Canadian Journal of Cardiology 35 (2019) 644–652

Clinical Research

Statin Use in Primary Prevention: A Simple Trial-Based Approach Compared With Guideline-Recommended Risk Algorithms for Selection of Eligible Patients

Kamlesh Khunti, MD, PhD,[a] Hyejung Jung, MSc,[b] Antonio L. Dans, MD,[c] Claes Held, MD, PhD,[d] Gilles R. Dagenais, MD,[e] Salim Yusuf, MB, BS, DPhil,[b,f] and Eva Lonn, MD[b,f]

[a] *Leicester Diabetes Centre, Leicester General Hospital, Leicester, United Kingdom*

[b] *Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada*

[c] *College of Medicine, University of the Philippines, Manila, Philippines*

[d] *Department of Medical Sciences, Cardiology, Uppsala Clinical Research Centre, Uppsala, Sweden*

[e] *Institut Universitaire de Cardiologie et Pneumologie de Québec, Université Laval, Québec, Quebec City, Canada*

[f] *Department of Medicine and Population Health Research Institute, Hamilton Health Sciences General Site, McMaster University, Hamilton, Ontario, Canada*

See editorial by Fitchett, pages 550–551 of this issue.

ABSTRACT

Background: Cardiovascular disease risk assessment tools help identify individuals likely to benefit from preventative therapies. In this study we compared outcomes using the American College of Cardiology/American Heart Association (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 10 mg rosuvastatin or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; second coprimary 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 for the first coprimary outcome according to risk categories of $\leq$ 10%, 10%-20%, and $\geq$ 20% using the ACC/AHA algorithm were 0.82 (95% confidence interval [CI],

RÉSUMÉ

Introduction : Les outils d'évaluation du risque de maladie cardiovasculaire permettent de repérer les patients qui pourraient bénéficier d'un traitement préventif. Nous avons donc comparé les résultats obtenus au moyen de l'algorithme d'évaluation du risque de l'American College of Cardiology/American Heart Association (ACC/AHA) et au moyen de l'outil d'évaluation du score de risque de Framingham (SRF) dans le cadre de l'étude HOPE-3 (***H**eart **O**utcomes **P**revention **E**valuation*).

Méthodes : Nous avons utilisé l'algorithme de l'ACC/AHA et le SRF pour évaluer les résultats obtenus au cours de l'étude HOPE-3, dans laquelle les participants ont été répartis aléatoirement pour recevoir de la rosuvastatine à 10 mg ou un placebo. Le premier coparamètre principal regroupait le décès d'origine cardiovasculaire, l'infarctus du myocarde non mortel et l'accident vasculaire cérébral non mortel; le deuxième coparamètre principal regroupait l'insuffisance cardiaque, l'arrêt cardiaque et la nécessité d'une revascularisation.

More than 80% of deaths from cardiovascular disease (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 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 effect 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,

Received for publication November 30, 2018. Accepted March 12, 2019.

Corresponding author: Dr Kamlesh Khunti, Leicester Diabetes Centre, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, United Kingdom. Tel.: +441162584005.

E-mail: kk22@leicester.ac.uk

See page 651 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.03.002

0.53-1.28), 0.72 (95% CI, 0.53-0.96), and 0.72 (95% CI, 0.55-0.93), and absolute risk reduction (ARR) of 0.18%, 1.33%, and 1.85%, respectively, over a median of 5.6 years. Corresponding results using the FRS were 0.69 (95% CI, 0.36-1.35), 0.73 (95% CI, 0.52-1.01), and 0.75 (95% CI, 0.60- 0.94); and ARR of 1.32%, 0.61%, and 1.43%. Hazard ratios for the second coprimary outcome were 0.77 (95% CI, 0.51-1.14), 0.73 (95% CI, 0.56-0.95), and 0.74 (95% CI, 0.58-0.94); and ARR of 0.36%, 1.49%, and 1.85%, using the ACC/AHA algorithm and 0.76 (95% CI, 0.41-1.41), 0.70 (95% CI, 0.52-0.95), and 0.76 (95% CI, 0.62-0.94); and ARR of 1.08%, 0.83%, and 1.56% using the FRS.

Conclusions: 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.

Résultats : Les risques relatifs établis selon les scores de risque étaient comparables à ceux observés dans le cadre de l'étude HOPE-3. Les rapports des risques instantanés relatifs au premier coparamètre principal correspondant aux catégories de risque $\leq$ 10 %, de 10 % à 20 % et $\geq$ 20 % définies selon l'algorithme de l'ACC/AHA s'établissaient respectivement à 0,82 (intervalle de confiance [IC] à 95 %, de 0,53 à 1,28), à 0,72 (IC à 95 %, de 0,53 à 0,96) et à 0,72 (IC à 95 %, de 0,55 à 0,93), et la réduction du risque absolu (RRA) à 0,18 %, à 1,33 % et à 1,85 % sur une période médiane de 5,6 ans. Les résultats correspondants obtenus au moyen du SRF étaient de 0,69 (IC à 95 %, de 0,36 à 1,35), de 0,73 (IC à 95 %, de 0,52 à 1,01) et de 0,75 (IC à 95 %, de 0,60 à 0,94), avec une RRA de 1,32 %, de 0,61 % et de 1,43 %. Les rapports des risques instantanés pour le deuxième coparamètre principal s'établissaient à 0,77 (IC à 95 %, de 0,51 à 1,14), à 0,73 (IC à 95 %, de 0,56 à 0,95) et à 0,74 (IC à 95 %, de 0,58 à 0,94), avec une RRA de 0,36 %, de 1,49 % et de 1,85 % selon l'algorithme de l'ACC/AHA, et à 0,76 (IC à 95 %, de 0,41 à 1,41), à 0,70 (IC à 95 %, de 0,52 à 0,95) et à 0,76 (IC à 95 %, de 0,62 à 0,94), avec une RRA de 1,08 %, de 0,83 % et de 1,56 % selon le SRF.

Conclusions : À l'aide de caractéristiques cliniques simples et sans recourir aux outils d'évaluation du risque complexes actuels, l'approche pragmatique mise en œuvre dans le cadre de l'étude HOPE-3 permet de repérer dans une population de patients de différentes origines ethniques en prévention primaire ceux qui présentent un risque intermédiaire et qui pourraient bénéficier d'un traitement par une statine.

especially those living in low- and middle-income countries. Previous studies have shown that risk prediction models are less accurate in nonwhite 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 according to the risk of the population, especially from trials involving participants from high- and low-income countries. There is also an increase in the 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 algorithms, 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 CVD (ASCVD) equations for risk assessment and focus on absolute cardiovascular risk and estimate the 10-year risk of major ASCVD.[7] Most guidelines recommend using risk assessment tools and categorizing at low risk ($<$ 10% ten-year cardiovascular risk), intermediate risk (10% to $<$ 20%), and high risk ($\geq$ 20%). However, these estimations are somewhat arbitrary and have been chosen largely according to 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 because 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 2 commonly recommended guideline-based risk scores, the ACC/AHA algorithm and the Framingham Risk Score,[10] with the outcomes in the **H**eart **O**utcomes **P**revention **E**valuation (HOPE) 3 study, which recruited an ethnically diverse population randomized to statin therapy using a more simple pragmatic risk factor-based approach.

Methods

Study design

This was a post hoc analysis on the basis of 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 2 $\times$ 2 factorial design to evaluate the effects of blood pressure-lowering, lipid-lowering, and their combination compared with 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 1 additional risk factor and women aged ≥ 60 with 2 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/1.73 m^2 in the absence of proteinuria, or blood pressure 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, an angiotensin-converting enzyme inhibitor, a thiazide diuretic, or a statin.

Procedures

Eligible participants completed a single-blind, 4-week run-in period of active drug (1 tablet each of candesartan/hydrochlorothiazide 16/12.5 mg and rosuvastatin 10 mg) to assess tolerance and adherence. Those who tolerated and adhered to the medication were randomized to receive daily, 1 tablet each of rosuvastatin 10 mg or placebo and fixed combination of candesartan/hydrochlorothiazide 16/12.5 mg or placebo. Participants were randomized using a blinded, central randomization system. Participants were seen at 6 weeks, 6 months, and then every 6 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], 0.64-0.91) and by 25% (hazard ratio, 0.75; 95% CI, 0.64-0.88), respectively.[11]

Statistical analysis

Continuous variables are expressed as mean ± 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 cholesterol. We defined patient groups according to 10-year projected modelled risks: < 10%, 10% to < 20%, and ≥ 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 a 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 the HOPE-3 trial on the basis of Kaplan-Meier estimates with their 95% CIs. We conducted subgroup analysis according to sex and major ethnic groups recruited in the HOPE-3 study (Asian, Hispanic, and white).

Results

Of the 12,705 participants randomized, 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 female. Their mean blood pressure was 138/82 mm Hg, body mass index 26.7, total cholesterol 201.7 mg/dL (5.2 mmol/L), low-density lipoprotein 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 on the basis of the ACC/AHA algorithm and the Framingham Risk Score of < 10%, 10% to < 20%, and ≥ 20% are presented in Table 1. Overall, using the ACC/AHA algorithm participants in the < 10% risk score group were younger (mean age, 62.4 years) compared with 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 according to different ethnicities in the different risk categories using either of the risk scores.

The mean risk scores using the ACC/AHA algorithm and Framingham Risk Scores were 14.9% (SD, 7.6) and 19.9% (SD, 7.9), respectively. At a threshold of ≥ 10% of the ACC/AHA algorithm and Framingham Risk Scores, 8353 (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 with the ACC/AHA algorithm. At a threshold of > 7.5% risk using the ACC/AHA algorithm, 10,117 (82.1%) participants would have been eligible for lipid-lowering therapy.

At a threshold of ≥ 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.

According to ethnicity, 4027 (65.7%) of Asian, 2300 (69.6%) Hispanic, and 1734 (69.8%) white patients would have been eligible for lipid-lowering therapy using the ACC/AHA algorithm at a threshold of ≥ 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 according to 10-year risk categories for the 2 co-primary outcomes in the HOPE-3 trial using the ACC/AHA algorithm and Framingham Risk Score. The relative risk reductions for co-primary outcomes 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

Table 1. Baseline characteristics of participants in the HOPE-3 trial stratified according to 10-year risk estimates defined by ACC/AHA or Framingham Risk Score

		10-Year ACC/AHA			10-Year Framingham Risk Score		
Variable	Total N = 12,317*	< 10% (low risk) n = 3964	10%-20% (intermediate risk) n = 5292	≥ 20% (high risk) n = 3061	< 10% (low risk) n = 1525	10%-20% (intermediate risk) n = 4881	≥ 20% (high risk) n = 5911
Rosuvastatin active	6155 (50.0)	2002 (50.5)	2616 (49.4)	1537 (50.2)	769 (50.4)	2452 (50.2)	2934 (49.6)
Rosuvastatin placebo	6162 (50.0)	1962 (49.5)	2676 (50.6)	1524 (49.8)	756 (49.6)	2429 (49.8)	2977 (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)
Female sex, n (%)	5647 (45.8)	2816 (71.0)	2136 (40.4)	695 (22.7)	1415 (92.8)	3012 (61.7)	1220 (20.6)
Systolic BP, mm Hg	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, mm Hg	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	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, 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, 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)

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.

ACC/AHA, 2013 American College of Cardiology/American Heart Association; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein cholesterol; HOPE-3, **H**eart **O**utcomes **P**revention **E**valuation-3 trial; LDL, low-density lipoprotein cholesterol; WHR, waist-to-hip ratio.

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

†Asian category includes South Asian, other Asian, and Chinese.

Table 2. Number of participants, event rates, incidence rates, and NNT* in the HOPE-3 trial according to outcome and ACC/AHA or Framingham Risk Score

		10-Year ACC/AHA			10-Year Framingham Risk Score		
Outcome	Total	< 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	6155	2002	2616	1537	769	2452	2934
Events, n (%)	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	6162	1962	2676	1524	756	2429	2977
Events, n (%)	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
HR (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	6155	2002	2616	1537	769	2452	2934
Events, n (%)	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	6162	1962	2676	1524	756	2429	2977
Events, n (%)	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
HR (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

ACC/AHA, 2013 American College of Cardiology/American Heart Association; CI, confidence interval; HOPE-3, **H**eart **O**utcomes **P**revention **E**valuation-3 trial; HR, hazard ratio; IR, incidence rates per 100 person-years; NNT, number needed to treat.

*NNT for 5.6 years (median follow-up for HOPE-3) using the Kaplan-Meier approach: calculated by inverting the absolute risk reduction (ie, difference in the cumulative incidence between 2 groups).

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

‡Co-primary outcome 2 is the second co-primary outcomes, which additionally include heart failure, cardiac arrest, or revascularization.

overall, according to risk categories of < 10%, 10% to < 20%, and ≥ 20% were: 0.82 (95% CI, 0.53-1.28), 0.72 (95% CI, 0.53-0.96), and 0.72 (95% CI, 0.55-0.93), respectively. Corresponding results using the Framingham Risk Score were 0.69 (95% CI, 0.36-1.35), 0.73 (95% CI, 0.52-1.01), and 0.75 (95% CI, 0.60-0.94), respectively. The overall NNT (ARR) for co-primary outcomes 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% to < 20%, and ≥ 20%, the NNT for co-primary outcome 1 for the ACC/AHA algorithm and Framingham Risk Scores was 547 (ARR, 0.18%), 75 (ARR, 1.33%), 54 (ARR, 1.85%), and 76 (ARR, 1.32%), 165 (ARR, 0.61%), and 70 (ARR, 1.43%), respectively. Similarly, the hazard ratios for co-primary outcome 2 for the same 3 categories using the ACC/AHA algorithm were 0.77 (95% CI, 0.51-1.14), 0.73 (95% CI, 0.56-0.95), and 0.74 (95% CI, 0.58-0.94), and for Framingham Risk Score 0.76 (95% CI, 0.41-1.41), 0.70 (95% CI, 0.52-0.95), and 0.76 (95% CI, 0.62-0.94), respectively. The corresponding NNT for co-primary outcome 2 was 278 (ARR, 0.36%), 67 (ARR, 1.49%), and 54 (ARR, 1.85%), and 93 (ARR, 1.08%), 121 (ARR, 0.83%), and 64 (ARR, 1.56%) using the ACC/AHA algorithm and Framingham Risk Scores, respectively.

Tables 3 and 4 show the incidence rates and hazards ratios for the 2 co-primary outcomes according to sex and ethnicity. Overall, the incidence rates and hazard rates were consistent across sex and ethnicities.

Discussion

ASCVD 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 safe[13] 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 on the basis of age and the presence of at least 1 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 might benefit from multifactorial intervention of statins instead of using accepted CVD risk algorithms. This study also showed that there were beneficial effects for statin therapy across a heterogeneous group of participants and irrespective of

Table 3. Event rates and HRs for co-primary outcomes 1 and 2 according to age, sex, and ethnicities for ACC/AHA

	10-Year ACC/AHA											
	< 10% (Low risk)				10%-20% (Intermediate risk)				≥ 20% (High risk)			
Outcome	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 (90.42- 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

Co-primary outcome 1 is the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Co-primary outcome 2 is the second co-primary outcomes, which additionally include heart failure, cardiac arrest, or revascularization.

ACC/AHA, 2013 American College of Cardiology/American Heart Association; CI, confidence interval; HR, hazard ratio; IR, incidence rates per 100 person-years;

* *P* for interaction.

Table 4. Event rates, HRs for co-primary outcomes 1 and 2 according to age, sex, and ethnicities for Framingham Risk Scores

	10-Year Framingham Risk Score											
	< 10% (Low risk)				10%-20% (Intermediate risk)				≥ 20% (High risk)			
Outcome	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)		0.33	0.52	0.64 (0.35-1.17)		0.82	1.14	0.72 (0.56-0.92)	
Female	0.36	0.49	0.71 (0.36-1.42)	0.21	0.54	0.70	0.77 (0.52-1.13)	0.62	0.67	0.71	0.96 (0.54-1.70)	0.35
Ethnicity												
White	0.29	0.54	0.55 (0.10-3.03)		0.22	0.55	0.40 (0.16-0.97)		0.63	0.99	0.63 (0.36-1.08)	
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)	0.27	0.54	0.72	0.76 (0.48-1.18)	0.38	0.79	0.95	0.83 (0.60-1.16)	0.66
Co-primary outcome 2												
Sex												
Male	0.33	0.66	0.51 (0.05-5.68)		0.41	0.71	0.57 (0.34-0.97)		1.03	1.39	0.74 (0.59-0.92)	
Female	0.44	0.55	0.78 (0.41-1.48)	0.34	0.60	0.77	0.77 (0.53-1.12)	0.35	0.79	0.87	0.92 (0.55-1.56)	0.68
Ethnicity												
White	0.44	0.55	0.80 (0.18-3.63)		0.38	0.72	0.52 (0.26-1.06)		0.81	1.27	0.63 (0.39-1.02)	
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)	0.19	0.56	0.80	0.70 (0.45-1.08)	0.46	0.93	1.11	0.84 (0.62-1.14)	0.64

Co-primary outcome 1 is the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Co-primary outcome 2 is the second co-primary outcomes, which additionally include heart failure, cardiac arrest, or revascularization.

CI, confidence interval; HR, hazard ratio; IR, incidence rate.

* *P* for interaction.

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 with 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 ≥ 7.5% risk, > 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 and this has been observed 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 who 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 low-density lipoprotein cholesterol thresholds or targets for statin therapy in certain patients would therefore be potentially useful in settings in which assessment of a blood test would be a barrier to treatment decisions.[10] As expected, the ARRs were greater with increasing baseline risk using both risk scores but the relative risk reductions were similar according to baseline risk and similar to those observed in the main HOPE-3 trial for both co-primary outcomes. This therefore translated to a 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 according to chemical parameters for cardiovascular stratification that might 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 on the basis of people from European descent in high-income countries and therefore might 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 randomized controlled trials did not recruit participants on the basis of 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 a robust real-world evidence base especially in terms of efficacy and equity effect.[21]

There have been a number of studies that compared risk-based approaches with trial-based approaches using population level data but mainly using observational data. One recent study compared the ACC/AHA risk-based approach compared with a 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 United States and European guidelines, for estimating global risk for CVD but more than three-quarters would be recommended a statin on the basis of 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 might not be representative of the global population, because they do not take into account different ethnic groups other than non-Hispanic, white, and African American subjects.[22] The HOPE-3 study included a global population with South and East Asian, Hispanic, 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.[22] Although this could be partially related to volunteer bias, this is consistent with other reports[22] and is likely related to the large effect 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 2 commonly used risk scores in clinical practice. Limitations include estimates in our analysis which were made on the basis of a number of assumptions. Because the median follow-up of HOPE-3 was 5.6 years, we assessed NNT on the basis of treatment over 5.6 years in 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 ASCVD of $> 7.5\%$, we used 10% to $< 20\%$ and $\geq 20\%$ because these are used in other international guidelines. For example, the United Kingdom'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% on the basis of the Framingham Risk Score.[25] HOPE-3 study participants were selected using a simple pragmatic approach on the basis of risk factors. However, other participants might have been recognized if a risk score-based approach was used that had not been identified when using a pragmatic approach. Further work could be considered to study the pragmatic risk factor approach compared with the Framingham Risk Score and ACC/AHA algorithm on a wider population level. Last, although some biomarkers such as high-sensitivity C-reactive protein 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.

In conclusion, 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 because of 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 inexpensive 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 begin low-cost statin treatment for patients without the need to use formal risk algorithms. These data have global implications on implementation of programs for primary prevention of CVD.

Acknowledgements

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: NCT00468923.

Funding Sources

The study was funded by the Canadian Institute of Health Research and an unrestricted grant from AstraZeneca.

The research was supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care East Midlands and the NIHR Leicester, Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health and Social Care.

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. Dr Yusuf reports receiving honoraria and travel support from Bayer, and grant support from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Bristol-Myers Squibb, and Cadila Pharmaceuticals. 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 GlaxoSmithKline, and Bristol-Myers Squibb. He serves on a Data Safety Monitoring Board for Idorsia. The other authors have no conflicts of interest to disclose.

References

1. Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med 2014;371:818-27.
2. Lim SS, Gaziano TA, Gakidou E, et al. Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs. Lancet 2007;370:2054-62.
3. Jackson R, Lawes CMM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet 2005;365:434-41.
4. Ridker PM, Wilson PW. A trial-based approach to statin guidelines. JAMA 2013;310:1123-4.
5. Nutbeam D. Health literacy as a public health goal: a challenge for contemporary health education and communication strategies into the 21st century. Health Promot Int 2000;15:259-67.
6. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-53.
7. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Circulation 2014;129:S1-45.
8. Anderson TJ, Gregoire J, Hegele RA, et al. 2012 Update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2013;29:151-67.
9. Kmietoqicz Z. New analysis fuels debate on merits of prescribing statins to low risk people. BMJ 2014;348:g2370.
10. Bonner C, Fajardo MA, Hui S, Stubbs R, Trevena L. Clinical validity, understandability, and actionability of online cardiovascular disease risk calculators: systematic review. J Med Internet Res 2018;20:e29.
11. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2021-31.
12. Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2009-20.
13. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388:2532-61.
14. Gupta A, Thompson D, Whitehouse A, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet 2017;389:2473-81.
15. Heller DJ, Coxson PG, Penko J, et al. Evaluating the impact and cost-effectiveness of statin use guidelines for primary prevention of coronary heart disease and stroke. Circulation 2017;136:1087-98.
16. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581-90.
17. Kavousi M, Leening MJ, Nanchen D, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. JAMA 2014;311:1416-23.
18. Modesti PA, Agostoni P, Agyemang C, et al. Cardiovascular risk assessment in low-resource settings: a consensus document of the European Society of Hypertension Working Group on Hypertension and Cardiovascular Risk in Low Resource Settings. J Hypertens 2014;32:951-60.
19. Finnikin S, Ryan R, Marshall T. Statin initiations and QRISK2 scoring in UK general practice: a THIN database study. Br J Gen Pract 2017;67:e881-7.
20. van Staa TP, Smeeth L, Ng ES, Goldacre B, Gulliford M. The efficiency of cardiovascular risk assessment: do the right patients get statin treatment? Heart 2013;99:1597-602.
21. Lee JT, Lawson KD, Wan Y, et al. Are cardiovascular disease risk assessment and management programmes cost effective? A systematic review of the evidence. Prev Med 2017;99:49-57.
22. Mortensen MB, Afzal S, Nordestgaard BG, Falk E. Primary prevention with statins: ACC/AHA risk-based approach versus trial-based approaches to guide statin therapy. J Am Coll Cardiol 2015;66:2699-709.
23. Pavlovic J, Greenland P, Deckers JW, et al. Comparison of ACC/AHA and ESC guideline recommendations following trial evidence for statin use in primary prevention of cardiovascular disease: results from the population-based Rotterdam Study. JAMA Cardiol 2016;1:708-13.
24. Rabar S, Harker M, O'Flynn N, Wierzbicki AS. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ 2014;349:g4356.
25. Anderson TJ, Gregoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2016;32:1263-82.
26. Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation 2011;124:146-53.