6%)	669 (54.3%)	<0.001
Premature CAD in 1st degree relative	66 (27.3%)	358 (29.0%)	0.58
ASCVD score, median (IQR)	6.0 (3.7, 10.5)	4.7 (2.7, 7.7)	<0.001
ASCVD Risk Category			
<5 %	97 (40.1%)	673 (54.6%)	<0.001
5-7.5 %	62 (25.6%)	236 (19.1%)	
7.5-20 %	60 (24.8%)	305 (24.7%)	
>20 %	23 (9.5%)	19 (1.5%)	

Online Table 7 – Analysis limited to patients with blood pressure available prior to MI (N=269)

Criteria	2013 ACC/AHA	2016 USPSTF
Statin Not Recommended	119 (44%)	179 (67%)
Statin Considered	57 (21%)	22 (8%)
Statin Recommended	93 (35%)	68 (25%)

Online Table 8 – Statin eligibility by NCEP III guidelines

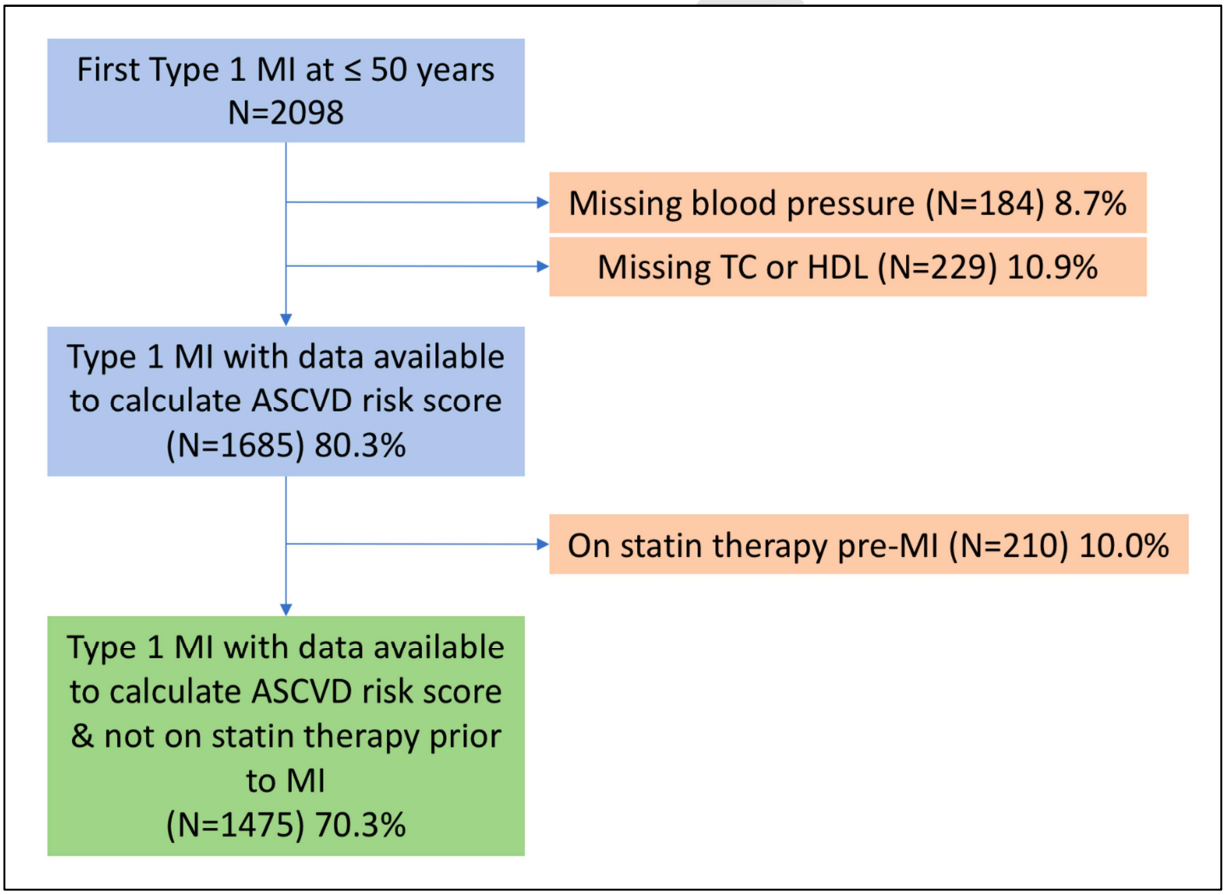
Criteria	NCEP III guidelines
Statin Not Recommended	968 (66%)
Statin Considered	160 (11%)
Statin Recommended	347 (23%)

3. Enhancement of Statin Eligibility

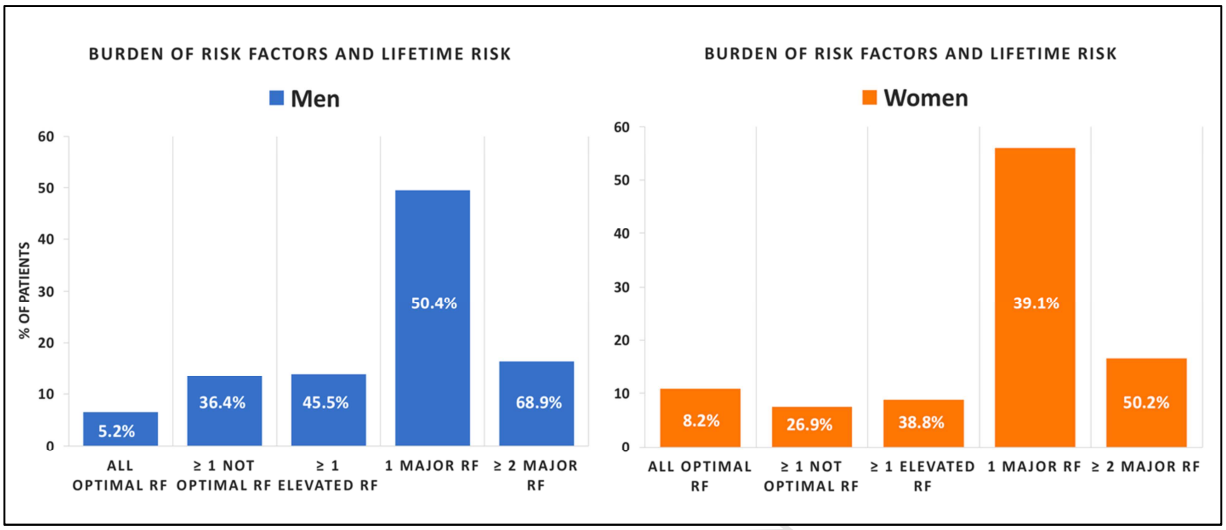
We estimated the effect of modifying the risk prediction and incorporating additional risk factors to increase statin eligibility. These were only applied to the 2013 ACC/AHA guidelines as, by design, it identifies more individuals than the 2016 USPSTF recommendations. When considering all statin ineligible individuals with LDL cholesterol >160 mg/dL and a family history of premature CAD, individually and then in combination, there was a significant increase in the proportion of patients considered for statins, as illustrated in **Online Figure 3.** Specifically, the addition of both variables increased the eligibility by 17% (n=244; p<0.001).

4.Online Figures

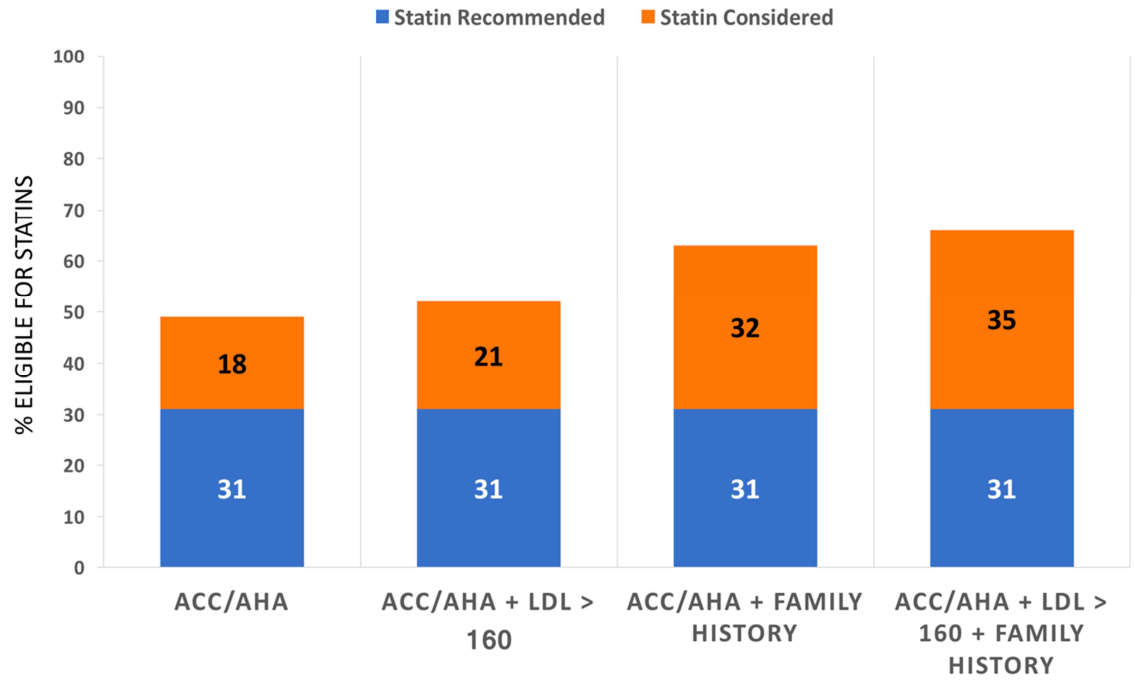
Online Figure 1



Online Figure 2



Online Figure 3



Online Figure 1: Consort diagram. Of the 2098 adults with a first type 1 myocardial infarction at ≤ 50 years of age, data on blood pressure and lipid profile was missing in 184 and 229 patients, respectively. Of the remaining 1685, 210 were on statin therapy prior to presentation. The final analytic cohort consisted of 1475 patients.

Online Figure 2: Burden of risk factors and lifetime risk stratified by sex. This figure illustrates the distribution of patients in various risk categories used to determine lifetime cardiovascular risk. The height of the bars is reflective of the proportion of patients in that risk factor category. The labeled percentages are the estimated lifetime risk for that category. Categories are as defined in Online Table 1. RF – Risk factor.

Online Figure 3: Enhancement of statin eligibility. This figure illustrates the effect of reclassifying patients with low density lipoprotein cholesterol > 160 mg/dL or family history of premature coronary artery disease as statin considered for the 2013 ACC / AHA guidelines. Vertical axis represents percent eligible for statin therapy. LDL – low density lipoprotein, ACC / AHA – American College of Cardiology / American Heart Association.