Supplementary Online Content

Mortensen MB, Blaha MJ, Nordestgaard BG. Eligibility and preventive potential for new evidence-based cardiovascular drugs in secondary prevention. *JAMA Cardiol*. Published online January 2, 2020. doi:10.1001/jamacardio.2019.4759

eFigure 8. Eligibility for number of drug classes simultaneously while allowing for multiple lipid-modifying drugs
eFigure 9. Eligibility by number of drug classes simultaneously while allowing for multiple lipid-modifying drugs but only drug from each of the other classes.
This supplementary material has been provided by the authors to give readers additional information about their work.

eMETHODS

Study population and setting

The Copenhagen General Population Study (CGPS) is an ongoing prospective cohort study of the white Danish general population[1-3]. Participants were selected through the Danish Civil Registration System in 2003-2015. All individuals of Danish descent aged 40+ years in selected parts of Copenhagen and surrounding country side were invited along with a random selection of 25% of individuals aged 20-39 years, with a participation rate of 43%. Thus, the CGPS covers all regions of Copenhagen including both high- and low-income areas.

The baseline examination included a questionnaire, a physical examination and blood sampling for biochemical measurements. Current smoking status and statin therapy was self-reported through the questionnaire. Blood pressure was measured using an automated Digital Blood Pressure Monitor (Kivex) after 5 min of rest with the individual in the sitting position. Plasma levels of total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, high-sensitivity C-reactive protein (hsCRP), triglycerides, and creatinine were measured with standard hospital assays. Missing data on these variables was <0.8%.

The study was approved by Herlev and Gentofte Hospital and by a Danish ethics committee. Written informed consent was obtained from all individuals.

Secondary prevention trials

Listed in chronological order by publication date, the following twelve studies are included in our analyses: The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (**IMPROVE-IT**)[4], Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction (**PEGASUS**)[5], the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus

Patients (**EMPA-REG**) [6], the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (**LEADER**)[7], the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (**SUSTAIN-6**)[8], Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (**FOURIER**)[9], CANagliflozin cardioVascular Assessment Study (**CANVAS**)[10], Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (**REVEAL**)[11], The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (**CANTOS**)[12], the Cardiovascular Outcomes for People Using Anticoagulation Strategies (**COMPASS**)[13], the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (**ODYSSEY-OUTCOMES**) [14] and the Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial (**REDUCE-IT**) [15]. The enrollment criteria used in these trials are shown in **Supplementary Table 1**. In order to assess the maximal potential eligibility in the general population over time by implementing RCT evidence from the twelve trials in clinical practice, we did not require strict adherence to the time-criteria for recent ASCVD used in the trials. For example, in the IMPROVE-IT trial individuals should have been hospitalized with an acute coronary syndrome within 10 days to be eligible for ezetimibe. In the main analyses, all patients with a previous acute coronary syndrome could therefore be eligible for ezetimibe if they met all the other inclusion criteria. However, in sensitivity analyses, we stringently followed the time-criteria for ASCVD used in clinical trials. These sensitivity analyses simulate the instant eligibility for new pharmacological therapies in the general population by immediate implementation of RCT evidence in clinical practice tomorrow.

It is unlikely that individuals will be assigned 2 of the novel drugs that targets the same biological pathway for cardiovascular disease prevention, (ie. two novel anti-thrombotic: ticagrelor + rivaroxaban). Thus, to determine if individuals potentially could be eligible for two or

more new drugs simultaneously, we divided the drug therapies into 4 different drug-classes: lipid-modifying, anti-thrombotic, anti-inflammatory, and anti-diabetic drugs.

Outcomes

Myocardial infarction, stroke, cardiovascular deaths and all-cause mortality were identified by linkage to the nation-wide Danish Patient Registry (covering all Danish Hospitals) and the nation-wide Danish Register of Causes of Death, using international Classification of Diseases, 10th Revision, codes I21-I22 for myocardial infarction, I20-I25 for ischemic heart disease, and I60, I61, I63, I64 and G45 for strokes. The validity of myocardial infarction diagnosis obtained from the Danish Patient Registry have been shown to be very high[16]. We validated stroke events using the World Health Organizations definition of stroke, that is, an acute disturbance of focal or global cerebral function with symptoms lasting longer than 24 hours or leading to death, with presumably no other reason than a vascular origin, as previously described[17]. Cardiovascular deaths were defined as deaths from ICD-10 codes I10-25, I44-51 and I61-73, obtained by linkage to the national Danish Cause of Death Registry

All residents in Denmark are assigned a personal identification number at birth or immigration, by which they can be traced in the national registries and therefore follow-up of all individuals in CGPS was without losses. The 448 individuals who emigrated had follow-up truncated at the date of emigration.

Statistical analysis

Baseline characteristics are presented as proportions for categorical variables and as medians (interquartile ranges) for continuous variables. We used Stata version 13.1 SE (StataCorp LP, College Station, Texas).

First, we determined the proportions of individuals in the general population overall as well as in those with IHD or MI who are eligible for novel preventive therapies by meeting enrollment criteria (inclusion as well as exclusion criteria) in the twelve RCTs. We assessed 1) the proportion of individuals eligible for at least 1 new drug, 2) the proportion meeting criteria in 0, 1, 2, 3 or ≥4 trials simultaneously, and 3) the proportion eligible for 0, 1, 2, 3 or 4 of the four different drug-classes simultaneously (lipid-modifying, anti-thrombotic, anti-inflammatory, and anti-diabetic drugs). We also calculated event rates per 1000 person-years among CGPS participants eligible for novel preventive therapies and compared them to those reported in the RCTs. If event-rates was not specifically reported in the RCTs, we estimated event-rates per 1000 person-years based on mean follow-up time and number of events in the placebo groups of the RCTs.

Second, we estimated the evidence-based potential for reduction of MI, stroke and all-cause mortality over 5 years through prescription of each novel therapy according to clinical trial criteria. We choose 5 years because this mimic the follow-up length in most trials. For these analyses, we first estimated the total number of MI, stroke and all-cause mortality events in 5 years in the overall population as well as in individuals with IHD and MI at baseline, using Kaplan-Meier analysis. Likewise, we estimated the total number of MI, stroke and all-cause mortality events in 5 years among trial eligible individuals. To estimate the potential reduction of events using each novel therapy, we used hazard ratios for each active therapy versus placebo for MI, stroke and all-cause mortality reduction as reported in the RCTs to calculate how many events that might have been averted by active treatment. The potential for event reduction in 5 years was then calculated as the number of events averted by assigning the novel preventive therapies according to clinical trial criteria divided by the total number of events. These calculations were performed in the overall population as well as among individuals with IHD or MI at baseline.

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eTable 1: Main inclusion criteria used in the 12 randomized controlled trials for prevention of atherosclerotic cardiovascular disease.

IMPROVE-IT	PEGASUS	EMPA-REG	LEADER	SUSTAIN-6	FOURIER	CANVAS	REVEAL	CANTOS	COMPASS	ODYSSEY Outcomes	REDUCE-IT
Age ≥18 years **Plus** maximum 10 days following hospital admission for ACS **Plus** LDL ≤ 125 mg/dL if not on statin **Or** LDL ≤ 100 mg/dL if on statin	Age ≥50 years **Plus** MI within 1-3 years ago **Plus** At least one additional risk factor: age ≥65 or diabetes or chronic, non-end-stage kidney disease	Age ≥18 years **Plus** Type 2 diabetes **Plus** BMI ≤ 45 kg/m^2 **Plus** A high cardiovascular risk defined as: known ischemic heart disease, previous stroke or peripheral artery disease (ankle brachial index <0.9)	Age ≥50 years **Plus** Type 2 diabetes **Plus** At least one of the following criteria: Prior MI, Prior stroke or TIA, Ischemic heart disease, chronic kidney disease (eGFR<60 mL/min) **Or** Age ≥60 and ankle brachial index <0.9	Age ≥50 years **Plus** Type 2 diabetes **Plus** Established cardiovascular disease defined as: prior MI, prior stroke, ischemic heart disease, chronic kidney disease (eGFR<60 mL/min). Cardiovascular events should be >90 days prior to inclusion. **Or** Age ≥60 and ankle brachial index <0.9	Age 40-85 years **Plus** Clinical evident atherosclerotic cardiovascular disease (MI or stroke) **Plus** LDL ≥70 mg/dL on statin therapy **Plus** Age ≥65 years **Or** Index event within 6 months to screening **Or** ≥2 of the following risk factors: low HDL (<40mg/dl in men and <50mg/dL in women), hsCRP >2.0 mg/L, current smoker, age>60 years, hyperlipidemia (LDL ≥130mg/dL or non-HDL ≥160 mg/dL) or metabolic syndrome	Age ≥30 years **Plus** Documented atherosclerotic cardiovascular disease defined as: prior MI, prior stroke, ischemic heart disease **Or** Age ≥50 years with 2 or more of the following: systolic blood pressure >140mmHg, smoking or HDL cholesterol <39mg/dL.	Age ≥50 years **Plus** Total cholesterol <155 mg/dL and creatinine < 200 µmol/L **Plus** Myocardial infarction **Or** Ischemic stroke **Or** Diabetes together with ischemic heart disease	Age ≥18 years **Plus** MI at least 30 days before randomization **Plus** hsCRP≥2 mg/L	Age ≥18 years **Plus** Coronary artery disease **Plus** Age ≥65 **Or** Age<65 with at least two additional risk factors: renal dysfunction (eGFR<60 ml/min), diabetes, smoking or ischemic stroke >1 month ago.	Age ≥40 years **Plus** Recently (<52 weeks) hospitalized for ACS **Plus** LDL ≥70 mg/dL on statin therapy	Age ≥45 years **Plus** Documented coronary artery disease or cerebrovascular disease **Plus** Triglycerides 135-499 mg/dL and LDL 41-100 mg/dL and on statin therapy **Or** Age ≥50 years **Plus** Diabetes with at least one additional risk factor: age ≥55 years in men or ≥65 years of age in women, current smoking, hypertension, HDL ≤ 40 mg/dL in men or ≤ 50 mg/dL in women, hsCRP >3 mg/dL or eGFR >30 and <60 mL/min **Plus** Triglycerides 135-499 mg/dL and LDL 41-100 mg/dL and on statin therapy

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (**IMPROVE-IT**), Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (**PEGASUS**), the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (**EMPA-REG**), the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (**LEADER**), the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (**SUSTAIN-6**), Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (**FOURIER**), CANagliflozin cardioVascular Assessment Study (**CANVAS**), Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (**REVEAL**), The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (**CANTOS**) and the Cardiovascular Outcomes for People Using Anticoagulation Strategies (**COMPASS**), Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (**ODYSSEY Outcomes**), Reduction of Cardiovascular Events with EPA – Intervention Trial (**REDUCE-IT**). LDL: low-density lipoprotein, MI: Myocardial infarction, BMI: body mass index, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, hsCRP: high-sensitive C-reaktive protein.

eTable 2. Event rates for major cardiovascular events, myocardial infarction, stroke and all-cause mortality per 1000 person-years among trial-eligible individuals and in the total Copenhagen General Population Study cohort.

Outcome	All	IMPROVE-IT	PEGASUS	EMPA-REG	LEADER	SUSTAIN-6	FOURIER	CANVAS	REVEAL	CANTOS	COMPASS	ODYSSEY	REDUCE-IT
Ischemic heart disease													
Major cardiovascular events*	31.5 (29.8-33.4)	41.5 (37.8-45.5)	37.3 (28.9-48.0)	44.8 (39.0-51.3)	47.0 (41.0-53.8)	47.0 (41.1-53.8)	40.5 (36.6-44.8)	44.7 (39.1-51.3)	42.8 (37.0-49.4)	54.6 (48.5-61.6)	41.8 (39.3-44.5)	39.9 (36.1-44.2)	35.0 (30.5-40.2)
MI	10.6 (9.7-11.6)	12.5 (10.7-14.5)	13.1 (11.2-15.5)	15.1 (12.2-.18.7)	15.4 (12.5-19.0)	15.4 (12.5-19.0)	12.7 (10.7-14.9)	15.2 (12.3-18.7)	12.9 (10.2-16.3)	15.1 (12.4-18.4)	12.2 (11.0-13.5)	12.6 (10.7-14.8)	13.0 (10.5-16.1)
Stroke	9.8 (8.9-10.7)	10.3 (8.8-12.0)	10.9 (9.2-12.9)	13.1 (10.5-16.4)	13.1 (10.5-16.4)	13.1 (10.5-16.4)	10.0 (8.4-11.9)	13.2 (10.6-16.4)	11.9 (9.4-15.0)	12.7 (10.4-15.6)	11.9 (10.8-13.2)	10.5 (8.8-12.4)	9.5 (7.5-12.0)
All-cause mortality	32.0 (30.3-33.7)	42.6 (39.4-46.2)	43.8 (35.4-54.4))	47.0 (41.6-53.1)	50.0 (44.3-56.2)	49.9 (44.3-56.2)	38.9 (35.5-42.5)	46.9 (41.6-53.0)	47.6 (42.2-53.8)	57.1 (51.6-63.2)	45.9 (43.4-48.5)	39.9 (36.5-43.6)	35.7 (31.5-40.4)
Myocardial infarction													
Major cardiovascular events*	39.9 (36.5-43.5)	41.5 (37.8-45.5)	37.3 28.9-48.0)	50.6 (41.2-62.2)	52.3 (42.6-64.1)	52.3 (42.6-64.1)	39.7 (35.7-44.1)	50.8 (41.3-62.4)	41.5 (34.9-49.3)	54.6 (48.5-61.6)	49.9 (45.3-55.0)	39.9 (36.1-44.2)	36.5 (36.5-44.7)
MI	12.5 (10.8-14.4)	12.5 (10.7-14.5)	13.1 (11.2-15.5)	14.7 (10.4-20.6)	15.1 (10.8-21.2)	15.1 (10.8-21.2)	12.7 (10.7-15.0)	15.0 (10.7-21.0)	11.9 (8.9-15.9)	15.1 (12.4-18.4)	13.4 (11.4-15.8)	12.6 (10.7-14.8)	12.7 (9.2-17.5)
Stroke	9.8 (8.4-11.3)	10.3 (8.8-12.0)	10.9 (9.2-12.9)	11.8 (8.3-16.7)	11.7 (8.2-16.6)	11.7 (8.2-16.6)	9.4 (7.8-11.3)	11.7 (8.2-16.6)	10.0 (7.5-13.4)	12.7 (10.4-15.6)	10.9 (9.2-12.9)	10.5 (8.8-12.4)	9.6 (6.9-13.4)
All-cause mortality	41.3 (38.3-44.6)	42.6 (39.4-46.2)	43.8 (35.4-54.4)	54.1 (45.4-64.4)	55.6 (46.8-66.2)	55.6 (46.8-66.2)	38.3 (34.8-42.0)	54.1 (45.4-64.4)	48.0 (41.7-55.1)	57.1 (51.6-63.2)	56.6 (52.3-61.3)	39.9 (36.5-43.6)	40.0 (33.8-47.4)

Event rates with 95% confidence interval. MI: Myocardial infarction. *Major cardiovascular events = myocardial infarction, stroke and cardiovascular death.

eTable 3. Estimated major cardiovascular events, myocardial infarctions, strokes and deaths prevented in 5 years among individuals with ischemic heart disease by each trial.

				Events in trial eligible participants								
Potential Outcomes	**All**	**IMPROVE-IT**	**PEGASUS**	**EMPA-REG**	**LEADER**	**SUSTAIN-6**	**FOURIER**	**CANVAS**	**REVEAL**	**CANTOS**	**COMPASS**	**ODYSSEY**	**REDUCE-IT**
Major cardiovascular event prevention*													
Kaplan-Meier estimated 5 year events	877	374	350	160	168	168	313	161	105*	230	725	305	141
Relative risk reduction from trial results		0.90 (0.84-0.96)	0.84 (0.74-0.95)	0.86 (0.74-0.99)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.80 (0.73-0.88)	0.86 (0.72-0.97)	0.89 (0.81-0.97)	0.88 (0.79-0.97)	0.76 (0.66-0.86)	0.85 (0.78-0.93)	0.74 (0.68-0.83)
Estimated events prevented in CGPS		37 (15-60)	56 (17-91)	22 (3-42)	22 (5-37)	44 (8-71)	63 (38-85)	23 (4-45)	12 (3-20)	28 (7-48)	174 (101-246)	46 (21-67)	37 (24-45)
Proportion of all events prevented, %		4.2 (1.7-6.8)	6.4 (1.9-10.4)	2.5 (0.3-4.8)	2.5 (0.6-4.2)	5.0 (0.9-8.1)	7.2 (4.3-9.7)	2.6 (0.5-5.1)	1.4 (0.3-2.3)	3.2 (0.8-5.5)	19.8 (11.5-28.0)	5.2 (2.4-7.6)	4.2 (2.7-5.1)
MI prevention													
Kaplan-Meier estimated 5 year events	343	139	118	61	63	63	120	62	60	81	267	117	64
Relative risk reduction from trial results		0.87 (0.80-0.95)	0.81 (0.69-0.95)	0.87 (0.70-1.09)	0.86 (0.73-1.0)	0.74 (0.51-1.08)	0.73 (0.65-0.82)	0.89 (0.73-1.09)	0.87 (0.78-0.96)	0.84 (0.73-0.97)	0.86 (0.70-1.05)	0.86 (0.77-0.96)	0.69 (0.58-0.81)
Estimated events prevented in CGPS		18 (7-28)	22 (6-37)	8 (-5-18)	9 (0-17)	16 (-5-31)	33 (22-42)	6 (-6-17)	8 (2-13)	13 (2-22)	37 (-13-80)	16 (5-27)	20 (12-27)
Proportion of all events prevented, %		5.2 (2.0-8.2)	6.4 (1.7-10.8)	2.3 (-1.6 – 5.2)	2.6 (0-5.0)	4.7 (-1.7-10.6)	9.6 (6.4-12.2)	1.7 (-1.7-5.0)	2.3 (0.5-3.8)	3.8 (0.6-6.4)	10.8 (-3.8-23.3)	4.5 (1.5-7.9)	5.8 (3.5-7.9)
Stroke prevention													
Kaplan-Meier estimated 5 year events	321	118	104	56	55	55	94	56	51	74	253	101	39
Relative risk reduction from trial results		0.86 (0.73-1.00)	0.75 (0.57-0.98)	1.18 (0.89-1.56)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.79 (0.66-0.95)	0.87 (0.69-1.09)	0.89 (0.65-1.22)	0.93 (0.72-1.20)	0.58 (0.44-0.76)	0.73 (0.57-0.93)	0.72 (0.55-0.93)

Estimated events prevented in CGPS		17 (0-32)	26 (2-45)	-10 (-31-6)	24 (-10-48)	21 (1-34)	20 (5-32)	7 (-5-17)	6 (-11-18)	5 (-15-21)	106 (61-142)	27 (7-43)	11 (2-18)	
Proportion of all events prevented, %		5.3 (0-10.0)	8.1 (0.6-14.0)	-3.1 (-9.7-1.9)	7.5 (-3.1-15.0)	6.5 (0.3-10.6)	6.2 (1.6-10.0)	2.2 (-1.6-5.3)	1.9 (-3.4-5.6)	1.6 (-4.7-6.5)	33.0 (19.0-44.3)	8.4 (2.2-13.4)	3.4 (0.6-5.6)	
All-cause mortality prevention														
Kaplan-Meier estimated 5 year events	727	302	315	139	149	147	234	139	143	201	674	243	118	
Relative risk reduction from trial results		0.99 (0.91-1.07)	0.89 (0.76-1.04)	0.68 (0.57-0.82)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	1.04 (0.91-1.19)	0.87 (0.74-1.01)	0.97 (0.89-1.05)	0.94 (0.83-1.06)	0.82 (0.71-.0.96)	0.85 (0.73-0.98)	0.87 (0.74-1.02)	
Estimated events prevented in CGPS		3 (-21-27)	35 (-13-76)	44 (25-60)	22 (4-39)	-7 (-74-38)	-9 (-44-21)	22 (-1-36)	4 (-7-26)	12 (-12-34)	121 (27-195)	36 (5-66)	15 (-2-31)	
Proportion of all events prevented, %		0.4 (-2.9-3.7)	4.8 (-1.8-10.5)	6.1 (3.4 – 8.3)	3.0 (0.6-5.4)	-1.0 (-10.2-5.2)	-1.2 (-6.1-2.9)	3.0 (-0.1-5.0)	0.6 (-1.0-3.6)	1.7 (-1.7-4.7)	16.6 (4.0-26.8)	5.0 (0.7-9.1)	2.1 (-0.2-4.3)	

MI: Myocardial infarction. CGPS: Copenhagen general Population Study.
*Major cardiovascular events = myocardial infarction, stroke and cardiovascular death. For REVEAL, the composite endpoint was coronary death and myocardial infarction.

eTable 4. Estimated major cardiovascular events, myocardial infarctions, strokes and deaths prevented in 5 years among individuals with prior myocardial infarction by each trial.

				Events in trial eligible participants								
Potential Outcomes	**All**	**IMPROVE-IT**	**PEGASUS**	**EMPA-REG**	**LEADER**	**SUSTAIN-6**	**FOURIER**	**CANVAS**	**REVEAL**	**CANTOS**	**COMPASS**	**ODYSSEY**	**REDUCE-IT**
Major cardiovascular event prevention*													
Kaplan-Meier estimated 5 year events	414	374	350	73	77	77	290	74	81*	230	344	305	76
Relative risk reduction from trial results		0.90 (0.84-0.96)	0.84 (0.74-0.95)	0.86 (0.74-0.99)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.80 (0.73-0.88)	0.86 (0.72-0.97)	0.89 (0.81-0.97)	0.88 (0.79-0.97)	0.76 (0.66-0.86)	0.85 (0.78-0.93)	0.74 (0.68-0.83)
Estimated events prevented in CGPS		37 (15-60)	56 (17-91)	10 (1-19)	10 (2-17)	20 (4-32)	58 (35-78)	10 (2-21)	9 (2-15)	28 (7-48)	83 (48-117)	46 (21-67)	20 (13-24)
Proportion of all events prevented, %		8.9 (3.6-14.5)	13.5 (4.1-22.0)	2.4 (0.2–4.6)	2.4 (0.5-4.1)	4.8 (1.0-7.7)	14.0 (8.5-18.8)	2.4 (0.5-5.1)	2.2 (0.5-3.6)	6.8 (1.7-11.6)	20.0 (11.6-28.3)	11.1 (5.1-16.2)	4.8 (3.1-5.8)
MI prevention													
Kaplan-Meier estimated 5 year events	157	139	118	25	28	28	114	25	44	81	117	117	34
Relative risk reduction from trial results		0.87 (0.80-0.95)	0.81 (0.69-0.95)	0.87 (0.70-1.09)	0.86 (0.73-1.0)	0.74 (0.51-1.08)	0.73 (0.65-0.82)	0.89 (0.73-1.09)	0.87 (0.78-0.96)	0.84 (0.73-0.97)	0.86 (0.70-1.05)	0.86 (0.77-0.96)	0.69 (0.58-0.81)
Estimated events prevented in CGPS		18 (7-28)	22 (6-37)	6 (-2-7)	4 (0-8)	7 (-2-14)	31 (21-40)	3 (-2-7)	6 (-2-10)	13 (2-22)	16 (-6-35)	16 (5-27)	11 (6-14)
Proportion of all events prevented, %		11.5 (4.5-17.8)	14.0 (3.8-23.6)	3.8 (-1.3-4.5)	2.5 (0.0-5.1)	4.5 (-1.2-8.9)	19.7 (13.4-25.5)	1.9 (-1.3-4.5)	3.8 (1.3-6.4)	8.3 (1.3-14.0)	10.2 (-3.8-22.3)	10.2 (3.2-17.2)	7.0 (3.8-8.9)
Stroke prevention													
Kaplan-Meier estimated 5 year events	128	118	104	22	22	22	83	22	35	74	100	101	22
Relative risk reduction from trial results		0.86 (0.73-1.00)	0.75 (0.57-0.98)	1.18 (0.89-1.56)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.79 (0.66-0.95)	0.87 (0.69-1.09)	0.89 (0.65-1.22)	0.93 (0.72-1.20)	0.58 (0.44-0.76)	0.73 (0.57-0.93)	0.72 (0.55-0.93)
Estimated events		17 (0-32)	26 (2-45)	-4 (-12-2)	3 (-1-5)	9 (1-14)	17 (4-28)	3 (-2-7)	4 (-8-12)	5 (-15-21)	42 (24-56)	27 (7-43)	6 (2-10)

prevented in CGPS														
Proportion of all events prevented, %		13.3 (0-25)	20.3 (1.6-35.2)	-3.1 (-9.4-1.6)	2.3 (-0.8-3.9)	7.0 (0.8-10.9)	13.3 (3.1-21.1)	2.3 (-1.6-5.5)	3.1 (-6.3-9.4)	3.9 (-11.7-16.4)	32.8 (18.8-43.8)	21.1 (5.5-33.6)	4.7 (1.6-7.8)	
All-cause mortality prevention														
Kaplan-Meier estimated 5 year events	336	302	315	60	63	62	213	60	105	201	313	243	61	
Relative risk reduction from trial results		0.99 (0.91-1.07)	0.89 (0.76-1.04)	0.68 (0.57-0.82)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	1.04 (0.91-1.19)	0.87 (0.74-1.01)	0.97 (0.89-1.05)	0.94 (0.83-1.06)	0.82 (0.71-.0.96)	0.85 (0.73-0.98)	0.87 (0.74-1.02)	
Estimated events prevented in CGPS		3 (-21-27)	35 (-13-76)	19 (11-24)	9 (2-16)	-3 (-31-16)	-9 (-40-19)	8 (-1-16)	3 (-5-12)	12 (-12-34)	56 (13-91)	36 (5-66)	8 (-1-16)	
Proportion of all events prevented, %		0.9 (-6.3-8.0)	10.4 (-3.9-22.6)	5.7 (3.3 – 7.1)	2.7 (0.6-4.8)	-0.9 (-9.2-4.8)	-2.7 (-11.9-5.7)	2.4 (-0.3-4.8)	0.9 (-1.5-3.6)	3.6 (-3.6-10.1)	16.7 (3.9-27.1)	10.7 (1.4-19.6)	2.4 (-0.3-4.8)	

MI: Myocardial infarction. CGPS: Copenhagen general Population Study.
*Major cardiovascular events = myocardial infarction, stroke and cardiovascular death. For REVEAL, the composite endpoint was coronary death and myocardial infarction.

eTable 5. Baseline characteristics of patients with ischemic heart disease or prior myocardial infarction from the Copenhagen General Population Study and of those eligible for new medication to prevent atherosclerotic cardiovascular disease according to inclusion and exclusion criteria used in ten different trials (strictly following ASCVD time-criteria used in clinical trials)

						Eligibility according to trial criteria							
Characteristics	**All**	**IMPROVE-IT**	**PEGASUS**	**EMPA-REG**	**LEADER**	**SUSTAIN-6**	**FOURIER**	**CANVAS**	**REVEAL**	**CANTOS**	**COMPASS**	**ODYSSEY**	**REDUCE-IT**
Ischemic heart disease													
Individuals, n	6292	1	253	806	809	802	1511	818	842	922	4176	80	977
Gender, male, n (%)	3861 (61)	-	175 (69)	554 (70)	551 (68)	546 (68)	1126 (75)	562 (69)	687 (82)	637 (69)	2682 (63)	52 (65)	743 (76)
Age, years	69 (62-76)	-	73 (69-79)	71 (65-77)	71 (65-77)	71 (65-77)	72 (66-78)	71 (65-77)	72 (66-78)	72 (65-79)	74 (69-79)	68 (61-77)	70 (64-76)
Blood pressure, mmHg													
Systolic,	144 (130-158)	-	143 (132-160)	144 (130-158)	144 (130-158)	144 (130-158)	142 (130-157)	144 (130-158)	140 (126-154)	143 (130-159)	145 (132-160)	140 (128-151)	142 (130-157)
Diastolic,	82 (75-90)	-	80 (72-88)	80 (71-86)	80 (71-86)	80 (71-86)	80 (72-88)	80 (71-86)	79 (71-85)	80 (72-89)	80 (73-89)	79 (70-87)	80 (73-88)
Cholesterol, mg/dL													
Total cholesterol	190 (163-224)	-	166 (143-193)	166 (143-197)	166 (143-197)	166 (143-197)	166 (147-189)	166 (143-197)	139 (128-147)	178 (151-213)	186 (159-217)	190 (163-217))	166 (151-182)
HDL cholesterol	55 (44-69)	-	54 (44-65)	48 (39-61)	48 (39-61)	47 (39-61)	51 (41-64)	48 (39-61)	46 (38-56)	49 (40-63)	56 (44-70)	48 (42-60)	45 (37-56)
LDL cholesterol	101 (76-130)	-	81 (66-104)	77 (60-104)	77 (60-104)	77 (60-104)	81 (66-101)	77 (61-104)	62 (50-73)	93 (70-120)	93 (72-124)	106 (85-124)	74 (62-85)
Triglycerides	137 (96-202)	-	134 (90-188)	168 (112-251)	169 (112-251)	169 (112-251)	144 (100-212)	168 (112-251)	124 (89-180)	153 (112-224)	136 (96-198)	147 (112-209)	210 (175-274)
C-reactive protein, mg/L	1.6 (1.0-2.9)	-	1.6 (1.0-3.2)	1.8 (1.1-3.5)	1.8 (1.1-3.7)	1.8 (1.1-3.6)	1.6 (1.0-2.9)	1.8 (1.1-3.6)	1.5 (1.0-3.1)	3.8 (2.6-5.9)	1.7 (1.1-3.2)	1.6 (1.1-3.6)	1.6 (1.1-2.9)
Current smokers, n (%)	984 (16)	-	34 (13)	115 (14)	113 (14)	114 (14)	289 (19)	118 (14)	126 (15)	206 (22)	593 (14)	11 (14)	134 (14)
Diabetes, n (%)	830 (13)	-	60 (24)	806 (100)	809 (100)	802 (100)	309 (20)	818 (100)	316 (38)	168 (18)	747 (17)	9 (11)	275 (28)
Statin use, n (%)	3535 (56)	-	202 (80)	637 (79)	645 (80)	638 (80)	1511 (100)	648 (79)	783 (93)	629 (68)	2633 (62)	55 (69)	977 (100)
Myocardial infarction													
Individuals, n	2277	1	253	330	334	331	1408	334	626	922	1608	80	474
Gender, male, n (%)	1637 (72)	-	175 (69)	254 (77)	255 (76)	252 (76)	1142 (75)	257 (77)	526 (84)	637 (69)	1189 (73)	52 (65)	387 (82)
Age, years	70 (63-77)	-	73 (69-79)	71 (66-77)	71 (66-77)	71 (66-77)	71 (65-77)	71 (66-76)	72 (66-78)	72 (65-79)	74 (69-79)	68 (61-77)	70 (63-76)
Blood pressure, mmHg													
Systolic,	142 (130-157)	-	143 (132-160)	144 (130-156)	144 (130-156)	144 (130-156)	142 (130-156)	144 (130-156)	140 (125-152)	143 (130-159)	144 (130-160)	140 (128-151)	141 (130-156)
Diastolic,	80 (73-89)	-	80 (72-88)	79 (70-86)	79 (70-86)	79 (70-86)	80 (72-88)	79 (70-86)	79 (70-85)	80 (72-89)	80 (72-88)	79 (70-87)	80 (72-88)
Cholesterol, mg/dL													
Total cholesterol	174 (151-209)	-	166 (143-193)	163 (143-190)	163 (139-190)	163 (139-190)	166 (147-190)	163 (143-190)	139 (128-147)	178 (151-213)	174 (151-205)	190 (163-217))	163 (147-178)
HDL cholesterol	52 (42-65)	-	54 (44-65)	47 (38-59)	46 (38-59)	46 (38-59)	51 (41-63)	46 (38-59)	46 (38-59)	49 (40-63)	53 (42-66)	48 (42-60)	44 (36-54)
LDL cholesterol	89 (70-116)	-	81 (66-104)	76 (58-102)	75 (58-101)	76 (58-101)	81 (66-101)	76 (58-102)	63 (51-73)	93 (70-120)	85 (67-112)	106 (85-124)	74 (62-85)
Triglycerides	140 (97-206)	-	140 (97-206)	174 (118-248)	174 (118-248)	174 (118-249)	144 (101-213)	174 (118-249)	121 (89-174)	153 (112-224)	139 (97-204)	147 (112-209)	214 (177-277)
C-reactive protein, mg/L	1.6 (1.0-3.0)	-	1.6 (1.0-3.2)	1.9 (1.1-3.9)	1.9 (1.1-3.9)	1.9 (1.1-3.9)	1.5 (1.0-2.8)	1.9 (1.1-3.9)	1.5 (1.0-3.1)	3.8 (2.6-5.9)	1.7 (1.1-3.3)	1.6 (1.1-3.6)	1.7 (1.1-3.0)
Current smokers, n (%)	412 (18)	-	34 (13)	63 (19)	62 (19)	62 (19)	278 (20)	64 (19)	107 (17)	206 (22)	276 (17)	11 (14)	80 (17)

Diabetes, n (%)	338 (15)	-	60 (24)	330 (100)	334 (100)	331 (100)	284 (19)	334 (100)	133 (21)	168 (18)	308 (21)	9 (11)	119 (25)
Satin use, n (%)	1671 (74)	-	202 (80)	282 (86)	287 (86)	284 (86)	1517 (100)	286 (86)	589 (94)	629 (68)	1228 (75)	55 (69)	474 (100)

Baseline characteristics are presented as proportions for categorical variables and as medians (interquartile range) for continuous variables.

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

Only 1 individual met inclusion criteria in IMPROVE-IT when ASCVD time-criteria was followed (acute coronary syndrome within 10 days).

eTable 6. Event rates for myocardial infarction, stroke and all-cause mortality per 1000 person-years among trial-eligible individuals and in the total Copenhagen General Population Study cohort (strictly following ASCVD time-criteria used in clinical trials).

Outcome	All	PEGASUS	EMPA-REG	LEADER	SUSTAIN-6	FOURIER	CANVAS	REVEAL	CANTOS	COMPASS	ODYSSEY	REDUCE-IT
Ischemic heart disease												
Major cardiovascular events*	31.5 (29.8-33.4)	37.4 (28.9-48.0)	45.2 (39.4-51.8)	47.2 (41.2-54.0)	47.4 (41.4-54.2)	44.8 (40.3-49.7)	44.7 (39.1-51.3)	42.7 (37.0-49.4)	54.8 (48.6-61.8)	41.8 (39.3-44.5)	34.9 (22.0-55.4)	35.0 (30.4-40.2)
MI	10.6 (9.7-11.6)	12.1 (8.1-18.0)	15.2 (12.3-18.8)	15.4 (12.5-19.0)	15.6 (12.6-19.2)	13.5 (11.3-16.0)	15.2 (12.3-18.7)	12.9 (10.2-16.4)	15.2 (12.4-18.5)	12.2 (11.0-13.5)	11.1 (5.3-23.3)	13.0 (10.5-16.1)
Stroke	9.8 (8.9-10.7)	9.1 (5.8-14.2)	13.2 (10.6-16.5)	13.1 (10.5-16.4)	13.3 (10.6-16.6)	11.0 (9.2-13.1)	13.2 (10.6-16.4)	11.9 (9.4-15.1)	12.8 (10.4-15.6)	11.9 (10.8-13.2)	7.5 (3.1-18.1)	9.5 (7.5-12.0)
All-cause mortality	32.0 (30.3-33.7)	43.9 (35.4-54.4)	47.4 (41.9-53.5)	50.0 (44.4-53.5)	50.0 (44.4-56.4)	44.2 (40.3-48.4)	46.9 (41.6-53.0)	47.6 (42.2-53.8)	57.1 (51.5-63.2)	45.9 (43.4-48.5)	40.1 (26.9-59.9)	35.7 (31.5-40.4)
Myocardial infarction												
Major cardiovascular events*	39.9 (36.5-43.5)	37.3 (28.9-48.0)	51.0 (41.5-62.7)	52.3 (42.6-64.1)	52.2 (42.5-64.1)	44.1 (39.5-49.2)	50.8 (41.3-62.4)	41.5 (34.9-49.3)	54.8 (48.6-61.8)	49.9 (45.3-55.0)	34.9 (22.0-55.4)	36.5 (29.7-44.7)
MI	12.5 (10.8-14.4)	12.1 (8.1-18.0)	14.8 (10.5-20.1)	15.1 (10.8-21.2)	15.3 (10.9-21.4)	13.4 (11.2-16.0)	15.0 (10.7-21.0)	12.0 (9.0-16.0)	15.2 (12.4-18.5)	13.4 (11.4-15.8)	11.1 (5.3-23.3)	12.7 (9.2-17.5)
Stroke	9.8 (8.4-11.3)	9.1 (5.8-14.2)	11.8 (8.3-16.8)	11.7 (8.2-16.8)	11.8 (8.3-16.8)	10.3 (8.5-12.4)	11.7 (8.2-16.6)	10.1 (7.5-13.5)	12.8 (10.4-15.6)	10.9 (9.2-12.9)	7.5 (3.1-18.1)	9.6 (6.9-13.4)
All-cause mortality	41.3 (38.3-44.6)	43.9 (35.4-54.4)	54.4 (45.7-64.8)	55.6 (46.8-66.2)	55.6 (46.7-66.1)	43.9 (39.9-48.3)	54.1 (45.4-64.4)	48.0 (41.7-55.2)	57.1 (51.5-63.2)	56.6 (52.3-61.3)	40.1 (26.9-59.9)	40.0 (33.8-47.4)

Event rates with 95% confidence interval. MI: Myocardial infarction. Major cardiovascular events = myocardial infarction, stroke and cardiovascular death.

Only 1 individual met inclusion criteria in IMPROVE-IT when ASCVD time-criteria was followed (acute coronary syndrome within 10 days), and is therefore not shown in this table.

eTable 7. Estimated major cardiovascular events, myocardial infarctions, strokes and deaths prevented in 5 years among individuals with ischemic heart disease by each trial (strictly following ASCVD time-criteria used in clinical trials).

					Events in trial eligible participants							
Potential Outcomes	**All**	**PEGASUS**	**EMPA-REG**	**LEADER**	**SUSTAIN-6**	**FOURIER**	**CANVAS**	**REVEAL**	**CANTOS**	**COMPASS**	**ODYSSEY**	**REDUCE-IT**
Major cardiovascular event prevention*												
Kaplan-Meier estimated 5 year events	877	45	160	168	168	297	161	105*	230	725	14	141
Relative risk reduction from trial results		0.84 (0.74-0.95)	0.86 (0.74-0.99)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.80 (0.73-0.88)	0.86 (0.72-0.97)	0.89 (0.81-0.97)	0.88 (0.79-0.97)	0.76 (0.66-0.86)	0.85 (0.78-0.93)	0.74 (0.68-0.83)
Estimated events prevented in CGPS		7 (2-12)	22 (3-42)	22 (5-37)	44 (8-71)	59 (36-80)	23 (4-45)	12 (3-20)	28 (7-48)	174 (101-246)	2 (1-3)	37 (24-45)
Proportion of all events prevented, %		0.8 (0.2-1.4)	2.5 (0.3-4.8)	2.5 (0.6-4.2)	5.0 (0.9-8.1)	6.7 (4.1-9.1)	2.6 (0.5-5.1)	1.4 (0.3-2.3)	3.2 (0.8-5.5)	19.8 (11.5-28.0)	0.2 (0.1-0.3)	4.2 (2.7-5.1)
MI prevention												
Kaplan-Meier estimated 5 year events	343	16	61	63	63	111	62	60	81	267	8	64
Relative risk reduction from trial results		0.81 (0.69-0.95)	0.87 (0.70-1.09)	0.86 (0.73-1.0)	0.74 (0.51-1.08)	0.73 (0.65-0.82)	0.89 (0.73-1.09)	0.87 (0.78-0.96)	0.84 (0.73-0.97)	0.86 (0.70-1.05)	0.86 (0.77-0.96)	0.69 (0.58-0.81)
Estimated events prevented in CGPS		3 (1-5)	8 (-5-18)	9 (0-17)	16 (-5-31)	30 (20-39)	6 (-6-17)	8 (2-13)	13 (2-22)	37 (-13-80)	1 (0-2)	20 (12-27)
Proportion of all events prevented, %		0.9 (0.3-1.5)	2.3 (-1.6 – 5.2)	2.6 (0-5.0)	4.7 (-1.7-10.6)	8.7 (6.4-11.4)	1.7 (-1.7-5.0)	2.3 (0.5-3.8)	3.8 (0.6-6.4)	10.8 (-3.8-23.3)	0.3 (0.1-0.6)	5.8 (3.5-7.9)
Stroke prevention												
Kaplan-Meier estimated 5 year events	321	16	56	55	55	91	56	51	74	253	3	39
Relative risk reduction from trial results		0.75 (0.57-0.98)	1.18 (0.89-1.56)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.79 (0.66-0.95)	0.87 (0.69-1.09)	0.89 (0.65-1.22)	0.93 (0.72-1.20)	0.58 (0.44-0.76)	0.73 (0.57-0.73)	0.72 (0.55-0.93)
Estimated events		4 (1-6)	-10 (-31-6)	24 (-10-48)	21 (1-34)	19 (5-31)	7 (-5-17)	6 (-11-18)	5 (-15-21)	106 (61-142)	1 (1-1)	11 (2-18)

prevented in CGPS													
Proportion of all events prevented, %		1.2 (0.3-1.9)	-3.1 (-9.7-1.9)	7.5 (-3.1-15.0)	6.5 (0.3-10.6)	5.9 (1.6-9.7)	2.2 (-1.6-5.3)	1.9 (-3.4-5.6)	1.6 (-4.7-6.5)	33.0 (19.0-44.3)	0.3 (0.3-0.3)	3.4 (0.6-5.6)	
All-cause mortality prevention													
Kaplan-Meier estimated 5 year events	727	35	139	149	147	229	139	143	201	674	11	118	
Relative risk reduction from trial results		0.89 (0.76-1.04)	0.68 (0.57-0.82)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	1.04 (0.91-1.19)	0.87 (0.74-1.01)	0.97 (0.89-1.05)	0.94 (0.83-1.06)	0.82 (0.71-.0.96)	0.85 (0.73-0.98)	0.87 (0.74-1.02)	
Estimated events prevented in CGPS		4 (-1-8)	44 (25-60)	22 (4-39)	-7 (-74-38)	-9 (-44-21)	22 (-1-36)	4 (-7-26)	12 (-12-34)	121 (27-195)	2 (1-3)	15 (-2-31)	
Proportion of all events prevented, %		0.6 (-0.1-1.1)	6.1 (3.4 – 8.3)	3.0 (0.6-5.4)	-1.0 (-10.2-5.2)	-1.2 (-6.1-2.9)	3.0 (-0.1-5.0)	0.6 (-1.0-3.6)	1.7 (-1.7-4.7)	16.6 (4.0-26.8)	0.3 (0.0-0.4)	2.1 (-0.2-4.3)	

MI: Myocardial infarction. CGPS: Copenhagen General Population Study.
Only 1 individual met inclusion criteria in IMPROVE-IT when ASCVD time-criteria was followed (acute coronary syndrome within 10 days), and is therefore not shown in this table.
*Major cardiovascular events = myocardial infarction, stroke and cardiovascular death. For REVEAL, the composite endpoint was coronary death and myocardial infarction.

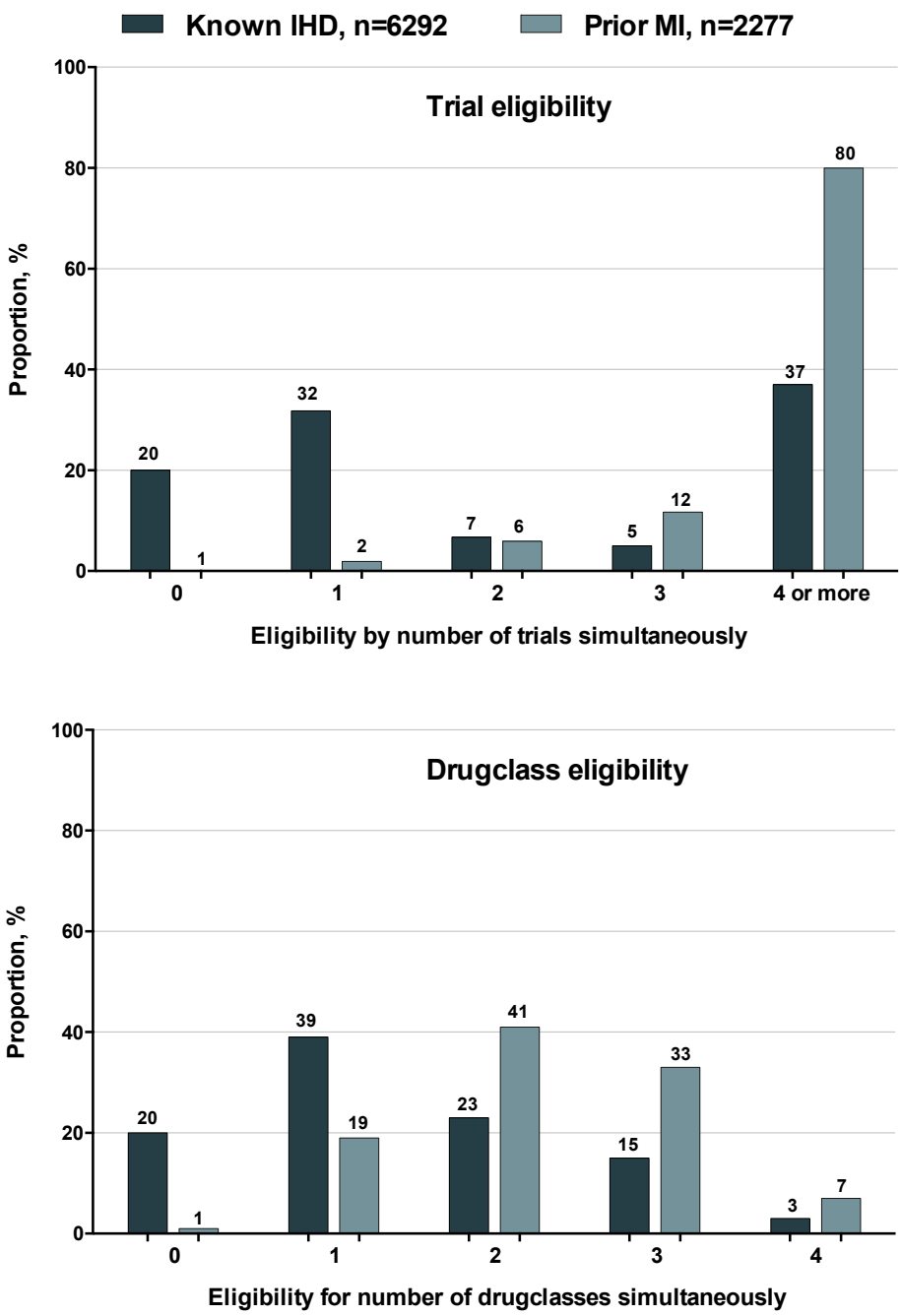
eTable 8. Estimated major cardiovascular events, myocardial infarctions, strokes and deaths prevented in 5 years among individuals with prior myocardial infarction by each trial (strictly following ASCVD time-criteria used in clinical trials).

					Events in trial eligible participants							
Potential Outcomes	**All**	**PEGASUS**	**EMPA-REG**	**LEADER**	**SUSTAIN-6**	**FOURIER**	**CANVAS**	**REVEAL**	**CANTOS**	**COMPASS**	**ODYSSEY**	**REDUCE-IT**
Major cardiovascular event prevention*												
Kaplan-Meier estimated 5 year events	414	45	73	77	77	274	74	81*	230	344	14	76
Relative risk reduction from trial results		0.84 (0.74-0.95)	0.86 (0.74-0.99)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.80 (0.73-0.88)	0.86 (0.72-0.97)	0.89 (0.81-0.97)	0.88 (0.79-0.97)	0.76 (0.66-0.86)	0.85 (0.78-0.93)	0.74 (0.68-0.83)
Estimated events prevented in CGPS		7 (2-12)	10 (1-19)	10 (2-17)	20 (4-32)	55 (33-74)	10 (2-21)	9 (2-15)	28 (7-48)	83 (48-117)	2 (1-3)	20 (13-24)
Proportion of all events prevented, %		1.7 (0.5-2.9)	2.4 (0.2–4.6)	2.4 (0.5-4.1)	4.8 (1.0-7.7)	13.3 (7.8-17.9)	2.4 (0.5-5.1)	2.2 (0.5-3.6)	6.8 (1.7-11.6)	20.0 (11.6-28.3)	0.5 (0.2-0.7)	4.8 (3.1-5.8)
MI prevention												
Kaplan-Meier estimated 5 year events	157	16	25	28	28	105	25	44	81	117	8	34
Relative risk reduction from trial results		0.81 (0.69-0.95)	0.87 (0.70-1.09)	0.86 (0.73-1.0)	0.74 (0.51-1.08)	0.73 (0.65-0.82)	0.89 (0.73-1.09)	0.87 (0.78-0.96)	0.84 (0.73-0.97)	0.86 (0.70-1.05)	0.86 (0.77-0.96)	0.69 (0.58-0.81)
Estimated events prevented in CGPS		3 (1-5)	6 (-2-7)	4 (0-8)	7 (-2-14)	28 (19-37)	3 (-2-7)	6 (-2-10)	13 (2-22)	16 (-6-35)	1 (0-2)	11 (6-14)
Proportion of all events prevented, %		1.9 (0.6-3.2)	3.8 (-1.3-4.5)	2.5 (0.0-5.1)	4.5 (-1.2-8.9)	17.8 (12.1-23.6)	1.9 (-1.3-4.5)	3.8 (1.3-6.4)	8.3 (1.3-14.0)	10.2 (-3.8-22.3)	0.6 (0.1-1.3)	7.0 (3.8-8.9)
Stroke prevention												
Kaplan-Meier estimated 5 year events	128	16	22	22	22	79	22	35	74	100	3	22
Relative risk reduction from trial results		0.75 (0.57-0.98)	1.18 (0.89-1.56)	0.86 (0.71-1.06)	0.61 (0.38-0.99)	0.79 (0.66-0.95)	0.87 (0.69-1.09)	0.89 (0.65-1.22)	0.93 (0.72-1.20)	0.58 (0.44-0.76)	0.73 (0.57-0.73)	0.72 (0.55-0.93)

Estimated events prevented in CGPS		4 (1-6)	-4 (-12-2)	3 (-1-5)	9 (1-14)	17 (4-27)	3 (-2-7)	4 (-8-12)	5 (-15-21)	42 (24-56)	1 (1-1)	6 (2-10)	
Proportion of all events prevented, %		3.1 (0.8-4.7)	-3.1 (-9.4-1.6)	2.3 (-0.8-3.9)	7.0 (0.8-10.9)	13.3 (3.1-21.1)	2.3 (-1.6-5.5)	3.1 (-6.3-9.4)	3.9 (-11.7-16.4)	32.8 (18.8-43.8)	0.8 (0.8-0.8)	4.7 (1.6-7.8)	
All-cause mortality prevention													
Kaplan-Meier estimated 5 year events	336	35	60	63	62	209	60	105	201	313	1	61	
Relative risk reduction from trial results		0.89 (0.76-1.04)	0.68 (0.57-0.82)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	1.04 (0.91-1.19)	0.87 (0.74-1.01)	0.97 (0.89-1.05)	0.94 (0.83-1.06)	0.82 (0.71-.0.96)	0.85 (0.73-0.98)	0.87 (0.74-1.02)	
Estimated events prevented in CGPS		4 (-1-8)	19 (11-24)	9 (2-16)	-3 (-31-16)	-8 (-34-19)	8 (-1-16)	3 (-5-12)	12 (-12-34)	56 (13-91)	2 (1-3)	8 (-1-16)	
Proportion of all events prevented, %		1.2 (-0.3-2.4)	5.7 (3.3 – 7.1)	2.7 (0.6-4.8)	-0.9 (-9.2-4.8)	-2.4 (-10.1-5.7)	2.4 (-0.3-4.8)	0.9 (-1.5-3.6)	3.6 (-3.6-10.1)	16.7 (3.9-27.1)	0.6 (0.3-0.9)	2.4 (-0.3-4.8)	

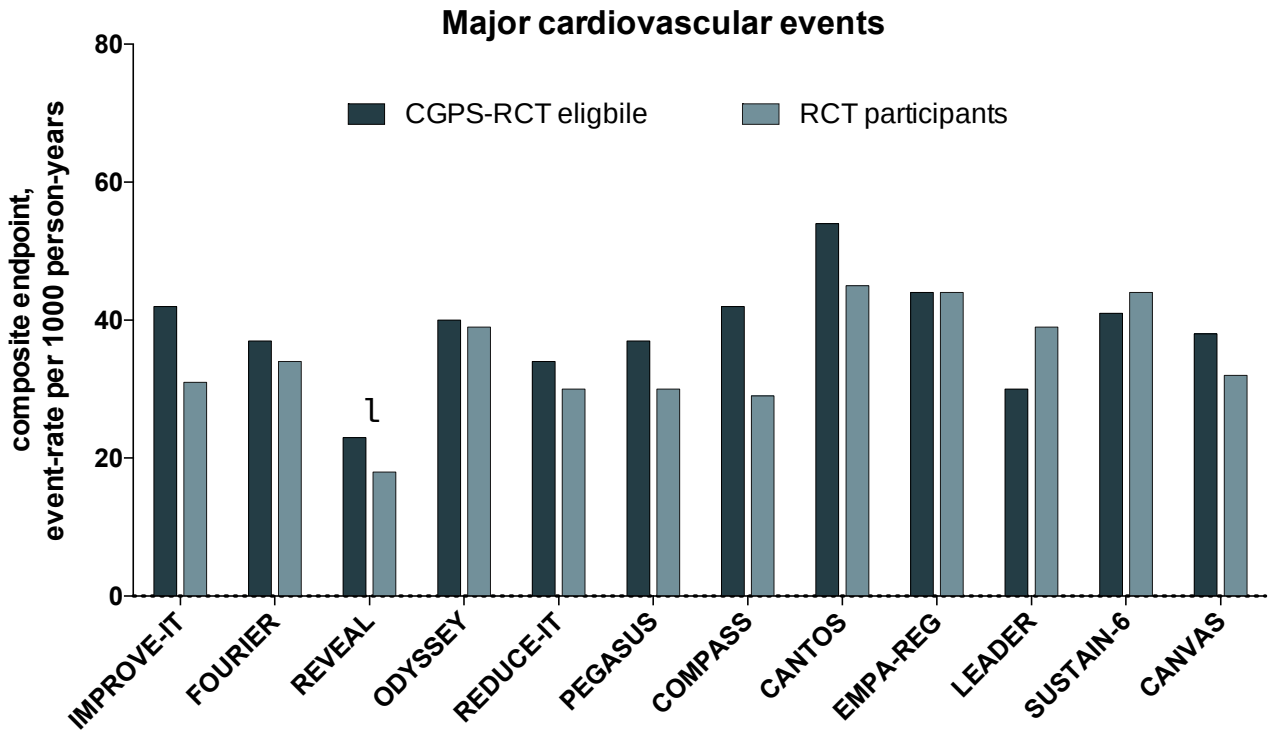
MI: Myocardial infarction. CGPS: Copenhagen General Population Study.
Only 1 individual met inclusion criteria in IMPROVE-IT when ASCVD time-criteria was followed (acute coronary syndrome within 10 days), and is therefore not shown in this table.
*Major cardiovascular events = myocardial infarction, stroke and cardiovascular death. For REVEAL, the composite endpoint was coronary death and myocardial infarction.

eFigure 1



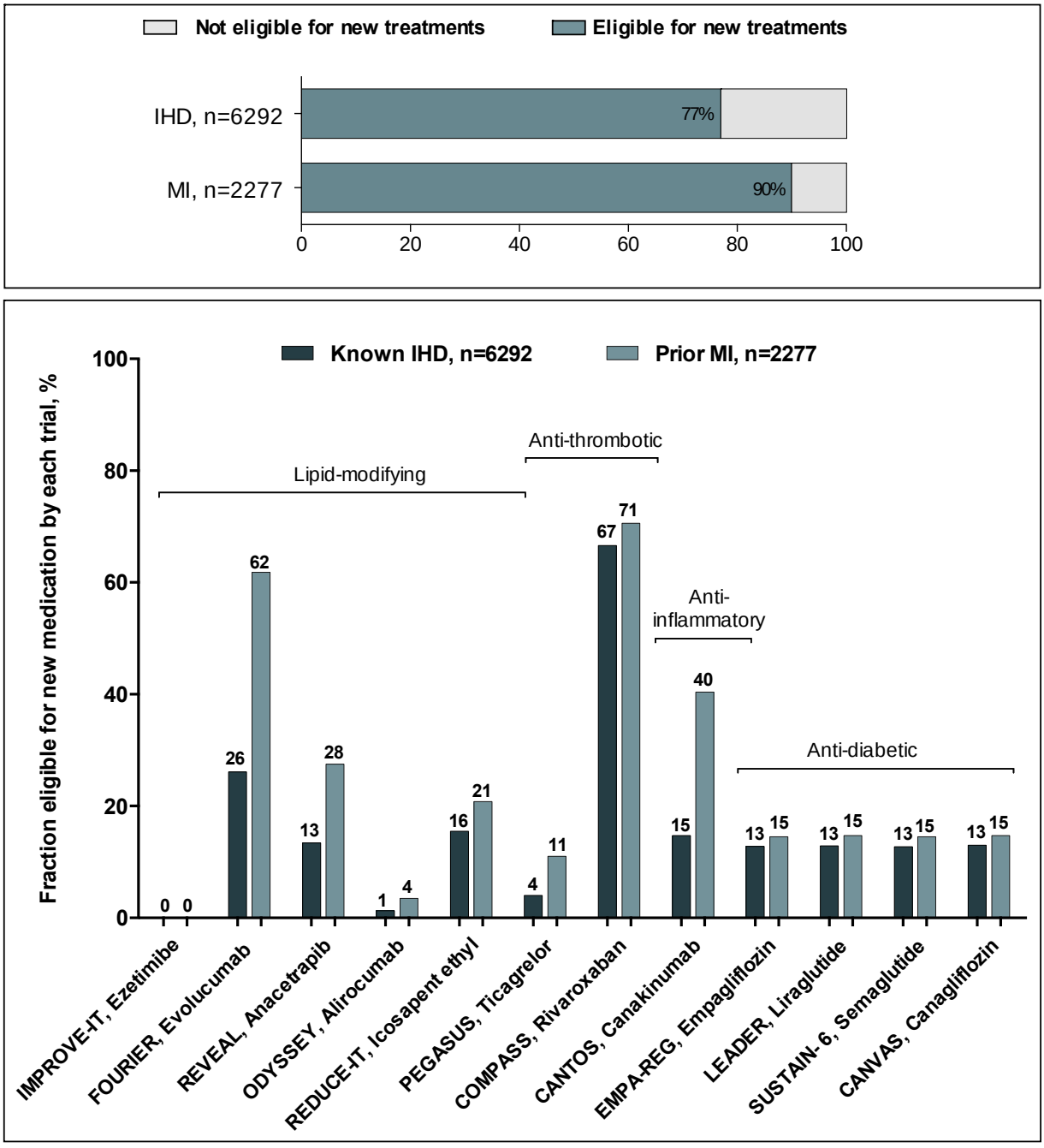
eFigure 1: Eligibility for novel therapies to prevent atherosclerotic cardiovascular disease and death by number of trials or drug classes simultaneously. Upper panel: Eligibility by number of different trials simultaneously. **Lower panel**: When divided into 4 potential drug classes (lipid-modifying, anti-thrombotic, anti-inflammatory, and anti-diabetic drugs), a large proportion of individuals with known IHD or previous MI met criteria for 2 or more different drug classes simultaneously. Based on patients from the Copenhagen General Population Study.

eFigure 2



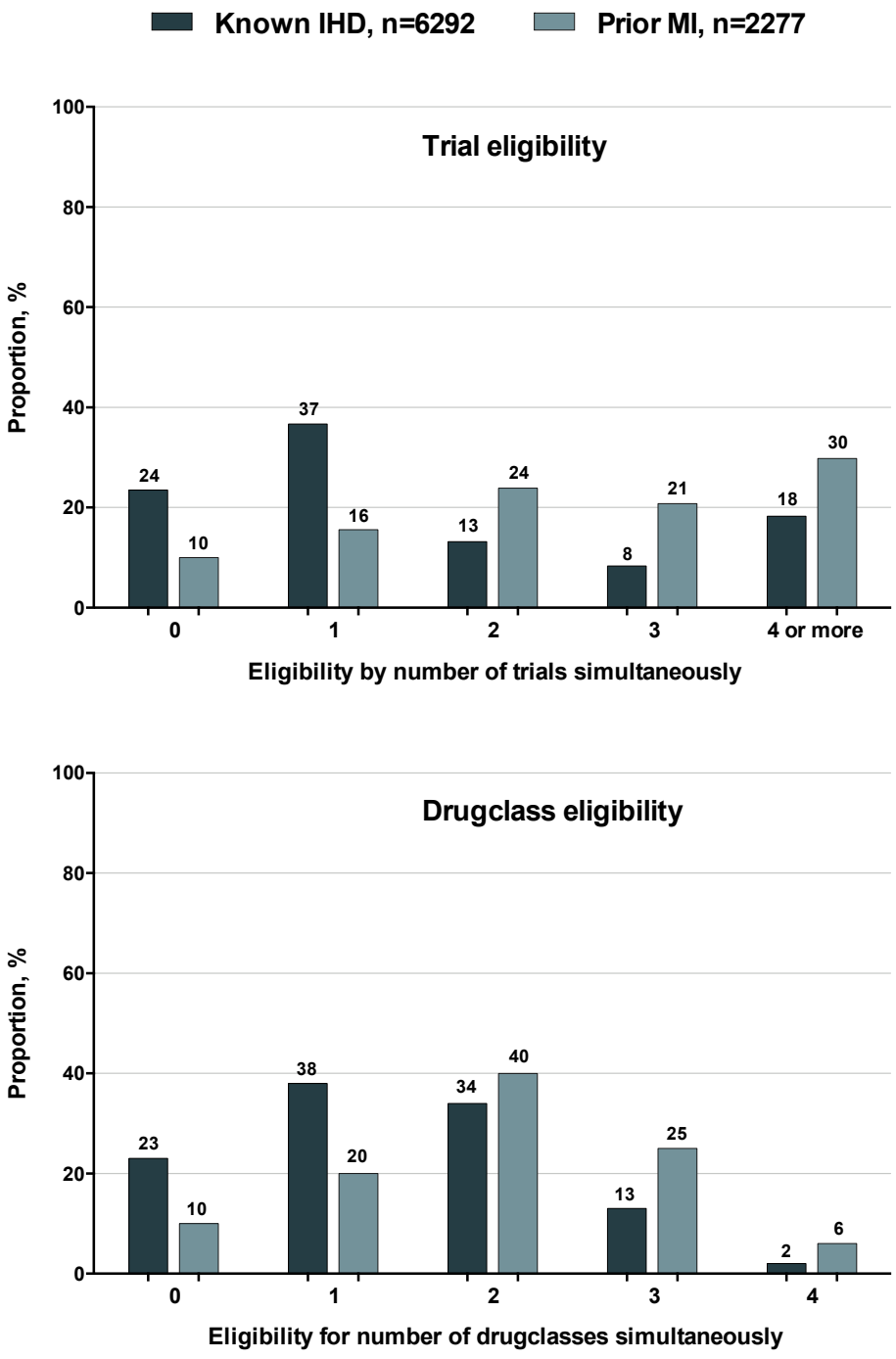
eFigure 2: Comparison of event rate per 1000 person-years of major cardiovascular events in trial-eligible Copenhagen General Population Study participant and actual patients from the randomized controlled trials. Major cardiovascular events were the composite endpoint of myocardial infarction, stroke and cardiovascular death. λ = As the REVEAL study did not use this endpoint, we compared event rates of a composite endpoint consisting of myocardial infarction and coronary death. RCT = randomized controlled trial. CGPS = Copenhagen General Population Study).

eFigure 3



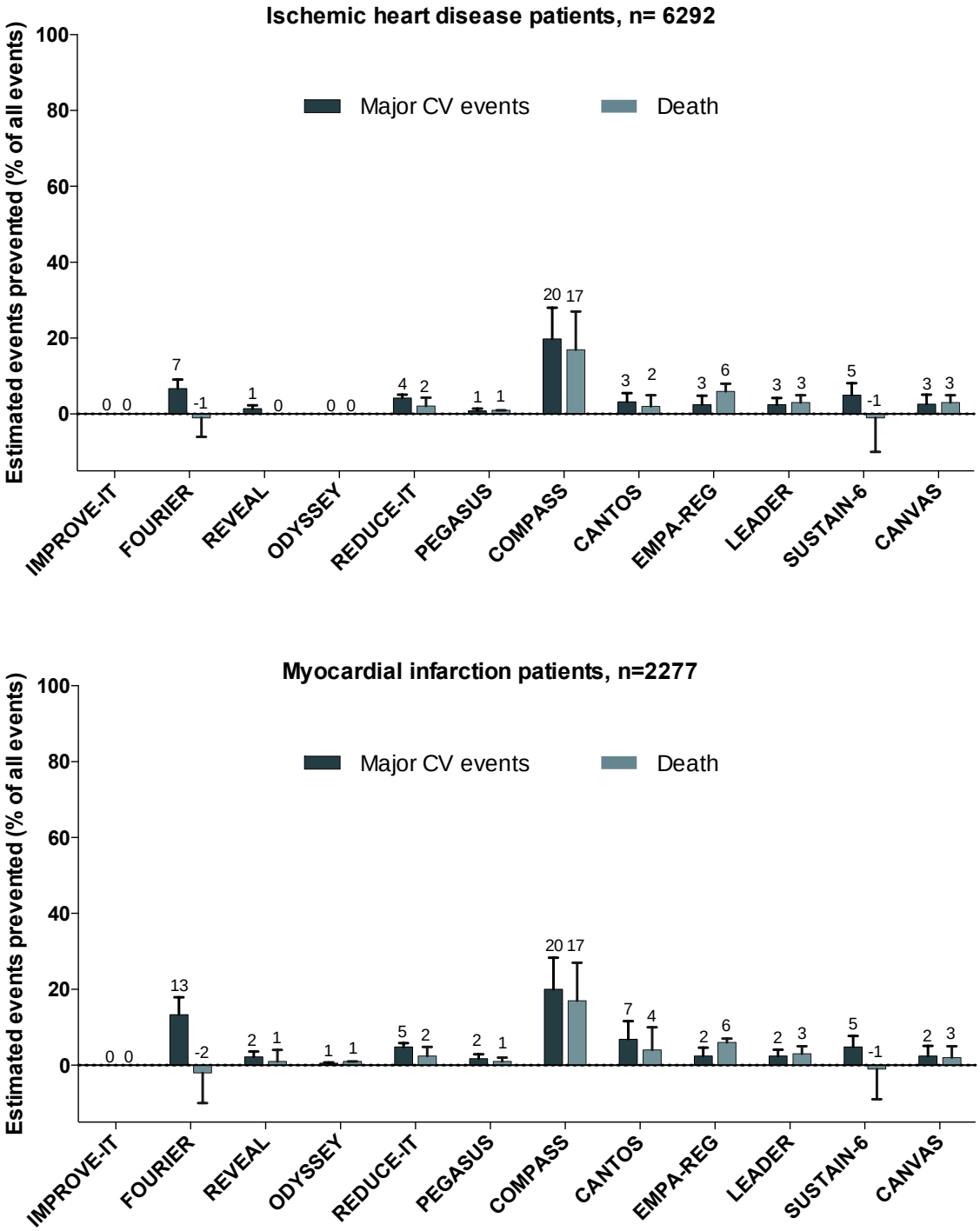
eFigure 3: Eligibility for novel therapies to prevent atherosclerotic cardiovascular disease and death in patients with known ischemic heart disease or prior myocardial infarction from a contemporary general population (strictly following ASCVD time-criteria used in clinical trials). Upper panel: Proportion eligible for at least one new secondary prevention medication**. Lower panel:** Eligibility by each trial individually ordered by drug classes**.** Only 1 individual in Copenhagen General Population Study met inclusion criteria in the IMPROVE-IT trial when ASCVD time-criteria was followed (acute coronary syndrome within 10 days). Based on patients from the Copenhagen General Population Study.

eFigure 4



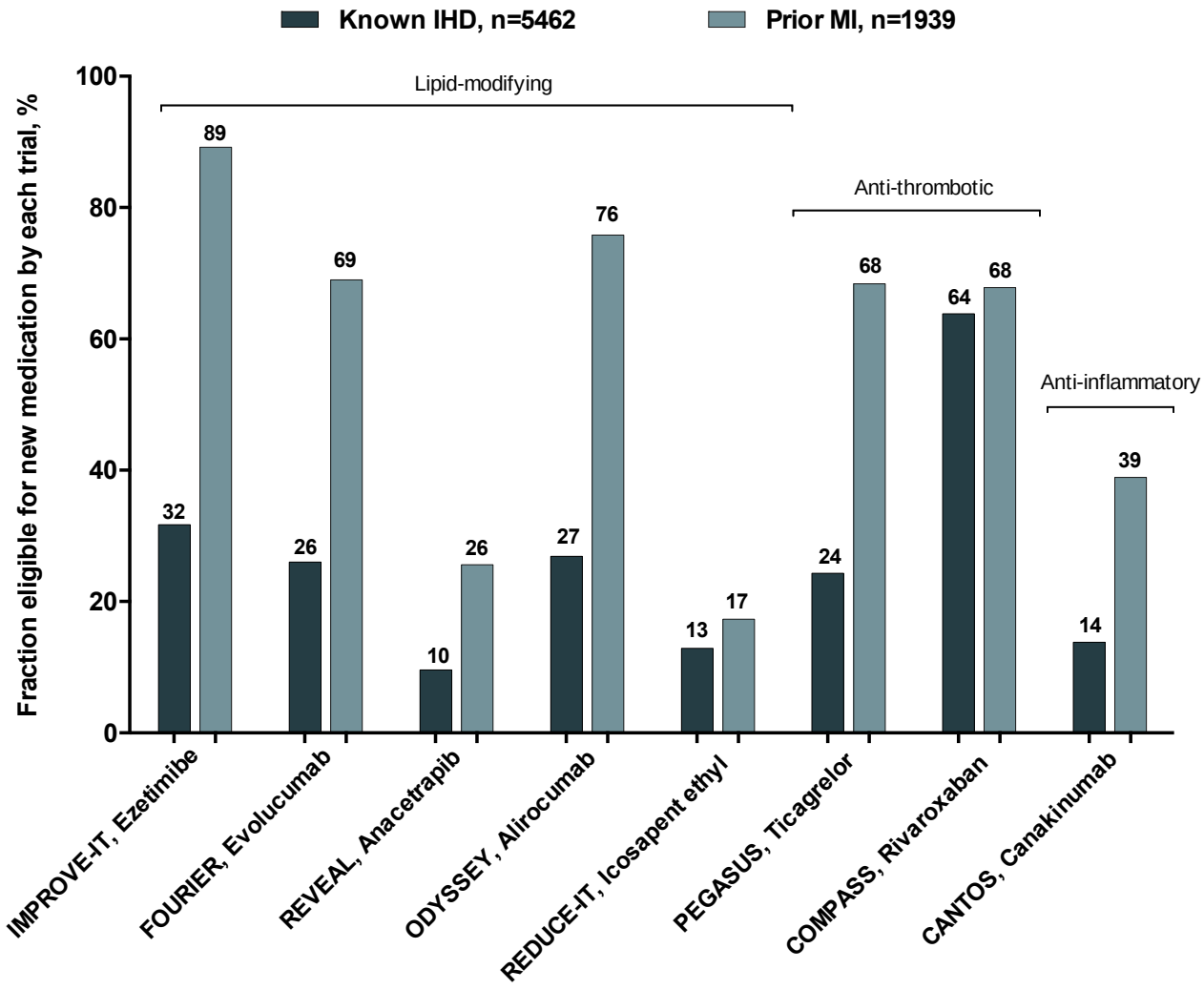
eFigure 4: Eligibility for novel therapies to prevent atherosclerotic cardiovascular disease and death by number of trials or drug classes simultaneously (strictly following ASCVD time-criteria used in clinical trials). Upper panel: Eligibility by number of different trials simultaneously. **Lower panel**: When divided into 4 potential drug classes (lipid-modifying, anti-thrombotic, anti-inflammatory, and anti-diabetic drugs), a large proportion of individuals with known IHD or previous MI met criteria for 2 or more different drug classes simultaneously. Based on patients from the Copenhagen General Population Study.

eFigure 5



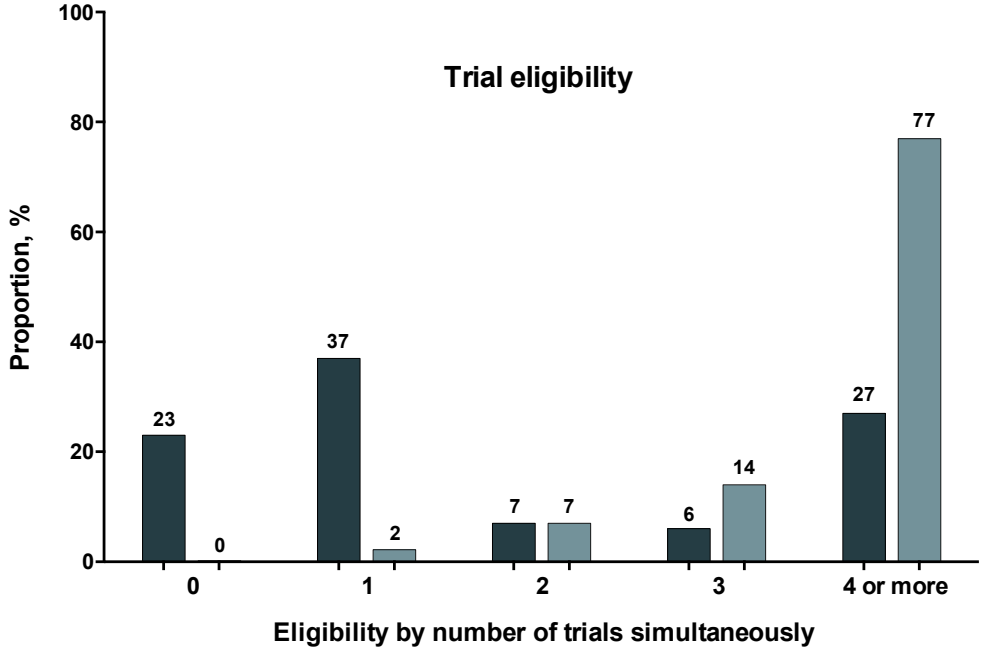
eFigure 5: Potential evidence-based prevention of major cardiovascular events, myocardial infarctions, strokes and all-cause mortality by each trial (strictly following ASCVD time-criteria used in clinical trials). Upper panel: Potential prevention of events in patients with ischemic heart disease at baseline. **Lower panel**: Potential prevention of events in patients with myocardial infarction at baseline. Based on patients from the Copenhagen General Population Study.

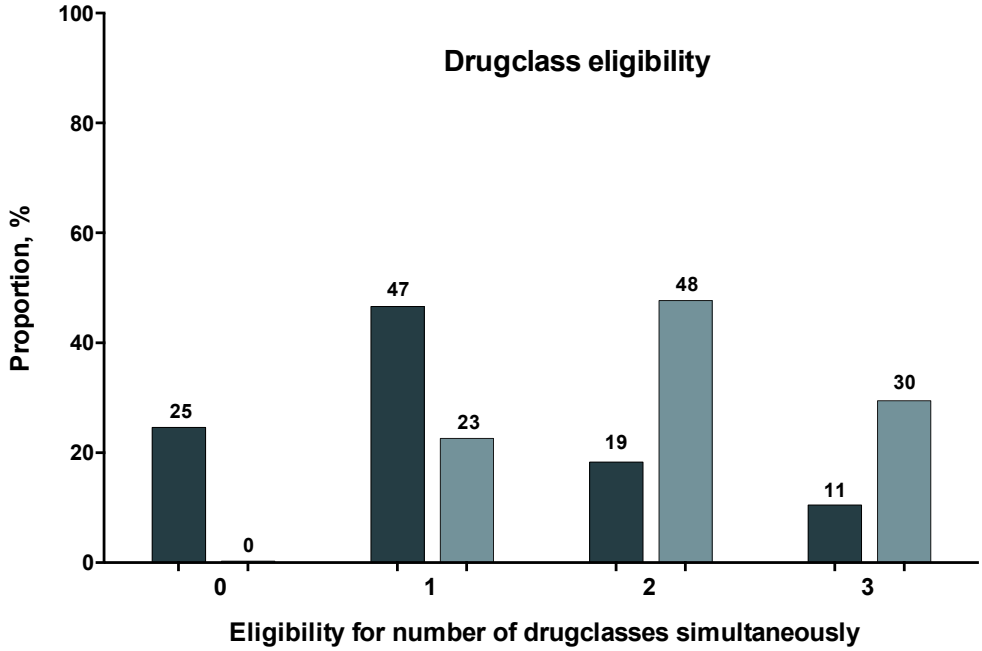
eFigure 6



eFigure 6: Eligibility by each trial individually in individuals without diabetes ordered by drug classes.

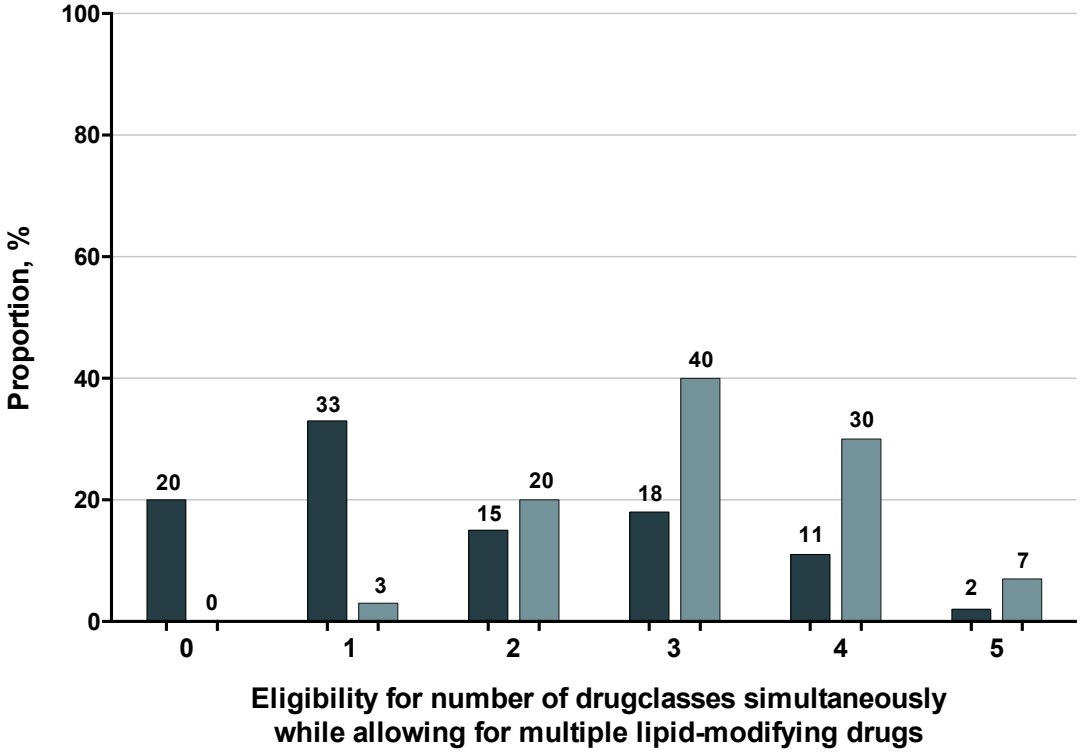
eFigure 7





eFigure 7: Eligibility by number of trials or drug classes simultaneously in individuals without diabetes. **Upper panel:** Eligibility by number of different trials simultaneously. **Lower panel**: When divided into 3 potential drug classes (lipid-modifying, anti-thrombotic, and anti-inflammatory drugs), a large proportion of non-diabetic patients with known IHD or previous MI met criteria for 2 or more different drug classes simultaneously.

eFigure 8



eFigure 9: Eligibility by number of drug classes simultaneously while allowing for multiple lipid-modifying drugs but only drug from each of the other classes.