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**STATIN USE IN PRIMARY PREVENTION; A SIMPLE TRIAL BASED APPROACH
COMPARED TO GUIDELINE RECOMMENDED RISK ALGORITHMS FOR
SELECTION OF ELIGIBLE PATIENTS**

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BRIEF SUMMARY

The Heart Outcomes Prevention Evaluation (HOPE) 3 study utilised a simple pragmatic risk factor approach to identify individuals that may benefit primary prevention therapy.

Comparing outcomes using the Framingham risk score and the 2013 American College of Cardiology / American Heart Association (ACC/AHA) algorithm to outcomes seen in the HOPE-3 trial, showed similar risk reductions in cardiovascular events. However, these risk tools did not identify all participants that were eligible as when using a simple pragmatic approach.

ABSTRACT

Background: Cardiovascular disease (CVD) risk assessment tools help identify individuals likely to benefit from preventative therapies. This study compared outcomes using the ACC/AHA risk algorithm and the Framingham risk score (FRS) tool in The Heart Outcomes Prevention Evaluation (HOPE) 3 study.

Methods: We compared outcomes using the ACC/AHA algorithm and the FRS with those seen in HOPE-3, which randomized participants to 10mg rosuvastatin or placebo. First co-primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke; second co-primary outcome additionally included heart failure, cardiac arrest and revascularization.

Results: Relative risks using risk scores were similar to those observed in the HOPE-3. Hazards ratios (HRs) for first co-primary outcome by risk categories of $\leq 10\%$, 10-20% and $\geq 20\%$ using the ACC/AHA algorithm were 0.82 (95% CI: 0.53, 1.28), 0.72 (0.53, 0.96) and 0.72 (0.55, 0.93) [absolute risk reduction (ARR) of 0.18, 1.33 and 1.85%, respectively, over a median of 5.6 years]. Corresponding results using FRS were 0.69 (0.36, 1.35), 0.73 (0.52, 1.01) and 0.75 (0.60, 0.94) [ARR 1.32, 0.61 and 1.43%]. HRs for second co-primary outcome were 0.77 (0.51, 1.14), 0.73 (0.56, 0.95) and 0.74 (0.58, 0.94) [ARR 0.36, 1.49 and 1.85%] using the ACC/AHA algorithm and 0.76 (0.41, 1.41), 0.70 (0.52, 0.95) and 0.76 (0.62, 0.94) [ARR of 1.08, 0.83 and 1.56%] using FRS.

Conclusion: The pragmatic HOPE-3 trial approach identifies in an ethnically diverse primary prevention population individuals at intermediate risk who benefit from statin therapy using simple clinical characteristics without the need for complex, currently used risk assessment tools.

INTRODUCTION

More than 80% of deaths from cardiovascular diseases (CVD) occur in low- and middle-income countries.¹ Statins reduce the risk of CVD but most of the data are from Western countries with few data from low and middle-income countries, especially for primary prevention.² However, meta-analysis of prospective observational studies both in developed and developing countries showed the same pattern of association between blood pressure and blood cholesterol level and relative risk of CVD in populations drawn from countries at different economic levels.³

The absolute cardiovascular risk is determined using various risk scores integrating the prognostic impact of several cardiovascular risk factors. Although risk scores have been developed to identify individuals without CVD who are relatively at high CVD risk, these are largely for Western populations with scant data from other ethnic groups, especially those living in low and middle-income countries. Previous studies have shown that risk prediction models are less accurate in non-White populations, for which there are currently no cardiovascular risk scores available for use in clinical practice.⁴ Furthermore, there are limited data on whether the benefits of statins are consistent or vary by the risk of the population, especially from trials involving participants from both high and low-income countries. There is also an increase in number of online risk algorithms including online risk tools; however there are major barriers for individuals in view of health literacy, access and ability to understand such risk algorithm, especially in low- and middle-income countries.⁵ Over the past decade, CVD risk scores have been developed to facilitate the clinicians' work for the identification of individuals who are at high risk and are most likely to benefit from preventive therapy. Several risk estimation scores are currently in existence for quantifying future cardiovascular risk, with the most widely used globally being the Framingham Risk Score.⁶ The 2013 American College of Cardiology/American Heart Association (ACC/AHA)

Guidelines on treatment of blood cholesterol developed the new Pooled Cohort atherosclerotic cardiovascular disease (ASCVD) equations for risk assessment and also focus on absolute cardiovascular risk and estimate the 10-year risk of major atherosclerotic CVD.⁷ Most guidelines recommend using risk assessment tools and categorising at low risk (<10% ten year cardiovascular risk), intermediate risk (10-20%) and high risk ($\geq 20\%$). However, these estimations are somewhat arbitrary and have been chosen largely by consensus rather than scientific evidence.⁸ Lack of conclusive data has led to controversy as to whether statin therapy in primary prevention should be guided by risk scores.⁹ In addition, there have been calls for moving away from estimated absolute risk based statin therapy as a trial based approach would provide simplicity in assessing eligibility for statin therapy.⁴ To our knowledge, such a pragmatic trial based approach has not been assessed in a global, ethnically diverse population targeted for primary prevention.

The aim of this present study was to compare the outcomes using two commonly recommended guideline based risk scores, the ACC/AHA algorithm and the Framingham risk score,¹⁰ with the outcomes in The Heart Outcomes Prevention Evaluation (HOPE) 3 study which recruited ethnically diverse population randomised to statin therapy using a more simple pragmatic risk factor based approach.

MATERIALS AND METHODS

Study Design

This is a post-hoc analysis based on prospectively acquired data in the HOPE-3 trial. Details of the HOPE-3 study design and main outcomes have been published.^{11, 12} In summary, HOPE-3 was a multicentre, international, double-blind, randomized, placebo-controlled trial that used a 2x2 factorial design to evaluate the effects of blood pressure (BP) lowering, lipid lowering, and their combination compared to placebo on the prevention of major cardiovascular (CVD) events with a median follow up of 5.6 years. The first co-primary outcome was composite of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. The second co-primary outcome additionally included heart failure, cardiac arrest and revascularization.

Participants

Participants from 21 countries (South and North America, Europe, Asia and Australia) were men aged ≥ 55 years and women ≥ 65 years with at least one additional risk factor and women aged ≥ 60 with two risk factors. The cardiovascular risk factors were: elevated waist-to-hip ratio (women ≥ 0.85 , men ≥ 0.90), history of low high-density lipoprotein (HDL) cholesterol (women < 50 mg/dl, men < 39 mg/dl), current or recent tobacco use, dysglycemia (impaired fasting glucose, impaired glucose tolerance or early diabetes treated with diet alone), family history of premature coronary disease or mild renal dysfunction (microalbuminuria or estimated glomerular filtration rate < 60 but > 45 mL/min/1.73m² in the absence of proteinuria or BP above 130/80 mm/Hg). The trial did not require participants to have a specific lipid or blood pressure levels for entry. Participants were excluded if they had pre-existing CVD or an indication or contraindication for an angiotensin receptor blocker (ARB), an angiotensin-converting enzyme inhibitor (ACE-I), a thiazide diuretic or a statin.

Procedures

Eligible participants completed a single blind, 4-week run in period on active drug (one tablet each of candesartan/hydrochlorothiazide (HCTZ) 16/12.5mg and rosuvastatin 10mg) to assess tolerance and adherence. Those who tolerated and adhered to the medication were randomised to receive daily, one tablet each of rosuvastatin 10mg or placebo and fixed combination of candesartan/HCTZ 16/12.5mg or placebo. Participants were randomised using a blinded, central randomization system. Participants were seen at 6 weeks, 6 months and then every six months thereafter until study end on October 31, 2015. All cardiovascular events were centrally adjudicated by physicians unaware of the medication allocation. In the main trial, rosuvastatin alone compared with placebo reduced the co-primary outcomes 1 and 2 by 24% (hazard ratio: 0.76; 95% confidence interval (CI): 0.64 to 0.91) and by 25% (hazard ratio, 0.75 (95% CI: 0.64 to 0.88), respectively.¹¹

Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD) and categorical ones are presented as number and percentage. We calculated the 10-year absolute predicted cardiovascular risk for all participants in the HOPE-3 study using the Pooled Cohort Risk Equations endorsed by the ACC/AHA algorithm and the global Framingham risk score using information on risk factors collected at baseline in HOPE-3 participants. Risk factors included age, sex, blood pressure, smoking history, diabetes, total cholesterol and HDL. We defined patient groups by 10-year projected modelled risks : <10%, 10-<20% and $\geq$ 20%. We determined the eligibility of participants from the HOPE-3 study using the ACC/AHA algorithm and the Framingham risk score.

We conducted the analysis on an intention-to-treat basis.¹¹ Arm-specific event rates and hazard ratios vs. placebo for the co-primary outcomes were calculated in each category of risks using stratified Cox regression model, according to the opposite group of the factorial.

We also calculated the absolute risk reduction (ARR) and the number needed to treat (NNT) for each of the risk categories over 5.6 years of median follow-up in HOPE-3 trial based on Kaplan-Meier estimates with their 95% CIs. We conducted subgroup analysis by sex and major ethnic groups recruited in the HOPE-3 study (Asian, Hispanic and White.)

RESULTS

Of the 12,705 participants randomised, 12,317 (96.9%) had all data required to calculate the ACC/AHA and Framingham risk scores. Participants had a mean age of 65.2 years and 45.8% were females. Their mean blood pressure was 138/82 mmHg, body mass index (BMI) 26.7 kg/m², total cholesterol 201.7 mg/dl (5.2 mmol/l), low-density lipoprotein (LDL) cholesterol 128.2 mg/dl (3.3 mmol/l), HDL 43.6 mg/dl (1.1 mmol/l) and triglycerides 127.5 mg/dl (1.4 mmol/l). Overall, 6126 participants (49.7%) were Asian, 3305 (26.8%) Hispanic, 2484 (20.2%) White and 402 (3.3%) other ethnicities.

Baseline characteristics of the participants based on the ACC/AHA algorithm and the Framingham risk score of <10%, 10-20% and ≥20% are presented in Table 1. Overall, using the ACC/AHA algorithm participants in the <10% risk score were younger (mean age 62.4 years) compared to those with a risk score ≥20% (69.6 years). However, there were no major differences in age within the different risk categories using the Framingham risk score. Overall there were no differences by different ethnicities in the different risk categories using either of the risk scores.

The mean (SD) risk scores using the ACC/AHA algorithm and Framingham risk scores were 14.9% (7.6) and 19.9% (7.9), respectively. At a threshold of ≥ 10% of the ACC/AHA algorithm and Framingham risk scores, 8,353 (67.8%) and 10,792 (87.6%) of participants would have been eligible for lipid lowering therapy, respectively. In total, 2439 (19.8%) more participants would have been eligible at a threshold of ≥10% for lipid lowering therapy using the Framingham risk score compared to the ACC/AHA algorithm. At a threshold of >7.5% risk using the ACC/AHA algorithm, 10117 (82.1%) participants would have been eligible for lipid lowering therapy.

At a threshold of $\geq 10\%$ of the same risk score measurement, 2831 (50.1%) and 4232 (74.9%) of women and 5522 (82.8%) and 6560 (98.4%) of men would have been eligible for lipid lowering therapies, respectively.

By ethnicity, 4027 (65.7%) of Asians, 2300 (69.6%) Hispanics, and 1734 (69.8%) Whites would have been eligible for lipid lowering therapy using the ACC/AHA algorithm at a threshold of $\geq 10\%$ estimated 10-year risk. The corresponding figures for Framingham Risk Score would have been 5405 (88.2%), 2831 (85.7%) and 2226 (89.6%), respectively.

Table 2 shows the number of people and events, incidence rates, hazard ratios, NNT and ARR by 10-year risk categories for the two co-primary outcomes in the HOPE-3 trial using the ACC/AHA algorithm and Framingham risk score. The relative risk reductions for both co-primary outcome 1 and 2 using risk scores were similar to those observed in the main HOPE-3 trial. The hazard ratios for co-primary outcome 1 for overall, by risk categories of $<10\%$, $10\text{--}<20\%$ and $\geq 20\%$ were: 0.82 (95% CI 0.53 to 1.28), 0.72 (95% CI 0.53 to 0.96) and 0.72 (95% CI 0.55 to 0.93), respectively. Corresponding results using the Framingham risk score were 0.69 (95% CI 0.36 to 1.35), 0.73 (95% CI 0.52 to 1.01) and 0.75 (95% CI 0.60 to 0.94), respectively. The overall NNT (ARR) for co-primary outcome 1 and 2 was 92 (1.09%) and 82 (1.22%) respectively, over the median 5.6 years of follow-up. For the risk categories $<10\%$, $10\text{--}<20\%$ and $\geq 20\%$, the NNT (ARR) for co-primary outcome 1 for the ACC/AHA algorithm and Framingham risk scores was 547 (0.18%), 75 (1.33%), 54 (1.85%) and 76 (1.32%), 165 (0.61%) and 70 (1.43%), respectively. Similarly, the hazard ratios for co-primary outcome 2 for the same three categories using ACC-AHA algorithm were 0.77 (95% CI 0.51 to 1.14), 0.73 (95% CI 0.56 to 0.95) and 0.74 (95% CI 0.58 to 0.94) and for Framingham risk score 0.76 (0.41 to 1.41), 0.70 (95% CI 0.52 to 0.95) and 0.76 (95% CI 0.62 to 0.94) respectively. The corresponding NNT (ARR) for co-primary outcome 2 was 278

(0.36%), 67 (1.49%) and 54 (1.85%) and 93 (1.08%), 121 (0.83%) and 64 (1.56%) using the ACC/AHA algorithm and Framingham risk scores, respectively.

Table 3a and 3b shows the incidence rates and hazards ratios for the two co-primary outcomes by sex and ethnicity. Overall, the incidence rates and hazards rates were consistent across sex and ethnicities.

DISCUSSION

Atherosclerotic cardiovascular disease is the leading cause of premature morbidity and mortality globally and a priority for public health policies worldwide. International guidelines therefore recommend statins for primary prevention of CVD in individuals above certain estimated levels of risk, which are calculated using various risk scores. Statins are generally very safe¹³ and in fact most adverse events reported in statin treated individuals are actually not causally related to the use of statins.¹⁴ Moreover statin use is cost-effective, especially with wide availability of generic preparations.¹⁵ The HOPE-3 trial was conducted in a primary prevention population with wide representation of women and participants from all continents. The trial used a pragmatic approach, by which the study population was selected based on age and the presence of at least one of a number of easily identifiable risk factors, without the use of more complex risk scores recommended by various guidelines for the selection of patients considered for statin therapy in primary prevention. In the present study using participants' data from the HOPE-3 study, we observed that benefits of statin therapy for primary prevention of CVD using a trial based approach were similar to that using the more complex modelled ACC/AHA algorithm and Framingham risk score based approaches. Indeed the data are also consistent with the relative risk reductions observed in the cholesterol Treatment Trialists' Collaboration.¹⁶ A simple pragmatic trial based criteria used in HOPE-3 trial can therefore be used to implement a simple strategy to identify people who may benefit from multifactorial intervention of statins instead of using accepted CVD risk algorithms. This study also found that there were beneficial effects for statin therapy across a heterogeneous group of participants and irrespective of baseline risk. In fact, the proportional risk reduction was similar across baseline risk categories.

Using the Framingham risk equation, a large proportion of participants in the HOPE-3 trial would have been eligible for statin therapy. Nearly 20% more participants were eligible for

lipid lowering therapy using the Framingham Risk Score compared to the ACC/AHA Risk algorithm. At a risk threshold of $>10\%$ using the ACC/AHA algorithm, nearly two thirds of the HOPE-3 participants would have been eligible for lipid lowering therapy and 87% of people using the Framingham risk score. Nearly three quarters of men were eligible for lipid lowering therapy in the HOPE-3 study using the ACC/AHA algorithm but nearly all men would have been eligible using the Framingham Risk Score. Using the ACC/AHA algorithm at a threshold of $\geq 7.5\%$ risk, over 82% of individuals would have been eligible for lipid lowering therapy. Overall using both risk algorithms, the proportion of individuals eligible for statin therapy varied substantially. Furthermore, both risk algorithms overestimated the risk as this has been seen in previous studies.¹⁷ This calls into question the use of complex risk algorithms when a simple pragmatic strategy using readily available characteristics could be used to identify individuals that would benefit from lipid lowering therapy. We found that the results were consistent across different age groups, in men and women and in different ethnicities. A HOPE-3 trial based approach with no LDL thresholds or targets for statin therapy in certain patients would therefore be potentially useful in settings where assessment of a blood test would be a barrier to treatment decisions.¹⁰ As expected, the absolute risk reductions were greater with increasing baseline risk using both risk scores but the relative risk reductions were similar by baseline risk and similar to those observed in the main HOPE-3 trial for both co-primary outcomes. This therefore translated to larger NNT with lower baseline risk.

Among the challenges faced by family physicians, is the use of risk prediction equations for primary prevention of CVD, including an availability of facilities to assess by chemical parameters for cardiovascular stratification that may not be available in low and some middle-income countries. There are a number of additional limitations using such risk tools, most of these equations have been developed to predict individual absolute risk of

cardiovascular events based on people from European descent in high-income countries and therefore may not be valid in other populations.¹⁸ A number of studies have shown that lipid lowering therapies are underused for primary prevention in intermediate risk populations.¹⁹ Furthermore, patients are being prescribed statins without assessment of their cardiovascular risk.^{19, 20} A number of cardiovascular risk prediction calculators are available. However, most of these calculators are not easily understandable and are not actionable in routine clinical practice.¹⁰ Most randomised controlled trials did not recruit participants based on global risk algorithms and therefore it has been argued that risk based algorithms do not reflect the existing evidence.⁴ A recent systematic review also concluded that recommendations for population wide risk assessment management programs, lack robust real world evidence base especially in terms of efficacy and equity impact.²¹

There have been a number of studies comparing risk based approaches to trial based approaches using population level data but mainly using observational data. One recent study compared the ACC/AHA risk based approach compared to trial based approach using the Copenhagen General Population observational study and showed that more subjects would be eligible for statin therapy with a trial based approach.²² The Rotterdam Population study showed that there was little alignment between different guidelines, including US and European guidelines, when estimating global risk for CVD but over three quarters would be recommended a statin based on recent primary prevention trial based approaches.²³ However, most of the participants in these population based studies were of white European origin. Many of the commonly used risk algorithms may not be representative of the global population, as they do not take into account of different ethnic groups other than non-Hispanic, white and African American subjects.²² HOPE-3 study included a global population with south and East Asians, Hispanics and White populations. Additionally, risk assessment algorithms used in practice, such as the modified Framingham and ACC/AHA,

appear to overestimate risk in middle-aged and elderly people in primary prevention settings [REF]. Although this could be partially related to volunteer bias, this is consistent with other reports [REF] and is likely related to the large impact of age on currently used risk scores.

There are a number of strengths to our study. The HOPE-3 study included an ethnically diverse population at intermediate cardiovascular risk; such ethnic diversity was not included in the Framingham Risk Score and the ACC/AHA algorithm. We included the major ethnic groups although we had limited power to conduct analysis for those of African ancestry. The study has further strengths: it was done in a large cohort with a very good follow-up and all events were adjudicated by an independent adjudication committee. In addition, we included all major cardiovascular events. We also report on the benefits of offering lipid-lowering therapy at different thresholds of risk, ethnicity and age allowing those implementing these strategies to make informed decisions depending on availability of resources and health care setting. We also estimated NNT for a wide range of outcomes with two commonly used risk scores in clinical practice. Limitations include estimates in our analysis based on a number of assumptions. As the median follow-up of HOPE-3 was 5.6 years, we assessed NNT based on treatment over 5.6 years in both the HOPE-3 study and using the ACC/AHA algorithm and Framingham risk score. Although the ACC/AHA algorithm recommend treating individuals with a predicted 10 year risk of any atherosclerotic cardiovascular disease of greater than 7.5%, we used 10 to <20% and $\geq 20\%$ as these are used in other international guidelines. For example, UK's National Institute for Health and Care Excellence guidelines recommend statin therapy for asymptomatic people aged 40 years or older with a 10 year risk for any ASCVD of at least 10%²⁴ and the Canadian Cardiovascular Society risk guidelines recommend statin therapy for asymptomatic people with a 10 year risk for any ASCVD of least 20% based on Framingham risk score.²⁵ HOPE-3 study participants were selected using a simple pragmatic approach based on risk factors. However, other participants may have

been recognised if a risk score based approach was used that have not been identified when using a pragmatic approach. Further work could be considered to study the pragmatic risk factor approach compared to the Framingham risk score and ACC/AHA algorithm on a wider population level. Lastly, although some biomarkers such as hs-CRP or carotid intimal-media thickness could further refine and stratify cardiovascular assessment, these are not included in the risk assessment used for subject selection in the HOPE-3 trial, but are also not considered in the Framingham and the ACC/AHA risk assessment models.

CONCLUSIONS

The simple pragmatic approach, as used in the HOPE-3 study, identifies people at intermediate risk who are likely to benefit from statin therapy. This approach can be used widely in primary prevention in high and low-income countries but appears particularly attractive in low and middle-income countries due to the simplicity of this approach. The pragmatic HOPE-3 trial based approach identifies intermediate risk ethnically diverse patients for primary prevention of CVD using simple phenotypical characteristics and medical history without the need for complex risk assessment tools and using limited laboratory testing. Statins are cheap and cost-effective for most people at moderately high cardiovascular risk.²⁶ A pragmatic approach using the HOPE-3 study criteria could be beneficial to commence people on low cost statins without the need to use formal risk algorithms. These data have global implications on implementation of programmes for primary prevention of CVD.

FOOTNOTES

Acknowledgement

Ethical approval of the HOPE-3 trial was obtained at all participating centres and all participants provided written informed consent. The HOPE-3 trial was funded by the Canadian Health Research Institute and Astra Zeneca and was registered at ClinicalTrials.gov, number NCT00468923.

Contribution Statement

KK, EL and SY designed the study. KK drafted the manuscript. HJ conducted the statistical analyses. All authors provided input into the manuscript and approved the final version.

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Disclosures

Professor Khunti has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme.

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Dr Lonn reports receiving fees for serving on advisory boards from Amgen, Sanofi, Novartis, Novo Nordisk and Servier, lecture fees from Amgen and Sanofi, and grant support through her institution from Bayer, GlaxoSmithKline, Merck/Schering-Plough, and Boehringer Ingelheim.

Dr Held reports receiving fees for serving on advisory boards and giving lectures from AstraZeneca, Bayer and Boehringer Ingelheim, institutional grants from GlaxoSmith Kline, Bristol-Myers Squibb. He serves on a DSMB for Idorsia.

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Table 1. Baseline characteristics of participants in the HOPE-3 trial stratified by 10-year risk estimates defined by (a) and ACC/AHA or (b) Framingham Risk Guideline Score

Variable	Total* N=12,317	10-year ACC/AHA			10-year Framingham Risk Score		
		<10% (Low risk) N=3,964	10-20% (Intermediate risk) N=5,292	≥20% (High risk) N=3,061	<10% (Low risk) N=1,525	10-20% (Intermediate risk) N=4,881	≥20% (High risk) N=5,911
Rosuvastatin Active	6,155 (50.0)	2,002 (50.5)	2,616 (49.4)	1,537 (50.2)	769 (50.4)	2,452 (50.2)	2,934 (49.6)
Rosuvastatin Placebo	6,162 (50.0)	1,962 (49.5)	2,676 (50.6)	1,524 (49.8)	756 (49.6)	2,429 (49.8)	2,977 (50.4)
Age, years	65.2 (5.7)	62.4 (4.0)	64.8 (5.3)	69.6 (5.7)	64.8 (4.4)	64.7 (5.7)	65.8 (6.0)
Females, n (%)	5,647 (45.8)	2,816 (71.0)	2,136 (40.4)	695 (22.7)	1,415 (92.8)	3,012 (61.7)	1,220 (20.6)
Systolic BP, mmHg	138.0 (14.7)	131.9 (13.6)	138.3 (13.7)	145.2 (14.6)	124.9 (12.0)	136.0 (12.5)	143.0 (14.7)
Diastolic BP, mmHg	82.0 (9.3)	80.5 (8.9)	82.4 (9.2)	83.2 (9.7)	76.7 (8.5)	81.3 (8.8)	83.9 (9.3)
BMI, kg/m ²	26.7 [24.1-29.7]	27.0 [24.3-29.9]	26.7 [24.1-29.7]	26.4 [23.9-29.4]	27.0 [24.2-30.0]	26.8 [24.1-30.0]	26.6 [24.1-29.4]
WHR	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)
Total cholesterol, mg/dl	201.7 (42.1)	200.3 (43.3)	202.2 (40.8)	202.4 (42.7)	185.8 (40.2)	201.6 (41.2)	205.4 (42.4)
LDL cholesterol, mg/dl	128.2 (36.0)	126.1 (37.1)	128.9 (35.1)	129.5 (36.2)	111.4 (33.8)	127.3 (35.1)	132.8 (36.1)
HDL cholesterol, mg/dl	43.6 (36.1-51.7)	45.9 [38.6-54.4]	43.2 [35.9-51.4]	40.9 [34.0-49.0]	49.0 [41.4-59.1]	45.9 [38.6-54.4]	40.5 [34.0-47.9]
Triglycerides, mg/dl	127.5 [92.9-177.0]	121.2 [89.4-167.3]	128.3 [92.9-179.6]	135.4 [96.5-189.4]	108.8 [82.2-147.8]	121.2 [89.4-168.1]	138.9 [100.0-193.8]
Ethnicity, n (%)							
Asian	6126 (49.7)	2,099 (53.0)	2,500 (47.2)	1,527 (49.9)	721 (47.3)	2,331 (47.8)	3074 (52.0)
Hispanic	3,305 (26.8)	1,005 (25.4)	1,429 (27.0)	871 (28.5)	474 (31.1)	1,323 (27.1)	1,508 (25.5)
White	2,484 (20.2)	750 (18.9)	1,175 (22.2)	559 (18.3)	258 (16.9)	1,061 (21.7)	1,165 (19.7)
Other	402 (3.3)	110 (2.8)	188 (3.6)	104 (3.4)	72 (4.7)	166 (3.4)	164 (2.8)

* Total HOPE-3 participants whose ASCVD risk score and Framingham risk score were derived

Shown are mean (SD) or median [interquartile range] unless stated otherwise.

To convert cholesterol (Total, LDL and HDL) to mmol/l, multiply by 0.02586; to convert Triglycerides to mmol/l, multiply by 0.01129.

HOPE-3=The Heart Outcomes Prevention Evaluation-3 trial; ACC/AHA=The 2013 American College of Cardiology/American Heart Association; BP=blood pressure; BMI=body mass index; WHR=waist-to-hip ratio; BMI = body mass index; HDL=high-density lipoprotein cholesterol; LDL=low-density lipoprotein cholesterol; Asian category=South Asian, Other Asian and Chinese.

Table 2. Number of participants, event rates, incidence rates, and NNT in HOPE-3 trial by outcome and ACC/AHA or Framingham Risk Scores

Outcome	Total	10-year ACC/AHA			10-year Framingham Risk Score		
		<10% (Low risk)	10-20% (Intermediate risk)	≥20% (High risk)	<10% (Low risk)	10-20% (Intermediate risk)	≥20% (High risk)
10-year mean (SD) Risk Score	NA	7.0 (1.9)	14.4 (2.8)	25.8 (3.6)	7.9 (1.5)	14.9 (2.8)	27.1 (3.5)
Co-primary outcome 1							
Rosuvastatin Active N	6,155	2,002	2,616	1,537	769	2,452	2,934
No. of events (%)	207 (3.4)	37 (1.9)	75 (2.9)	95 (6.2)	15 (2.0)	63 (2.6)	129 (4.4)
IR		0.33	0.51	1.11	0.36	0.46	0.79
Rosuvastatin Placebo N	6,162	1,962	2,676	1,524	756	2,429	2,977
No. of events (%)	279 (4.5)	44 (2.2)	106 (4.0)	129 (8.5)	21 (2.8)	85 (3.5)	173 (5.8)
IR		0.41	0.71	1.55	0.51	0.63	1.05
Hazard Ratio (95% CI)	0.74 (0.61, 0.88)	0.82 (0.53, 1.28)	0.72 (0.53, 0.96)	0.72 (0.55, 0.93)	0.69 (0.36, 1.35)	0.73 (0.52, 1.01)	0.75 (0.60, 0.94)
NNT	92	547	75	54	76	165	70
Absolute risk reduction (%)	1.09	0.18	1.33	1.85	1.32	0.61	1.43
Co-primary outcome 2							
Rosuvastatin Active N	6,155	2,002	2,616	1,537	769	2,452	2,934
No. of events (%)	249 (4.0)	43 (2.1)	92 (3.5)	114 (7.4)	18 (2.3)	72 (2.9)	159 (5.4)
IR		0.39	0.63	1.35	0.43	0.52	0.98
Rosuvastatin Placebo N	6,162	1,962	2,676	1,524	756	2,429	2,977
No. of events (%)	333 (5.4)	55 (2.8)	128 (4.8)	150 (9.8)	23 (3.0)	101 (4.2)	209 (7.0)
IR		0.51	0.86	1.82	0.56	0.75	1.28
Hazard Ratio (95% CI)	0.74 (0.63, 0.87)	0.77 (0.51, 1.14)	0.73 (0.56, 0.95)	0.74 (0.58, 0.94)	0.76 (0.41, 1.41)	0.70 (0.52, 0.95)	0.76 (0.62, 0.94)
NNT	82	278	67	54	93	121	64
Absolute risk reduction (%)	1.22	0.36	1.49	1.85	1.08	0.83	1.56

HOPE-3=The Heart Outcomes Prevention Evaluation-3 trial; ACC/AHA=The 2013 American College of Cardiology/American Heart Association; SD=standard deviation; CI=confidence interval; NNT=number needed to treat for 5.6 years (median follow-up for HOPE-3) using the Kaplan Meier approach: calculated by inverting the absolute risk reduction, i.e. difference in the cumulative incidence between two groups; IR=Incidence rates per 100 person-years.

Co-primary outcome 1=the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Co-primary outcome 2=the second co-primary outcomes additionally include heart failure, cardiac arrest, or re-vascularization.

Table 3a. Event rates, hazard ratios (HR) for co-primary outcomes one and two by age, sex, and ethnicities for ACC/AHA

Outcome	10-year ACC/AHA											
	<10% (Low risk)				10-20% (Intermediate risk)				≥20% (High risk)			
	IR Rosuvastatin	IR Placebo	HR (95% CI)	P*	IR Rosuvastatin	IR Placebo	HR (95% CI)	P*	IR Rosuvastatin	IR Placebo	HR (95% CI)	P*
Co-primary outcome 1												
Sex												
Male	0.30	0.37	0.81 (0.35, 1.87)		0.43	0.68	0.63 (0.42, 0.95)		1.18	1.64	0.71 (0.53, 0.96)	
Female	0.35	0.42	0.83 (0.50, 1.39)	0.57	0.62	0.75	0.83 (0.54, 1.28)	0.38	0.91	1.26	0.71 (0.38, 1.30)	0.27
Ethnicity												
White	0.14	0.39	0.36 (0.10, 1.37)		0.30	0.69	0.43 (0.21, 0.90)		1.00	1.44	0.69 (0.37, 1.30)	
Hispanic	0.31	0.32	1.00 (0.40, 2.52)		0.55	0.83	0.67 (0.40, 1.13)		1.08	1.27	0.85 (0.51, 1.42)	
Asian	0.39	0.47	0.83 (0.47, 1.46)	0.22	0.53	0.60	0.87 (0.56, 1.37)	0.99	1.16	1.66	0.70 (0.48, 1.02)	0.81
Co-primary outcome 2												
Sex												
Male	0.36	0.60	0.61 (0.30, 1.26)		0.56	0.86	0.65 (0.45, 0.93)		1.45	1.94	0.74 (0.57, 0.97)	
Female	0.40	0.47	0.85 (0.53, 1.37)	0.41	0.73	0.86	0.85 (0.57, 1.28)	0.33	1.01	1.42	0.70 (0.39, 1.25)	0.47
Ethnicity												
White	0.28	0.53	0.52 (0.19, 1.42)		0.45	0.80	0.56 (0.30, 1.04)		1.25	1.92	0.64 (0.36, 1.11)	
Hispanic	0.38	0.49	0.78 (0.35, 1.72)		0.70	1.08	0.65 (0.41, 1.04)		1.42	1.48	0.96 (0.06, 1.52)	
Asian	0.40	0.50	0.80 (0.46, 1.39)	0.23	0.62	0.72	0.86 (0.56, 1.30)	0.88	1.31	1.90	0.69 (0.49, 0.99)	0.46

ASCVD=The 2013 American College of Cardiology/American Heart Association; SD=standard deviation; CI=confidence interval; IR=Incidence rates per 100 person-years; Co-primary outcome 1=the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Co-primary outcome 2=the second co-primary outcomes additionally include heart failure, cardiac arrest, or re-vascularization. P*=P for interaction

Table 3b. Event rates, hazard ratios (HR) for co-primary outcomes one and two by age, sex, and ethnicities for Framingham Risk Scores

Outcome	10-year Framingham Risk Score											
	<10% (Low risk)				10-20% (Intermediate risk)				≥20% (High risk)			
	IR Rosuvastatin	IR Placebo	HR (95% CI)	p*	IR Rosuvastatin	IR Placebo	HR (95% CI)	p*	IR Rosuvastatin	IR Placebo	HR (95% CI)	p*
Co-primary outcome 1												
Sex												
Male	0.33	0.66	0.51 (0.05, 5.68)	0.21	0.33	0.52	0.64 (0.35, 1.17)	0.62	0.82	1.14	0.72 (0.56, 0.92)	0.35
Female	0.36	0.49	0.71 (0.36, 1.42)		0.54	0.70	0.77 (0.52, 1.13)		0.67	0.71	0.96 (0.54, 1.70)	
Ethnicity												
White	0.29	0.54	0.55 (0.10, 3.03)	0.27	0.22	0.55	0.40 (0.16, 0.97)	0.38	0.63	0.99	0.63 (0.36, 1.08)	0.66
Hispanic	0.38	0.44	0.81 (0.25, 2.65)		0.47	0.55	0.84 (0.45, 1.57)		0.82	1.11	0.73 (0.48, 1.13)	
Asian	0.30	0.54	0.55 (0.20, 1.52)		0.54	0.72	0.76 (0.48, 1.18)		0.79	0.95	0.83 (0.60, 1.16)	
Co-primary outcome 2												
Sex												
Male	0.33	0.66	0.51 (0.05, 5.68)	0.34	0.41	0.71	0.57 (0.34, 0.97)	0.35	1.03	1.39	0.74 (0.59, 0.92)	0.68
Female	0.44	0.55	0.78 (0.41, 1.48)		0.60	0.77	0.77 (0.53, 1.12)		0.79	0.87	0.92 (0.55, 1.56)	
Ethnicity												
White	0.44	0.55	0.80 (0.18, 3.63)	0.19	0.38	0.72	0.52 (0.26, 1.06)	0.46	0.81	1.27	0.63 (0.39, 1.02)	0.64
Hispanic	0.45	0.44	0.98 (0.32, 3.03)		0.55	0.71	0.76 (0.43, 1.35)		1.10	1.45	0.76 (0.52, 1.11)	
Asian	0.35	0.60	0.59 (0.23, 1.51)		0.56	0.80	0.70 (0.45, 1.08)		0.93	1.11	0.84 (0.62, 1.14)	

ACC/AHA=The 2013 American College of Cardiology/American Heart Association; SD=standard deviation; CI=confidence interval; IR1=Incidence rates per 100 person-years in the Rosuvastatin Arm. IR2=Incidence rates per 100 person-years in the Rosuvastatin Placebo Arm. Co-primary outcome 1=the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Co-primary outcome 2=the second co-primary outcomes additionally include heart failure, cardiac arrest, or re-vascularization. P*=P for interaction