JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 76, NO. 23, 2020

VLDL Cholesterol Accounts for One-Half of the Risk of Myocardial Infarction Associated With apoB-Containing Lipoproteins

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ABSTRACT

BACKGROUND Plasma apolipoprotein B (apoB) is a composite measure of all apoB-containing lipoproteins causing atherosclerotic cardiovascular disease; however, it is unclear which fraction of risk is explained by cholesterol and triglycerides, respectively, in very low-density lipoproteins (VLDLs).

OBJECTIVES The authors tested the hypothesis that VLDL cholesterol and triglycerides each explain part of the myocardial infarction risk from apoB-containing lipoproteins.

METHODS Nested within 109,751 individuals from the Copenhagen General Population Study, the authors examined 25,480 subjects free of lipid-lowering therapy and myocardial infarction at study entry. All had measurements of plasma apoB (quantitating number of apoB-containing lipoproteins) and cholesterol and triglyceride content of VLDL, intermediate-density lipoproteins (IDLs), and low-density lipoproteins (LDLs).

RESULTS During a median 11 years of follow-up, 1,816 were diagnosed with myocardial infarction. Per 1-mmol/l higher levels, multivariable-adjusted hazard ratios for myocardial infarction were 2.07 (95% confidence interval [CI]: 1.81 to 2.36) for VLDL cholesterol, 1.19 (95% CI: 1.14 to 1.25) for VLDL triglycerides, 5.38 (95% CI: 3.73 to 7.75) for IDL cholesterol, and 1.86 (95% CI: 1.62 to 2.14) for LDL cholesterol. Per 1-g/l higher plasma apoB, the corresponding value was 2.21 (95% CI: 1.90 to 2.58). In a step-up Cox regression, risk factors for myocardial infarction entered by importance as VLDL cholesterol, systolic blood pressure, smoking, and IDL + LDL cholesterol, whereas VLDL triglycerides did not enter the model. VLDL cholesterol explained 50% and IDL + LDL cholesterol 29% of the risk of myocardial infarction from apoB-containing lipoproteins, whereas VLDL triglycerides did not explain risk.

CONCLUSIONS VLDL cholesterol explained one-half of the myocardial infarction risk from elevated apoB-containing lipoproteins, whereas VLDL triglycerides did not explain risk. (J Am Coll Cardiol 2020;76:2725–35) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

In 1979, Donald B. Zilversmit suggested that atherogenesis is a postprandial phenomenon, as triglyceride-rich remnants are particularly elevated postprandially, and as such, remnants in addition to low-density lipoprotein (LDL) lead to atherosclerosis (1). Since then, numerous human observational and causal, genetic studies have documented that elevated triglyceride-rich remnants or very low-density lipoproteins (VLDLs) are associated with increased risk of atherosclerotic cardiovascular disease (2–17). The exact mechanism behind this causal relationship is currently not understood;

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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 *JACC* author instructions page.

Manuscript received June 17, 2020; revised manuscript received September 10, 2020, accepted September 29, 2020.

ISSN 0735-1097/$36.00

https://doi.org/10.1016/j.jacc.2020.09.610

ABBREVIATIONS AND ACRONYMS

CV = coefficients of variation

HDL = high-density lipoprotein

IDL = intermediate-density lipoprotein

LDL = low-density lipoprotein

NMR = nuclear magnetic resonance

VLDL = very low-density lipoprotein

however, likely triglyceride-rich remnants penetrate the arterial wall where hydrolysis of triglycerides releases toxic free fatty acids inducing inflammation and where cholesterol after macrophage uptake accumulates in the intima, causing atherosclerosis and eventually atherosclerotic cardiovascular disease.

SEE PAGE 2736

Randomized clinical trials using triglyceride-lowering therapies mainly in individuals without elevated triglycerides yielded conflicting results on cardiovascular endpoints (18–27). Recently, in individuals with elevated triglycerides, the REDUCE-IT (Reduction of Cardiovascular Event Icosapent Ethyl Intervention Trial) found that reduction in triglycerides by 20% led to a 25% reduction in atherosclerotic cardiovascular events (28); however, the mechanism behind this cardiovascular benefit is not fully understood.

Higher levels of VLDL or triglyceride-rich remnants imply higher levels of plasma apolipoprotein B (apoB) due to more apoB-containing lipoproteins in plasma. Total plasma apoB is a composite measure of all apoB-containing lipoproteins causing atherosclerotic cardiovascular disease, including myocardial infarction, encompassing VLDL, intermediate-density lipoprotein (IDL), and LDL, the latter also including lipoprotein(a). Each of these lipoproteins have 1 apoB molecule per particle. It is unclear which fraction of risk is explained by respectively cholesterol and triglycerides in VLDL.

We tested the hypothesis that VLDL cholesterol and triglycerides each explain part of the myocardial infarction risk from apoB-containing lipoproteins; we chose to study myocardial infarction, as this is the best reported hard endpoint within atherosclerotic cardiovascular disease. To do so, we used measurements of plasma apoB (quantitating number of apoB-containing lipoproteins) and cholesterol and triglyceride content of VLDL, IDL, and LDL in 25,480 individuals nested within the Copenhagen General Population study.

METHODS

STUDY POPULATION. The Copenhagen General Population Study is an ongoing study initiated in 2003 including 109,751 individuals and with a 43% participation rate (7). Individuals were invited at random based on the Danish Civil Registration System to obtain a cohort reflecting the general population. Those participating filled in a questionnaire, underwent a physical examination, and had blood samples drawn. The present study of 25,480 individuals is nested within the Copenhagen General Population Study, excluding individuals with myocardial infarction before baseline and individuals receiving lipid-lowering therapy. The study was approved by the Ethics Committee of the Capital Region of Denmark (H-KF-01-144/01) and by Herlev and Gentofte Hospital. Written informed consent was obtained from all individuals.

MYOCARDIAL INFARCTION. Myocardial infarction during follow-up (World Health Organization International Classification of Diseases [ICD]: ICD-8: 410, ICD-10: I21 to I22) was identified through hospitalization from the national Danish Patient Registry (29) or through death certificates from the national Danish Causes of Death Registry (30). Information on death and emigration was retrieved from the Danish Civil Registration System where information on all Danes are registered continuously (31). End of follow-up was December 2018.

LIPOPROTEINS. Cholesterol and triglyceride content of VLDL, IDL, and LDL were measured using Nightingale Health's nuclear magnetic resonance (NMR) spectroscopy platform. Cholesterol and triglyceride contents of all non-high-density lipoproteins (non-HDL) were calculated by adding respectively triglycerides and cholesterol in VLDL, IDL, and LDL. Lipoprotein(a) is included in LDL.

Plasma samples were stored at −80°C before measurement. Nightingale Health's NMR spectroscopy platform has been widely used in epidemiological studies (a publication list is available online). A previous study found that coefficients of variation (CV%) for this platform typically were below 5% for lipoprotein subclass measures, and CV% for total cholesterol was 2.1% and for total triglycerides was 1.2% (32). Another study found CV% for the NMR measurements with a median value on 5.0% and an interquartile range of 2.7% to 6.7% (33). More details on the application, validation, and experimentation of Nightingale Health's NMR spectroscopy platform have been reported in previous studies (33–35).

ApoB, total cholesterol, total triglycerides, and HDL cholesterol were measured on fresh samples using standard hospital assays (Konelab and Cobas) subjected to daily internal quality control for imprecision and monthly external quality control for accuracy. LDL cholesterol was calculated using the Friedewald equation when plasma triglycerides were ≤4 mmol/l (354 mg/dl), and was otherwise measured directly (Konelab and Cobas). Calculated remnant cholesterol was total cholesterol minus HDL

cholesterol minus LDL cholesterol. Nonfasting blood samples were used, as described previously (36).

COVARIATES. Information on covariates was collected at baseline. Smoking was self-reported, whereas blood pressure was measured.

STATISTICAL ANALYSES. Analyses were conducted with Stata/S.E. version 13 (StataCorp, College Station, Texas). Multivariable chained imputation was performed for the 0.04% of missing data. The imputation model included age, sex, and the missing potential confounders (smoking status and systolic blood pressure). Results were similar without imputation. Content of cholesterol and triglycerides in VLDL, IDL, and LDL were corrected for recovery according to total plasma cholesterol and triglyceride levels measured on fresh samples at baseline for each individual, and similar to standard practice for ultracentrifugation measurement of cholesterol and triglyceride content of VLDL, IDL, and LDL subfraction, as described previously (37–39). For comparison of those with and without myocardial infarction, p values were calculated using Pearson's chi-square test for categorical variables and Kruskal-Wallis test for continuous variables. Spearman's correlation coefficients (abbreviated r) and r^2 as coefficient of determination (r × r) between lipoprotein lipid subclasses were calculated. A composite of LDL cholesterol and IDL cholesterol was used in some statistical models, because of a high correlation (R^2 = 93%). Such high correlation may lead to spurious findings when, for example, LDL cholesterol is positively associated with risk of myocardial infarction while IDL cholesterol in the same model is negatively associated with such risk, or vice versa.

Associations of VLDL cholesterol, IDL cholesterol, LDL cholesterol, non-HDL cholesterol, VLDL triglycerides, non-HDL triglycerides, and apoB with risk of myocardial infarction were examined using Cox regression analyses with time of follow-up as the timescale. We also conducted parallel analyses with age as the underlying timescale and delayed entry at study examination (= left truncation); left truncation means that an individual first enters the model at the day of examination and is followed prospectively thereafter. Individuals were followed to incident myocardial infarction (n = 1,816), death (n = 7,545), emigration (n = 82), or end of follow-up at December 2018, whichever occurred first. Analyses were multivariable adjusted for age, sex, smoking, and systolic blood pressure when using time of follow-up as the time scale and for sex, smoking, and systolic blood pressure when using age as the underlying timescale (the latter automatically adjusts for age). The median follow-up time was 11 years (range 0 to 15 years). Using multivariable-adjusted hazard ratios on restricted cubic splines with 3 knots (best fit according to Akaike's and Schwarz's Bayesians information criteria), the association of VLDL cholesterol, IDL

TABLE 1 Baseline Characteristics of Individuals in the Copenhagen General Population Study Free of Lipid-Lowering Therapy and Myocardial Infarction at Study Entry

	All (N = 25,480)	Myocardial Infarction During Follow-Up		p Value
		Yes (n = 1,816)	No (n = 23,664)	
Age, yrs	61 (50–71)	66 (56–75)	60 (50–71)	<0.001
Women	13,504 (53)	689 (38)	12,815 (54)	<0.001
Smokers	6,170 (24)	500 (28)	5,670 (24)	0.001
Systolic blood pressure, mm Hg	140 (128–156)	149 (135–162)	140 (127–155)	<0.001
VLDL cholesterol				
mmol/l	0.88 (0.66–1.20)	1.0 (0.77–1.30)	0.87 (0.65–1.20)	<0.001
mg/dl	34 (26–45)	39 (30–51)	34 (25–45)	<0.001
IDL cholesterol				
mmol/l	0.87 (0.74–1.00)	0.93 (0.79–1.10)	0.87 (0.74–1.01)	<0.001
mg/dl	34 (29–39)	36 (31–41)	34 (29–39)	<0.001
LDL cholesterol				
mmol/l	2.0 (1.7–2.4)	2.2 (1.8–2.5)	2.0 (1.7–2.4)	<0.001
mg/dl	78 (65–92)	84 (70–97)	78 (65–92)	<0.001
Non-HDL cholesterol				
mmol/l	3.8 (3.2–4.5)	4.1 (3.5–4.8)	3.8 (3.2–4.5)	<0.001
mg/dl	147 (123–174)	160 (135–186)	146 (122–173)	<0.001
VLDL triglycerides				
mmol/l	0.95 (0.58–1.50)	1.2 (0.73–1.80)	0.93 (0.57–1.50)	<0.001
mg/dl	84 (51–134)	104 (65–162)	82 (51–132)	<0.001
Non-HDL triglycerides				
mmol/l	1.3 (0.87–1.90)	1.5 (1.0–2.3)	1.3 (0.86–1.90)	<0.001
mg/dl	114 (77–171)	136 (92–203)	113 (76–169)	<0.001
apoB				
g/l	1.1 (0.93–1.40)	1.2 (1.0–1.5)	1.1 (0.92–1.40)	<0.001
mg/dl	110 (93–140)	120 (100–150)	110 (92–140)	<0.001

Values are median (interquartile range) or n (%). Number of individuals in each covariate varies slightly due to availability of data. The p values are calculated using Pearson's chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.

apoB = apolipoprotein B; HDL= high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

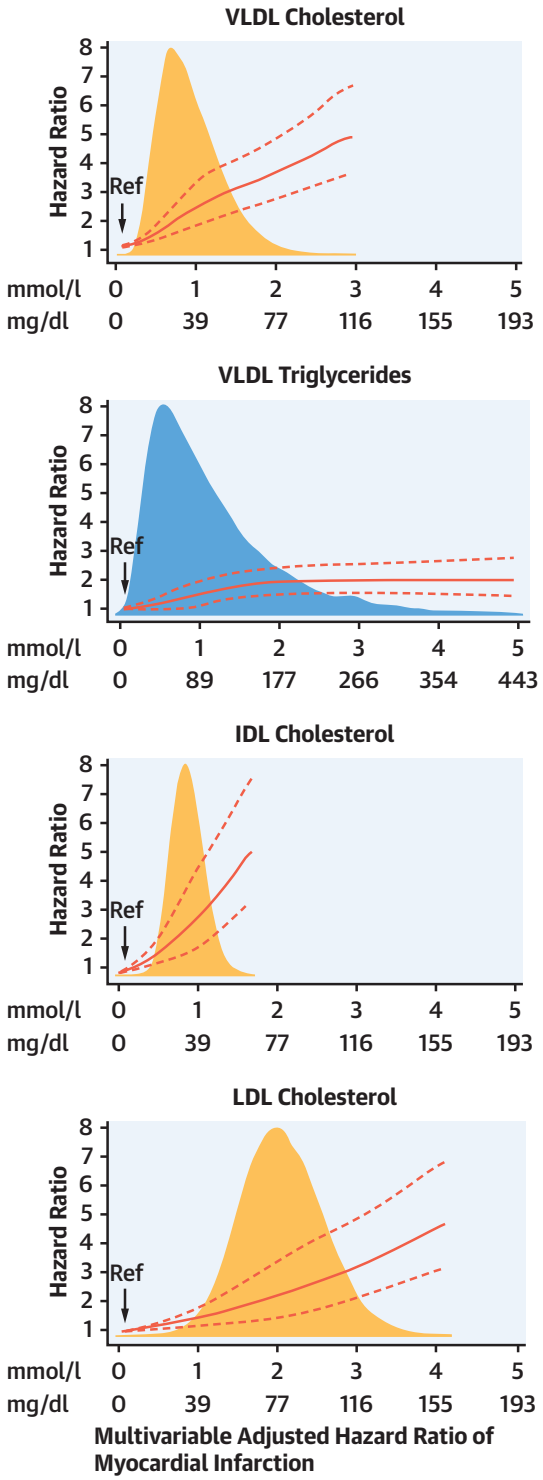
TABLE 2 Intercorrelation of Lipoprotein Cholesterol and Triglyceride Contents in 25,477 Individuals in the Copenhagen General Population Study Free of Lipid-Lowering Therapy and Myocardial Infarction at Study Entry

r / r^2	VLDL Cholesterol	VLDL Triglycerides	IDL Cholesterol	LDL Cholesterol
VLDL cholesterol		0.88	0.61	0.50
VLDL triglycerides	77%		0.27	0.17
IDL cholesterol	37%	7%		0.96
LDL cholesterol	25%	3%	93%	

All p values <0.001. r was the Spearman's correlation coefficient, while r^2 (r times r) was also shown to illustrate percentage of variation explained between 2 covariates.

Abbreviations as in Table 1.

FIGURE 1 Hazard Ratio for Myocardial Infarction by Cholesterol Content of VLDL, IDL, and LDL and by Triglyceride Content of VLDL on a Continuous Scale With No Assumption of Linearity



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cholesterol, LDL cholesterol, and VLDL triglycerides with myocardial infarction was examined. The reference values were 0.1 mmol/l (4 mg/dl) for VLDL cholesterol, IDL cholesterol, and LDL cholesterol and 0.1 mmol/l (9 mg/dl) for VLDL triglycerides. The reference values were chosen to visualize the risk estimates with increase in triglycerides and cholesterol content over the whole concentration span. Furthermore, to rank lipoprotein lipid subfractions and other risk factors for myocardial infarction, a step-up adding of risk factors based on lowest p values using a Cox regression analysis adjusted for sex and age with time of follow-up as the timescale was performed. A parallel analysis with age as the underlying timescale was also conducted. An analysis with triglycerides forced into the model was also performed.

The proportional hazard assumption was assessed graphically, and no major violations were observed.

Hazard ratios including 95% confidence intervals (CIs) were corrected for regression dilution bias (40). Regression dilution bias is the designation for the fluctuations of a parameter (in this case lipids and systolic blood pressure) within individuals and random measurement errors over time. Most commonly, regression dilution bias leads to underestimation of an association. Using replicated measurements in ~500 individuals without lipid-lowering therapy participating in the Copenhagen General Population Study for the first time in 2003 to 2004 and for the second time in 2014 to 2016, the regression dilution ratio was 0.74 for VLDL cholesterol, 0.60 for IDL cholesterol, 0.62 for LDL cholesterol, 0.63 for IDL + LDL cholesterol, 0.62 for non-

FIGURE 1 Continued

Hazard ratios with 95% confidence intervals for myocardial infarction, according to VLDL cholesterol, IDL cholesterol, LDL cholesterol, and VLDL triglycerides on continuous scales, are from Cox regression restricted cubic splines. **Yellow areas** show distribution of cholesterol levels while the **blue area** shows the distribution of triglycerides within each lipoprotein fraction. Multivariable adjusted for age, sex, smoking, and systolic blood pressure. The analyses comprised 25,477 individuals from the Copenhagen General Population Study including 1,816 cases of myocardial infarction developed during a median of 11 years of follow-up. VLDL triglycerides were truncated at 5 mmol/l (443 mg/dl) corresponding to the 99.3 percentile. The cholesterol measurements were truncated at the 99.9 percentile. Ref = reference level, which was 0.1 mmol/l (4 mg/dl) for cholesterol values and 0.1 mmol/l (9 mg/dl) for triglyceride values. IDL= intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

HDL cholesterol, 0.81 for VLDL triglycerides, 0.62 for non-HDL triglycerides, 0.74 for plasma apoB, and 0.77 for systolic blood pressure.

The degree to which VLDL cholesterol, IDL + LDL cholesterol, and VLDL triglycerides explained the relationship between apoB-containing lipoproteins and risk of myocardial infarction (the fraction of risk explained) was examined by the Karlson-Holm-Breen method (41) using bootstrap to calculate CIs. When values in the CIs were below 0%, they were truncated to 0%. VLDL cholesterol, IDL + LDL cholesterol, and VLDL triglycerides were examined separately. Corresponding analyses were also carried out with calculated remnant cholesterol. The logarithm of apoB, VLDL cholesterol, VLDL triglycerides, and calculated remnant cholesterol and the square root of IDL + LDL cholesterol were taken to obtain normally distributed variables. A logistic regression model was first adjusted for age and sex and afterwards additionally for smoking and systolic blood pressure.

RESULTS

Baseline characteristics of 1,816 individuals with, and 23,664 without myocardial infarction during follow-up are shown in **Table 1**. Individuals with myocardial infarction during follow-up were older, were more often men and smokers, had higher systolic blood pressure, and had higher levels of non-HDL cholesterol, VLDL cholesterol, IDL cholesterol, LDL cholesterol, non-HDL triglycerides, VLDL triglycerides, and apoB.

Coefficient of determination, r^2, of VLDL cholesterol was 77% with VLDL triglycerides, 37% with IDL cholesterol, and 25% with LDL cholesterol (**Table 2**). For VLDL triglycerides, r^2 was 7% with IDL cholesterol and 3% with LDL cholesterol. LDL cholesterol and IDL cholesterol were highly correlated with an r^2 of 93%.

RISK OF MYOCARDIAL INFARCTION. The multivariable-adjusted hazard ratios increased with higher levels of VLDL cholesterol, VLDL triglycerides, IDL cholesterol, and LDL cholesterol (**Figure 1**). However, for VLDL triglycerides, the risk estimates reached a plateau from around ~2 mmol/l (~177 mg/dl) through to higher concentrations, shown in the Cox regression restricted cubic spline model.

For a 1-mmol/l (39 mg/dl) higher cholesterol content, multivariable-adjusted hazard ratios for myocardial infarction were 2.07 (95% CI: 1.81 to 2.36) for VLDL, 5.38 (95% CI: 3.73 to 7.75) for IDL, 1.86 (95% CI: 1.62 to 2.14) for LDL, and 1.49 (95% CI: 1.39 to 1.60) for non-HDL (**Figure 2**). Corresponding estimates for a 1-mmol/l (89-mg/dl) higher triglyceride content were 1.19 (95% CI: 1.14 to 1.25) for VLDL triglycerides and 1.17 (95% CI: 1.12 to 1.22) for non-HDL triglycerides. Multivariable-adjusted hazard ratio for myocardial infarction for a 1 g/l (100 mg/dl) higher concentration of apoB was 2.21 (95% CI: 1.90 to 2.58).

When using age rather than time of follow-up as the timescale, similar results were found (Supplemental Figures 1 and 2).

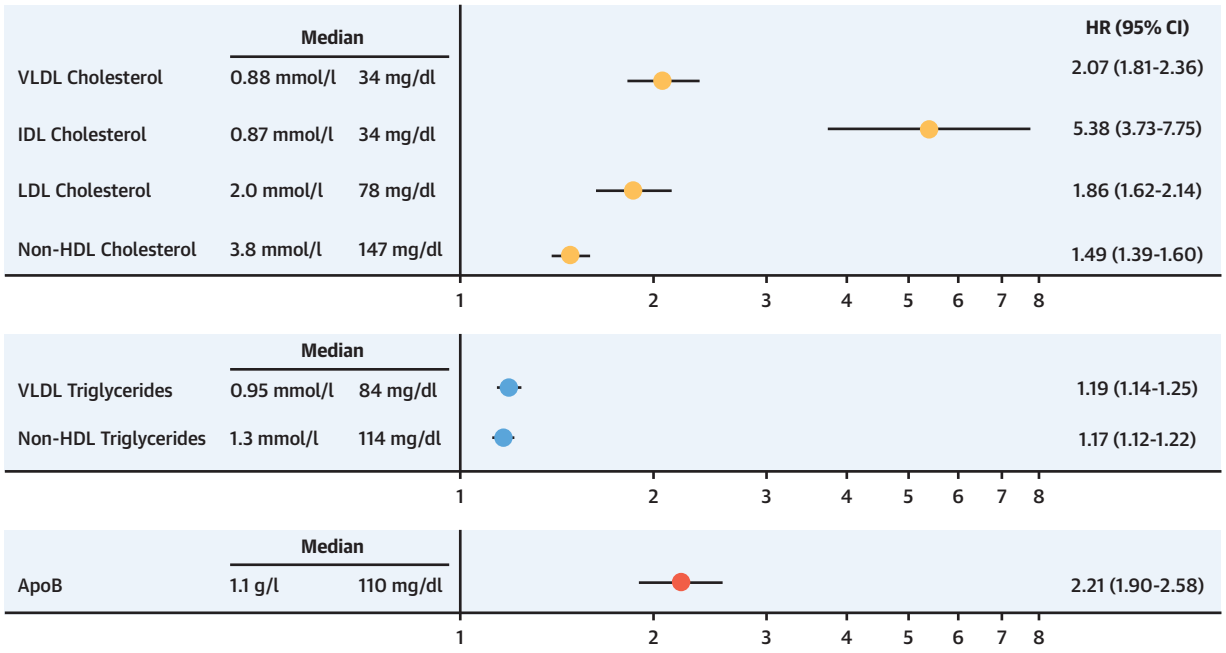
RANKING OF RISK FACTORS. In a Cox regression analysis adjusted for sex and age, step-up addition by lowest p value of risk factors for myocardial infarction first entered VLDL cholesterol, followed by systolic blood pressure, smoking, and IDL + LDL cholesterol (**Table 3**). If IDL and LDL cholesterol were included in the same model as separate variables, estimates were in opposing directions, potentially a spurious finding due to high correlation of IDL and LDL cholesterol (r^2 = 93%). VLDL triglycerides had a p value >0.1 and did not enter the model. In the final step-up model, the hazard ratio was 1.77 (95% CI: 1.52 to 2.05) for 1-mmol/l (39-mg/dl) higher VLDL cholesterol, 1.11 (95% CI: 1.07 to 1.23) for 10-mm Hg higher systolic blood pressure, 1.31 (95% CI: 1.18 to 1.46) for smokers versus nonsmokers, and 1.32 (95% CI: 1.19 to 1.46) for 1-mmol/l (39-mg/dl) higher IDL + LDL cholesterol. In a corresponding model with age as the underlying timescale, results were similar (Supplemental Table 1). When VLDL triglycerides were forced into the model, the hazard ratio was 0.98 (95% CI: 0.89 to 2.46) for 1-mmol/l (88-mg/dl) higher VLDL triglycerides (Supplemental Table 2).

apoB-CONTAINING LIPOPROTEINS, MYOCARDIAL INFARCTION, AND RISK EXPLAINED BY SUBFRACTIONS. VLDL cholesterol statistically explained 46% (95% CI: 21% to 72%; p = 0.001) and IDL + LDL cholesterol 25% (95% CI: 10% to 39%; p = 0.001) of the risk in the association between apoB-containing lipoproteins and myocardial infarction in models adjusted for age and sex (**Figure 3**). Corresponding values in multivariable-adjusted models were 50% (95% CI: 22% to 78%; p = 0.001) for VLDL cholesterol and 29% (95% CI: 13% to 45%; p < 0.001) for IDL + LDL cholesterol. VLDL triglycerides did not explain significant risk, that is, 8% (95% CI: 0% to 23%; p = 0.31) and 8% (95% CI: 0% to 24%; p = 0.35). In corresponding models, calculated remnant cholesterol explained 10% (95% CI: 0% to 24%; p = 0.17) when adjusted for age and sex, and 10% (95% CI: 0% to 26%; p = 0.19) when multivariable adjusted.

DISCUSSION

In this prospective study of 25,480 individuals nested within 109,751 individuals from the Copenhagen

FIGURE 2 Hazard Ratio for Myocardial Infarction According to Cholesterol and Triglyceride Content in Lipoprotein Fractions and to Plasma apoB on Linear Continuous Scales



Multivariable Adjusted Hazard Ratio (95% CI) for Myocardial Infarction per 1 mmol/l Higher Cholesterol or Triglyceride Content or 1 g/l Higher apoB Concentration

Hazard ratios for myocardial infarction from Cox regression analyses by 1-mmol/l (39-mg/dl) higher cholesterol content in VLDL, IDL, LDL, and non-HDL, by 1-mmol/l (89-mg/dl) higher triglyceride content in VLDL and non-HDL, and by 1-g/l (100-mg/dl) higher plasma apoB. Multivariable adjusted for age, sex, smoking, and systolic blood pressure. The analyses comprised 25,477 individuals from the Copenhagen General Population Study including 1,816 cases of myocardial infarction developed during 11 years of follow-up. apoB = apolipoprotein B; CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

General Population Study, we found that VLDL cholesterol explained one-half of the risk of myocardial infarction from elevated levels of apoB-containing lipoproteins, whereas VLDL triglycerides did not materially add to the explanation of risk (Central Illustration). This finding is novel.

TABLE 3 Ranking of Risk Factors for Myocardial Infarction by p Values for Hazard Ratios in 25,376 Individuals From the Copenhagen General Population Study

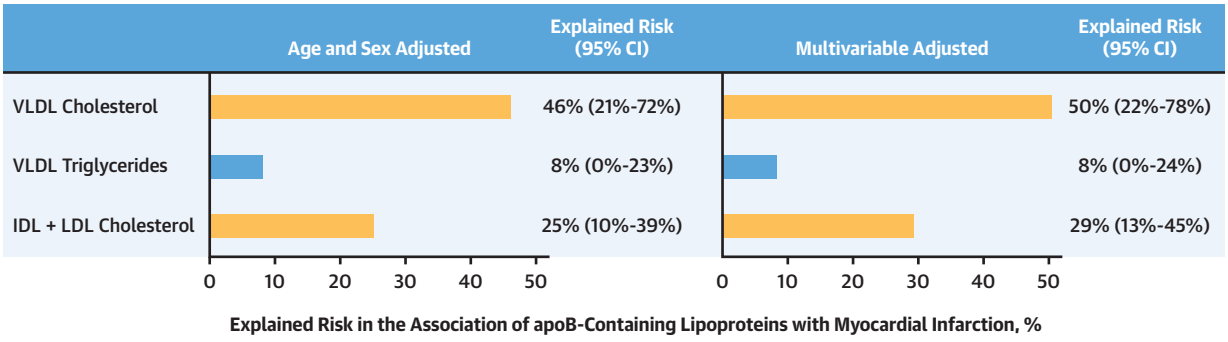
Ranking	HR	95% CI
1. VLDL cholesterol, per 1 mmol/l (39 mg/dl)	1.77	(1.52-2.05)
2. Systolic blood pressure, per 10 mm Hg	1.11	(1.07-1.23)
3. Smoking, yes vs. no	1.31	(1.18-1.46)
4. IDL+ LDL cholesterol, per 1 mmol/l (39 mg/dl)	1.32	(1.19-1.46)
VLDL triglycerides, per 1 mmol/l (89 mg/dl)	Did not enter the model	

Step-up addition of risk factors for myocardial infarction using Cox regression analysis. Adjusted for sex and age with time of follow-up as the timescale. Significance level for addition to the model was $p < 0.10$.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

The mechanism behind our finding likely is straightforward for the following reasons (Central Illustration). First, VLDL or triglyceride-rich remnants can, like LDL, penetrate the arterial wall to enter into the intima, the anatomical location of atherosclerosis (2,42-45). Second, at the surface of endothelial cells, or within the intima, lipoprotein lipase likely hydrolyses triglycerides and thereby liberates toxic free fatty acids causing inflammation (2,44-46). Third, triglyceride-rich remnants may get trapped preferentially within the intima because of their larger size relative to LDL (2,44,45,47). Fourth, triglyceride-rich remnants can directly be taken up by macrophages that turn into foam cells, giving rise to atherosclerotic plaques with cholesterol accumulation in the intima (2,44-46). Fifth, it is cholesterol and not triglycerides that accumulates in the atherosclerotic plaque. For these reasons, it seems biologically plausible that particularly the cholesterol content of VLDL explained a main fraction of risk

FIGURE 3 **Explained Risk in the Causal Association From Plasma apoB-Containing Lipoproteins to Myocardial Infarction**



Multivariable adjusted for age, sex, smoking, and systolic blood pressure. The logarithm of apoB, VLDL cholesterol, and VLDL triglycerides, and the square root of IDL + LDL cholesterol were taken to obtain normally distributed variables. The analyses comprised 25,474 individuals from the Copenhagen General Population Study including 1,816 cases of myocardial infarction. Abbreviations as in Figures 1 and 2.

from apoB-containing lipoproteins to the development of atherosclerotic cardiovascular disease including myocardial infarction.

A causal association between elevated triglyceride-rich remnants and atherosclerotic cardiovascular disease including myocardial infarction is well documented (2–17). This is further supported by the fact that type III hyperlipidemia, also called remnant hyperlipidemia, is a condition accompanied by a high risk of atherosclerotic cardiovascular disease (48). Hitherto, it was unclear whether such risk was mainly explained through the cholesterol or triglyceride content of these lipoproteins; however, we here document for the first time by head-to-head comparison that the cholesterol and not the triglyceride content of triglyceride-rich lipoproteins explains a large fraction of the increased risk of myocardial infarction from elevated concentrations of apoB-containing lipoproteins. This is further supported by our step-up regression model, where VLDL cholesterol was entered first into the model while VLDL triglycerides did not meet the inclusion criteria of a p value <0.1. In support of our findings, the Emerging Risk Factors Collaboration found that an SD higher concentration of plasma triglycerides was associated with 37% higher risk of coronary heart disease; however, after adjusting for non-HDL cholesterol and HDL cholesterol, the association attenuated substantially (49).

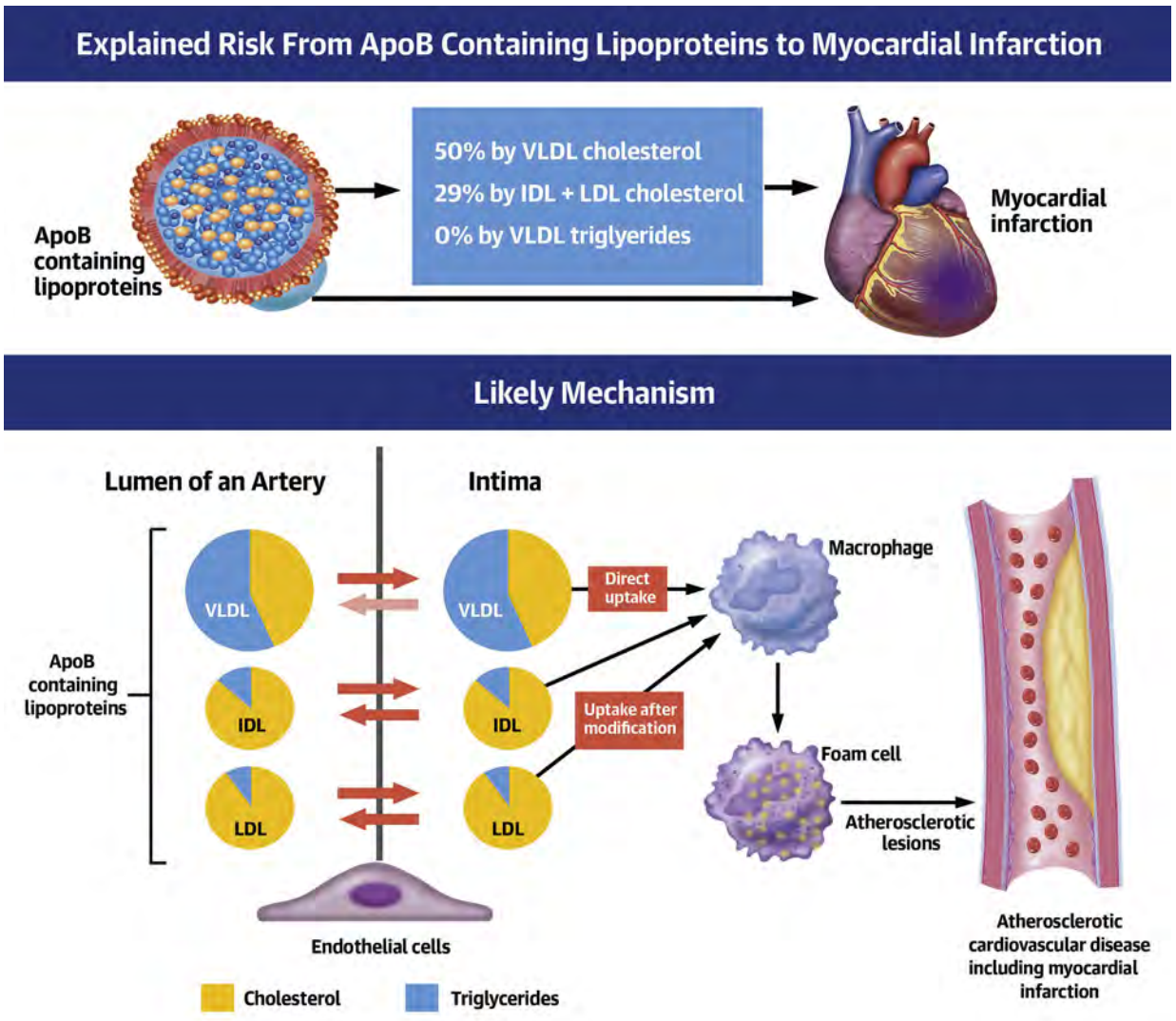
It may seem surprising that for a 1-mmol/l (39-mg/dl) increase in cholesterol content, the myocardial infarction risk is 3-fold higher for IDL than for LDL, both of which are normally part of the "normal measured LDL cholesterol." This points to the notion that if elevated, particularly the IDL part of the "normal measured LDL cholesterol" leads to the highest myocardial infarction risk. In other words, the cholesterol in proper LDL particles within the "normal measured LDL cholesterol" leads to the lowest risk of myocardial infarction. That said, in most individuals, the proper LDL cholesterol constitutes the largest fraction of "normal measured LDL cholesterol," whereas the contribution from IDL cholesterol is minor.

As non-HDL cholesterol constitutes the total atherogenic lipoprotein burden in plasma, it may seem odd that for a 1-mmol/l (39-mg/dl) increase in cholesterol content, the hazard ratio for myocardial infarction is lower for non-HDL cholesterol than for VLDL, IDL, and LDL separately. This is likely explained by the fact that the reference groups differ in the different analyses. In other words, some individuals have very low levels of cholesterol in either VLDL, IDL, or LDL, whereas very few have very low levels of non-HDL cholesterol. If a person has very low levels of LDL cholesterol, they often have relatively high levels of VLDL cholesterol, and vice versa.

Calculated remnant cholesterol and VLDL cholesterol were not comparable in mediation analyses. This may be explained by total triglycerides being a surrogate measure of calculated remnant cholesterol, and it is therefore not possible to compare triglycerides and cholesterol content in VLDL using calculated remnant cholesterol.

In this paper, we equate VLDL particles with remnant lipoproteins. Some agree with this approach, and others disagree. Typically, VLDL is considered a

CENTRAL ILLUSTRATION **Likely Mechanism Behind the Risk From apoB-Containing Triglyceride-Rich Remnants to Atherosclerotic Cardiovascular Disease Including Myocardial Infarction**



Balling, M. et al. J Am Coll Cardiol. 2020;76(23):2725–35.

Suggested mechanism from apoB-containing triglyceride-rich remnants or VLDL to atherosclerotic cardiovascular disease including myocardial infarction. Fractions of risk explained by VLDL cholesterol, IDL + LDL cholesterol, and VLDL triglycerides were examined using the Karlson-Holm-Breen method. VLDL cholesterol explained 50% of the risk from apoB-containing lipoproteins to myocardial infarction. apoB = apolipoprotein B; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

parent lipoprotein produced and secreted by the hepatocytes, while remnant lipoproteins (small VLDL and IDL) are produced when the VLDL is progressively lipolyzed (triglyceride mass removed). However, as soon as VLDL is secreted from the hepatocytes triglyceride hydrolysis starts, and therefore, any triglyceride-rich lipoprotein measured in the VLDL fraction in plasma can be considered a "remnant." This is also the case for any chylomicron entering plasma from the intestine via lymph. Because of this chain of thought, we often use the term remnant cholesterol (7,9,36,45) corresponding

to VLDL cholesterol used here, as this includes all cholesterol in plasma not found in HDL, LDL, and lipoprotein(a).

STRENGTHS AND LIMITATIONS. Strengths of our study include a large number of individuals recruited from the general population, a median follow-up time of 11 years without losing track of any individual, and a large number of myocardial infarctions during follow-up, an endpoint with an estimated accuracy of ~99.5% (50). Furthermore, because we had measurements of plasma total cholesterol and total triglycerides at baseline in all individuals, it was possible to correct for recovery after measurement of lipoprotein lipid fractions using NMR spectroscopy, just as is routine procedure for the gold standard method of ultracentrifugation to measure cholesterol and triglycerides in lipoprotein fractions (37–39). The correction for recovery makes the NMR spectroscopy measurements clinically relatable. Our correction for regression dilution bias that otherwise leads to underestimation of the hazard ratios (40) is a further strength.

A limitation is the observational design, because the associations could be affected by residual confounding and reverse causation; however, we had nearly complete information on known confounders, which decreases the risk of major residual confounding. Also, it is well documented that triglyceride-rich lipoproteins are causally related to atherosclerotic cardiovascular disease through human genetics (2–17), studies where confounding and reverse causation generally do not represent a problem (51). Another limitation is collinearity, because some of the lipid measurements were highly correlated. It is unlikely that the differences among VLDL cholesterol, IDL cholesterol, LDL cholesterol, and VLDL triglycerides can all be explained by collinearity, because neither VLDL cholesterol nor VLDL triglycerides were highly correlated with IDL and LDL cholesterol. That said, IDL and LDL cholesterol were highly correlated, and therefore, in some analyses were examined jointly. Also, VLDL cholesterol and VLDL triglycerides were highly correlated, and if VLDL triglycerides vary more than VLDL cholesterol, this could by error lead to the false conclusion that VLDL cholesterol rather than VLDL triglycerides is the most important fraction for risk of myocardial infarction. Finally, we included solely White individuals, and therefore, our results may not necessarily be generalizable to other ethnicities. That said, we are not aware of data to suggest that our results cannot be applied to most ethnicities.

A key assumption in mediation analysis is that apoB-containing lipoproteins are causally related to increased risk of myocardial infarction and atherosclerotic cardiovascular disease. However, such causal relationships have been documented amply for all apoB-containing lipoproteins including LDL, lipoprotein(a), and triglyceride-rich lipoproteins (2,45,52–55).

CLINICAL RELEVANCE. Our data illustrate that elevated levels of VLDL cholesterol can explain a large part of residual risk of myocardial infarction when LDL cholesterol is relatively low. Therefore, the current focus on mainly LDL cholesterol reduction likely needs to be re-evaluated with more focus on reduction of triglyceride-rich remnants. Most important seems reduction of cholesterol in these particles, as reduction in VLDL cholesterol, IDL cholesterol, or the composite of cholesterol in all triglyceride-rich lipoproteins referred to as remnant cholesterol (7,9,36,45). However, the measures of plasma apoB or non-HDL cholesterol are also very useful clinically, as both of these measurements include LDL, triglyceride-rich lipoproteins, as well as lipoprotein(a).

Until now, no randomized controlled intervention trial has recruited patients solely due to high remnant cholesterol levels, to reduce residual atherosclerotic cardiovascular disease risk. However, the REDUCE-IT trial recruited patients with elevated triglyceride-rich lipoproteins and high residual atherosclerotic cardiovascular risk (28). We recently estimated that roughly one-half of the risk reduction observed in the REDUCE-IT trial using icosapent ethyl 4 g daily can be explained by reduction in remnant cholesterol (56). Further, post hoc subanalyses of trials using fibrates have shown that fibrates lowered triglyceride-rich lipoproteins concentrations and reduced the risk of atherosclerotic cardiovascular disease (57). In addition, it is possible that part of the effect on reducing atherosclerotic cardiovascular disease and mortality risk by statins (58,59) could be due to reduction in triglyceride-rich lipoproteins (60). Further light on whether reduction in triglyceride-rich remnants or remnant cholesterol will lead to reduced risk of atherosclerotic cardiovascular disease will come from the STRENGTH (Long-Term Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia) (61) and PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) (62) trials.

CONCLUSIONS

VLDL cholesterol explained one-half of the myocardial infarction risk from elevated apoB-containing lipoproteins, whereas VLDL triglycerides did not explain risk.

ACKNOWLEDGMENTS The authors thank the staff and participants from the Copenhagen General Population Study for their valuable contributions.

AUTHOR DISCLOSURES

This study was funded by the Danish Heart Foundation, Denmark grant no.: 18-R124-A8511-22089 and by the Novo Nordisk Foundation, Denmark grant no.: NNF18OC0052893. The funders did not participate in the design or conduct of the study; in the collection, analysis, or interpretation of data; and in preparation, review, or approval of the paper. Dr. Varbo is a current employee of Novo Nordisk. Dr. Davey Smith was supported by the Medical Research Council Integrative Epidemiology Unit at the University of Bristol MC_UU_00011/1. Dr. Nordestgaard has consultancies with AstraZeneca, Sanofi, Regeneron, Akcea, Amgen, Kowa, Denka Seiken, Amarin, Novartis, Novo Nordisk, and Silence Therap. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with elevated apoB-containing lipoproteins, VLDL cholesterol accounts for a substantial fraction of causal risk of myocardial infarction, whereas VLDL triglycerides did not.

TRANSLATIONAL OUTLOOK: These findings should be considered in the design of randomized trials of triglyceride-lowering therapies in patients with elevated triglyceride-rich remnants.

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KEY WORDS cardiovascular disease, general population, ischemic heart disease, lipoprotein, remnant cholesterol, triglycerides

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