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Elevated Remnant Cholesterol Reclassifies Risk of Ischemic Heart Disease and Myocardial Infarction

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ABSTRACT

BACKGROUND Elevated remnant cholesterol causes ischemic heart disease.

OBJECTIVES We tested the hypothesis that the inclusion of elevated remnant cholesterol will lead to appropriate reclassification of individuals who later experience myocardial infarction and ischemic heart disease.

METHODS For >10 years we followed up 41,928 white Danish individuals from the Copenhagen General Population Study without a history of ischemic cardiovascular disease, diabetes, and statin use. Using predefined cut points for elevated remnant cholesterol, we calculated net reclassification index (NRI) from below to above 5%, 7.5%, and/or 10% 10-year occurrence of myocardial infarction and ischemic heart disease defined as a composite of death from ischemic heart disease, myocardial infarction, and coronary revascularization.

RESULTS For individuals with remnant cholesterol levels ≥95th percentile (≥1.6 mmol/L, 61 mg/dL), 23% ($P < 0.001$) of myocardial infarction and 21% ($P < 0.001$) of ischemic heart disease were reclassified correctly from below to above 5% for 10-year occurrence when remnant cholesterol levels were added to models based on conventional risk factors, whereas no events were reclassified incorrectly. Consequently, the addition of remnant cholesterol levels yielded NRI of 10% (95% CI: 1%-20%) for myocardial infarction and 5% (95% CI: −3% to 13%) for ischemic heart disease. Correspondingly, when reclassifications were combined from below to above 5%, 7.5%, and 10% risk of events, 42% ($P < 0.001$) of individuals with myocardial infarction and 41% ($P < 0.001$) with ischemic heart disease were reclassified appropriately, leading to NRI of respectively 20% (95% CI: 9%-31%) and 11% (95% CI: 2%-21%).

CONCLUSIONS Elevated remnant cholesterol levels considerably improve myocardial infarction and ischemic heart disease risk prediction. (J Am Coll Cardiol 2022;79:2383-2397) © 2022 by the American College of Cardiology Foundation.

Elevated remnant cholesterol is considered a causal risk factor for ischemic heart disease.[1,2] Epidemiologic and Mendelian randomized studies have demonstrated robust associations of elevated remnant cholesterol with increased risk of ischemic heart disease including myocardial infarction.[3-9]

Remnant cholesterol is total cholesterol minus low-density lipoprotein (LDL) cholesterol minus high-density lipoprotein (HDL) cholesterol and includes the cholesterol content of the triglyceride-rich very-low-density lipoproteins, intermediate-density lipoproteins, and chylomicron remnants in the non-fasting state.[10,11] When these particles enter the arterial wall, they are taken up by macrophages to produce foam cells, and therefore elevated remnant cholesterol likely enhance accumulation of cholesterol in the arterial wall, leading to progression of

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

HDL = high-density lipoprotein

IDI = integrated discrimination index

LDL = low-density lipoprotein

NIH = National Institutes of Health

NRI = net reclassification index

atherosclerosis and in consequence ischemic heart disease.[1,2]

Most guidelines for assessment of the 10-year risk of ischemic heart and atherosclerotic cardiovascular disease include levels of total and HDL cholesterol.[12-15] However, remnant cholesterol levels are not included. Risk stratification of ischemic heart disease with the application of remnant cholesterol levels in addition to conventional risk factors could improve the selection of individuals for statin therapy appropriately, which may contribute to a reduction in the burden of ischemic heart disease for long periods.

We tested the hypothesis that elevated remnant cholesterol will lead to appropriate reclassification of individuals who later experience myocardial infarction and ischemic heart disease. For this purpose, we used 41,928 white Danish individuals from the Copenhagen General Population Study without a history of ischemic cardiovascular disease, diabetes, and statin use; individuals with diabetes were excluded because most such individuals are already given statins.

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METHODS

STUDY POPULATION. The Copenhagen General Population Study was recruited in 2003-2015 with a 43% participation rate, and clinical diagnoses were collected until December 13, 2018. Individuals were randomly invited from the Danish Civil Registration System to obtain a cohort reflecting the White Danish general population. Information on lifestyle, health, and medication including statin therapy was obtained through a questionnaire. Furthermore, participants underwent physical examinations and had nonfasting blood samples drawn for biochemical measurements.[11] We included 41,928 individuals aged 40-100 years enrolled before December 13, 2008, with possibly >10 years of follow-up and without a history of ischemic cardiovascular disease, diabetes, and statin use at baseline. The median follow-up time was 12.0 years (IQR: 10.7-13.5 years). Individuals experiencing endpoints, death, or emigration were censored before completing 10 years of follow-up but were still included in the study.

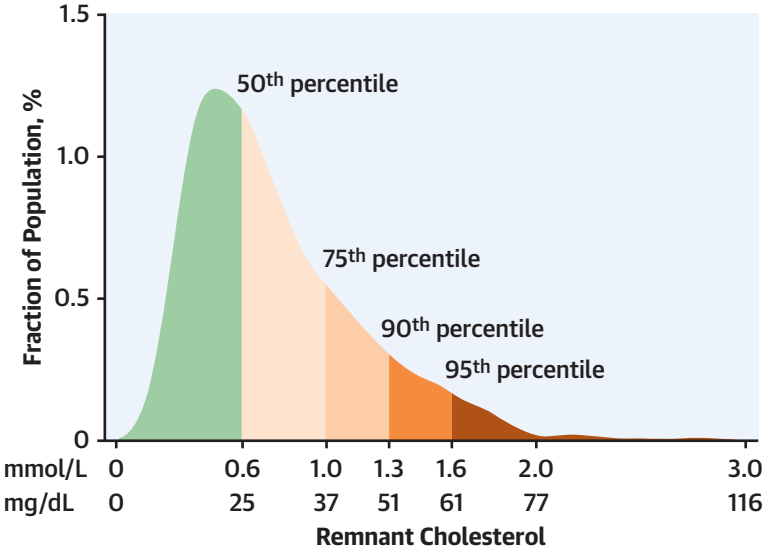
ISCHEMIC HEART DISEASE. Information on diagnoses of myocardial infarction and ischemic heart disease—that is, death of ischemic heart disease, nonfatal myocardial infarction, and coronary revascularization—was collected from the national Danish Causes of Death Registry and all hospital admissions and diagnoses entered in the national Danish Patient Registry. The World Health Organization International Classification of Diseases-10th edition (ICD-10) codes I20-I25 were used for death of ischemic heart disease and I21-I22 for myocardial infarction, whereas coronary revascularization was registered according to the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures as coronary artery bypass graft (NOMESCO: KFNA-KFNE) and percutaneous coronary intervention (NOMESCO: KFNG00-05).

The study was approved by an Institutional Review Board and a Danish Ethics Committee (H-KF-01-144/01). The study was conducted according to the Declaration of Helsinki. Written informed consent was given by each participant.

LABORATORY ANALYSES. Plasma total cholesterol, HDL cholesterol, and triglycerides were measured at baseline by the use of standard hospital assays. When triglycerides were <4 mmol/L (<354 mg/dL), LDL cholesterol was calculated by the Friedewald method[16] and otherwise was measured directly. LDL cholesterol levels calculated by the Martin-Hopkins method[17] or the Sampson-National Institute of Health (NIH) method[18] were also used for sensitivity analyses. Nonfasting remnant cholesterol was calculated as total cholesterol minus LDL cholesterol (Friedewald et al,[16] Martin et al,[17] or Sampson et al[18]) minus HDL cholesterol.

STATISTICAL ANALYSES. We used Stata version 15.1 SE. Correlation coefficients between remnant cholesterol and other lipids, lipoproteins, and apolipoprotein B were calculated by Spearman rank correction coefficients. In the baseline model, covariates for adjustment were chosen according to known associations with ischemic heart disease, including age, sex, smoking status (current or former/never smoker), LDL cholesterol, and systolic blood pressure. In the main analyses, HDL cholesterol was deliberately omitted as covariate for adjustment because it influences lipid traits through biological pathways; HDL cholesterol levels are inversely related to plasma triglycerides and remnant cholesterol levels.[5,19] Missing information on continuous covariates (0.1%) for adjustment were imputed by regression based on age and sex. However, if only individuals with complete data were included, the results were similar. Cox proportional hazard regressions with time from study entry as the underlying time scale, and censoring at the occurrence of myocardial infarction (or ischemic heart disease), emigration (0.3%), and death or end of follow-up, whichever came first, were used to estimate hazard ratios for myocardial infarction (or ischemic heart

FIGURE 1 **Distribution of Nonfasting Remnant Cholesterol in the General Population**



Graph is based on 41,928 individuals aged 40-100 years from the Copenhagen General Population Study without ischemic cardiovascular disease, diabetes, and statin use. The graph was truncated at remnant cholesterol >3.0 mmol/L (116 mg/dL) because of the limited number of individuals outside this cut point.

disease). The assumption of proportional hazards was tested by the use of Schoenfeld residuals; no major deviations were observed. We further used the competing risk model of Fine and Gray[20] using emigration and death of other causes than ischemic heart disease as competing events.

First, for estimating measures of reclassification and discrimination, we constructed a Cox regression model analyzing time to event including only conventional risk factors (age, sex, smoking, systolic blood pressure, and LDL cholesterol). We here derived the baseline survival at 10 years, S_0(10 years) and the beta-coefficients, β_1, β_2, … β_p, for the included covariates, x_1, x_2, … x_p. Supplemental Table 1 lists all beta-coefficients included in the risk prediction models. The probability of survival beyond 10 years, $P_{survival}$ (10 years) after baseline without experiencing an event was calculated as follows:

$$P_{survival}\ (10\ years) = S_0(10\ years)^{exp\ (\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p)}$$

and the probability of an event within 10 years after baseline was 1 minus the survival probability:

$$P_{event}\ (10\ years) = 1 - P_{survival}\ (10\ years)$$

Second, we constructed a similar Cox proportional hazards model including conventional risk factors plus remnant cholesterol as a new risk factor. We calculated the new probability of survival beyond 10 years, $P_{survival\_new}$ (10 years), as described in the previous paragraph. The Cox regression models were fitted to data for all individuals, and their predictive ability was assessed by the use of measures of reclassification and discrimination as described below.

We assessed reclassification for individuals with known event status at 10 years of follow-up, excluding individuals censored for other reasons before this, under the assumption that models derived from data on all individuals were still applicable. Using the estimated 10-year risk predictions of $P_{survival}$ (10 years) and $P_{survival\_new}$ (10 years), individuals were classified into a priori defined standard 10-year risk categories of <5% and ≥5%, <7.5% and ≥7.5%, and <10% and ≥10%. Cross-tabulation of the risk categories was stratified by event status (myocardial infarction or ischemic heart disease) at 10 years, and reclassifications of individuals between risk categories using $P_{survival}$ (10 years) versus $P_{survival\_new}$ (10 years) were examined. Reclassification was appropriate for individuals with events moving up in risk category and for individuals without events moving down in risk category when remnant cholesterol was added as a new risk factor. Reclassification was summarized by use of the net reclassification index (or improvement)

TABLE 1 Baseline Characteristics of Individuals From the Copenhagen General Population Study

		Remnant Cholesterol Percentiles				
	All (N = 41,928)	<50th (n = 20,877)	≥50th (n = 21,051)	≥75th (n = 10,496)	≥90th (n = 4,203)	≥95th (n = 2,100)
Age, y	57 (49-66)	56 (48-65)	59 (50-67)	58 (50-67)	57 (49-66)	56 (48-64)
Women	57.0	67.0	46.0	39.0	33.0	29.0
Smoking	22.0	19.0	26.0	28.0	31.0	33.0
Body mass index, kg/m^2	26 (23-28)	24 (22-27)	27 (24-30)	27 (25-30)	28 (26-31)	28 (26-31)
Systolic blood pressure, mm Hg	140 (126-155)	136 (123-150)	141 (130-156)	144 (130-159)	145 (132-160)	145 (132-160)
Total cholesterol						
mmol/L	5.7 (5.1-6.5)	5.5 (4.8-6.1)	6.0 (5.4-6.7)	6.2 (5.6-6.9)	6.4 (5.8-7.1)	6.5 (5.9-7.2)
mg/dL	220 (197-251)	213 (186-236)	232 (209-259)	240 (217-267)	247 (224-275)	251 (228-278)
Non-HDL cholesterol						
mmol/L	4.1 (3.4-4.8)	3.6 (3.0-4.2)	4.6 (4.0-5.3)	4.9 (4.3-5.6)	5.3 (4.6-5.9)	5.4 (4.8-6.1)
mg/dL	157 (131-187)	138 (117-162)	177 (153-205)	190 (165-217)	203 (178-230)	210 (185-237)
LDL cholesterol						
mmol/L	3.3 (2.8-4.0)	3.1 (2.6-3.7)	3.5 (2.9-4.2)	3.6 (3.0-4.2)	3.6 (2.9-4.2)	3.5 (2.9-4.2)
mg/dL	128 (108-155)	120 (101-143)	135 (112-162)	139 (116-162)	139 (112-162)	135 (112-162)
HDL cholesterol						
mmol/L	1.6 (1.3-2.0)	1.8 (1.5-2.2)	1.4 (1.1-1.7)	1.3 (1.0-1.5)	1.1 (0.9-1.4)	1.1 (0.9-1.3)
mg/dL	62 (50-77)	70 (58-85)	54 (43-66)	50 (39-58)	43 (35-54)	43 (35-50)
Triglycerides						
mmol/L	1.4 (1.0-2.1)	1.0 (0.8-1.2)	2.1 (1.7-2.8)	2.8 (2.4-3.5)	3.6 (3.2-4.5)	4.0 (3.4-5.3)
mg/dL	124 (89-186)	89 (71-106)	186 (151-248)	248 (213-310)	319 (283-399)	354 (301-469)
Remnant cholesterol						
mmol/L	0.6 (0.4-1.0)	0.4 (0.4-0.5)	0.9 (0.8-1.2)	1.2 (1.1-1.5)	1.6 (1.4-1.8)	1.8 (1.7-2.0)
mg/dL	23 (15-39)	15 (15-19)	35 (31-46)	46 (43-58)	62 (54-70)	70 (66-77)
Apolipoprotein B						
g/L	1.1 (0.9-1.3)	0.9 (0.8-1.1)	1.3 (1.1-1.5)	1.5 (1.3-1.7)	1.6 (1.4-1.9)	1.8 (1.5-2.0)
mg/dL	110 (91-133)	94 (81-109)	129 (111-152)	145 (125-168)	163 (142-188)	175 (152-200)
Lipoprotein(a)[a]						
nmol/L	17 (6-58)	17 (7-59)	17 (6-58)	17 (6-56)	16 (5-53)	15 (5-57)
mg/dL	10 (5-29)	10 (5-29)	10 (5-28)	9 (4-27)	9 (4-26)	8 (4-28)

Values are median (IQR) or %. Nonfasting remnant cholesterol was calculated as total cholesterol minus LDL cholesterol (Friedewald et al[16]) minus HDL cholesterol. [a]Not all individuals have lipoprotein(a) levels. Conversion of lipoprotein(a) from mg/dL to nmol/L was done using the equation 2.18·lipoprotein(a), mg/dL−3.83.[30]

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

(NRI) and the integrated discrimination index (or improvement) (IDI).[21] Furthermore, we assessed discrimination over the entire concentration levels by computing C index and difference in C indices between model with and without remnant cholesterol.

Because the distribution of remnant cholesterol is skewed with a tail toward higher levels (Figure 1), we focused on individuals with extremely high remnant cholesterol levels *a priori*, exactly as physicians typically would do in a clinical setting. Thus, we conducted analyses including only individuals with remnant cholesterol levels in the ≥50th, ≥75th, ≥90th, or ≥95th percentile. When these cut points were examined for remnant cholesterol levels, individuals not included were dropped before the assessment of reclassification and discrimination, whereas underlining Cox regression models fitted data from all individuals. For comparison, we also performed analyses including the entire range of remnant cholesterol levels.

In sensitivity analysis, we: 1) adjusted for plasma triglycerides or apolipoprotein B in the baseline model; 2) used non-HDL cholesterol or total and HDL cholesterol instead of LDL cholesterol in the baseline model; 3) analyzed reclassification as a function of elevated apolipoprotein B instead of elevated remnant cholesterol; 4) stratified the study population according to smokers and nonsmokers or body mass index ≥30 kg/m^2 and <30 kg/m^2; and 5) included only individuals at intermediate risk of fatal or nonfatal cardiovascular events defined as 1%-10% 10-year risk by the SCORE2 risk prediction algorithm.[22]

RESULTS

The baseline characteristics of the 41,928 individuals are shown in Table 1. We observed 1,063 and 1,460

FIGURE 2 Risk of Ischemic Heart Disease by Elevated Nonfasting Remnant Cholesterol

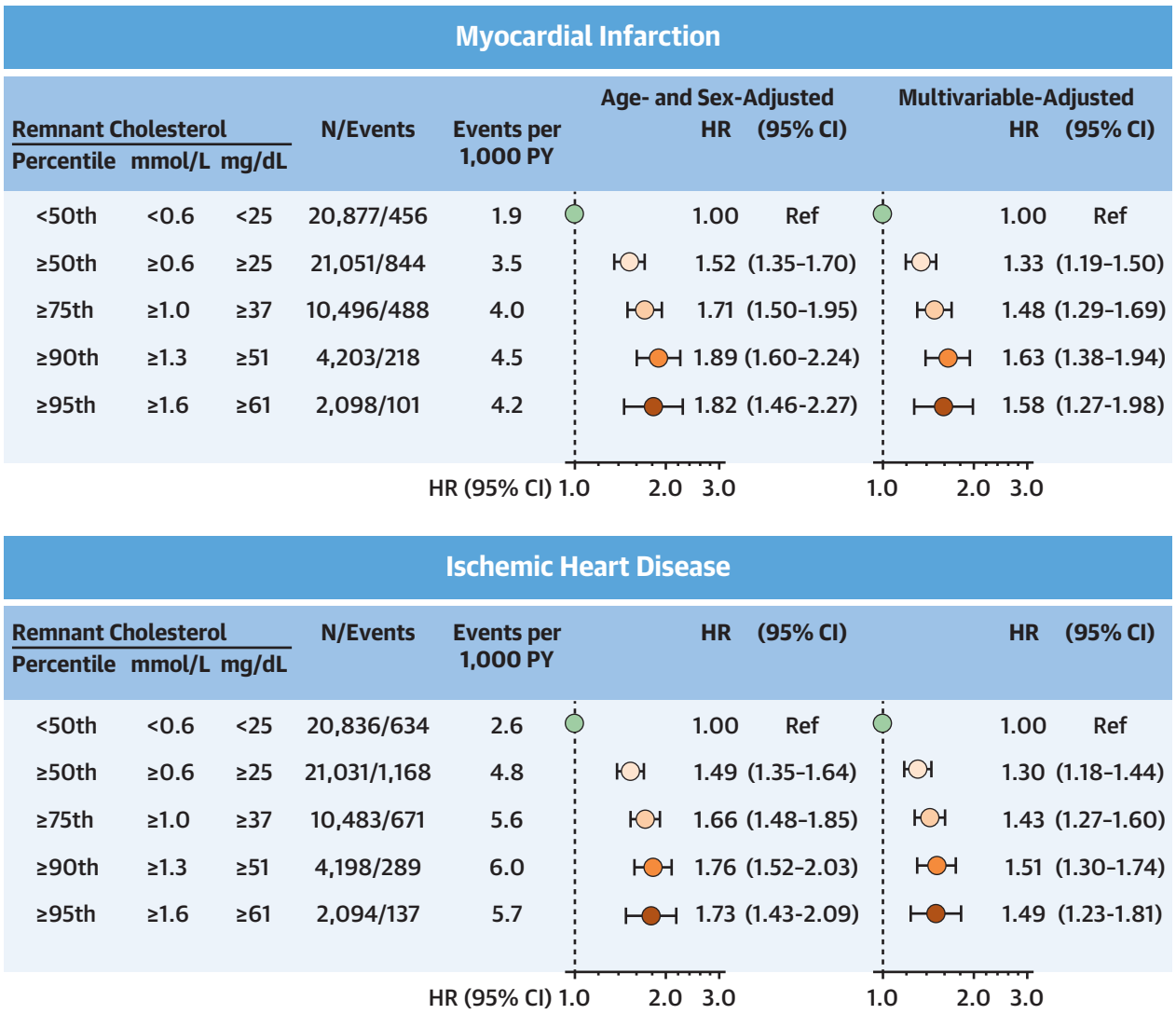


Figure is based on 41,928 individuals aged 40-100 years from the Copenhagen General Population Study without ischemic cardiovascular disease, diabetes, and statin use. Analyses are multivariable adjusted for age, sex, smoking (current, former/never), systolic blood pressure, and LDL cholesterol. LDL = low-density lipoprotein; PY = person-years; Ref = reference.

first-time myocardial infarction and ischemic heart disease events during the first 10 years of follow-up. The correlation coefficients between remnant cholesterol and other lipids, lipoproteins, and apolipoprotein B are shown in Supplemental Table 2.

RISK OF MYOCARDIAL INFARCTION AND ISCHEMIC HEART DISEASE. For remnant cholesterol levels ≥95th percentile (≥1.6 mmol/L, 61 mg/dL) or ≥75th percentile (≥1.0 mmol/L, 37 mg/dL), the multivariable adjusted hazard ratios were 1.58 (95% CI: 1.27-1.98) and 1.48 (95% CI: 1.29-1.69) for myocardial infarction and 1.49 (95% CI: 1.23-1.81) and 1.43 (95% CI: 1.27-1.60) for ischemic heart disease, respectively, in comparison with individuals with remnant cholesterol levels <50th percentile (<0.6 mmol/L, <25 mg/dL) (Figure 2).

RECLASSIFICATION FROM BELOW TO ABOVE 5% 10-YEAR RISK. In models based on conventional risk factors estimating above or below 5% risk in 10 years, at ≥95th percentile (≥1.6 mmol/L, 61 mg/dL)

levels of remnant cholesterol, 23% ($P < 0.001$) of individuals with myocardial infarction and 21% ($P < 0.001$) of individuals with ischemic heart disease were reclassified appropriately when remnant cholesterol was added to the model (**Figure 3**). At remnant cholesterol levels ≥75th percentile (≥1.0 mmol/L, 37 mg/dL), the corresponding numbers were 10% ($P < 0.001$) and 8% ($P < 0.001$), respectively. For both cut points, no events were reclassified inappropriately for either endpoint. For these 2 cut points for elevated remnant cholesterol, inappropriate reclassifications of experiencing no event were 13% ($P < 0.001$) and 6% ($P < 0.001$) for myocardial infarction, and 16% ($P < 0.001$) and 7% ($P < 0.001$) for ischemic heart disease, respectively. Therefore, the total NRIs for individuals with remnant cholesterol levels ≥95th percentile (≥1.6 mmol/L, 61 mg/dL) were 10% (95% CI: 1%-20%) for myocardial infarction and 5% (−3% to 13%) for ischemic heart disease, and the corresponding NRIs for remnant cholesterol levels ≥75th percentile (≥1.0 mmol/L, 37 mg/dL) were 4% (95% CI: 1%-6%) and 2% (95% CI: −1% to 4%), respectively (**Figure 3**). The IDIs for myocardial infarction were 0.007 (95% CI: 0.003-0.010) for individuals with remnant cholesterol levels ≥95th percentile (≥1.6 mmol/L, 61 mg/dL) and 0.004 (0.002-0.005) for individuals with remnant cholesterol levels ≥75th percentile (≥1.0 mmol/L, 37 mg/dL); the corresponding IDIs for ischemic heart disease were 0.007 (0.004-0.011) and 0.004 (0.003-0.005), respectively.

The addition of remnant cholesterol over the entire concentration range yielded insignificant improvements of reclassification by NRI of 0% (95% CI: −1% to 2%) and a C index change of 0.003 (95% CI: −0.005 to 0.008) for myocardial infarction but slightly improved reclassification by NRI of 2% (95% CI: 1%-3%) and a C index change of 0.007 (95% CI: 0.003-0.012) for ischemic heart disease. Discrimination was improved correspondingly by IDIs of, respectively, 0.0008 (95% CI: 0.0002-0.0014) and 0.0007 (95% CI: 0.0002-0.0013).

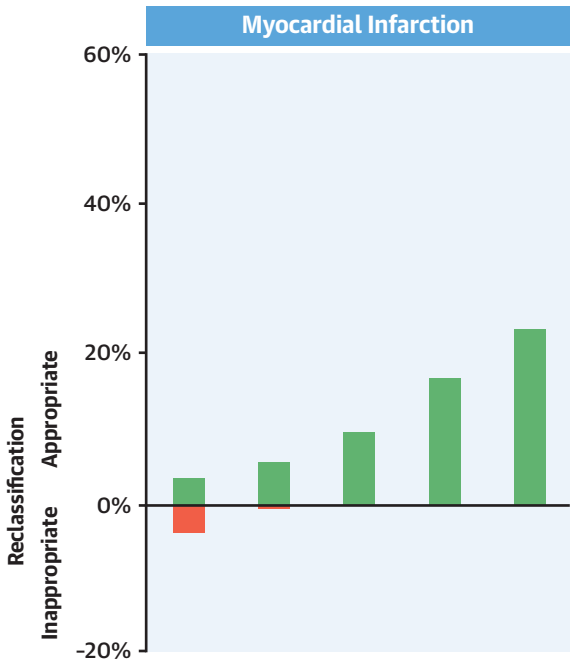
In a similar model for remnant cholesterol levels ≥95th percentile (≥1.3 mmol/L, 51 mg/dL, or ≥1.6 mmol/L, 62 mg/dL) with LDL cholesterol calculated by the Martin-Hopkins or the Sampson-NIH method, the NRIs for myocardial infarction were 4% (95% CI: −3% to 11%) and 9% (95% CI: 0%-17%), respectively (**Figure 4**). For remnant cholesterol levels ≥75th percentile (≥0.8 mmol/L, 32 mg/dL, or ≥0.9 mmol/L, 34 mg/dL), the corresponding NRIs were 2% (95% CI: 0%-4%) and 4% (95% CI: 1%-7%), respectively (**Figure 4**).

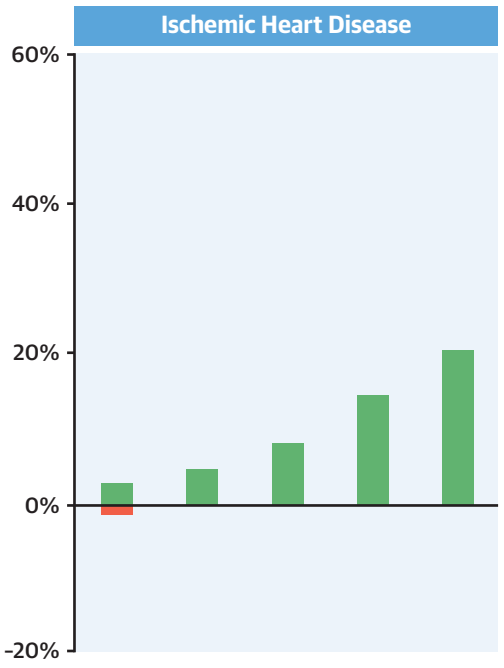
RECLASSIFICATION FROM BELOW TO ABOVE 7.5% OR 10% 10-YEAR RISK. For remnant cholesterol levels ≥95th percentile (≥1.6 mmol/L, 61 mg/dL) and ≥75th percentile (≥1.0 mmol/L, 37 mg/dL), myocardial infarction reclassifications were appropriate for 14% ($P < 0.001$) and 9% ($P < 0.001$) from below to above 7.5%, and for 14% ($P < 0.001$) and 6% ($P < 0.001$) from below to above 10% (**Figure 5**). For these cut points, inappropriate reclassifications of no events were 7% ($P < 0.001$) and 3% ($P < 0.001$) from below to above 7.5%, yielding NRIs of 7% (95% CI: −1% to 15%) and 6% (95% CI: 3%-9%), whereas inappropriate reclassifications of no events were 4% ($P < 0.001$) and 2% ($P < 0.001$) from below to above 10%, yielding NRIs of 10% (95% CI: 2%-17%) and 5% (95% CI: 2%-7%), respectively (**Figure 5**).

COMBINING RECLASSIFICATION FROM BELOW TO ABOVE 5%, 7.5%, AND 10% 10-YEAR RISK. The addition of remnant cholesterol to models based on conventional risk factor combining reclassification from below to above 5%, 7.5%, and 10% risk for remnant cholesterol levels ≥95th percentile (≥1.6 mmol/L, 61 mg/dL), 42% ($P < 0.001$) of individuals with myocardial infarction and 41% ($P < 0.001$) with ischemic heart disease were reclassified appropriately (**Figure 6**). For remnant cholesterol levels ≥75th percentile (≥1.0 mmol/L, 37 mg/dL), the corresponding numbers were 23% ($P < 0.001$) and 22% ($P < 0.001$), respectively. Taken together, this yielded corresponding NRIs of 20% (95% CI: 9%-31%) and 13% (95% CI: 9%-17%) for myocardial infarction and 11% (95% CI: 2%-21%) and 9% (95% CI: 5%-13%) for ischemic heart disease, respectively.

SENSITIVITY ANALYSES. After additional adjustment for plasma triglycerides or apolipoprotein B in the baseline model, the percentages of individuals reclassified appropriately were lower than in the main model, with lower NRIs (compare Supplemental Figures 1 and 2 with **Figure 3**). When non-HDL cholesterol or total plus HDL cholesterol was used instead of LDL cholesterol in the baseline model, NRIs likewise were lower (compare Supplemental Figures 3 and 4 with **Figure 3**). Furthermore, reclassification as a function of elevated apolipoprotein B instead of elevated remnant cholesterol yielded lower NRIs (compare Supplemental Figure 5 with **Figure 3**). When analyses were stratified for smokers versus nonsmokers, a higher percentage of individuals were reclassified appropriately, and higher NRIs were found in nonsmokers compared with smokers (**Figure 7**), whereas analyses stratified for body mass index ≥30 kg/m^2 compared with <30 kg/m^2 showed similar results (Supplemental Figure 6). In

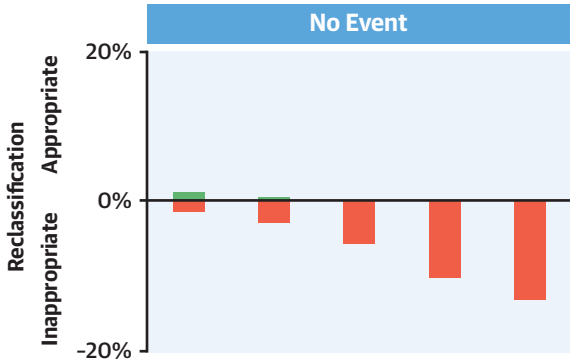
FIGURE 3 **Reclassification From <5% to ≥5% 10-Year Risk**

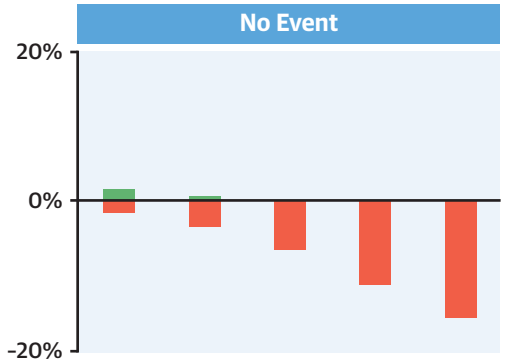




N	1,063	681	385	177	81
Reclassification					
Appropriate, %	4	6	10	17	23
Inappropriate, %	4	0	0	0	0
P Value	0.56	0.003	< 0.001	< 0.001	< 0.001

	1,460	938	530	229	107
	3	5	8	15	21
	1	0	0	0	0
	0.001	< 0.001	< 0.001	< 0.001	< 0.001



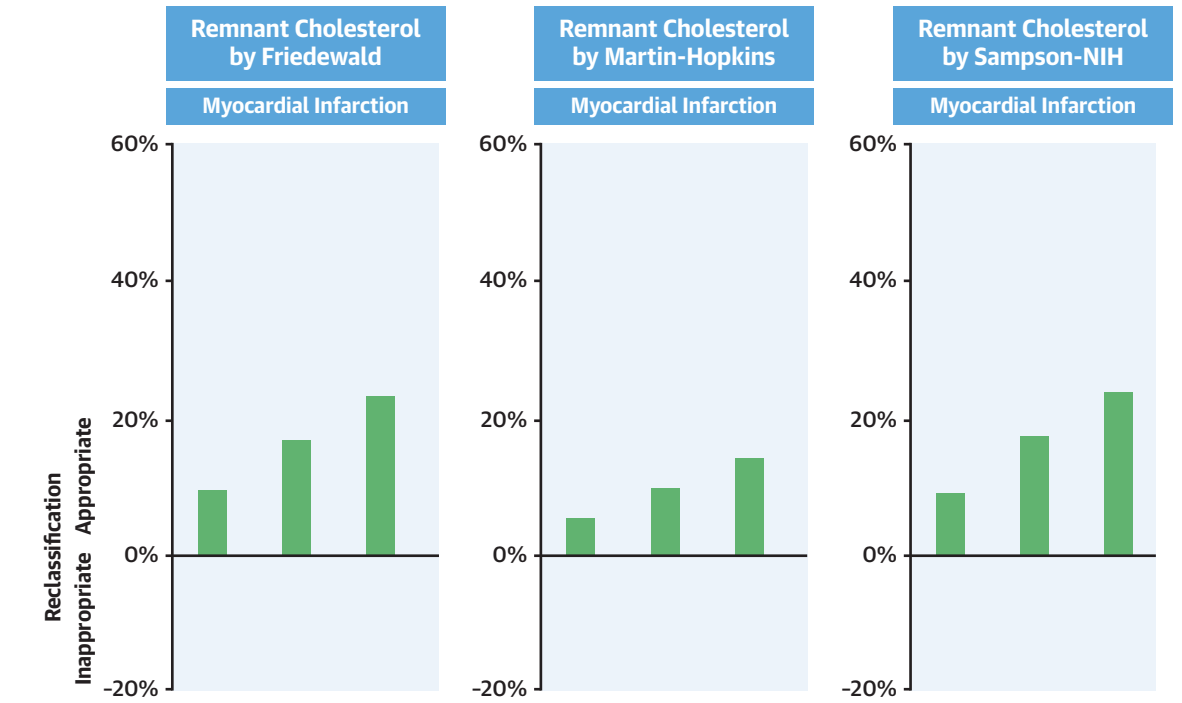


N	36,927	18,230	9,074	3,603	1,824
Reclassification					
Appropriate, %	1	1	0	0	0
Inappropriate, %	1	3	6	10	13
P Value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
NRI, %	0	3	4	7	10
95% CI	-1-2	1-5	1-6	1-12	1-20
Remnant Cholesterol					
Percentile	All	≥50th	≥75th	≥90th	≥95th
mmol/L	≥0	≥0.6	≥1.0	≥1.3	≥1.6
mg/dL	≥0	≥25	≥37	≥51	≥61

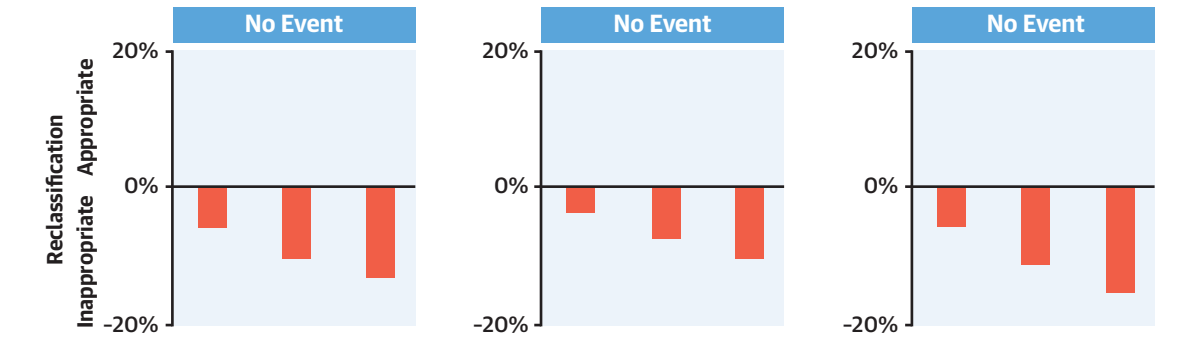
	36,625	18,031	8,961	3,560	1,798
	1	1	0	0	0
	2	3	7	11	16
	0.06	< 0.001	< 0.001	< 0.001	< 0.001
	2	2	2	3	5
	1-3	1-3	-1-4	-1-8	-3-13
	All	≥50th	≥75th	≥90th	≥95th
	≥0	≥0.6	≥1.0	≥1.3	≥1.6
	≥0	≥25	≥37	≥51	≥61

Chart is based on 41,928 individuals aged 40-100 years from the Copenhagen General Population Study without ischemic cardiovascular disease, diabetes, and statin use. Proportions of population are shown in **green bars** for those appropriately reclassified as a function of elevated nonfasting remnant cholesterol and in **red bars** for those inappropriately reclassified, when nonfasting remnant cholesterol was added to the baseline model. LDL = low-density lipoprotein; NRI = net reclassification index.

FIGURE 4 **Reclassification When Calculating LDL Cholesterol by Different Methods**



	Myocardial Infarction			Myocardial Infarction			Myocardial Infarction		
N	385	177	81	389	190	97	391	182	92
Reclassification									
Appropriate, %	10	17	23	6	10	14	9	18	24
Inappropriate, %	0	0	0	0	0	0	0	0	0
P Value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001



	No Event			No Event			No Event		
N	9,074	3,603	1,824	9,095	3,617	1,809	9,080	3,621	1,810
Reclassification									
Appropriate, %	0	0	0	0	0	0	0	0	0
Inappropriate, %	6	10	13	4	8	10	6	11	15
P Value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
NRI, %	4	7	10	2	2	4	4	6	9
95% CI	1-6	1-12	1-20	0-4	-2-7	-3-11	1-7	1-12	0-17
Remnant Cholesterol									
Percentile	≥75th	≥90th	≥95th	≥75th	≥90th	≥95th	≥75th	≥90th	≥95th
mmol/L	≥1.0	≥1.3	≥1.6	≥0.8	≥1.1	≥1.3	≥0.9	≥1.3	≥1.6
mg/dL	≥37	≥51	≥61	≥32	≥40	≥51	≥34	≥50	≥62

Chart is based on 41,928 individuals aged 40-100 years in the Copenhagen General Population Study without ischemic cardiovascular disease, diabetes, and statin use. Proportions of population are shown in **green bars** for those appropriately reclassified from <5% to ≥5% 10-year risk as a function of elevated nonfasting remnant cholesterol and in **red bars** for those inappropriately reclassified, when nonfasting remnant cholesterol was added to the baseline model. Nonfasting remnant cholesterol was calculated as total cholesterol minus LDL cholesterol (Friedewald et al,[6] Martin et al,[17] or Sampson et al[18]) minus high-density lipoprotein cholesterol. NIH = National Institutes of Health; other abbreviations as in Figure 3.

FIGURE 5 **Reclassification by Different Cut Points of Event Rates**

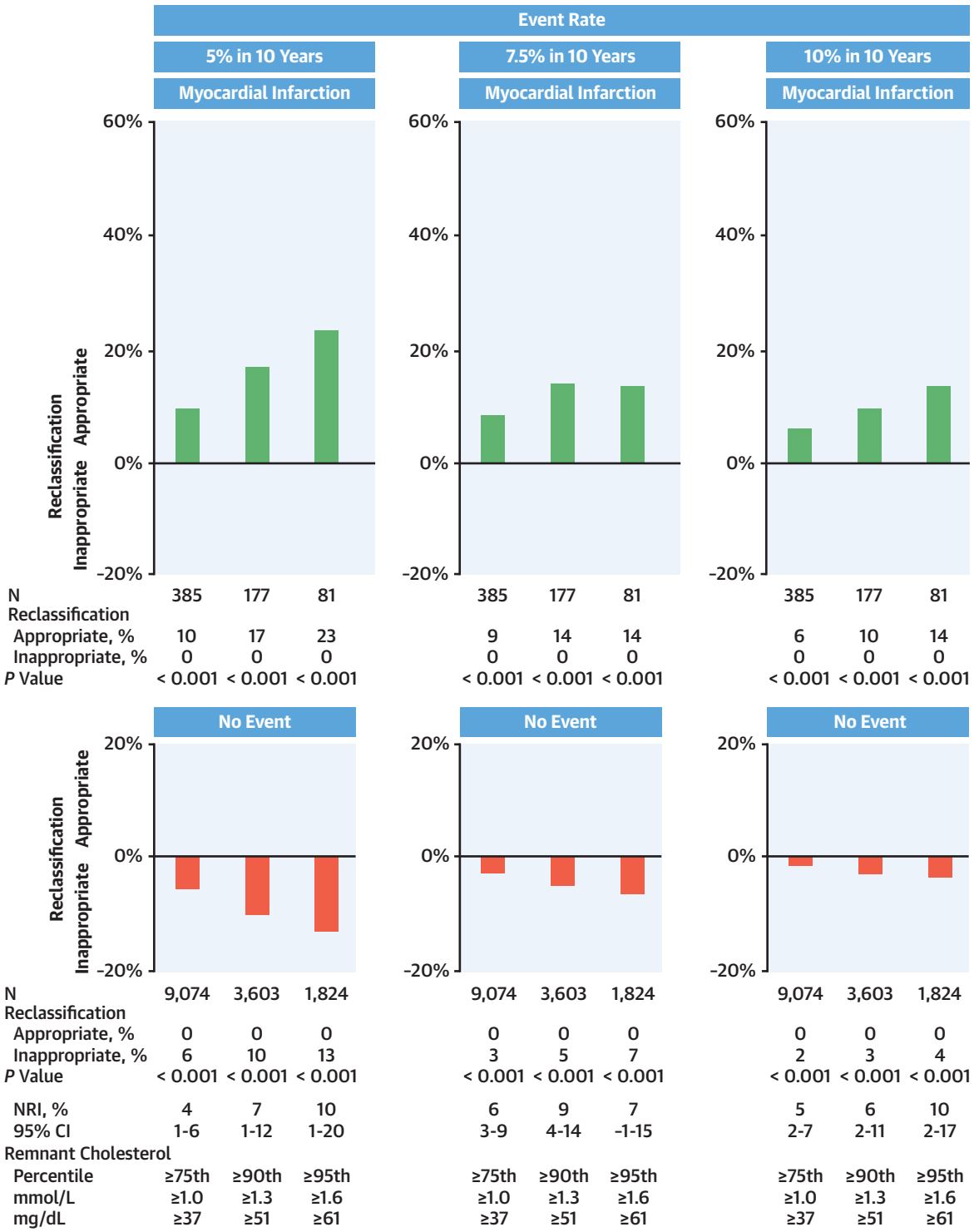
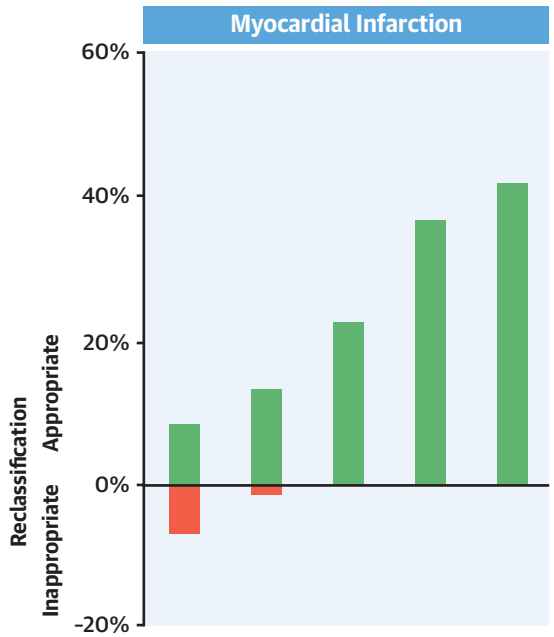
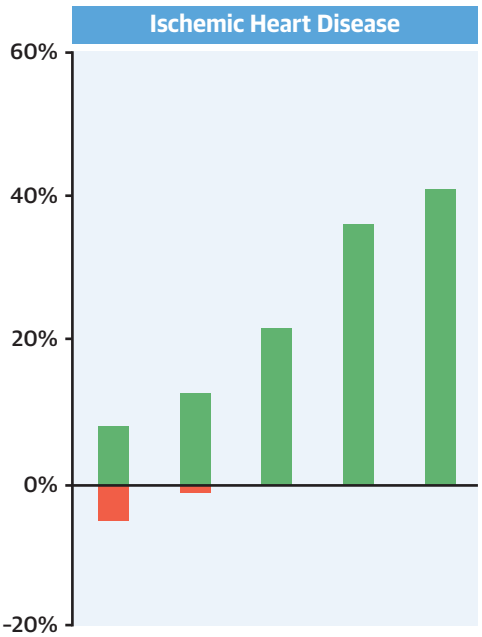


Chart is based on 41,928 individuals aged 40-100 years in the Copenhagen General Population Study without ischemic cardiovascular disease, diabetes, and statin use. Proportions of population are shown in **green bars** for those appropriately reclassified from <5% to ≥5%, 7.5%, or 10% 10-year risk as a function of elevated nonfasting remnant cholesterol and in **red bars** for those inappropriately reclassified, when nonfasting remnant cholesterol was added to the baseline model. Abbreviations as in Figure 3.

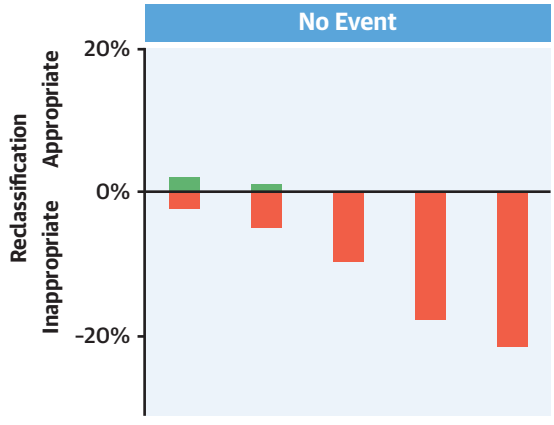
FIGURE 6 **Combined Reclassification from <5% to ≥5%, 7.5%, and 10% 10-Year Risk**

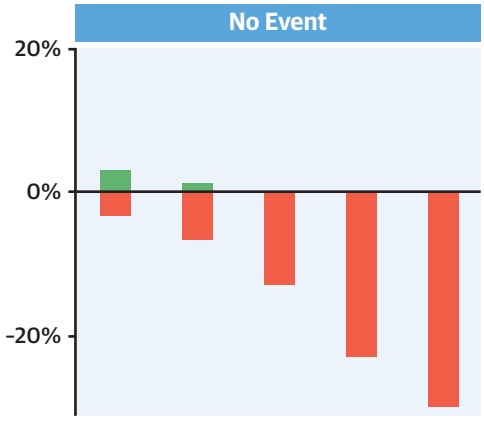




N	1,063	681	385	177	81
Reclassification					
Appropriate, %	9	13	23	37	42
Inappropriate, %	7	1	0	0	0
P Value	0.14	< 0.001	< 0.001	< 0.001	< 0.001

1,460	938	530	229	107	
8	13	22	36	41	
5	1	0	0	0	
< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	



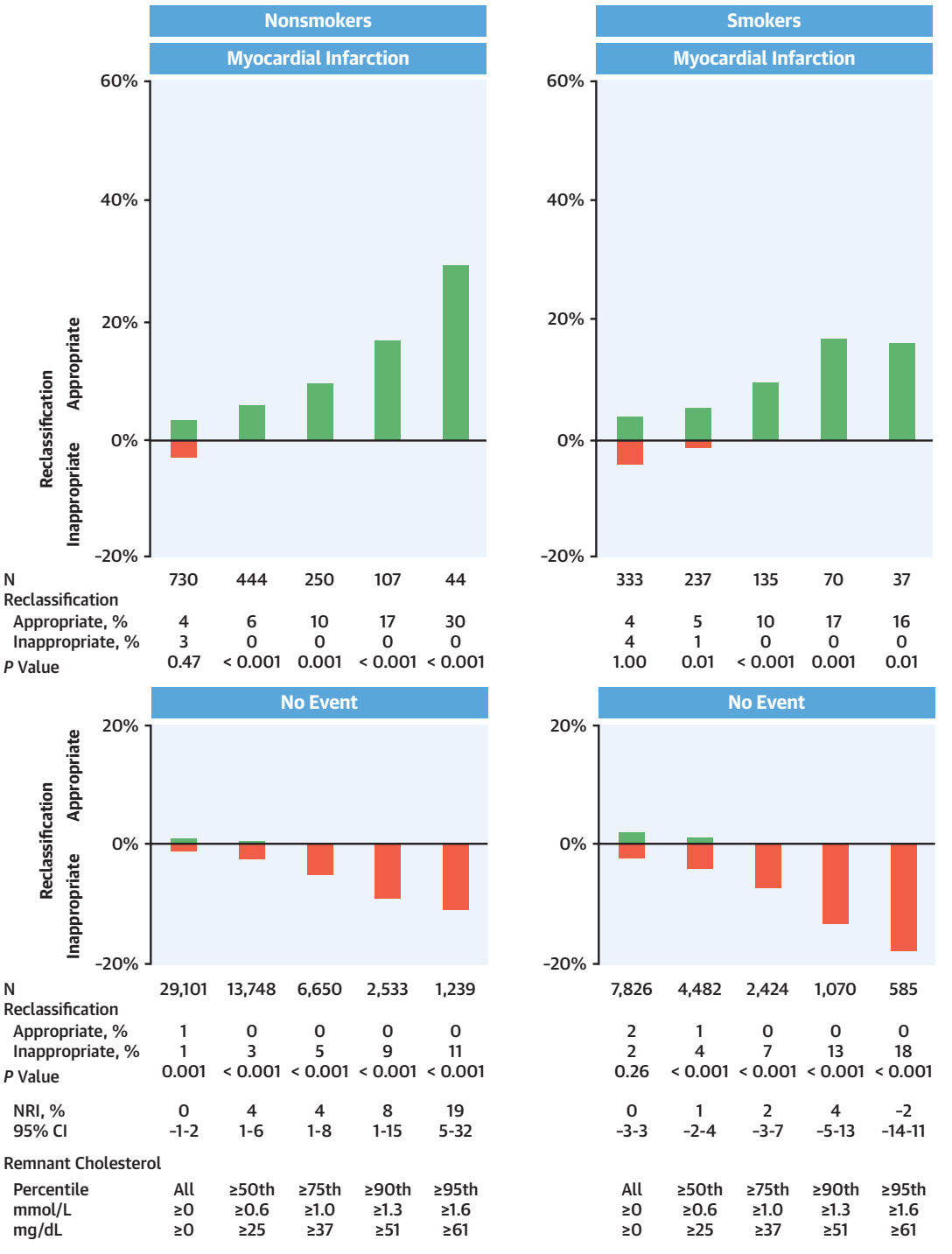


N	36,927	18,230	9,074	3,603	1,824
Reclassification					
Appropriate, %	2	1	0	0	0
Inappropriate, %	2	5	10	18	22
P Value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
NRI, %	1	8	13	19	20
95% CI	-1-4	5-11	9-17	12-26	9-31
Remnant Cholesterol					
Percentile	All	≥50th	≥75th	≥90th	≥95th
mmol/L	≥0	≥0.6	≥1.0	≥1.3	≥1.6
mg/dL	≥0	≥25	≥37	≥51	≥61

36,625	18,031	8,961	3,560	1,798	
3	1	0	0	0	
3	7	13	23	30	
0.002	< 0.001	< 0.001	< 0.001	< 0.001	
3	6	9	13	11	
1-5	4-9	5-13	7-20	2-21	
All	≥50th	≥75th	≥90th	≥95th	
≥0	≥0.6	≥1.0	≥1.3	≥1.6	
≥0	≥25	≥37	≥51	≥61	

Chart is based on 41,928 individuals aged 40-100 years in the Copenhagen General Population Study without ischemic cardiovascular disease, diabetes, and statin use. Proportions of population are shown in **green bars** for those appropriately reclassified from <5% to ≥5%, 7.5%, and 10% 10-year risk combined as a function of elevated nonfasting remnant cholesterol and in **red bars** for those inappropriately reclassified, when nonfasting remnant cholesterol was added to the baseline model. Abbreviations as in Figure 3.

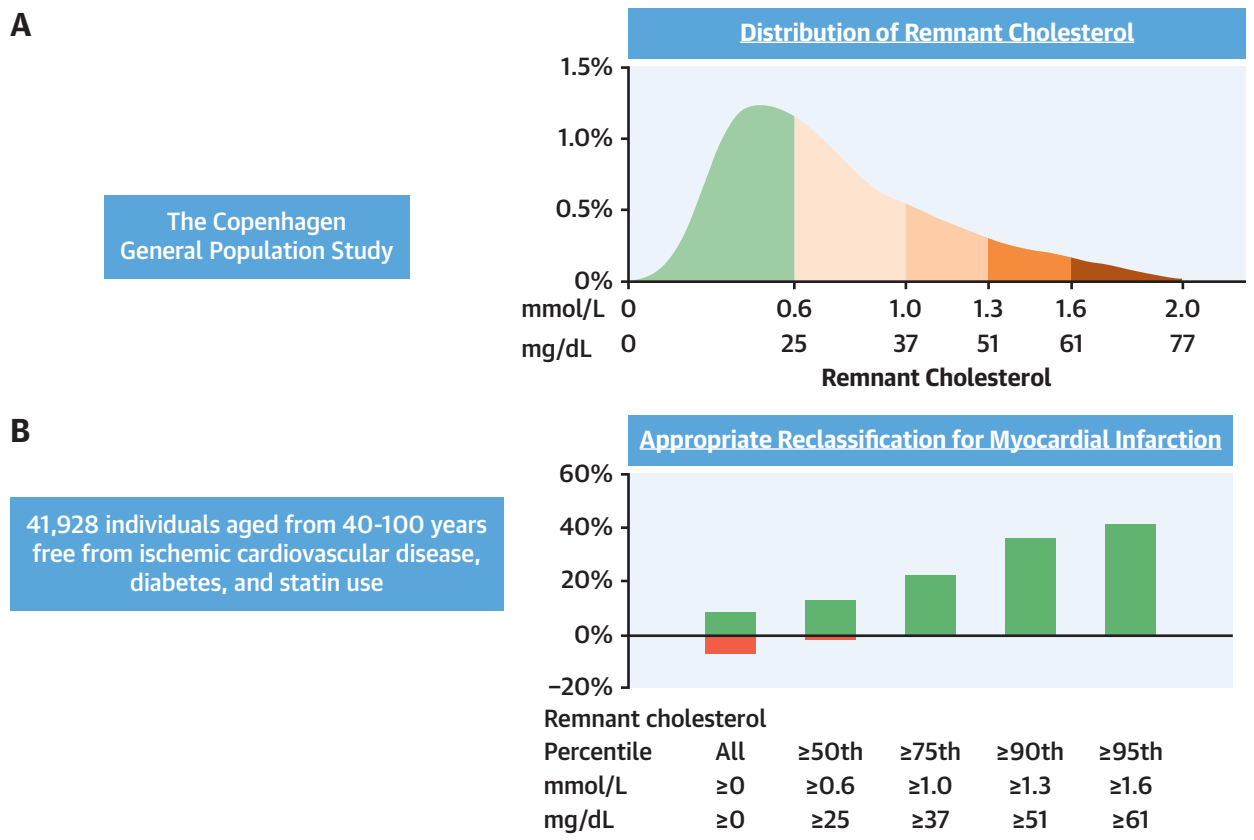
FIGURE 7 **Reclassification for Myocardial Infarction in Smokers or Nonsmokers**



	Nonsmokers MI					Smokers MI				
N	730	444	250	107	44	333	237	135	70	37
Reclassification										
Appropriate, %	4	6	10	17	30	4	5	10	17	16
Inappropriate, %	3	0	0	0	0	4	1	0	0	0
P Value	0.47	< 0.001	0.001	< 0.001	< 0.001	1.00	0.01	< 0.001	0.001	0.01
N	29,101	13,748	6,650	2,533	1,239	7,826	4,482	2,424	1,070	585
Reclassification										
Appropriate, %	1	0	0	0	0	2	1	0	0	0
Inappropriate, %	1	3	5	9	11	2	4	7	13	18
P Value	0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.26	< 0.001	< 0.001	< 0.001	< 0.001
NRI, %	0	4	4	8	19	0	1	2	4	-2
95% CI	-1-2	1-6	1-8	1-15	5-32	-3-3	-2-4	-3-7	-5-13	-14-11
Remnant Cholesterol										
Percentile	All	≥50th	≥75th	≥90th	≥95th	All	≥50th	≥75th	≥90th	≥95th
mmol/L	≥0	≥0.6	≥1.0	≥1.3	≥1.6	≥0	≥0.6	≥1.0	≥1.3	≥1.6
mg/dL	≥0	≥25	≥37	≥51	≥61	≥0	≥25	≥37	≥51	≥61

Chart is based on 41,928 individuals aged 40-100 years from the Copenhagen General Population Study without ischemic cardiovascular disease, diabetes, and statin use. Underlining Cox regression models fitted data from all individuals. Proportions of population are shown in **green bars** for those appropriately reclassified and in **red bars** for those inappropriately reclassified, when remnant cholesterol was added to the baseline model. Abbreviations as in Figure 3.

CENTRAL ILLUSTRATION **Reclassification of Myocardial Infarction by Elevated Remnant Cholesterol**



Doi T, et al. J Am Coll Cardiol. 2022;79(24):2383–2397.

Distribution of **(A)** nonfasting remnant cholesterol and **(B)** combined reclassification from <5% to ≥5%, 7.5% and 10% 10-year risk of later myocardial infarction as a function of elevated nonfasting remnant cholesterol. Proportions of population are shown in **green bars** for those appropriately reclassified and in **red bars** for those inappropriately reclassified.

individuals with a 1%-10% 10-year risk of cardiovascular disease in the SCORE2 risk prediction algorithm, the results were similar to the main analyses (compare Supplemental Figure 7 with **Figure 3**). Finally, analyses using the competing risk model of Fine and Gray[20] instead of a Cox regression model gave similar results (compare Supplemental Figure 8 with **Figure 3**).

DISCUSSION

We found that elevated remnant cholesterol appropriately reclassified up to 40% of those who later experienced myocardial infarction and ischemic heart disease, leading to NRI of up to 20% in statin-naïve individuals without a history of ischemic cardiovascular disease and diabetes (**Central Illustration**). These novel results in individuals with elevated remnant cholesterol suggest that adding this causal risk factor to guideline prediction models will improve the identification of individuals who would benefit the most from statin treatment.

Elevated remnant cholesterol is known for its causal association with increased risk of myocardial infarction and ischemic heart disease.[1,2,5] Mechanistically, human and animal studies have demonstrated that remnant lipoproteins can enter into the arterial intima like LDL.[2,23,24] Because neither LDL nor remnants can penetrate farther into the media because of their large size relative to the fenestra of the media, and although the rate at which large remnants enter into the intima itself is slightly slower than that of the smaller LDL particles, remnant lipoproteins may be trapped preferentially within the intima. Indeed, remnants like LDL have difficulty returning into the bloodstream because of the blood pressure gradient

from the arterial lumen through to the adventitia. As when LDL is trapped in the intima, trapping of remnants leads to intimal accumulation of cholesterol, development of atherosclerosis, and finally myocardial infarction and ischemic heart disease. On the basis of accumulated evidence establishing a causal association between elevated remnant cholesterol and increased risk of atherosclerotic cardiovascular disease, we here performed a clinically focused study to evaluate to what extent elevated remnant cholesterol levels contribute to reclassify the risk of myocardial infarction and ischemic heart disease.

A distinctive feature of remnant cholesterol levels, compared with levels of LDL cholesterol, is the skewed concentration distribution with a tail toward higher levels (**Central Illustration**). Previous studies have shown that although the risk of atherosclerotic cardiovascular disease may already be high at moderately high remnant cholesterol levels, the risk is very high for extremely high levels.[5,25,26] Therefore, in the present study we selectively examined reclassification if only individuals with various degrees of extremely high remnant cholesterol (eg, ≥95th percentile [≥1.6 mmol/L, 61 mg/dL] or ≥75th percentile [≥1.0 mmol/L, 37 mg/dL]) were taken into account, exactly as would be done in a typical clinical situation. Above these cut points, substantial appropriate reclassification was observed; however, the remnant cholesterol levels over the entire concentration range showed little or no significant increases in NRIs, which is in line with recent results from the Framingham Offspring Study.[27]

When remnant cholesterol was calculated as total cholesterol minus LDL cholesterol minus HDL cholesterol, LDL cholesterol was calculated either with the classic Friedewald method[16] or at individual levels of plasma triglycerides and non-HDL cholesterol using the Martin-Hopkins[17] or Sampson-NIH[18] methods; however, all 3 values of remnant cholesterol provided similar trends of increased NRIs. Moreover, our recent study in a primary prevention setting[9] and other studies in secondary prevention settings[28,29] have also demonstrated significant increases in NRIs after the addition of remnant cholesterol to risk prediction models. Although minor discrepancies exist among remnant cholesterol calculated by these 3 methods and between calculated and directly measured remnant cholesterol on an individual patient basis,[9] remnant cholesterol calculated by the Friedewald method has the advantage that it can be obtained from a standard lipid profile without additional cost. Of note, in a previous study we found that calculated remnant cholesterol levels reclassified more appropriately future myocardial infarction events than did directly measured remnant cholesterol.[9] However, that study had less statistical power than the present study.

STUDY STRENGTHS AND LIMITATIONS. The strengths of the current study include a high number of individuals with long follow-up periods in a primary prevention setting, available lipid traits required to calculate remnant cholesterol, and the large availability of relevant data. Furthermore, cardiovascular outcomes were obtained from nationwide Danish health registries, and no individuals were lost to follow-up. Moreover, following current guidelines using cut points of 5%, 7.5%, and 10% 10-year risk of atherosclerotic cardiovascular disease for the initiation of statins for primary prevention purposes in individuals without a history of diabetes, we used these same cut points for myocardial infarction and ischemic heart disease to determine appropriate and inappropriate reclassification. It is also a strength that remnant cholesterol was analyzed in the nonfasting state, which included very-low-density lipoproteins, intermediate-density lipoproteins, and chylomicron remnants. Taken together, the present results may provide key insights when cholesterol, dyslipidemia, and cardiovascular disease prevention guidelines in the United States, Europe, the United Kingdom, Japan, and elsewhere need revision.[12-15]

A limitation of our study is that we analyzed only white individuals. Therefore, the results may not necessarily apply to other ethnicities; however, we are not aware of data to suggest that our results should not be applicable in most countries having fractions of the population with elevated remnant cholesterol. It could be argued that the novelty of the current study is limited by previous reports suggesting that remnant cholesterol may help to predict the risk of cardiovascular outcomes. However, in the present study we examined reclassification in individuals with extremely high remnant cholesterol, which is similar to what physicians do in their daily clinical practice, representing a clear novel aspect of our study. Further, no standardized method or definition of remnant cholesterol exists. Finally, in our net reclassification analyses, the results are shown as percentages, which is the standard approach; however, it is worth noticing that in terms of absolute numbers, there is a considerably larger number of inappropriately reclassified nonevents than of appropriately reclassified events.

CLINICAL IMPLICATIONS. The clinical implications of our study include that doctors and patients should be aware of remnant cholesterol levels to prevent

future risk of myocardial infarction and ischemic heart disease. The development of a cardiovascular risk algorithm (like SCORE and PCE) including remnant cholesterol together with LDL cholesterol would help to better identify high-risk individuals who could be candidates for statins in a primary prevention setting. Further, physicians are encouraged to evaluate non-HDL cholesterol and/or apolipoprotein B rather than LDL cholesterol and certainly not yet remnant cholesterol, possibly because of the limited availability of remnant cholesterol values in some parts of the world. However, remnant cholesterol can be calculated with a standard lipid profile without additional cost, which is currently already the standard procedure in the greater Copenhagen area in Denmark. This means that the use of remnant cholesterol is easy to introduce into daily clinical practice.

CONCLUSIONS

Elevated remnant cholesterol appropriately reclassified up to 40% of individuals who later experienced myocardial infarction and ischemic heart disease, leading to a net reclassification index of up to 20% in statin-naïve individuals without a history of ischemic cardiovascular disease and diabetes. These findings may contribute to direct future efforts to evaluate risk of cardiovascular events and promote statin initiation for primary prevention purposes in those at the highest risk with elevated remnant cholesterol.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In individuals without a history of ischemic cardiovascular disease, diabetes, or statin therapy, elevated remnant cholesterol appropriately reclassified up to 40% of patients who later experienced ischemic heart disease or myocardial infarction.

TRANSLATIONAL OUTLOOK: Further research is needed to assess the efficacy of statin therapy in individuals without diabetes or manifest ischemic cardiovascular disease whose risk of disease is reclassified as high when remnant cholesterol is added to the conventional risk model.

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KEY WORDS atherosclerotic cardiovascular disease, primary prevention, reclassification, triglyceride-rich lipoproteins, very-low-density lipoprotein

APPENDIX For supplemental tables and figures, please see the online version of this paper.