Supplementary Online Content

Mortensen MB, Nordestgaard BG. Statin use in primary prevention of atherosclerotic cardiovascular disease according to 5 major guidelines for sensitivity, specificity, and number needed to treat. *JAMA Cardiol*. Published online October 2, 2019. doi:10.1001/jamacardio.2019.3665

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplementary Methods

Recommendations for statin therapy by the 5 guidelines

The UK NICE guideline recommends statin therapy to asymptomatic individuals aged 40 years and older with a 10-year risk for any ASCVD of ≥10% estimated using the QRISK2[1] prediction model or to individuals with non-dialysis dependent chronic kidney disease (CKD) (Should be offered)[2]. The USPSTF statement (referred to as guideline in our paper) recommend statin therapy to asymptomatic individuals aged 40-75 who have 1 or more ASCVD risk factors and a 10-year risk of any ASCVD ≥10% estimated using PCE (Grade B recommendation, offer or provide this service)[3]. The CCS guideline recommends statin therapy to asymptomatic individuals aged 40-75 with a 10-year risk of any ASCVD ≥20% estimated with the Framingham Risk Score (FRS)[4] or with a 10-year risk of any ASCVD ≥10% and <20% combined with a low-density lipoprotein cholesterol (LDL-C) ≥193 mg/dL (5.0 mmol/L) (Strong recommendations, High-Quality Evidence). Further, the CCS guideline recommend statins to individuals with diabetes or with CKD (age≥50 years)[5]. The ESC/EAS guideline recommends risk-based statin therapy to asymptomatic individuals aged 40-65 (age-range of the Systematic Coronary Risk Evaluation (SCORE)) with an LDL-C ≥97 mg/dL (2.5 mmol/L) combined with a 10-year risk for fatal ASCVD of ≥10% estimated using the SCORE prediction model or to individuals with an LDL-C ≥155 mg/dL (4.0 mmol/L) combined with a 10-year risk of fatal ASCVD of ≥5% and <10% (Class I recommendations)[6]; for individuals aged ≤65 as well as >65, there are class I recommendations for statin therapy to asymptomatic individuals with familial hypercholesterolemia (LDL-C ≥232 mg/dL (6.0 mmol/L) or total cholesterol ≥309 mg/dL (8.0 mmol/L)), non-dialysis dependent CKD or with diabetes. The ACC/AHA guideline recommend statin therapy to asymptomatic individuals aged 40-75 with LDL-C ≥190 mg/dL (4.9 mmol/L), diabetes or an estimated 10-year risk for any ASCVD of ≥7.5% estimated using the Pooled Cohort Equations (PCE)[7,8] prediction model (Class I recommendations)[9].

As the USPSTF, ESC/EAS and ACC/AHA guidelines also provide weaker class IIa (ESC/EAS), C (USPSTF) or IIb (ACC/AHA) recommendations for statin therapy, we assessed the performance of these criteria in sensitivity analyses. The USPSTF C recommendation lowers the 10-year PCE threshold from 10% to 7.5%. The ESC/EAS Class IIa recommendation lowers the LDL-C based threshold to ≥70 mg/dL (1.8 mmol/L) for individuals with a 10-year SCORE risk ≥10% and to ≥97 mg/dL (2.5 mmol/L) for individuals with a 10-year SCORE risk ≥5% and <10% [6]. Finally, the ACC/AHA Class IIb recommendation lowers the 10-year PCE threshold from 7.5% to 5%

("borderline risk"). In contrast to the 2013 ACC/AHA guidelines[10], the 2018 ACC/AHA guidelines state that statin therapy should only be initiated if risk-enhancing factors are present (such as family history of premature ASCVD, metabolic syndrome and chronic kidney disease). A full list of risk-enhancers is shown in **Supplementary Table 1**[9].

References

1. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, Brindle P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* British Medical Journal Publishing Group; 2008;**336**:1475–1482.

2. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. BMJ Publishing Group Ltd and British Cardiovascular Society; 2014. p. ii1–ii67.

3. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FAR, Gillman MW, Kemper AR, Krist AH, Kurth AE, Landefeld CS, LeFevre ML, Mangione CM, Phillips WR, Owens DK, Phipps MG, Pignone MP. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* American Medical Association; 2016;**316**:1997–2007.

4. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* American Heart Association, Inc; 2008;**117**:743–753.

5. Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest J, Grover S, Gupta M, Hegele RA, Lau DC, Leiter LA, Lonn E, Mancini GBJ, McPherson R, Ngui D, Poirier P, Sievenpiper JL, Stone JA, Thanassoulis G, Ward R. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol* Elsevier; 2016;**32**:1263–1282.

6. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.

7. Lloyd-Jones DM, Braun LT, Ndumele CE, Smith SC, Sperling LS, Virani SS, Blumenthal RS. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease: A Special Report From the American Heart Association and American College of Cardiology. *Journal of the American College of Cardiology* 2018.

8. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PWF, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014. p. 2935–2959.

9. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology* 2018.

10. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Watson K, Wilson PWF, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. American Heart Association, Inc; 2014. p. S1–S45.

eTable 1: Atherosclerotic cardiovascular disease risk enhancers according to the 2018 ACC/AHA cholesterol guidelines.

- Family history of ASCVD
- Persistently elevated LDL-C ≥ 160 mg/dL (4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome

Lipid/biomarkers:

- Persistently elevated triglycerides ≥ 175 mg/dL (2.0 mmol/L)

In selected individuals if measured:

- hs-CRP ≥ 2.0 mg/dL
- Lp(a) > 50 mg/dL
- apoB ≥ 130 mg/dL
- Ankle-brachial index < 0.9

ASCVD: Atherosclerotic cardiovascular disease; LDL-C: Low-density lipoprotein cholesterol; hs-CRP: High-sensitive C-reactive protein; Lp(a): Lipoprotein(a); apoB: Apolipoprotein(B).

eTable 2. Baseline characteristics of all men from the Copenhagen General Population Study and men eligible for statin therapy according to 5 major statin guidelines for primary prevention of atherosclerotic cardiovascular disease.

		Statin eligibility according to guidelines				
Characteristics	**All men**	**CCS**	**ACC/AHA**	**NICE**	**USPSTF**	**ESC/EAS**
Individuals, n	19870	11431	11785	9947	9200	2547
Gender, male %	100	100	100	100	100	100
Age, median (IQR), year	56 (48-64)	61 (54-67)	62 (56-68)	64 (59-69)	64 (59-69)	62 (57-65)
Systolic blood pressure, median (IQR), mmHg	140 (130-155)	148 (135-161)	148 (135-160)	149 (135-162)	150 (140-164)	155 (140-170)
Diastolic blood pressure, median (IQR), mmHg	85 (80-93)	88 (80-96)	88 (80-95)	88 (80-95)	89 (80-96)	90 (82-100)
Plasma cholesterol, median (IQR)						
Total cholesterol, mg/dL	220 (197-247)	236 (213-259)	232 (205-259)	228 (201-251)	232 (205-255)	252 (221-283)
mmol/L	5.7 (5.1-6.4)	6.1 (5.5-6.7)	6.0 (5.3-6.7)	5.9 (5.2-6.5)	6.0 (5.3-6.6)	6.5 (5.7-7.3)
HDL cholesterol, mg/dL	53 (43-65)	50 (41-62)	51 (42-64)	51 (41-64)	51 (41-63)	50 (43-66)
mmol/L	1.4 (1.1-1.7)	1.3 (1.1-1.6)	1.3 (1.1-1.7)	1.3 (1.1-1.7)	1.3 (1.1-1.7)	1.3 (1.1-1.7)
LDL cholesterol, md/dL	131 (108-155)	143 (124-166)	139 (116-162)	135 (112-159)	139 (116-162)	163 (128-186)
mmol/L	3.4 (2.8-4.0)	3.7 (3.2-4.3)	3.6 (3.0-4.2)	3.5 (2.9-4.1)	3.6 (3.0-4.2)	4.2 (3.3-4.8)
Current smokers, %	23	31	32	32	36	38
Diabetes, %	2	4	4	5	4	19
10-year PCE risk, median (IQR), %	9.7 (4.3-18.0)	16.2 (10.6-24.0)	15.9 (10.9-23.5)	18.0 (13.2-25.3)	18.7 (13.8-26.0)	20.9 (15.6-28.3)

HDL=high-density lipoprotein; LDL=low-density lipoprotein; ASCVD=atherosclerotic cardiovascular disease. IQR=interquartile range. PCE=Pooled Cohort Equations; ACC=American College of Cardiology; AHA=American Heart Association; CCS=Canadian Cardiovascular Society; NICE=National Institute for Health and Care Excellence; USPSTF=US Preventive Services Task Force; ESC= European Society of Cardiology; EAS= European Atherosclerosis Society.

eTable 3. Baseline characteristics of all <u>women</u> from the Copenhagen General Population Study and of women eligible for statin therapy according to 5 major statin guidelines for primary prevention of atherosclerotic cardiovascular disease.

		Statin eligibility according to guidelines				
Characteristics	**All women**	**CCS**	**ACC/AHA**	**NICE**	**USPSTF**	**ESC/EAS**
Individuals, n	25880	8522	7615	8249	4766	4323
Gender, male %	0	0	0	0	0	0
Age, median (IQR), year	56 (48-64)	64 (59-69)	67 (62-71)	67 (62-71)	70 (66-73)	64 (58-69)
Systolic blood pressure, median (IQR), mmHg	135 (122-150)	150 (136-165)	150 (136-165)	147 (132-162)	155 (142-170)	144 (130-160)
Diastolic blood pressure, median (IQR), mmHg	81 (75-90)	85 (80-94)	85 (79-92)	84 (78-91)	86 (80-94)	84 (77-90)
Plasma cholesterol, median (IQR)						
Total cholesterol, mg/dL	224 (197-251)	252 (228-275)	247 (220-278)	243 (216-271)	243 (220-271)	352 (224-286)
mmol/L	5.8 (5.1-6.5)	6.5 (5.9-7.1)	6.4 (5.7-7.2)	6.3 (5.6-7.0)	6.3 (5.7-7.0)	6.5 (5.8-7.4)
HDL cholesterol, mg/dL	68 (56-82)	66 (54-81)	65 (52-80)	65 (52-80)	65 (52-80)	70 (54-85)
mmol/L	1.8 (1.4-2.1)	1.7 (1.4-2.1)	1.7 (1.3-2.1)	1.7 (1.3-2.1)	1.7 (1.3-2.1)	1.8 (1.4-2.2)
LDL cholesterol, md/dL	128 (104-151)	150 (135-174)	151 (124-182)	143 (120-170)	147 (124-170)	151 (128-181)
mmol/L	3.3 (2.7-3.9)	3.9 (3.5-4.5)	3.9 (3.2-4.7)	3.7 (3.1-4.4)	3.8 (3.2-4.4)	3.9 (3.3-4.7)
Current smokers, %	21	28	32	28	35	23
Diabetes, %	1	4	5	6	4	7
10-year PCE risk, median (IQR), %	3.2 (1.1-7.9)	9.4 (5.6-15.8)	12.0 (8.7-17.7)	11.5 (7.9-17.2)	15.9 (12.4-21.3)	8.9 (4.1-15.5)

HDL=high-density lipoprotein; LDL=low-density lipoprotein; ASCVD=atherosclerotic cardiovascular disease. IQR=interquartile range. PCE=Pooled Cohort Equations; ACC=American College of Cardiology; AHA=American Heart Association; CCS=Canadian Cardiovascular Society; NICE=National Institute for Health and Care Excellence; USPSTF=US Preventive Services Task Force; ESC= European Society of Cardiology; EAS= European Atherosclerosis Society.

eTable 4: Positive and negative predictive values for statin allocation according to 5 guidelines

				Guideline eligibility		
		CCS	**ACC/AHA**	**NICE**	**USPSTF**	**ESC/EAS**
PPV		14%	15%	15%	17%	15%
NPV		95%	95%	95%	94%	92%

PPV=positive predictive value; NPV=negative predictive value; ACC=American College of Cardiology; AHA=American Heart Association; CCS=Canadian Cardiovascular Society; NICE=National Institute for Health and Care Excellence; USPSTF=US Preventive Services Task Force; ESC= European Society of Cardiology; EAS= European Atherosclerosis Society.

eTable 5: Event rates per 1000 person-years for atherosclerotic cardiovascular disease in individuals eligible for statin therapy for primary prevention according to 5 guidelines

				Guideline eligibility			
Event rates		**ALL**	**CCS**	**ACC/AHA**	**NICE**	**USPSTF**	**ESC/EAS**
ASCVD		6.7 (6.5-9.0)	11.1 (10.6-11.7)	11.6 (11.1-12.2)	12.2 (11.7-12.8)	13.6 (12.9-14.3)	11.7 (10.8-12.6)

ASCVD= Atherosclerotic cardiovascular disease; ACC=American College of Cardiology; AHA=American Heart Association; CCS=Canadian Cardiovascular Society; NICE=National Institute for Health and Care Excellence; USPSTF=US Preventive Services Task Force; ESC= European Society of Cardiology; EAS= European Atherosclerosis Society.

eTable 6. Calculations of the number needed to treat to prevent one ASCVD event in 10 years among individuals aged 40-75. The calculations are based on assuming a 25% relative risk reduction per 1 mmol/L LDL-C reduction and a 50% versus 30% LDL-C reduction with high- and moderate-intensity statin treatment, respectively.

		Events by guidelines				
Potential Outcomes	**All events**	**CCS**	**ACC/AHA**	**NICE**	**USPSTF**	**ESC/EAS**
Kaplan-Meier estimated 10 year events	3097	2200	2265	2225	1913	780
High-intensity statins						
50% LDL-C reduction, mmol/L		1.92 (1.92-1.93)	1.89 (1.88-1.90)	1.82 (1.81-1.82)	1.85 (1.84-1.85)	2.02 (2.01-2.03)
Relative risk reduction, %		42 (42-42)	42 (42-43)	41 (41-41)	41 (41-41)	44 (44-45)
Events prevented		924 (924-980)	951 (951-974)	913 (913-913)	784 (784-784)	343 (343-351)
Absolute risk reduction, %		4.7 (4.7-5.0)	4.9 (4.9-5.0)	5.0 (5.0-5.0)	5.6 (5.6-5.6)	5.0 (5.0-5.1)
NNT-10 to prevent 1 ASCVD event		21 (20-21)	20 (20-20)	20 (20-20)	18 (18-18)	20 (20-20)
Moderate-intensity statins						
30% LDL-C reduction, mmol/L		1.15 (1.15-1.16)	1.13 (1.13-1.14)	1.09 (1.09-1.09)	1.11 (1.10-1.11)	1.21 (1.20-1.22)
Relative risk reduction, %		28 (28-28)	28 (28-28)	27 (27-27)	27 (27-27)	29 (29-30)
Events prevented		616 (616-616)	634 (634-642)	601 (601-601)	517 (517-517)	226 (226-234)
Absolute risk reduction, %		3.1 (3.1-3.1)	3.3 (3.3-3.3)	3.3 (3.3-3.3)	3.7 (3.7-3.7)	3.3 (3.3-3.4)
NNT-10 to prevent 1 ASCVD event		32 (32-32)	30 (30-30)	30 (30-30)	27 (27-27)	29 (29-29)

Numbers are means (95% CI). ACC=American College of Cardiology; AHA=American Heart Association; CCS=Canadian Cardiovascular Society; NICE=National Institute for Health and Care Excellence; USPSTF=US Preventive Services Task Force; ESC= European Society of Cardiology; EAS= European Atherosclerosis Society.

eTable 7. Calculations of the number needed to treat to prevent one ASCVD event in 10 years among individuals aged 40-65. The calculations are based on assuming a 25% relative risk reduction per 1 mmol/L LDL-C reduction and a 50% versus 30% LDL-C reduction with high- and moderate-intensity statin treatment, respectively.

		Events by guidelines				
Potential Outcomes	**All events**	**CCS**	**ACC/AHA**	**NICE**	**USPSTF**	**ESC/EAS**
Kaplan-Meier estimated 10 year events	1833	1109	1027	948	755	458
High-intensity statins						
50% LDL-C reduction, mmol/L		1.97 (1.96-1.98)	1.97 (1.96-1.97)	1.87 (1.86-1.88)	1.91 (1.89-1.92)	2.07 (2.05-2.08)
Relative risk reduction, %		43 (43-43)	43 (43-43)	42 (41-42)	42 (42-42)	45 (45-45)
Events prevented		477 (477-477)	442 (442-442)	398 (389-398)	316 (316-316)	206 (206-206)
Absolute risk reduction, %		3.6 (3.6-3.6)	4.0 (4.0-4.0)	4.0 (3.9-4.0)	4.4 (4.4-4.4)	4.3 (4.3-4.3)
NNT-10 to prevent 1 ASCVD event		27 (27-27)	25 (25-25)	25 (25-26)	23 (23-23)	23 (23-23)
Moderate-intensity statins						
30% LDL-C reduction, mmol/L		1.18 (1.18-1.19)	1.18 (1.17-1.18)	1.12 (1.12-1.13)	1.14 (1.14-1.15)	1.24 (1.23-1.25)
Relative risk reduction, %		29 (29-29)	29 (29-29)	28 (28-28)	28 (28-28)	30 (30-30)
Events prevented		324 (324-322)	298 (298-298)	265 (265-265)	209 (209-209)	137 (137-137)
Absolute risk reduction, %		2.4 (2.4-2.4)	2.6 (2.6-2.6)	2,7 (2,7-2,7)	2.9 (2.9-2.9)	2.9 (2.9-2.9)
NNT-10 to prevent 1 ASCVD event		40 (40-40)	38 (38-38)	37 (37-37)	35 (34-34)	35 (35-35)

Numbers are means (95% CI). ACC=American College of Cardiology; AHA=American Heart Association; CCS=Canadian Cardiovascular Society; NICE=National Institute for Health and Care Excellence; USPSTF=US Preventive Services Task Force; ESC= European Society of Cardiology; EAS= European Atherosclerosis Society.

eTable 8. Calculations of the number needed to treat to prevent one ASCVD event in 10 years among individuals aged 66-75. The calculations are based on assuming a 25% relative risk reduction per 1 mmol/L LDL-C reduction and a 50% versus 30% LDL-C reduction with high- and moderate-intensity statin treatment, respectively.

		Events by guidelines				
Potential Outcomes	**All events**	**CCS**	**ACC/AHA**	**NICE**	**USPSTF**	**ESC/EAS**
Kaplan-Meier estimated 10 year events	1264	1101	1243	1281	1160	321
High-intensity statins						
50% LDL-C reduction, mmol/L		1.83 (1.82-1.84)	1.78 (1.77-1.79)	1.76 (1.75-1.77)	1.78 (1.78-1.80)	1.92 (1.89-1.94)
Relative risk reduction, %		41 (41-41)	40 (40-40)	40 (40-40)	40 (40-40)	42 (42-43)
Events prevented		451 (451-451)	497 (497-497)	512 (512-512)	464 (464-464)	135 (135-138)
Absolute risk reduction, %		6.5 (6.6-6.6)	6.2 (6.2-6.2)	6.1 (6.1-6.1)	6.6 (6.6-6.6)	6.3 (6.3-6.3)
NNT-10 to prevent 1 ASCVD event		15 (15-15)	16 (16-16)	16 (16-16)	15 (15-15)	16 (15-16)
Moderate-intensity statins						
30% LDL-C reduction, mmol/L		1.10 (1.09-1.11)	1.07 (1.06-1.07)	1.05 (1.05-1.06)	1.07 (1.07-1.08)	1.15 (1.14-1.16)
Relative risk reduction, %		28 (28-28)	28 (28-28)	27 (27-27)	27 (27-27)	29 (29-30)
Events prevented		308 (308-308)	348 (348-348)	346 (346-346)	313 (313-313)	93 (93-93)
Absolute risk reduction, %		4.5 (4.5-4.5)	4.3 (4.3-4.3)	4.2 (4.2-4.2)	4.5 (4.5-4.5)	4.4 (4.4-4.4)
NNT-10 to prevent 1 ASCVD event		22 (22-22)	23 (23-23)	24 (24-24)	22 (22-22)	23 (23-23)

Numbers are means (95% CI). ACC=American College of Cardiology; AHA=American Heart Association; CCS=Canadian Cardiovascular Society; NICE=National Institute for Health and Care Excellence; USPSTF=US Preventive Services Task Force; ESC= European Society of Cardiology; EAS= European Atherosclerosis Society.

eTable 9. Baseline characteristics of individuals without known atherosclerotic cardiovascular disease or statin use at baseline from the Copenhagen General Population Study (CGPS=, Multi Ethnic Study of Atherosclerosis (MESA) and the Reasons for Geographic and Racial Differences in Stroke (REGARDS) studies.

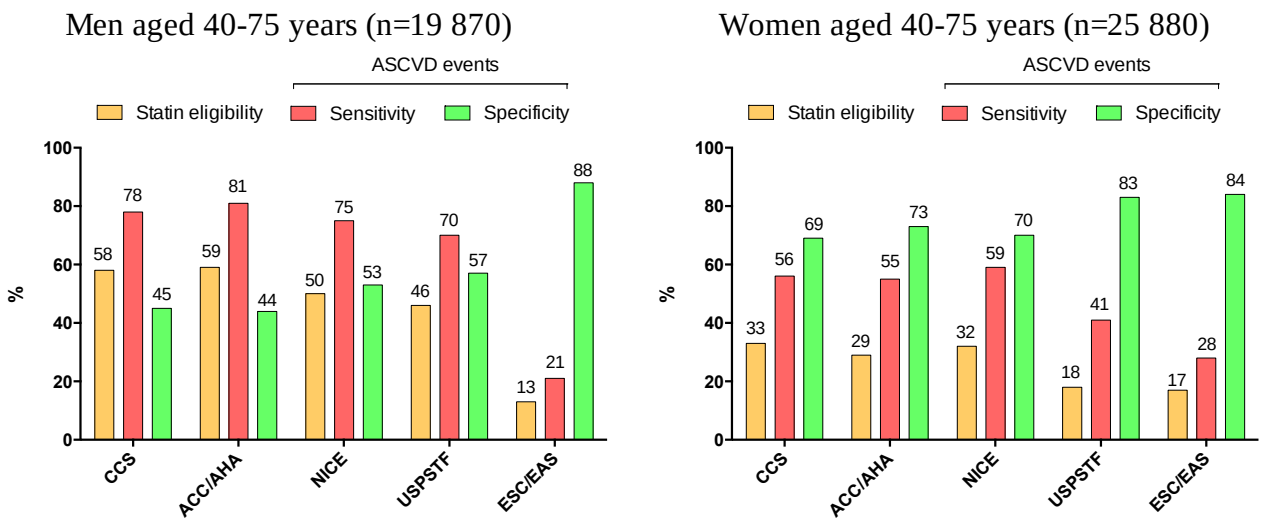
Characteristics	CGPS	MESA*	REGARDS**
Gender, male %	43	47	41
Age, mean	56	61	62
Systolic blood pressure, mean, mmHg	140	123	125
Plasma cholesterol, mean			
Total cholesterol, mg/dL	220	194	203
mmol/L	5.7	5.0	5.2
HDL cholesterol, mg/dL	61	46	54
mmol/L	1.6	1.2	1.4
LDL cholesterol, mg/dL	128	120	125
mmol/L	3.3	3.1	3.2
Current smokers, %	21	13	15
Diabetes, %	2	11	-

HDL=high-density lipoprotein; LDL=low-density lipoprotein;

*Data from: Mortensen et al. Statin Trials, Cardiovascular Events, and Coronary Artery Calcification. JACC Cardiovascular Imaging, 2018 Feb;11(2 Pt 1):221-230

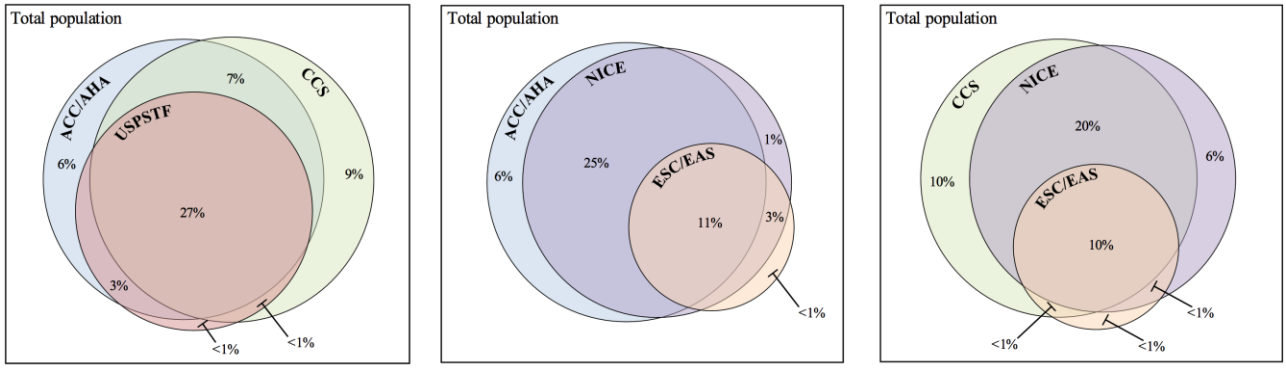
**Data from Muntner et al. Validation of the Atherosclerotic Cardiovascular Disease Pooled Cohort Risk Equations. JAMA, 2014 (311): 1406-1415.

Supplementary Figure 1



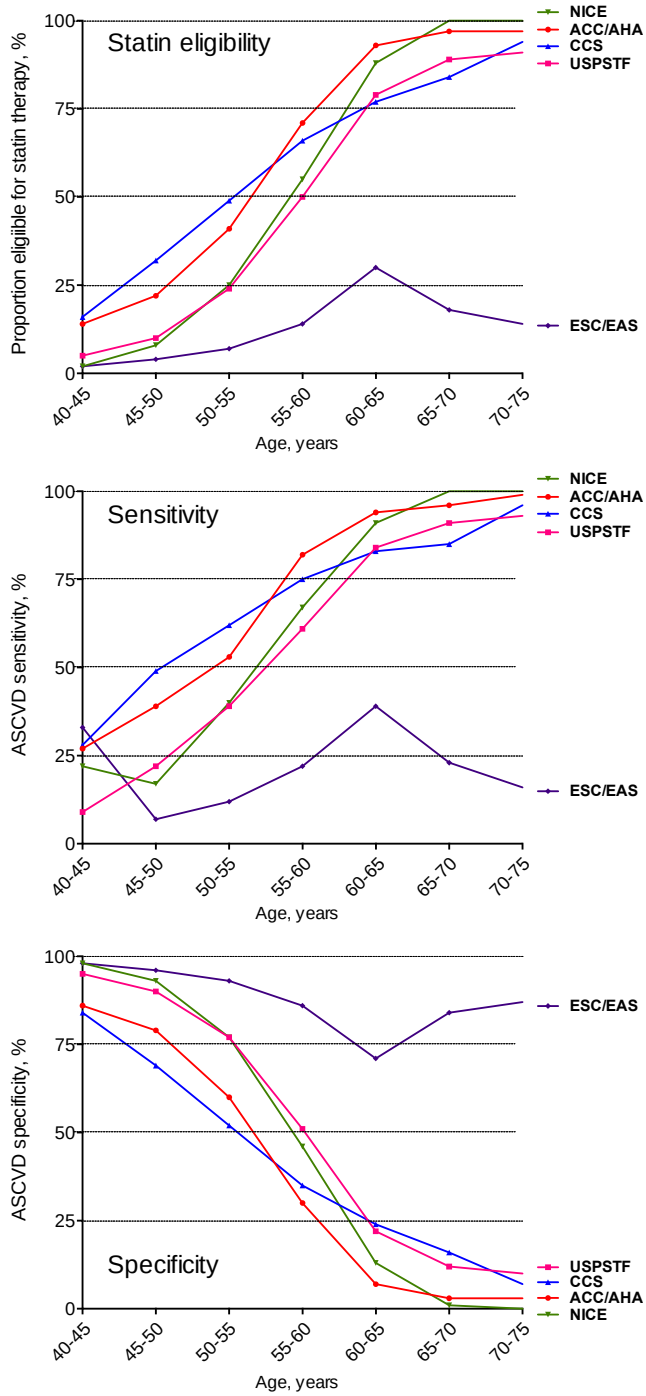
eFigure 1. Clinical performance of 5 major guidelines on cholesterol treatment for primary prevention of ASCVD <u>stratified by gender</u> in the Copenhagen General Population Study. ASCVD events: non-fatal myocardial infarction, fatal coronary heart disease, and stroke. ASCVD=Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.

Supplementary Figure 2



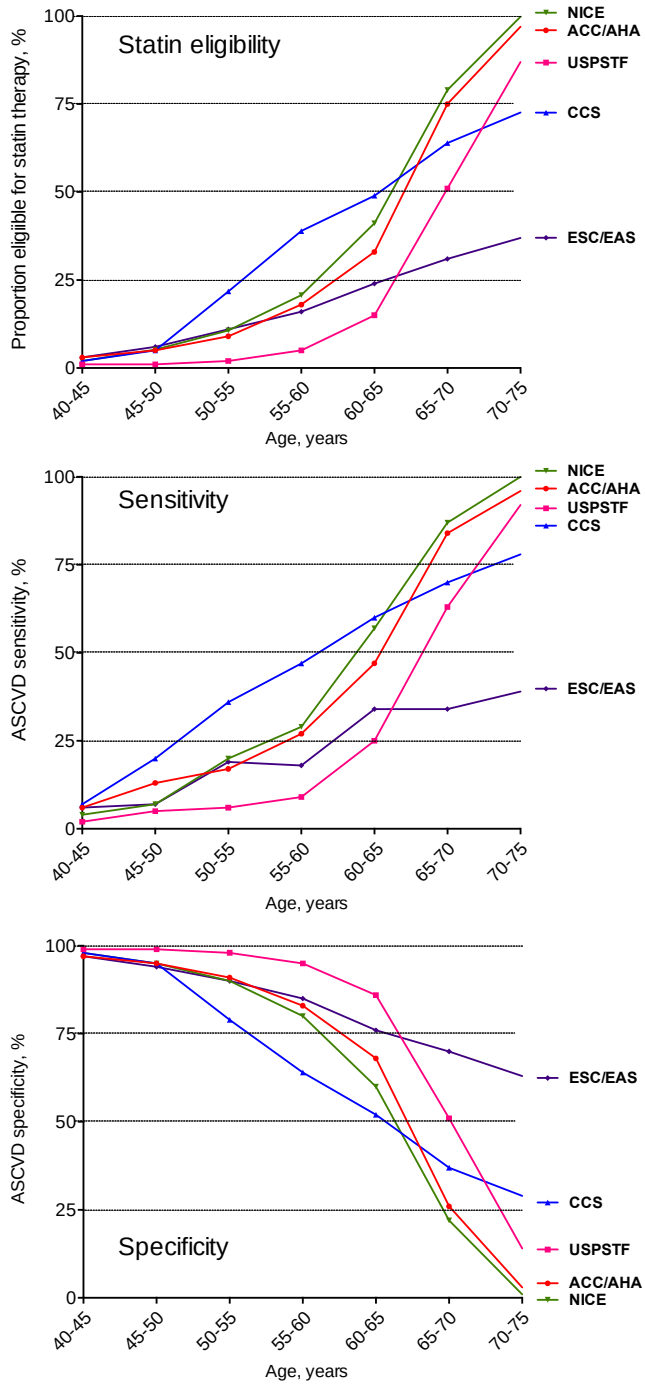
eFigure 2. Area-proportional Venn diagrams demonstrating overlap in statin eligibility by 5 major guidelines on statin use for primary prevention. ASCVD: Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.

Supplementary Figure 3



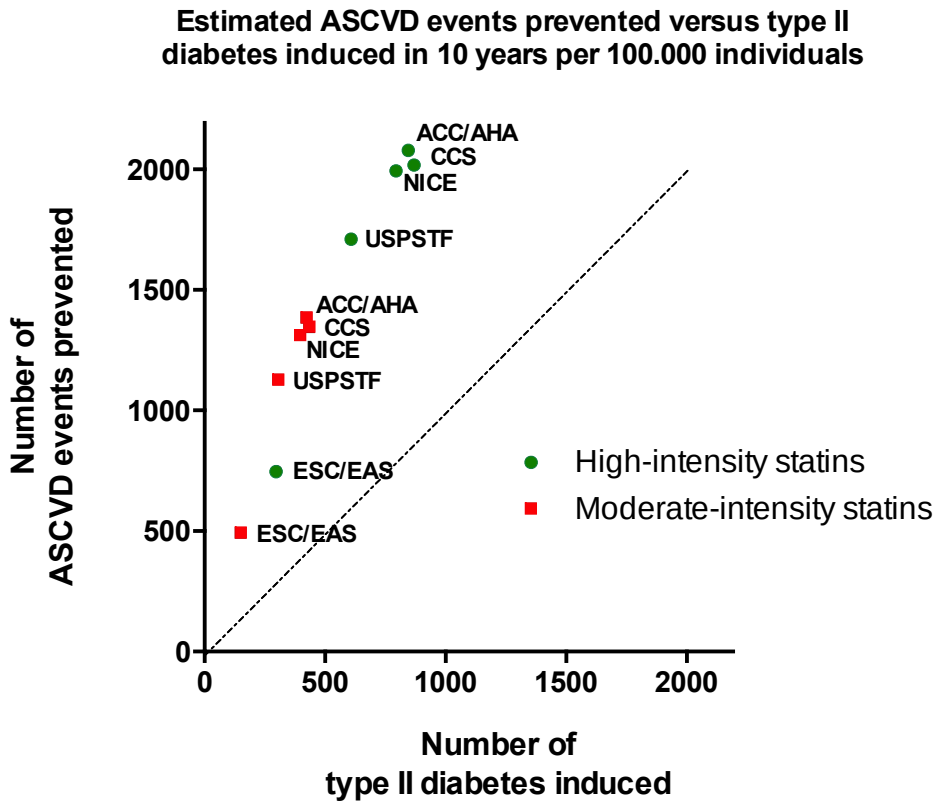
eFigure 3. Statin eligibility, ASCVD sensitivity and specificity of five major guidelines for primary prevention of ASCVD stratified by 5-year age groups in <u>men</u> in the Copenhagen General Population Study. ASCVD=Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.

Supplementary Figure 4



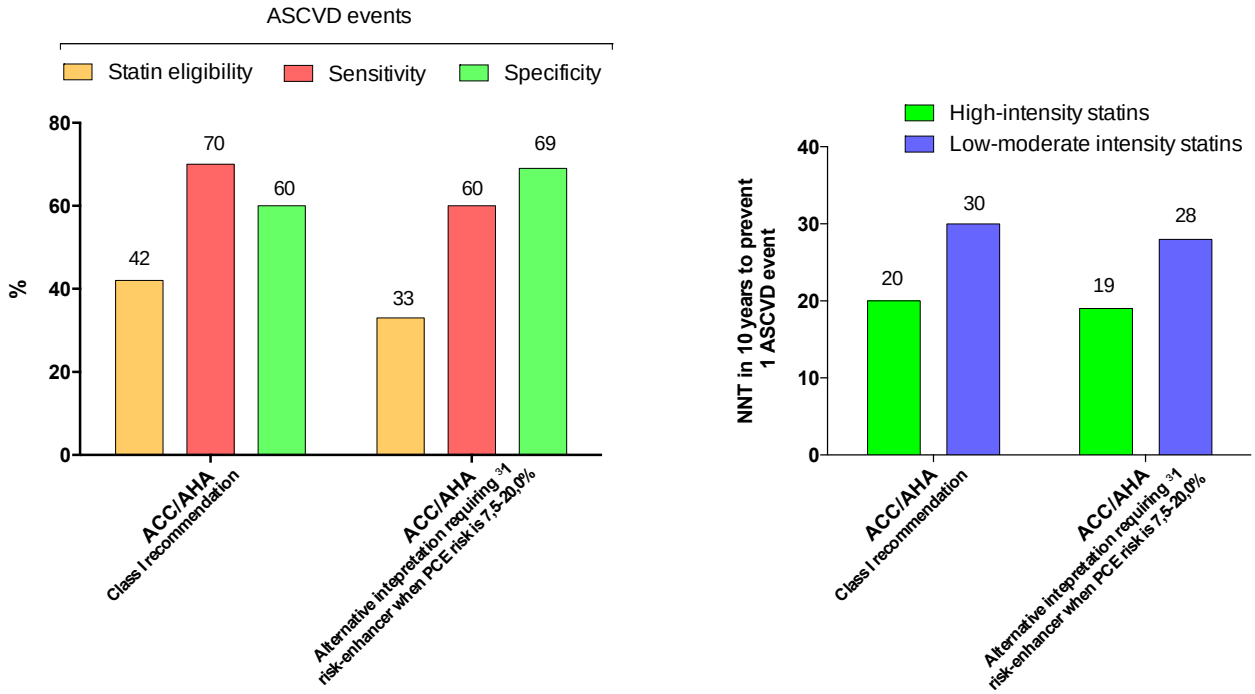
eFigure 4. Statin eligibility, ASCVD sensitivity and specificity for primary prevention of ASCVD of five major guidelines stratified by 5-year age groups in <u>women</u> in the Copenhagen General Population Study. ASCVD=Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.

Supplementary Figure 5



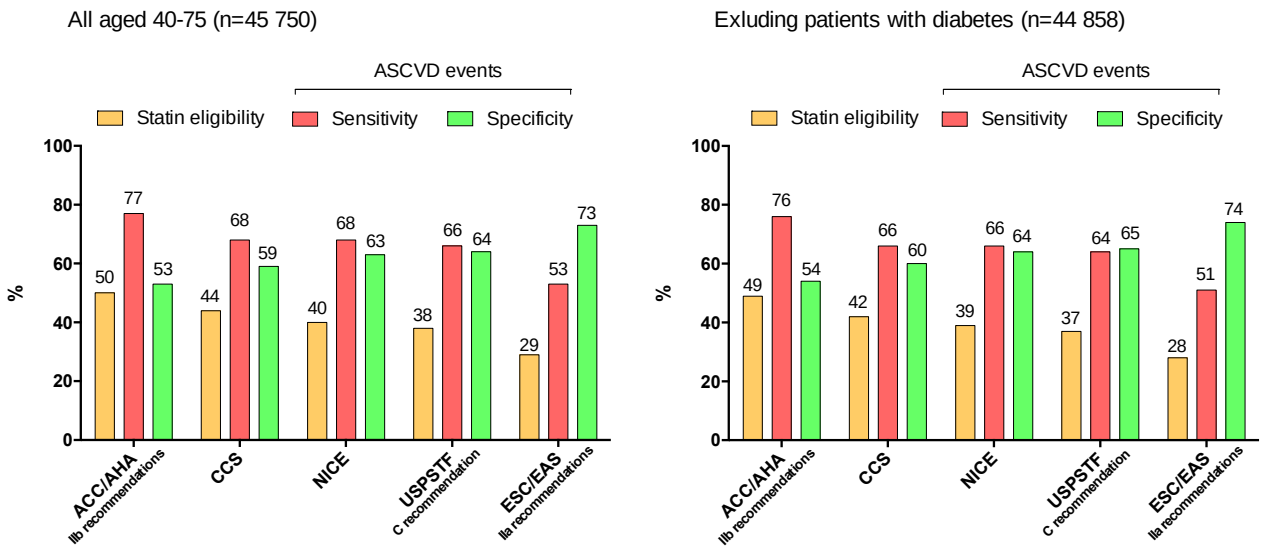
eFigure 5. Total number of ASCVD events prevented versus total number of additional diabetes diagnoses per 100.000 Copenhagen General Population participants by following the 5 major statin guidelines. For all the guidelines and for both high-intensity and moderate-intensity statin therapy, the estimated number of ASCVD events prevented was several times higher than expected additional diabetes diagnoses. ASCVD=Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.

Supplementary Figure 6



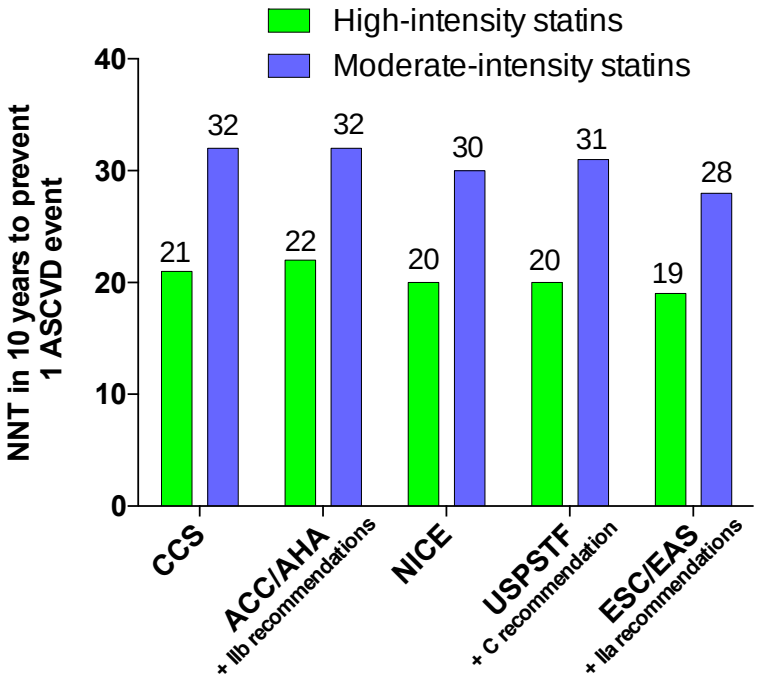
eFigure 6. Clinical performance of two different interpretations of ACC/AHA class I recommendations. In the usual approach, individuals with PCE risk ≥7.5% to 20% does not need risk-enhancers to be statin eligible. In the alternative interpretation, all individuals with with PCE risk ≥7.5% to 20% should also have at least one risk-enhancer to qualify for statin theraphy. ASCVD events: non-fatal myocardial infarction, fatal coronary heart disease, and stroke. ASCVD=Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association.

Supplementary Figure 7



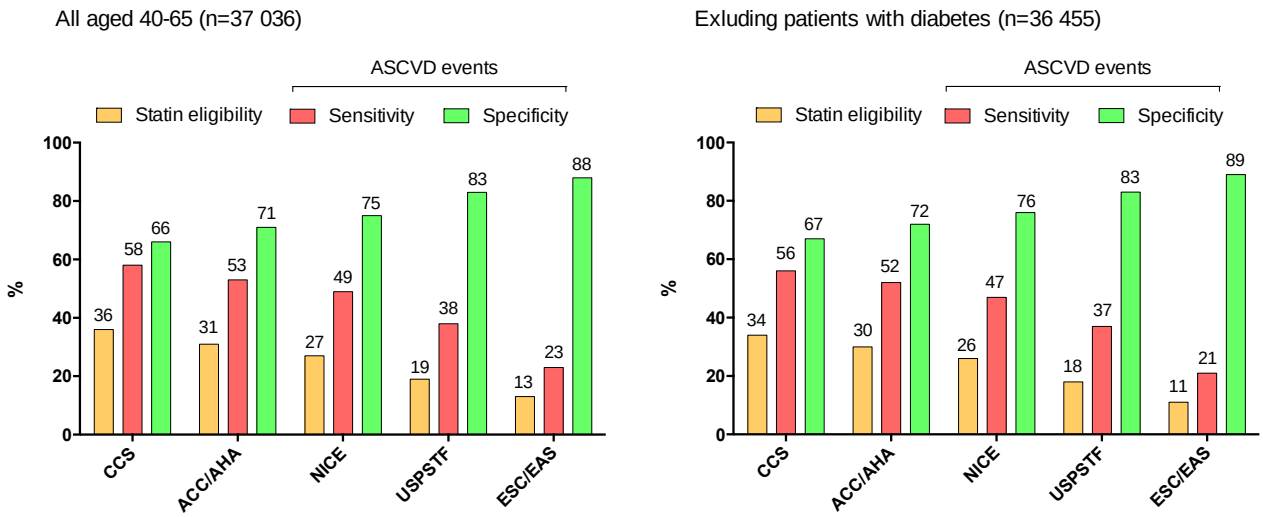
eFigure 7. Clinical performance of 5 major guidelines on cholesterol treatment for primary prevention of ASCVD among individuals aged 40 to 75 also <u>including the weaker class IIa (for ESC/EAS), IIb (for ACC/AHA) and C recommendation (for USPSTF)</u> in the Copenhagen General Population Study. ASCVD events: non-fatal myocardial infarction, fatal coronary heart disease, and stroke. ASCVD=Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.

Supplementary Figure 8



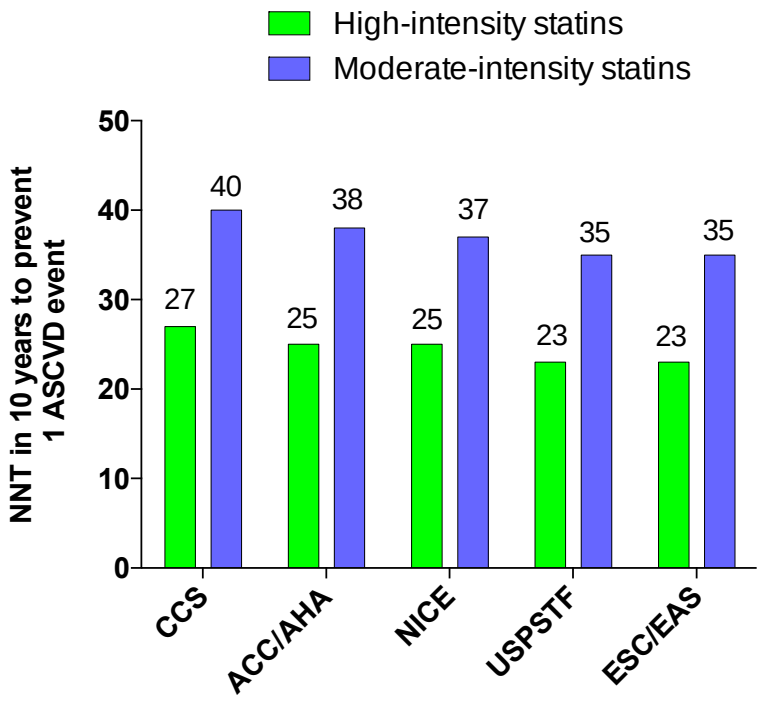
eFigure 8. The number needed to treat to prevent one ASCVD event in primary prevention in individuals aged 40-75 also <u>including the weaker class IIa (ESC/EAS), IIb (ACC/AHA) and C recommendation (for USPSTF)</u>. ASCVD: Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.

Supplementary Figure 9

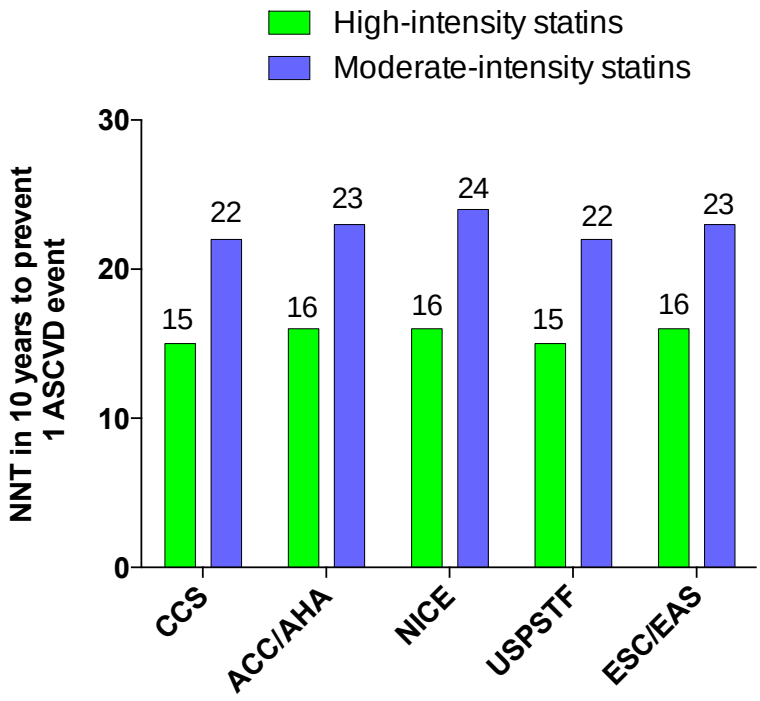


eFigure 9. Clinical performance of 5 major guidelines on cholesterol treatment for primary prevention of ASCVD among individuals aged 40 to 65 in the Copenhagen General Population Study. ASCVD events: non-fatal myocardial infarction, fatal coronary heart disease, and stroke. ASCVD=Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.

Supplementary Figure 10



eFigure 10. The number needed to treat (NNT) to prevent one ASCVD event in primary prevention in individuals aged 40-65.
ASCVD: Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.



eFigure 11. The number needed to treat (NNT) to prevent one ASCVD event in primary prevention in individuals aged 66-75.
ASCVD: Atherosclerotic cardiovascular disease. ACC: American College of Cardiology. AHA: American Heart Association. CCS: Canadian Cardiovascular Society. NICE: National Institute for Health and Care Excellence. USPSTF: US Preventive Services Task Force. ESC: European Society of Cardiology. EAS: European Atherosclerosis Society.