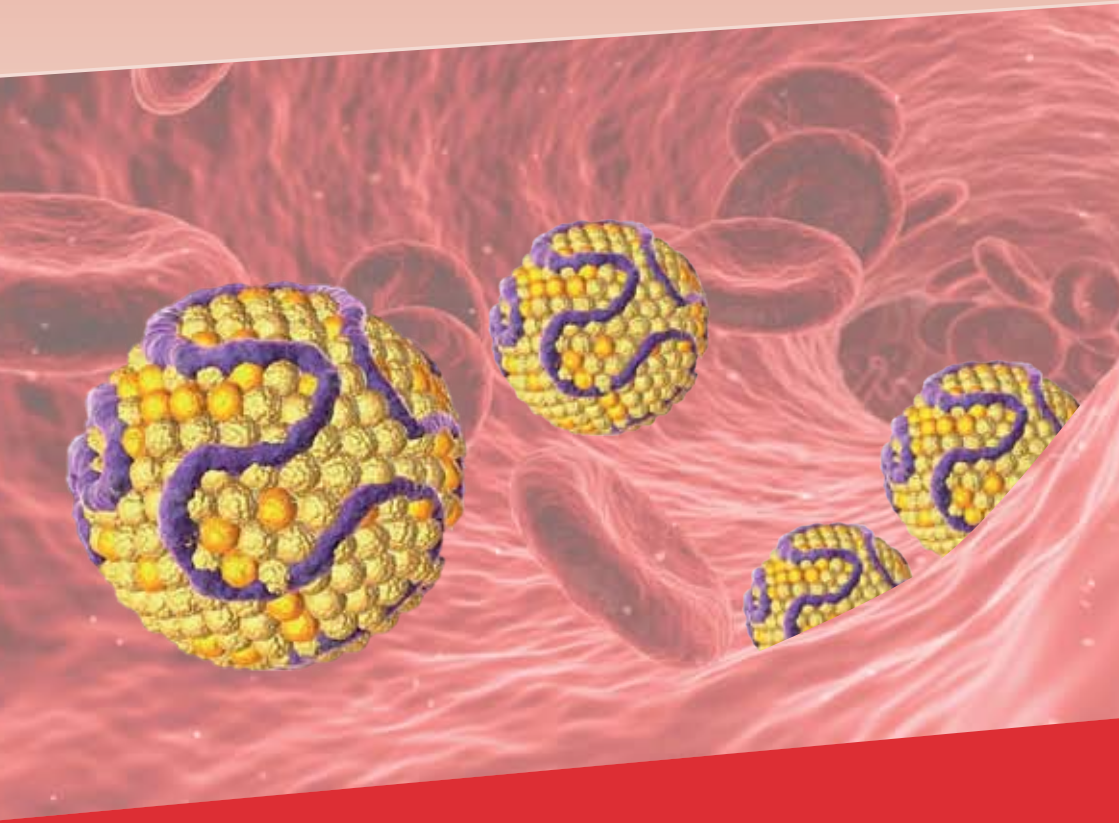
R3i
Residual Risk Reduction initiative

Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease

Professors Børge G. Nordestgaard MD, DMSc,
Michel P. Hermans MD,
and Jean-Charles Fruchart PharmD, PhD



DEFINING TOMORROW'S VASCULAR STRATEGIES

R3i Residual Risk Reduction initiative

Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease

Professors Børge G. Nordestgaard MD, DMSc[1], Michel P. Hermans MD[2], and Jean-Charles Fruchart PharmD, PhD[3]

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Preface

Lowering low-density lipoprotein cholesterol (LDL-C) is the primary lipid target to prevent atherosclerotic cardiovascular disease (ASCVD). Yet even at very low LDL-C levels, high-risk patients continue to experience cardiovascular events.

In the search for possible lipid contributors to this high residual cardiovascular risk, attention focuses on atherogenic dyslipidemia, the combination of low plasma concentration of high-density lipoprotein cholesterol (HDL-C) and elevated triglycerides. The 'HDL hypothesis', which proposed that HDL-C could be protective against ASCVD has been largely abandoned after trials testing numerous HDL-C raising strategies, against a background of best evidence-based medicine including statins, failed to show cardiovascular benefit.

The stage is now set for reconsideration of triglyceride-rich lipoproteins as a causal cardiovascular risk factor. Since 2007, there has been renewed interest in elevated plasma triglycerides, a surrogate for triglyceride-rich lipoproteins and their remnants. This sea-change in thinking has been driven by new genetic insights showing that triglyceride-rich lipoproteins are implicated in the causal pathway for ASCVD. Accumulating epidemiologic evidence also supports an association between triglyceride-rich lipoproteins and ASCVD risk.

The critical test is whether lowering elevated levels of triglycerides reduces residual cardiovascular risk. The PROMINENT trial (Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabetes) is a critical test of the hypothesis that lowering elevated triglycerides with the novel selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα) pemafibrate, will reduce the high residual cardiovascular risk in type 2 diabetes patients (with and without ASCVD) on intensive statin therapy.

This booklet provides a critical background to triglyceride-rich lipoproteins and their role in ASCVD, concluding with discussion of the trials – past and present – that have targeted elevated triglycerides to lower residual cardiovascular risk.

Contents

What are triglyceride-rich lipoproteins?

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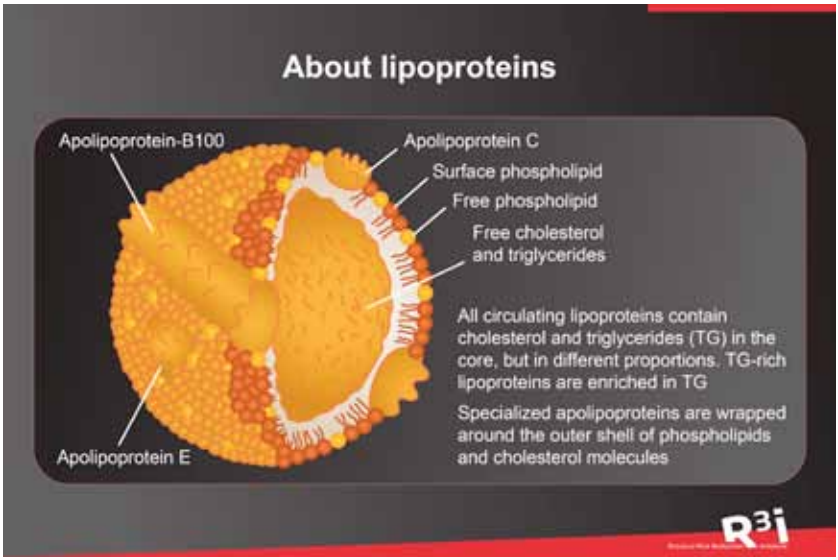
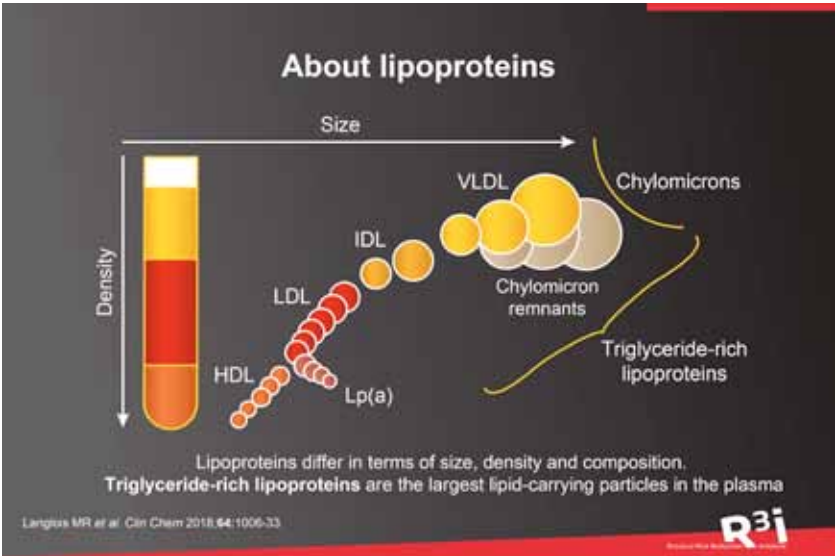
Residual Risk Reduction initiative



About lipoproteins

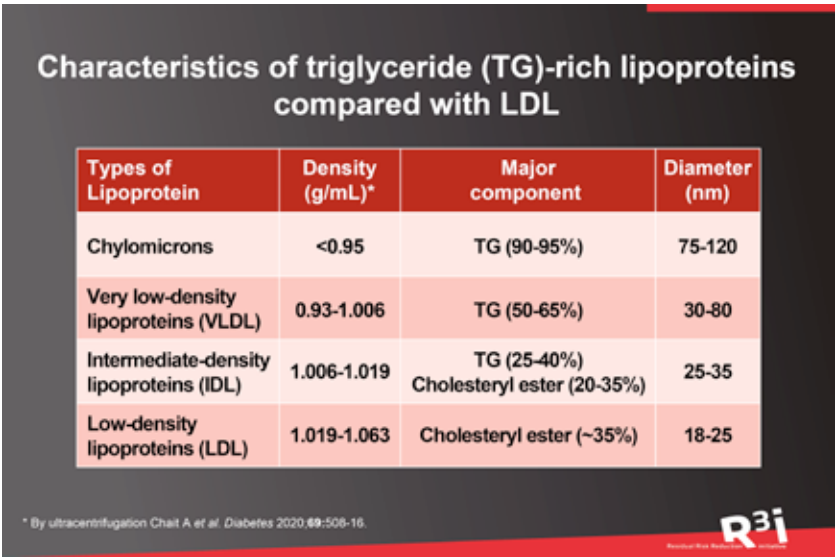
All lipoproteins comprise a core of triglyceride (TG) and esterified cholesterol, varying in proportions. These lipophilic triglycerides are covered by a surface layer of phospholipids, free cholesterol and apolipoproteins, each of which have lipophilic parts facing the centre of the lipoprotein and hydrophilic parts facing the aqueous phase of the plasma, resulting in a spherical form.



About lipoproteins

Triglyceride-rich lipoproteins, which comprise chylomicrons and their remnants, very low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL), are the largest lipid-carrying particles that circulate in the plasma.

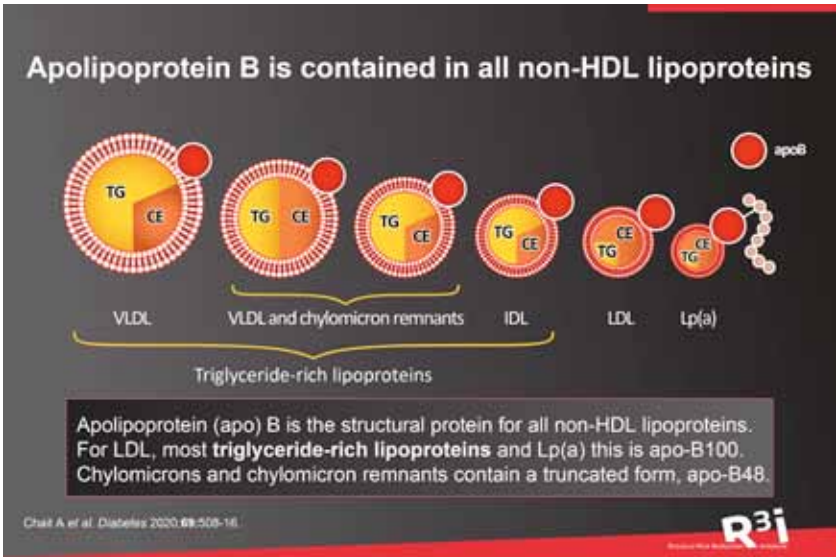
Langlois MR *et al. Clin Chem* 2018;**64**:1006-33.



Characteristics of triglyceride-rich lipoproteins

Triglyceride-rich lipoproteins represent a heterogenous group of lipoproteins that vary in terms of size, density, protein cargo, and core lipid composition.

Chait A *et al. Diabetes* 2020;**69**:508-16.

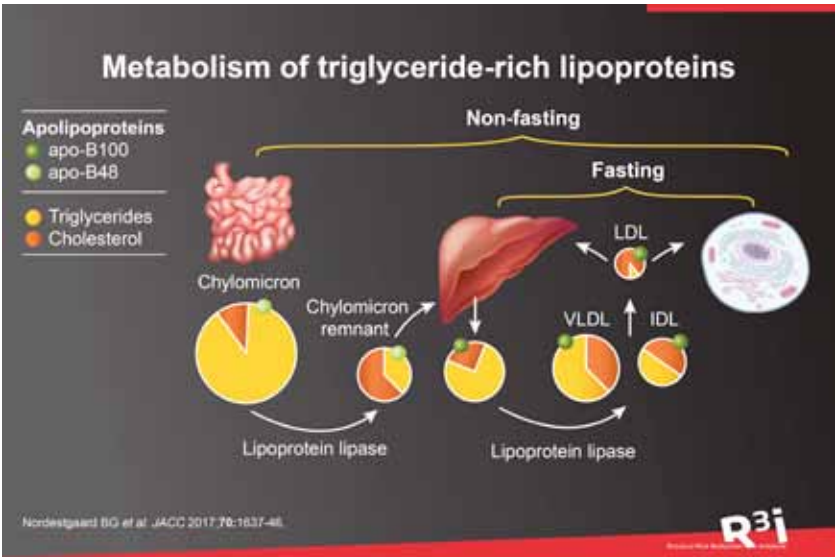


Apolipoprotein B is contained in all non-HDL lipoproteins

All lipoproteins causing ASCVD have one molecule of apolipoprotein B (apoB), the ligand for the LDL-receptor. Chylomicrons and chylomicron remnants have a truncated form of apoB (apo-B48) with 48% the molecular size of full size apo-B100.

Triglyceride-rich lipoproteins also carry several other proteins notably apolipoproteins C and E.

Chait A *et al. Diabetes* 2020;**69**:508-16.

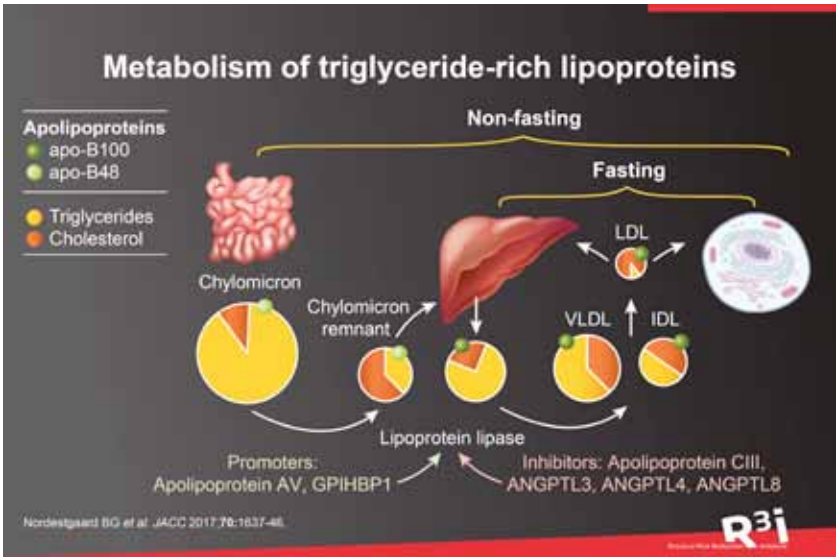


Metabolism of triglyceride-rich lipoproteins

After intake of a fatty meal, dietary TG are hydrolyzed to fatty acids and 2-monoacylglycerol in the stomach and small intestine, absorbed by enterocytes and incorporated into apo-B48-containing chylomicrons after resynthesis of TG. These are then transported via the lymph system to the circulation. Here, lipoprotein lipase (LpL) on the luminal surface of capillaries hydrolyzes TG in the core of chylomicrons to form smaller, cholesterol-enriched chylomicron remnants, which are then taken up by the liver.

In the liver, TG are re-secreted together with esterified cholesterol producing VLDL particles. Once VLDL particles are secreted into the plasma, LpL on the luminal surface of capillaries hydrolyzes TG in the core of VLDL particles. As fatty acids are liberated from VLDL, TG-rich lipoproteins undergo a cascade of remodelling to smaller and denser VLDL and IDL particles, and eventually LDL. This process also involves cholesteryl ester enrichment of VLDL, IDL and LDL in exchange for TG from other lipoproteins.

Nordestgaard BG *et al. JACC* 2017;**70**:1637-46; Sandesara PB *et al. Endocr Rev* 2019;**40**:537-57.

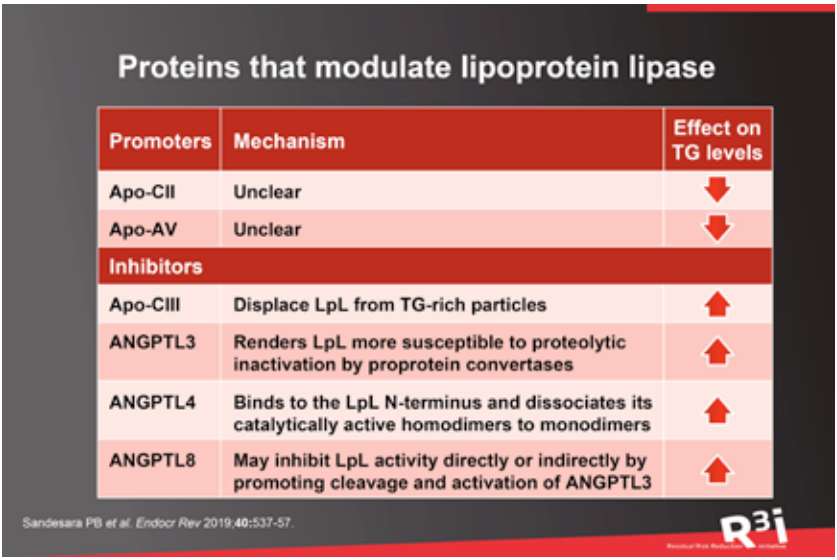


Metabolism of triglyceride-rich lipoproteins

Several proteins influence the activity of lipoprotein lipase (LpL), the key regulator of TG-rich lipoprotein metabolism. Those that promote the activity of LpL include GPIHBP1 (glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1), an endothelial protein which provides a platform for LpL-mediated lipolytic processing along the capillary lumen, and apolipoprotein (apo)AV.

Other proteins act to inhibit the activity of LpL; these include apo-CIII, and the angiopoietin-like proteins ANGPTL3, ANGPTL4, and ANGPTL8. Importantly, apo-CIII also has a pleiotropic role in the regulation of TG-rich lipoprotein metabolism which is independent of LpL pathways. These activities include inhibition of hepatic lipase (HL) activity and inhibition of hepatic TG-rich lipoprotein remnant clearance.

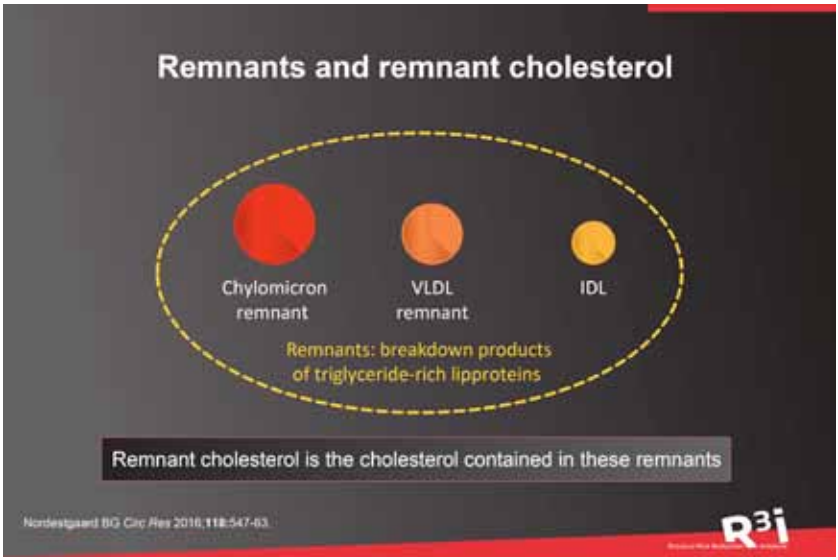
Nordestgaard BG *et al. JACC* 2017;**70**:1637-46; Sandesara PB *et al. Endocr Rev* 2019;**40**:537-57.



Proteins that modulate lipoprotein lipase

This table summarizes the effects and possible mechanisms of proteins that modulate the activity of LpL.

Sandesara PB *et al. Endocr Rev* 2019;**40**:537-57.

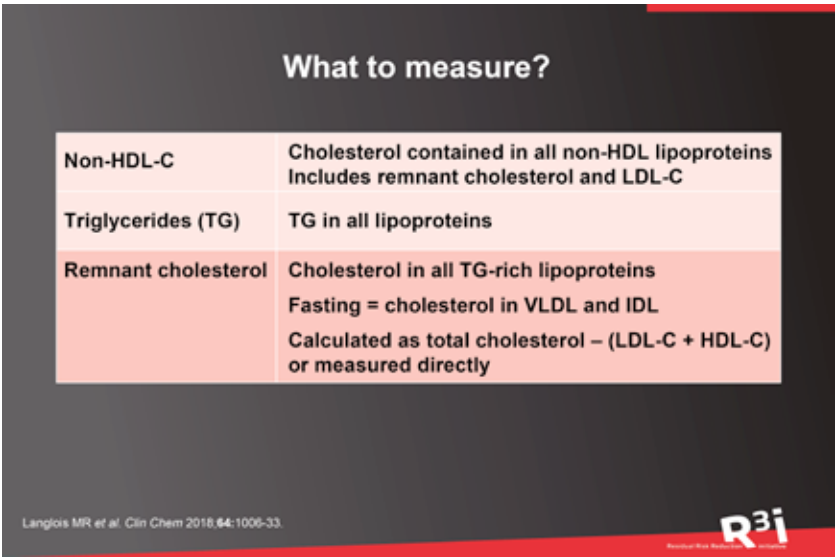


Remnants and remnant cholesterol

Remnant cholesterol refers to the cholesterol content of partially lipolyzed TG-rich lipoproteins, i.e., the cholesterol cargo of VLDL and IDL in the fasting state and additionally of chylomicron remnants in the nonfasting state.

When chylomicrons and VLDL are released into the blood, lipoprotein lipase will immediately start degrading their triglycerides. This means that essentially all TG-rich lipoproteins can be considered as remnants. Because of this, TG contained in these lipoproteins do not directly lead to plaque formation. This suggests that the cholesterol content in TG-rich lipoproteins, i.e., remnant cholesterol, is more important in atherogenesis.

Nordestgaard BG. *Circ Res* 2016;**118**:547-63.

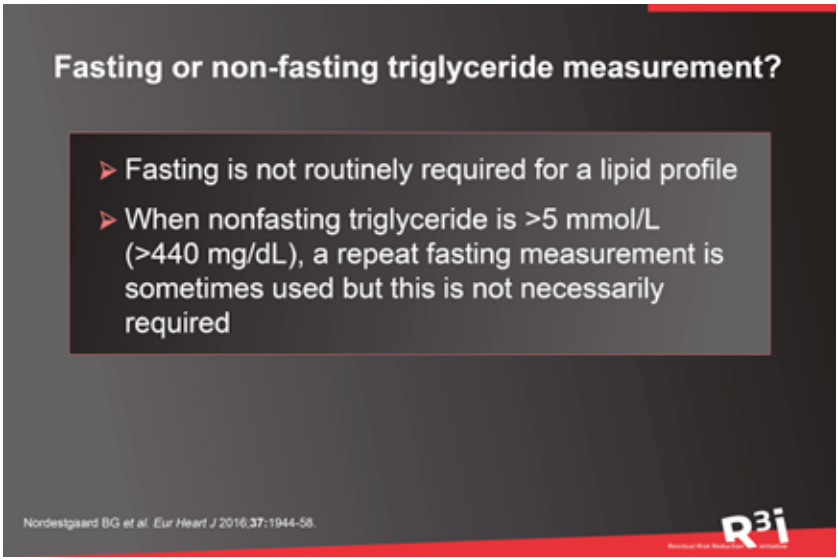


What to measure?

For clinical use, TG-rich lipoproteins and their remnants can be considered as one group. Various measures have been proposed to capture the cholesterol content of TG-rich lipoproteins and their remnants.

Remnant cholesterol can be calculated from a standard lipid profile as: total cholesterol – (LDL-C + HDL-C), with LDL-C calculated using the Friedewald equation provided TG are <5.7 mmol/L (<500 mg/dL). Alternatively, remnant cholesterol can be directly measured using a variety of analytical methods, including ultracentrifugation, nuclear magnetic resonance spectroscopy, or a direct automated assay.

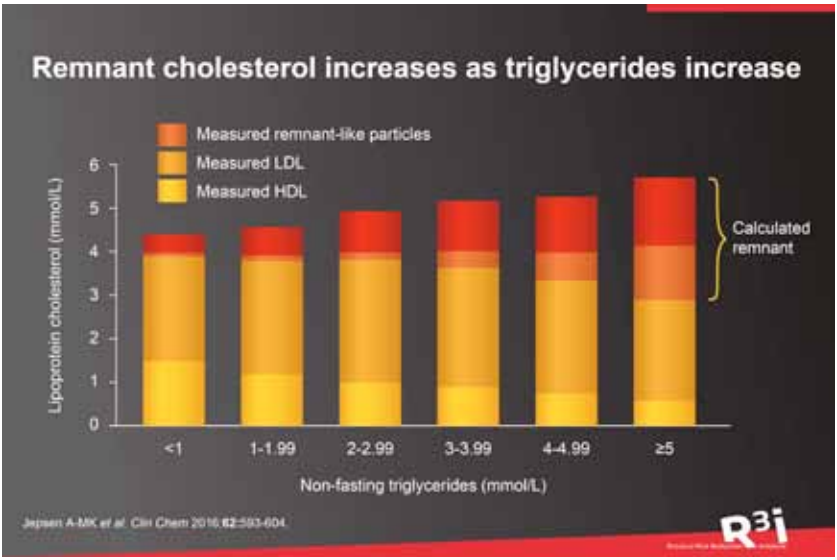
Langlois MR *et al. Clin Chem* 2018;**64**:1006-33.



Fasting or nonfasting triglyceride measurement?

Fasting measurement is generally recommended if fasting TG are >5 mmol/L (>440 mg/dL). Either fasting or nonfasting TG concentrations can serve as a marker of increased risk of cardiovascular events.

Nordestgaard BG *et al. Eur Heart J* 2016;**37**:1944-58.

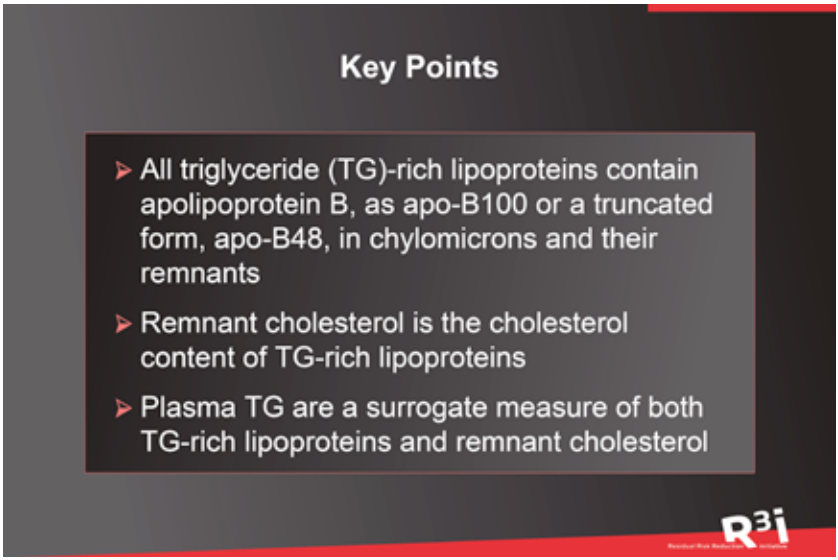


Remnant cholesterol increases as triglycerides increase

At higher plasma concentrations of nonfasting TG, measured remnant cholesterol captures an increasingly larger portion of measured remnant-like particle cholesterol. At TG levels <1 mmol/L (89 mg/dL), measured remnant cholesterol comprised 9% of calculated remnant cholesterol; this increased to 43% for TG levels ≥5 mmol/L (≥443 mg/dL).

It is now also possible to measure all remnant cholesterol directly (=TG-rich lipoprotein cholesterol).

Jepsen A-MK *et al. Clin Chem* 2016;**62**:593-604.


Key Points
All triglyceride (TG)-rich lipoproteins contain apolipoprotein B, as apo-B100 or a truncated form, apo-B48, in chylomicrons and their remnants
Remnant cholesterol is the cholesterol content of TG-rich lipoproteins
Plasma TG are a surrogate measure of both TG-rich lipoproteins and remnant cholesterol
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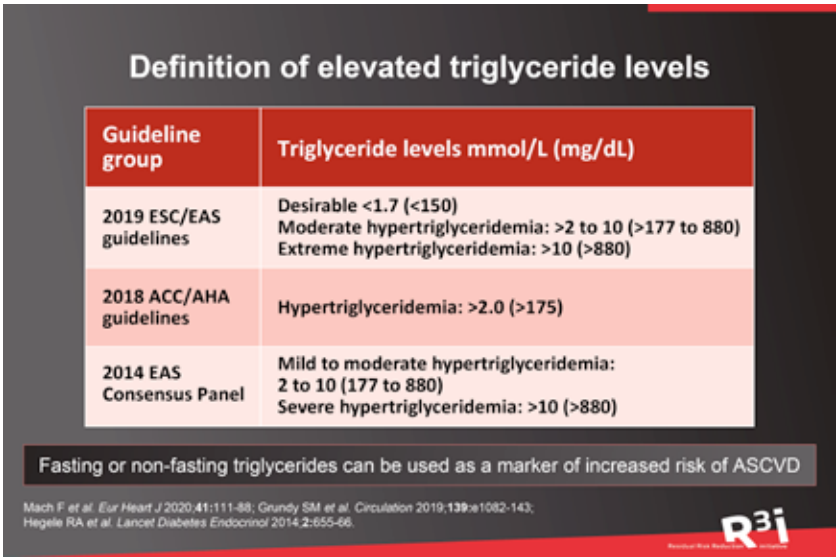
Do elevated levels of triglyceride-rich lipoproteins play a role in atherosclerosis?

SECTION

2

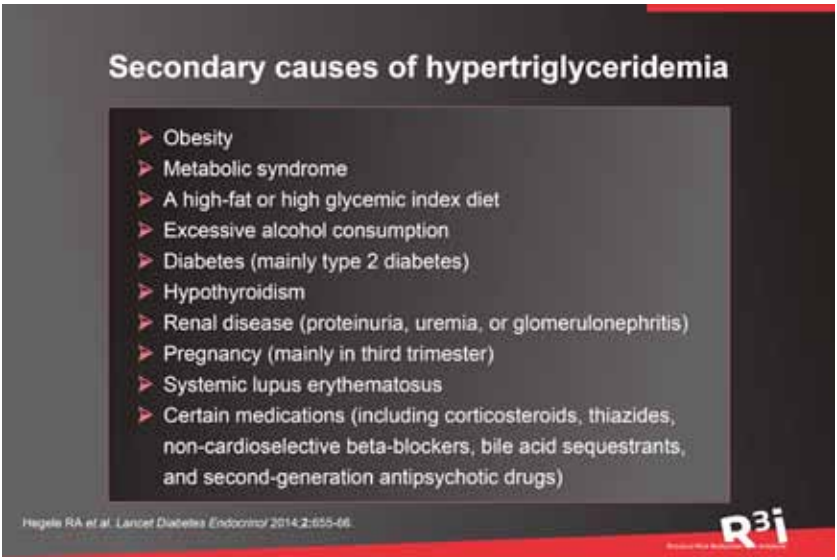
Residual Risk Reduction initiative



Definition of elevated triglyceride levels

There is no consensus on the definition of elevated TG levels across different guidelines. The 2019 European Society of Cardiology/European Atherosclerosis Society dyslipidemia guidelines recommend that a TG level <1.7 mmol/L (<150 mg/dL) is desirable. Moderate hypertriglyceridemia is defined as >2.0 mmol/L (>177 mg/dL); extreme TG levels (>10 mmol/L or >880 mg/dL) are associated with an increased risk for acute pancreatitis.

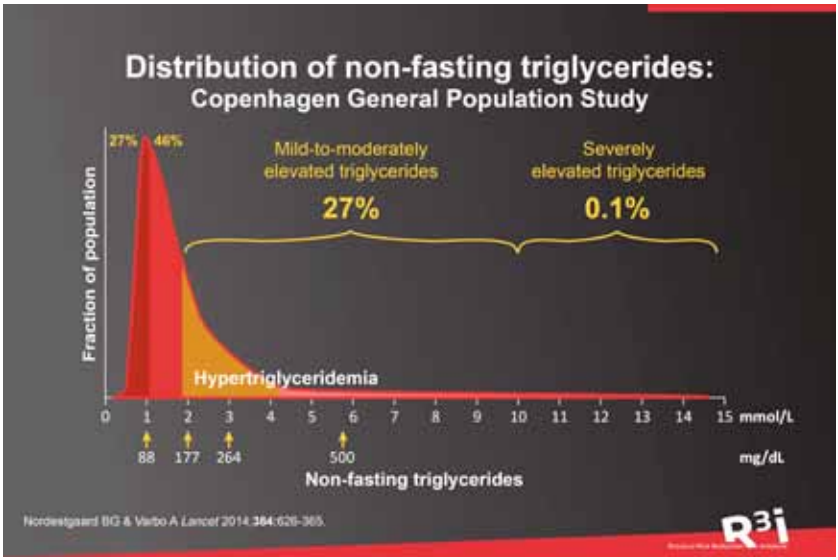
Mach F *et al. Eur Heart J* 2020;**41**:111-88.



Secondary causes of hypertriglyceridemia

Hypertriglyceridemia is often associated with other disorders that independently increase plasma TG levels, notably type 2 diabetes, obesity, metabolic syndrome, and excessive alcohol intake. Diet (high-fat, high glycemic index) and excessive consumption of fructose are also important secondary causes.

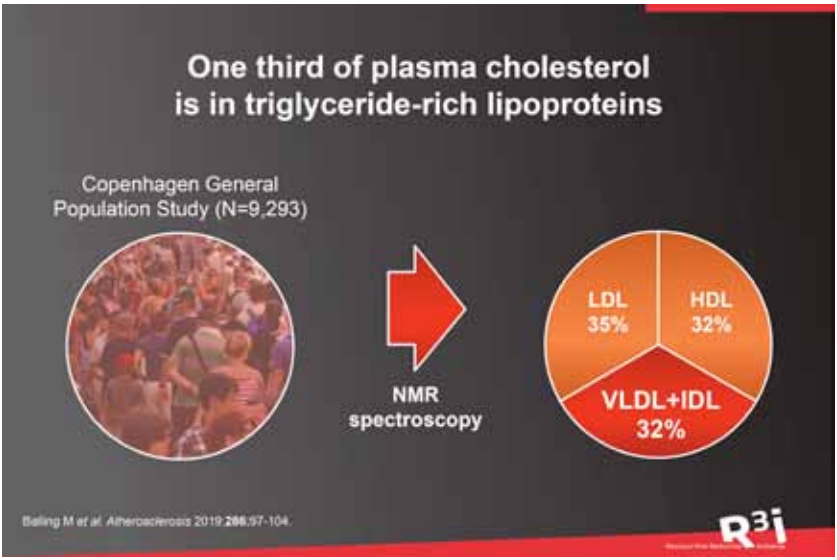
Hegele RA *et al. Lancet Diabetes Endocrinol* 2014;**2**:655-66.



Distribution of nonfasting triglycerides

Triglyceride levels in the general population have a skewed distribution. In the Copenhagen General Population Study, 27% of adults had mild-to-moderately elevated TG (2 to 10 mmol/L or 177 to 880 mg/dL), whereas only 0.1% of adults had severely elevated TG >10 mmol/L (>880 mg/dL). In contrast, only 27% of individuals had normal TG levels (<1.0 mmol/L or <88 mg/dL).

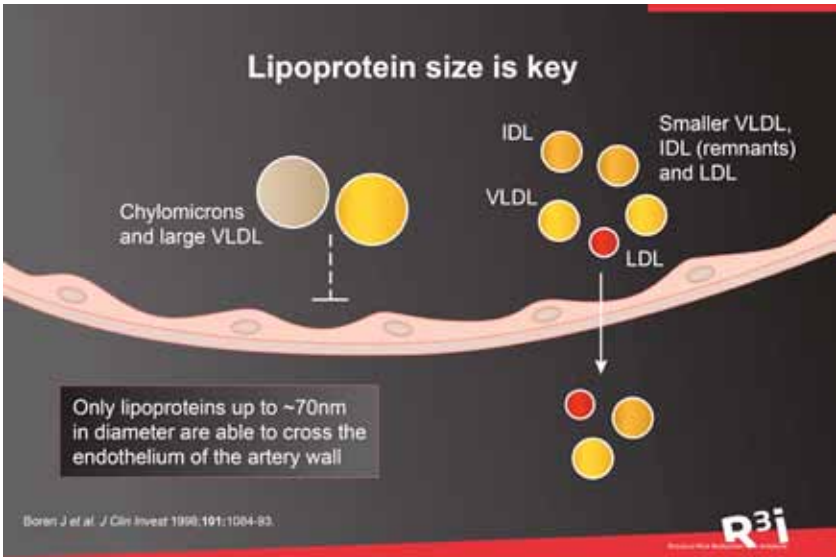
Nordestgaard BG & Varbo A. *Lancet* 2014;**384**:626-35.



One-third of plasma cholesterol is in triglyceride-rich lipoproteins

Nuclear magnetic resonance spectroscopy was used to measure total cholesterol, free- and esterified cholesterol, TG, phospholipids, and particle concentration in 14 classes of lipoproteins in individuals in the Copenhagen General Population Study (n=9,293). Overall, one third of total cholesterol in plasma was present in remnant lipoproteins, *i.e.*, the TG-rich lipoproteins IDL and VLDL.

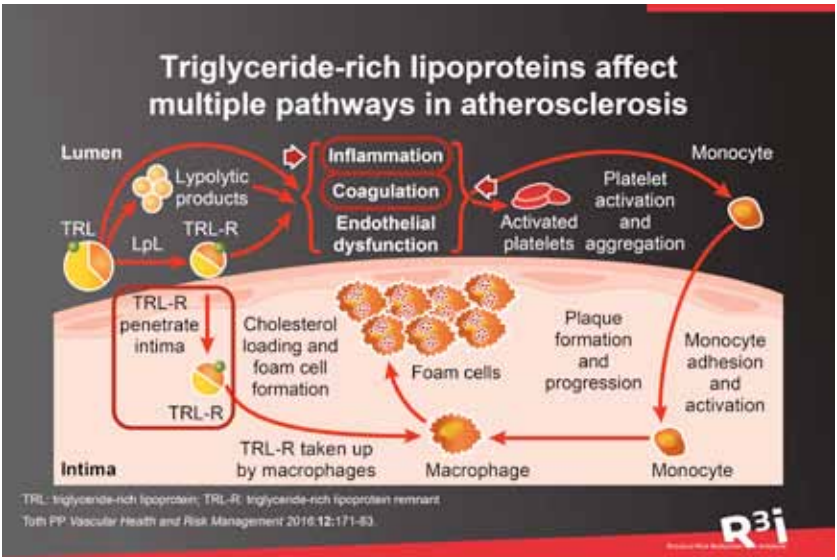
Balling M *et al. Atherosclerosis* 2019; **286**:97-104.



Lipoprotein size is key

Only lipoproteins up to ~70 nm in diameter are able to enter the artery wall. Consequently, chylomicrons and larger VLDL particles are likely too large to effectively cross the endothelium of the artery wall, in contrast to the smaller remnant lipoproteins (VLDL remnants and IDL). This is supported by evidence from individuals with familial chylomicronemia syndrome due to lipoprotein lipase deficiency, who despite severe hypertriglyceridemia, do not develop atherosclerosis in the absence of other cardiovascular risk factors.

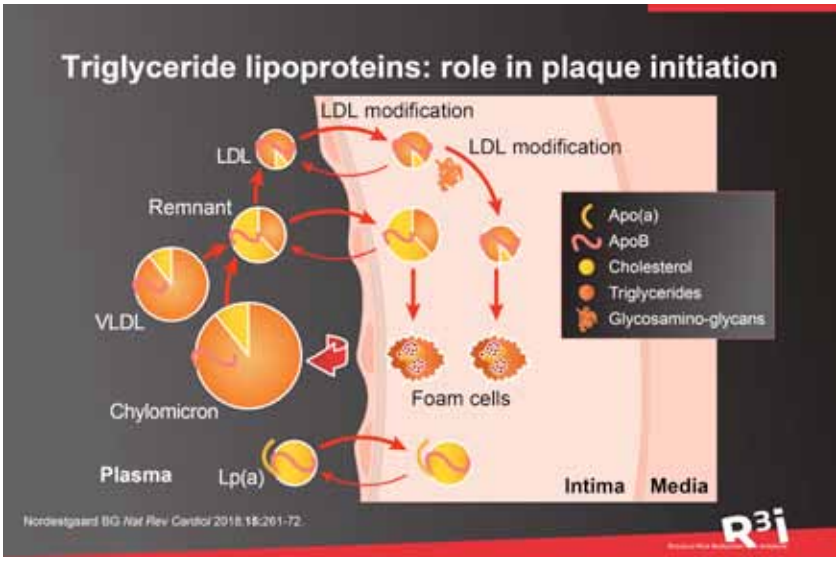
Teramoto R, *et al. Atherosclerosis* 2018;**269**:272-8.



Triglyceride-rich lipoproteins affect multiple pathways in atherosclerosis

The exact underlying mechanisms by which TG-rich lipoproteins are involved in atherosclerotic plaque formation are unclear. This figure provides an overview of proposed pathophysiological pathways likely to contribute to the initiation and progression of atherosclerosis.

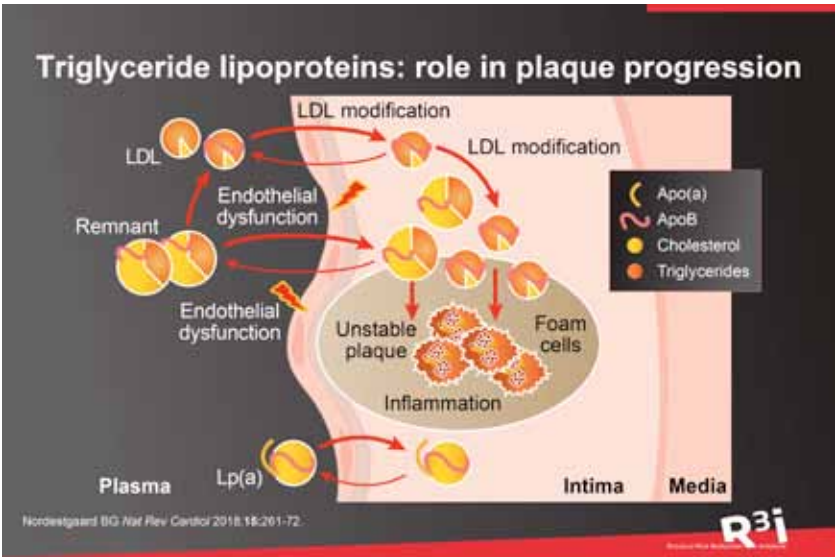
Toth PP. *Vasc Health Risk Manag* 2016;**12**:171-83.



Triglyceride-rich lipoproteins: role in plaque initiation

Cholesterol-enriched, smaller TG-rich lipoproteins and their remnants readily penetrate the arterial wall and are retained in the connective tissue matrix. Because of their larger size, these TG-rich lipoproteins and remnants carry more cholesterol per particle than LDL. Accumulation of cholesterol in macrophages results in foam cell formation and initiation of atherosclerosis. Unlike LDL, TG-rich lipoproteins are also taken up by arterial wall macrophages directly without modification. TG-rich lipoproteins and their remnants may also promote endothelial dysfunction, which precedes atherosclerosis.

Sandesara PB *et al. Endocr Rev* 2019;**40**:537-57. Rosenson RS *et al. J Am Coll Cardiol* 2014;**64**:2525-40.



Triglyceride-rich lipoproteins: role in plaque progression

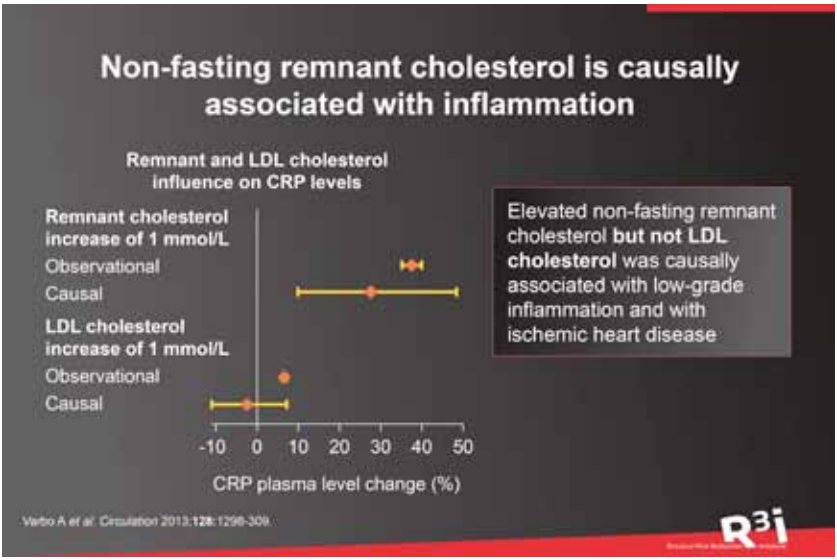
The action of lipoprotein lipase (LpL) on TG-rich lipoproteins leads to the activation of proinflammatory, procoagulant, and proapoptotic signalling pathways that contribute to atherosclerosis progression. TG-rich lipoproteins and their remnants also enhance platelet aggregation and amplify the coagulation cascade, via assembly of the prothrombinase complex and upregulation of the expression of the plasminogen activator inhibitor-1 gene and the plasminogen activator inhibitor-1 antigen. Collectively, these processes lead to enhanced platelet aggregation and thrombus formation.

Nordestgaard BG *et al. Nat Rev Cardiol* 2018;**15**:261-72; Rosenson RS *et al. J Am Coll Cardiol* 2014;**64**:2525-40.

Triglyceride-rich lipoproteins are pro-inflammatory

The lipolytic products of triglyceride-rich lipoproteins and their remnants induce the production of cytokines, interleukins (i.e., IL-1, IL-6, IL-8), and proatherogenic adhesion molecules (i.e., intracellular adhesion molecule-1 and vascular cell adhesion molecule-1) which facilitate migration of leukocytes to the site of inflammation. The inflammatory response is characterized by monocyte adhesion to the endothelium and neutrophil activation.

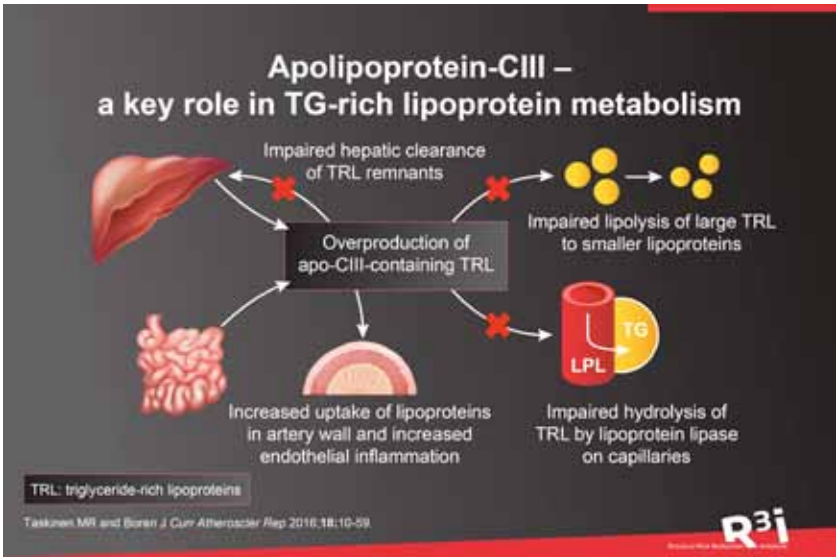
Toth PP. *Vasc Health Risk Manag* 2016;**12**:171-83.



Nonfasting remnant cholesterol is causally associated with inflammation

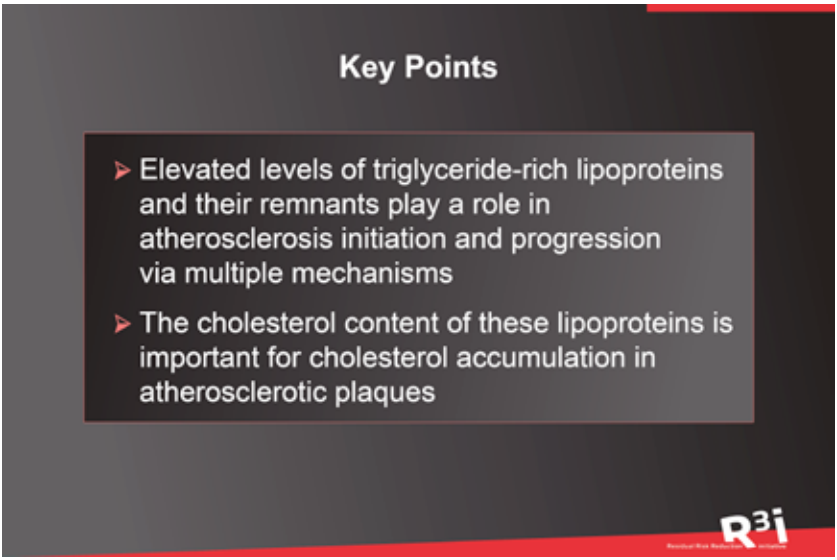
In a Mendelian randomization study including data from over 60,000 individuals from the Copenhagen General Population Study, the Copenhagen City Heart Study, and the Copenhagen Ischemic Heart Disease study, elevated nonfasting remnant cholesterol was shown to be causally associated with low-grade inflammation (as indicated by elevated C-reactive protein, CRP) and with ischemic heart disease. In contrast, elevated LDL-C was only associated causally with ischemic heart disease.

Varbo A et al. *Circulation* 2013;**128**:1298-309.



Apolipoprotein-CIII – a key role in TG-rich lipoprotein metabolism

Apolipoprotein-CIII (apo-CIII) is a multifaceted protein that has a key role in TG-rich lipoprotein metabolism.


Key Points
Elevated levels of triglyceride-rich lipoproteins and their remnants play a role in atherosclerosis initiation and progression via multiple mechanisms
The cholesterol content of these lipoproteins is important for cholesterol accumulation in atherosclerotic plaques
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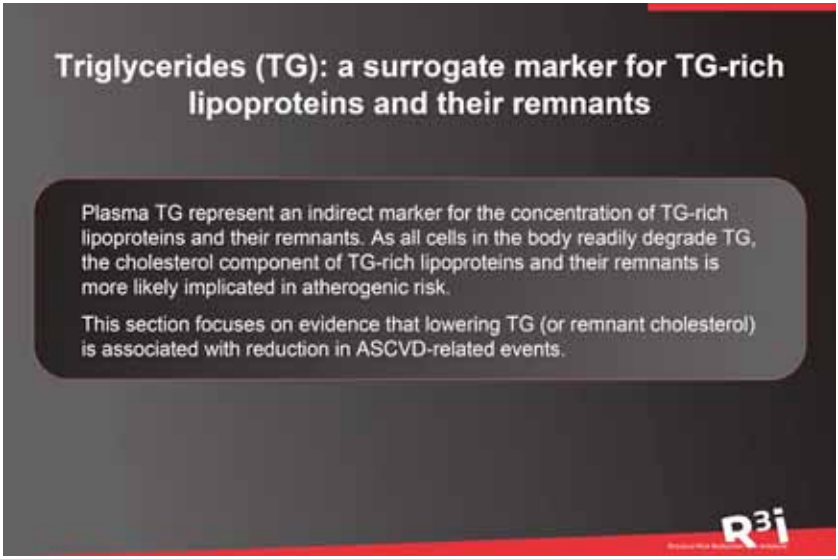
Triglyceride-rich lipoproteins and ASCVD – what is the evidence?

SECTION

3

Residual Risk Reduction initiative


Triglycerides (TG): a surrogate marker for TG-rich lipoproteins and their remnants
Plasma TG represent an indirect marker for the concentration of TG-rich lipoproteins and their remnants. As all cells in the body readily degrade TG, the cholesterol component of TG-rich lipoproteins and their remnants is more likely implicated in atherogenic risk.
This section focuses on evidence that lowering TG (or remnant cholesterol) is associated with reduction in ASCVD-related events.
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Population studies
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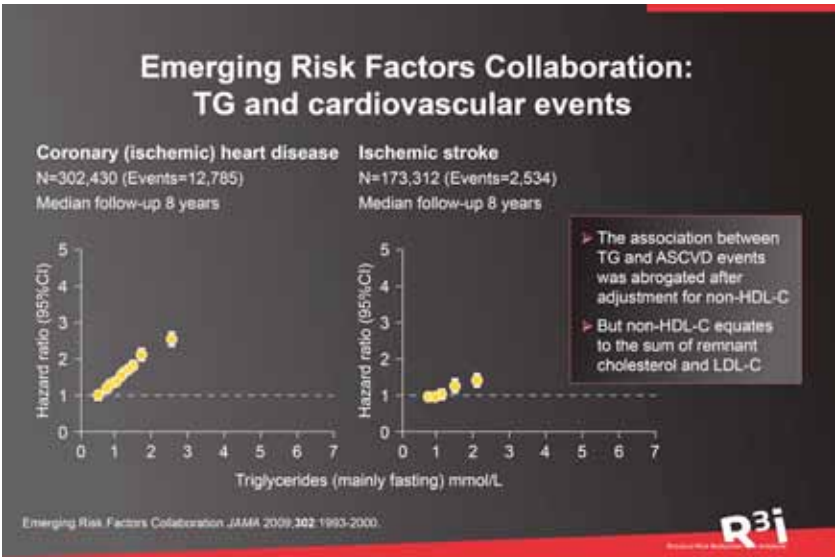
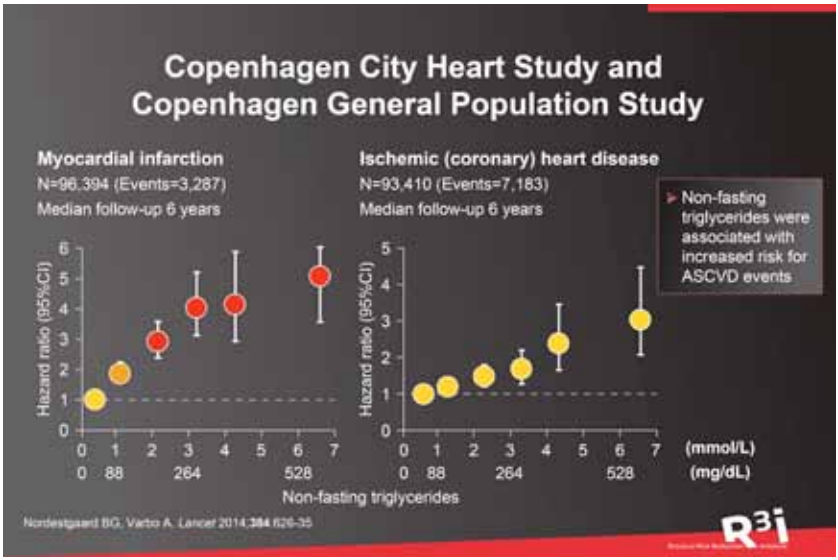


Emerging Risk Factors Collaboration: TG and cardiovascular events

The Emerging Risk Factors Collaboration analysed data from more than 300,000 individuals in 68 long-term prospective studies. In unadjusted analyses increasing plasma TG was associated with increased risk of ASCVD-related events. This association was attenuated after adjustment for HDL-C and abrogated after additional adjustment for non-HDL-C. It should be remembered, however, that non-HDL-C captures the cholesterol contained in LDL-C and remnant lipoproteins.

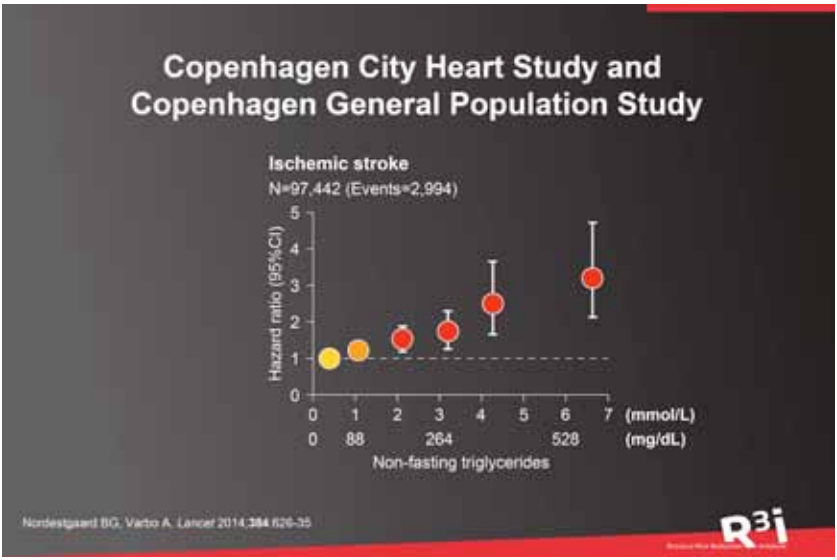
Emerging Risk Factors Collaboration *JAMA* 2009;**302**:1993-2000.



Copenhagen City Heart Study and Copenhagen General Population Study: TG and ischemic heart disease risk

Combined analyses from the Copenhagen City Heart Study and the Copenhagen General Population Study including more than 100,000 individuals, showed that increasing non-fasting TG concentrations were associated with increased risk of ischemic heart disease events such as myocardial infarction (MI). When compared with individuals with optimal TG levels (<1.0 mmol/L or <88 mg/dL) those with non-fasting TG levels >5 mmol/L (440 mg/dL) had a 5-fold higher risk for MI.

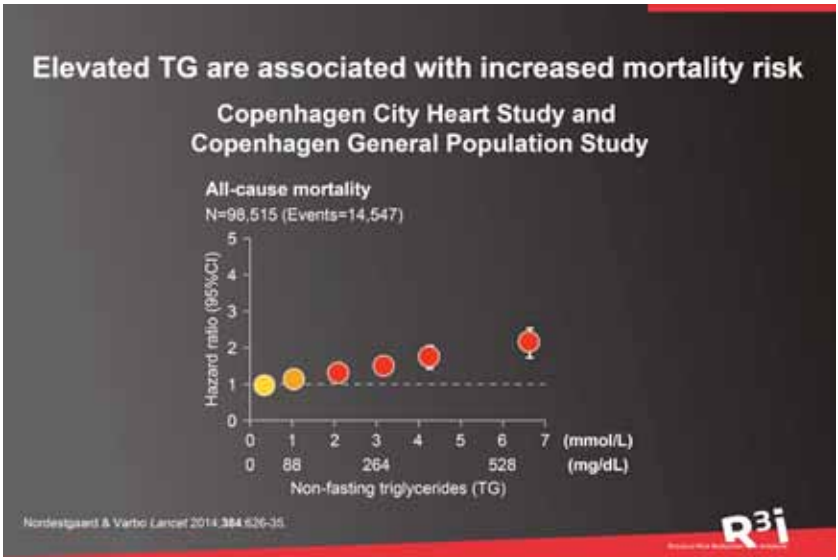
Nordestgaard BG, Varbo A. *Lancet* 2014;**384**:626-35.



Copenhagen City Heart Study and Copenhagen General Population Study: TG and ischemic stroke risk

Analyses from the Copenhagen City Heart Study and the Copenhagen General Population Study also showed an increasing risk of ischemic stroke with increasing TG. When compared with individuals with optimal TG levels (<1.0 mmol/L or <88 mg/dL) those with non-fasting TG levels >5 mmol/L (>440 mg/dL) had about 3-fold higher risk of ischemic stroke.

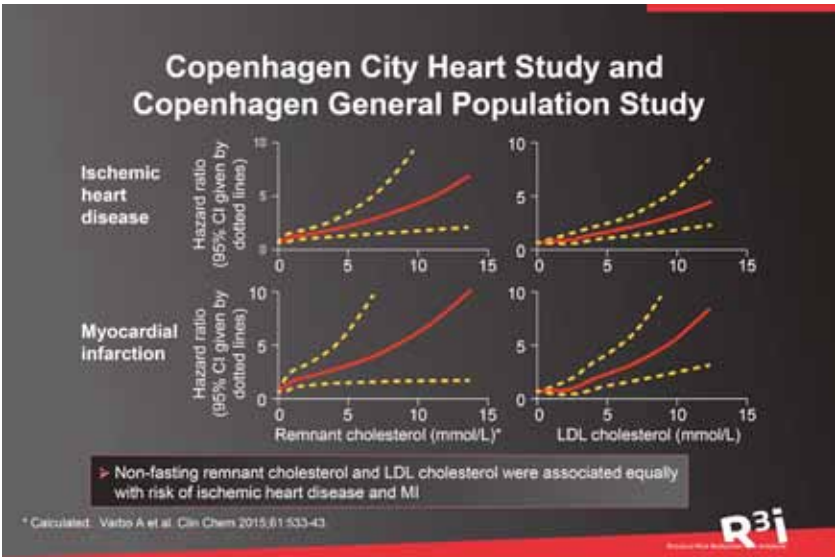
Nordestgaard BG, Varbo A. *Lancet* 2014;**384**:626-35.



Copenhagen City Heart Study and Copenhagen General Population Study: TG and increased mortality

Analyses from the Copenhagen City Heart Study and the Copenhagen General Population Study also showed an increasing risk of all-cause mortality with increasing TG. When compared with individuals with optimal TG levels (<1.0 mmol/L or <88 mg/dL) those with non-fasting TG levels >5 mmol/L (>440 mg/dL) had a 2-fold higher risk for all-cause death.

Nordestgaard BG, Varbo A. *Lancet* 2014;**384**:626-35.

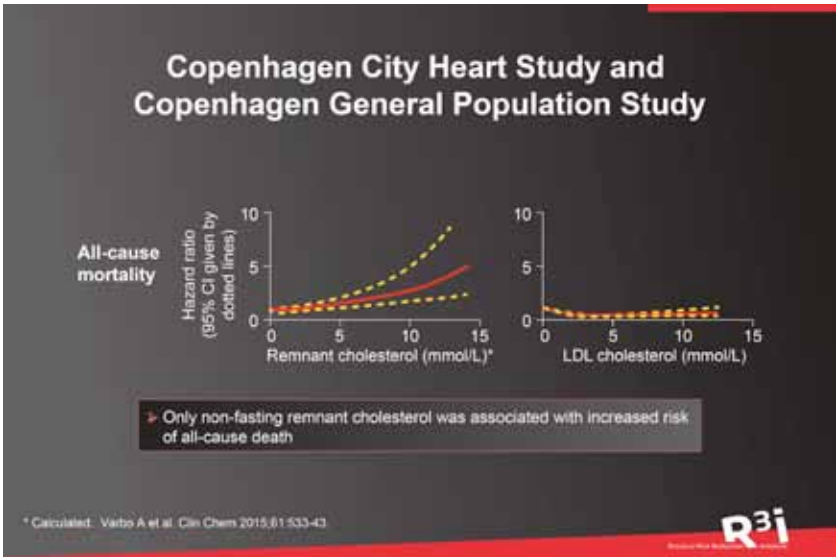


Copenhagen City Heart Study and Copenhagen General Population Study: remnant cholesterol and IHD risk

Analyses based on data for about 90,000 individuals in both of these Danish studies investigated the association between non-fasting calculated remnant cholesterol or LDL-C and risk of ischemic heart disease (IHD) and MI. Over 22 years of follow-up, 4,435 subjects developed IHD, 1,722 developed MI, and 8,121 died.

Increasing levels of remnant cholesterol or LDL-C were associated with a similar increase in risk of IHD and MI.

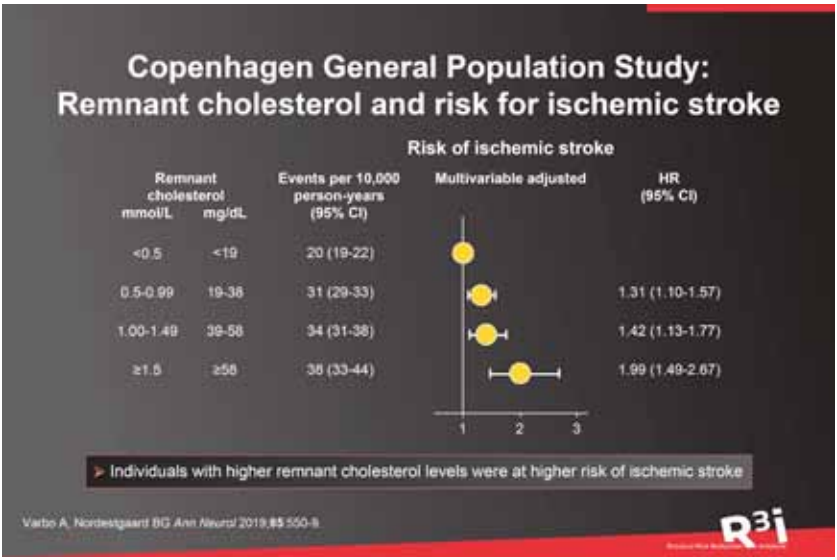
Varbo A *et al. Clin Chem* 2015;**61**:533-43.



Copenhagen City Heart Study and Copenhagen General Population Study: remnant cholesterol and mortality

Analyses based on data for about 90,000 individuals in these Danish studies showed that the risk of all-cause mortality increased continuously as remnant cholesterol concentration increased. This was not observed with increasing LDL-C concentration. These data agreed with prior evidence from the Copenhagen studies that increasing plasma TG (a marker of remnant cholesterol) were associated with increasing all-cause mortality.

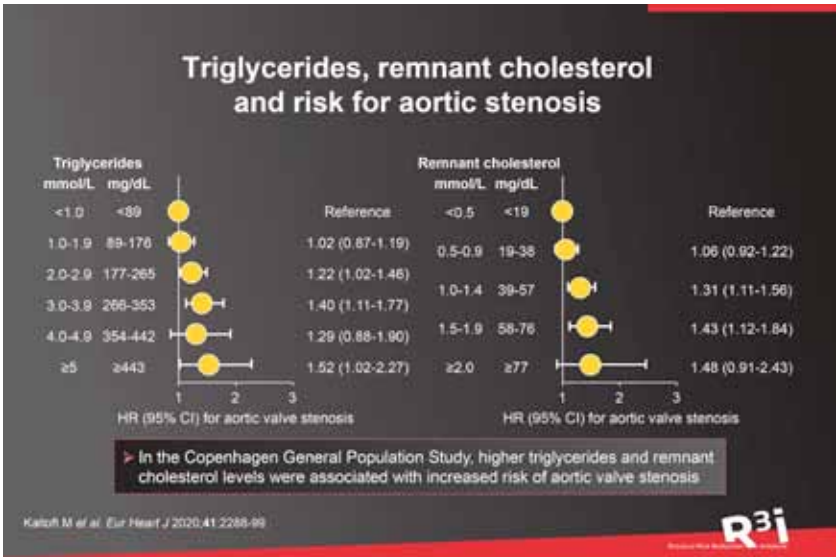
Varbo A *et al. Clin Chem* 2015;**61**:533-43.



Copenhagen General Population Study: Remnant cholesterol and risk for ischemic stroke

This observational study investigated the association of non-fasting remnant cholesterol with risk of ischemic stroke in over 100,000 individuals in the Copenhagen General Population Study. Individuals with remnant cholesterol concentration ≥1.5 mmol/L (≥58 mg/dL) had ~2-fold increase in risk compared with individuals with remnant cholesterol concentration <0.5 mmol/L (<19 mg/dL).

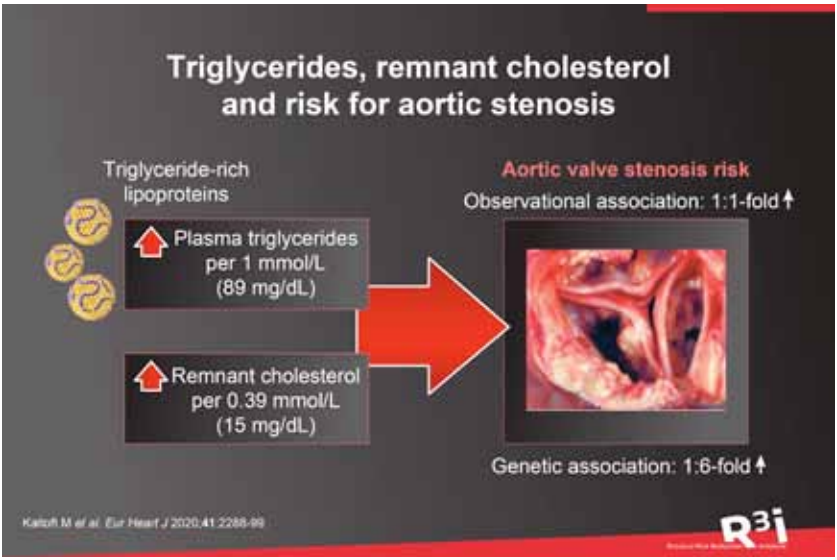
Varbo A, Nordestgaard BG. *Ann Neurol* 2019;**85**:550-9.



Copenhagen studies: Triglycerides, remnant cholesterol and risk for aortic stenosis

Aortic valve stenosis is the most common heart valve disease, with increasing prevalence among older populations. A Mendelian randomization study using data from 108,559 individuals in the Copenhagen General Population Study showed that higher plasma TG and calculated remnant cholesterol were associated with a higher risk of aortic valve stenosis. When compared with individuals with optimal TG levels (<1.0 mmol/L or <88 mg/dL) those with non-fasting TG levels >5 mmol/L (>440 mg/dL) had a ~1.5-fold increase in risk for aortic stenosis.

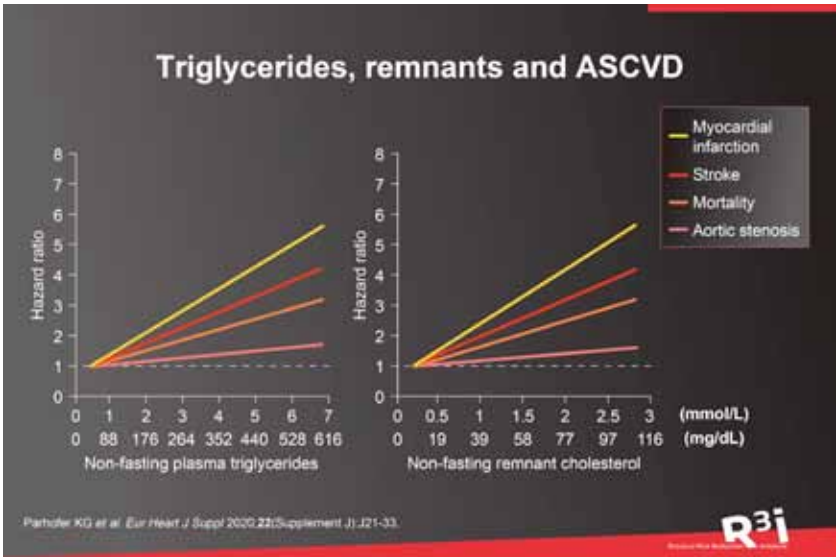
Kaltoft M *et al. Eur Heart J* 2020;**41**:2288-99.



Copenhagen studies: Triglycerides, remnant cholesterol and risk for aortic stenosis

This study concluded that higher plasma TG and calculated remnant cholesterol were observationally and genetically associated with increased risk of aortic valve stenosis. These findings suggest that high levels of TG-rich remnant lipoproteins might be one of the factors facilitating the evolution of aortic valve stenosis.

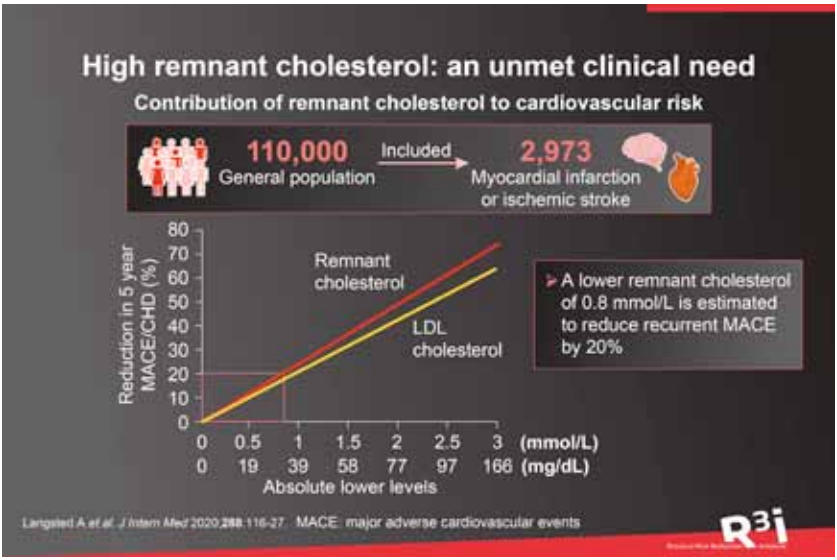
Kaltoft M *et al. Eur Heart J* 2020;**41**:2288-99.



Triglycerides, remnants and ASCVD

Among the general population, findings from the Copenhagen City Heart Study and Copenhagen General Population Study, showed that progressive increases in non-fasting plasma TG and (calculated) remnant cholesterol were associated with increased risk of ASCVD-related events, aortic stenosis and all-cause mortality. It should be noted that risk for acute pancreatitis is mainly associated with extreme TG levels (>10 mmol/L or >880 mg/dL).

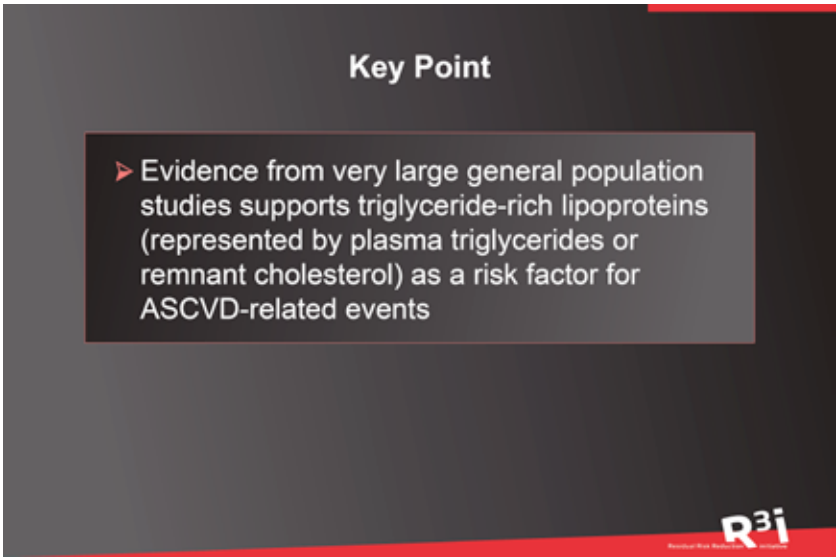
Parhofer KG *et al. Eur Heart J Suppl* 2020;**22(Supplement J)**:J21-J33; Hegele RA *et al. Lancet Diabetes Endocrinol* 2014;**2**:655-66.



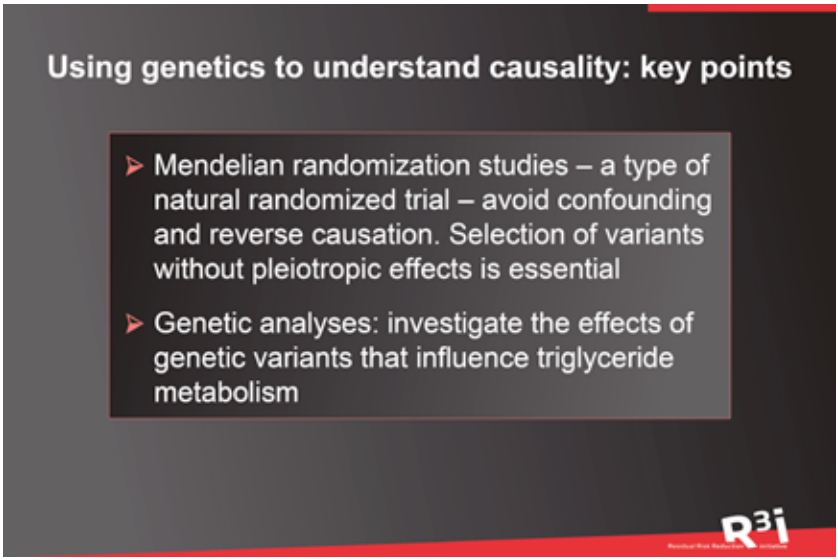
High remnant cholesterol: an unmet clinical need

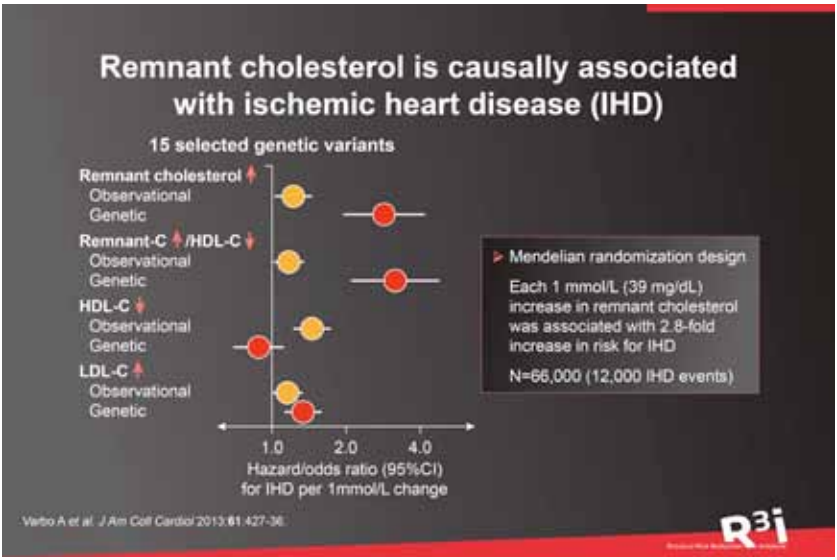
From more than 100,000 individuals in the Copenhagen General Population Study, 2,973 were identified with a previous diagnosis of MI, ischemic stroke or both events. Lower remnant cholesterol levels (by 0.8 mmol/L or 32 mg/dL) is estimated to reduce the risk of recurrent MI or ischemic stroke by 20% in this group. These findings indicate that high remnant cholesterol levels represent an unmet clinical need to prevent recurrent cardiovascular events.

Langsted A *et al. J Intern Med* 2020;**288**:116-27.


Key Point
Evidence from very large general population studies supports triglyceride-rich lipoproteins (represented by plasma triglycerides or remnant cholesterol) as a risk factor for ASCVD-related events
R3i

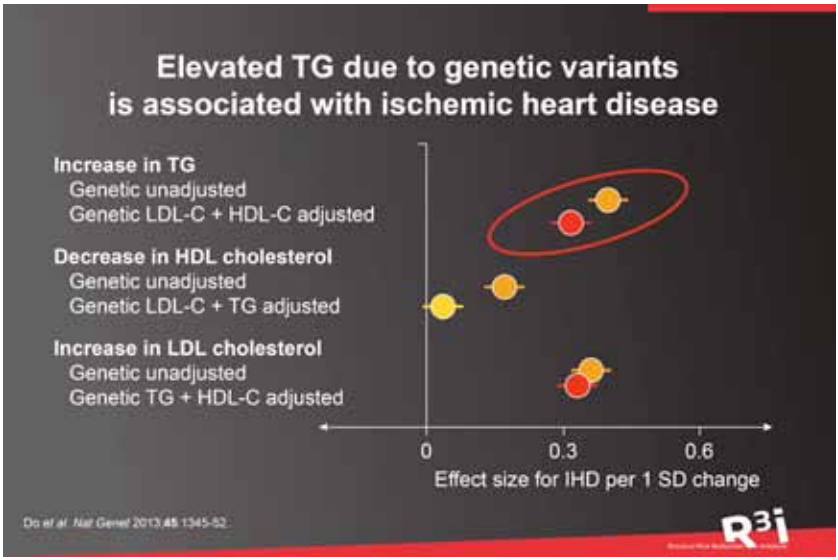
Genetic studies
R3i


Using genetics to understand causality: key points
Mendelian randomization studies – a type of natural randomized trial – avoid confounding and reverse causation. Selection of variants without pleiotropic effects is essential
Genetic analyses: investigate the effects of genetic variants that influence triglyceride metabolism
R3i



Remnant cholesterol is causally associated with ischemic heart disease

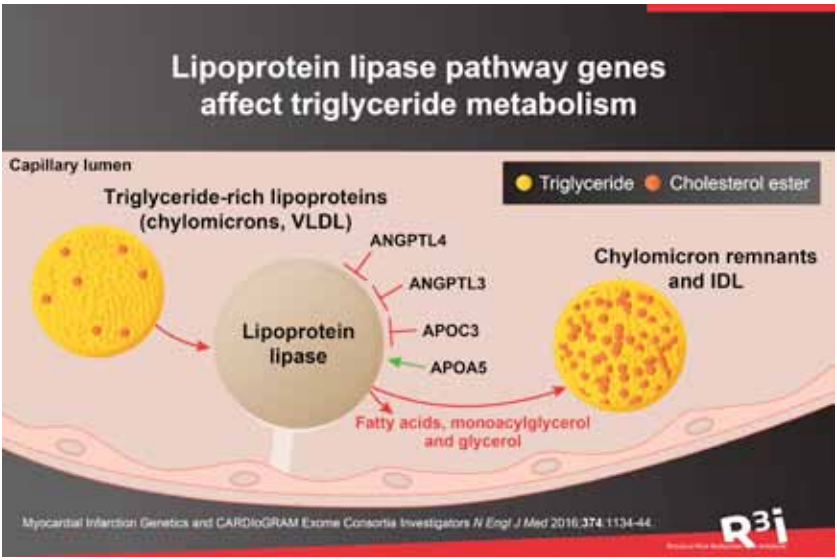
In this Mendelian randomization study in 73,513 Danish subjects, 11,984 with IHD, 15 genetic variants were selected that either affected non-fasting remnant cholesterol alone; non-fasting remnant cholesterol and HDL-C combined; HDL-C alone; or LDL-C alone. A 1 mmol/L (39 mg/dL) genetic increase in non-fasting remnant cholesterol was associated with 2.8 increase in IHD risk; for observational data, there was a 1.4-fold increase in risk. Both were independent of HDL-C. These findings imply a causal role for the cholesterol content of TG-rich lipoprotein particles in IHD.
Varbo A *et al. J Am Coll Cardiol* 2013;**61**:427-36.



Elevated TG due to genetic variants is associated with ischemic heart disease

This genetic analysis was based on 185 genetic variants (single nucleotide polymorphisms) shown to be associated with blood lipids. Genetically determined elevated TG concentration was strongly associated with risk for IHD.

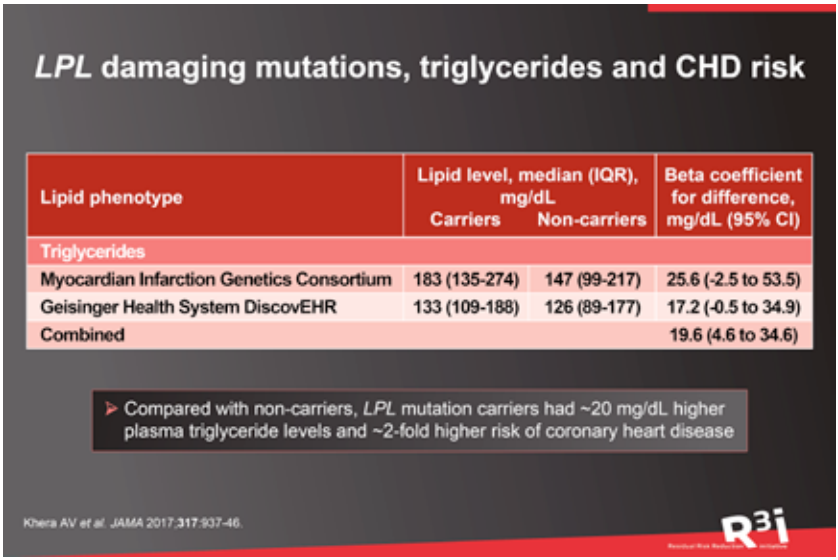
Do R *et al. Nature Genet* 2013;**45**;1345-52.



Lipoprotein lipase pathway genes affect triglyceride metabolism

Lipoprotein lipase has a central role in the regulation of plasma concentration of TG-rich lipoproteins. Key genes – *APOC3, ANGPTL4, ANGPTL3, APOA5* – impact this pathway and potentially, plasma TG levels and IHD risk.

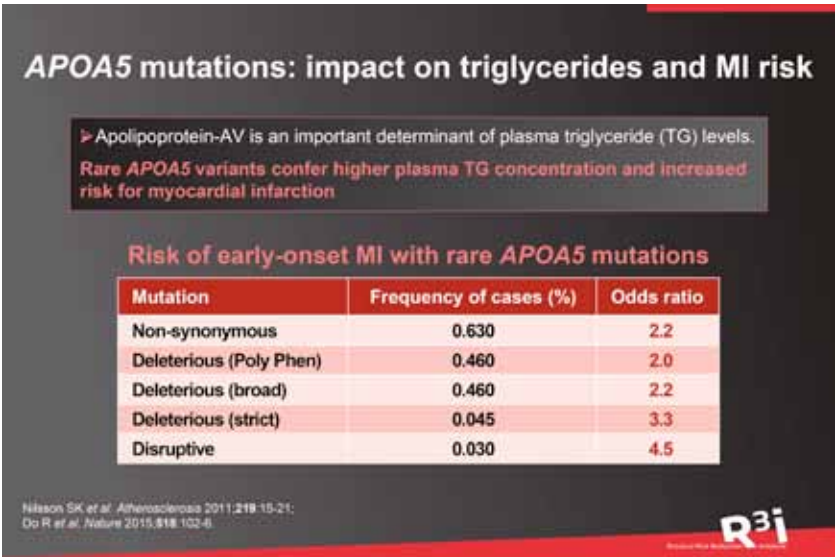
Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators *N Engl J Med* 2016;**374**:1134-44.



LPL damaging mutations, triglycerides and CHD risk

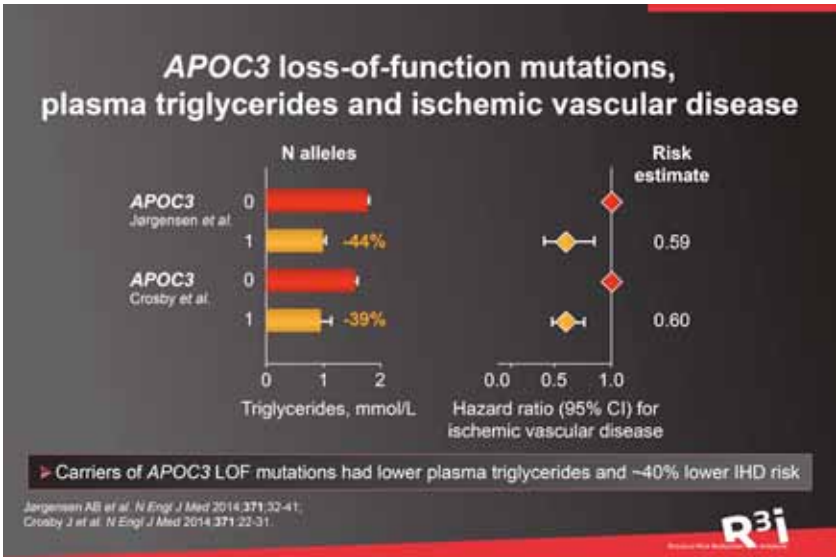
Lipoprotein lipase has a central role in clearing TG-rich lipoproteins from the circulation. In this cross-sectional analysis of coronary artery disease case-control studies, gene sequencing identified a damaging mutation in the *LPL* gene in 188 of 46,891 individuals. Carriers of this mutation had higher plasma TG levels (19.6 mg/dL, 95% CI, 4.6-34.6 mg/dL) and a higher risk of coronary heart disease (odds ratio 1.84; 95% CI, 1.35-2.51) compared with noncarriers.

Khera AV *et al. JAMA* 2017;**317**:937-46.



***APOA5* mutations: impact on triglycerides and MI risk**

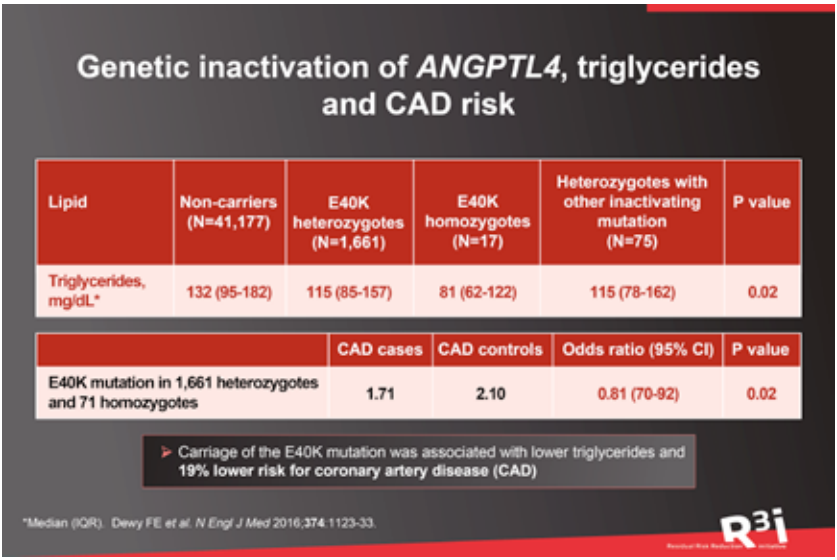
Apolipoprotein-AV is an important regulator of plasma TG levels. Among genetic data from 9,793 patients with early-onset MI (≤50 years in males and ≤60 years in females), carriers of a rare *APOA5* variant were identified. These individuals had a 2.2-fold higher risk of MI compared with noncarriers. These observations suggest that disordered metabolism of TG-rich lipoproteins contributes to MI risk.
Nilsson SK *et al. Atherosclerosis* 2011;**219**:15-21; Do R *et al. Nature* 2015;**518**:102-6.



APOC3 loss-of-function mutations, plasma triglycerides and ischemic vascular disease

Apolipoprotein-CIII has a key role in the regulation of TG-rich lipoprotein metabolism, inhibiting hydrolysis by lipoprotein lipase and attenuating hepatic uptake of TG-rich lipoproteins remnants. Two genetic studies, including data from more than 75,000 and 110,000 individuals, respectively, consistently showed that carriage of *APOC3* LOF variants was associated with lower plasma TG and ~40% decrease in the risk of ischemic vascular disease. These findings suggest that apolipoprotein-CIII is a relevant drug target for reducing residual cardiovascular risk.

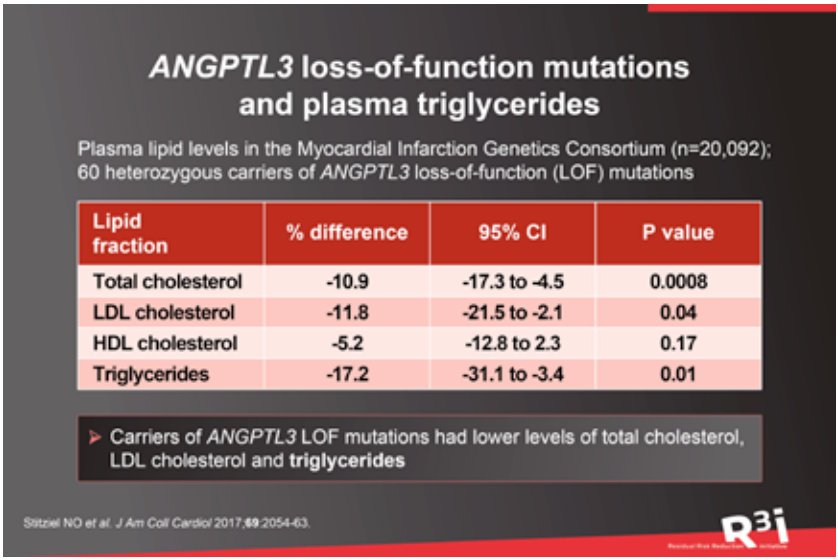
Jørgensen AB *et al. N Engl J Med* 2014;**371**:32-41; Crosby J *et al. N Engl J Med* 2014;**371**:22-31.



Genetic inactivation of *ANGPTL4*, triglycerides and CAD risk

Angiopoietin-like proteins 3 and 4 (*ANGPTL3*, *ANGPTL4*) inhibit lipoprotein lipase and modulate the uptake of free fatty acids during fasting and non-fasting states. Genetic inactivation of *ANGPTL4*, as evident with the missense E40K variant, is known to be associated with decreased levels of plasma TG. Human genetic studies showed that carriers of the E40K variant or other inactivating *ANGPTL4* mutations had lower plasma TG levels (by 13% per allele). Lifelong carriage of the E40K variant was associated with a 19% lower risk of coronary artery disease.

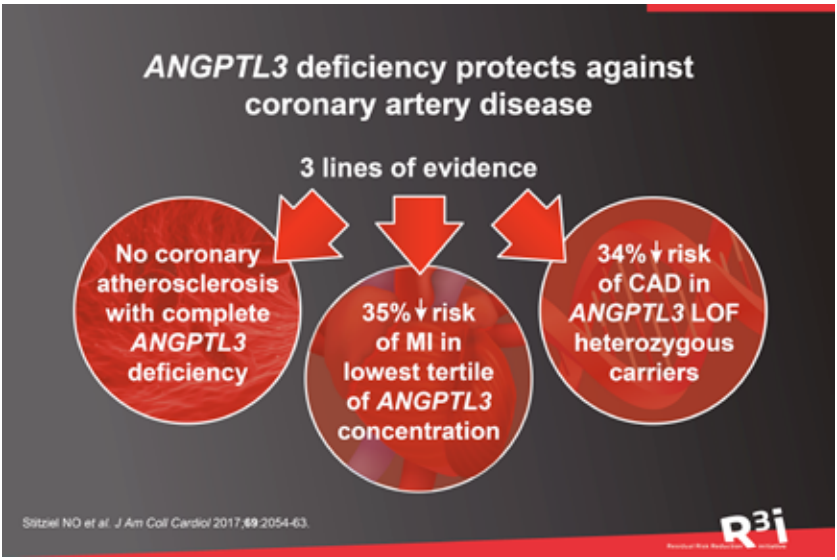
Dewey FE *et al. N Engl J Med* 2016;**374**:1123-33.



***ANGPTL3* loss-of-function mutations and plasma triglycerides**

Data from the Myocardial Infarction Genetics Consortium (n=20,092) showed that heterozygous carriers of *ANGPTL3* LOF mutations had 17% lower plasma TG and 12% lower levels of LDL-C.

Stitziel NO *et al. J Am Coll Cardiol* 2017;**69**:2054-63.

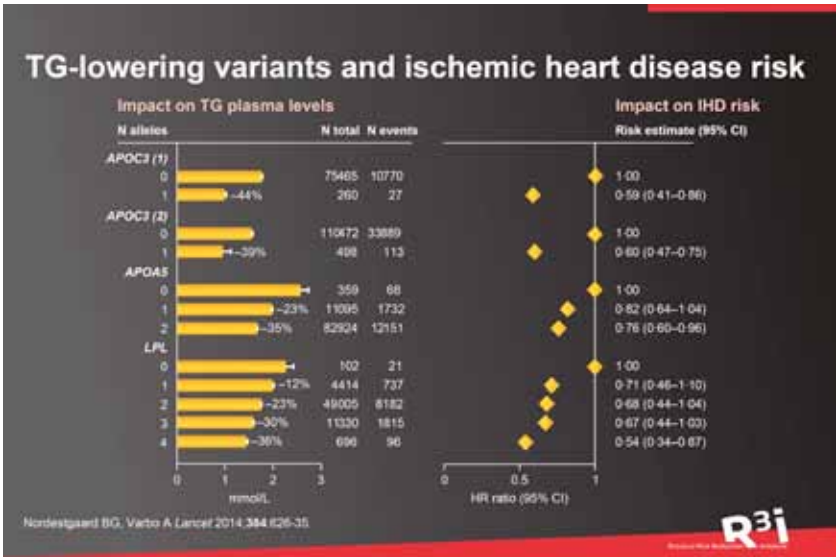


ANGPTL3 deficiency protects against coronary artery disease

Three points of evidence showed that *ANGPTL3* deficiency protected against coronary artery disease (CAD).

- Heterozygous carriers of *ANGPTL3* LOF mutations had a 34% decrease in risk for CAD (odds ratio 0.66, 95% CI 0.44 to 0.98, p=0.04)
- Individuals with the lowest tertile of plasma *ANGPTL3* levels had a 35% decrease in risk for MI (adjusted odds ratio 0.65, 95% CI 0.55 to 0.77, p<0.001)
- Individuals homozygous for *ANGPTL3* LOF mutations had no evidence of coronary atherosclerosis on intravascular ultrasound.

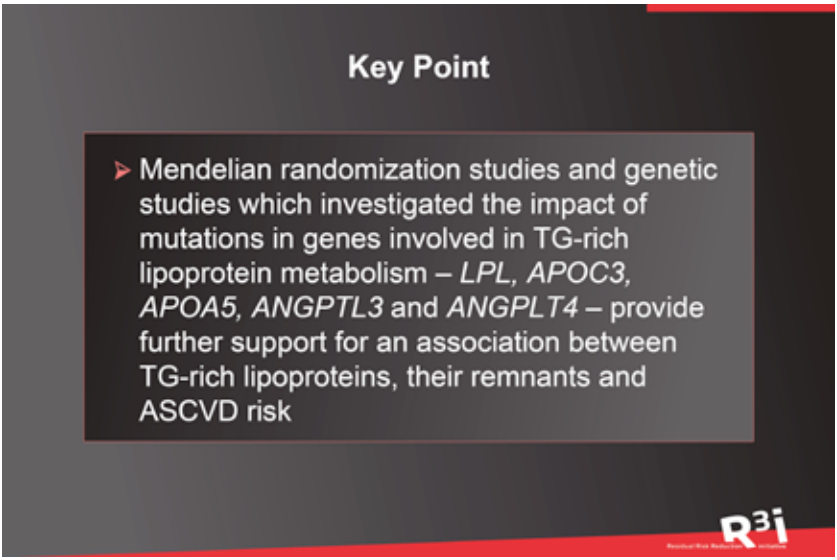
Stitziel NO *et al. J Am Coll Cardiol* 2017;**69**:2054-63.



TG-lowering variants and ischemic heart disease risk

In summary, studies show that variants of genes regulating TG-rich lipoprotein metabolism resulted in lower plasma TG levels and a reduced risk for IHD.

Nordestgaard BG, Varbo A. *Lancet* 2014;**384**:626-35.


Key Point
Mendelian randomization studies and genetic studies which investigated the impact of mutations in genes involved in TG-rich lipoprotein metabolism – *LPL, APOC3, APOA5, ANGPTL3* and *ANGPLT4* – provide further support for an association between TG-rich lipoproteins, their remnants and ASCVD risk
R3i

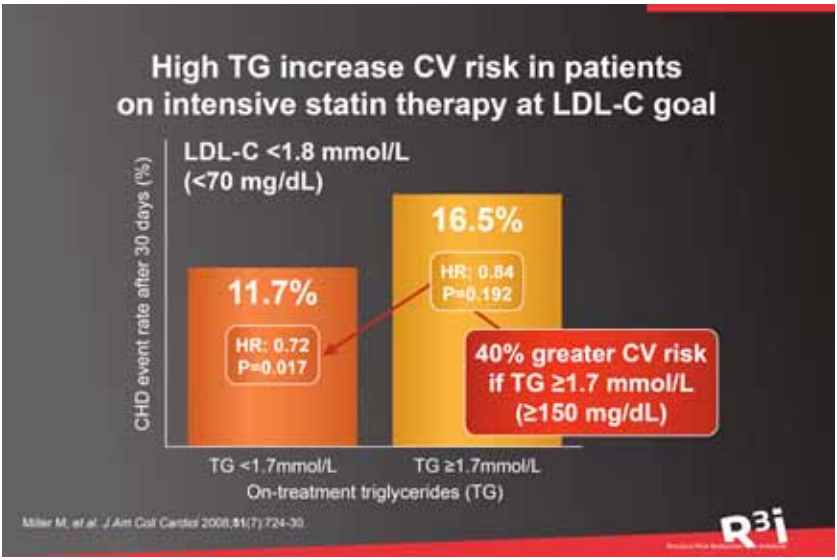
Triglyceride-rich lipoproteins and ASCVD – insights from clinical trials

SECTION

4

Residual Risk Reduction initiative

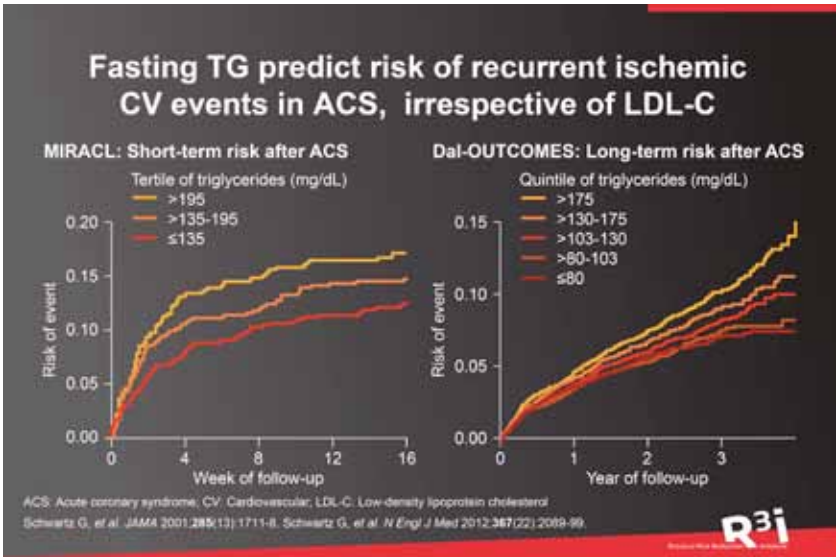

Statin trials
R3i



High TG increase CV risk in ACS patients on intensive statin therapy at LDL-C goal

Insights from statin trials indicate that part of the residual cardiovascular risk in high-risk patients is due to elevated TG-rich lipoproteins (either as plasma TG or remnant cholesterol). The PROVE IT-TIMI (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) 22 trial, which compared the effect of atorvastatin 80 mg or pravastatin 40 mg daily in acute coronary syndrome (ACS) patients, provides an example. On-treatment plasma TG ≥1.7 mmol/L (≥150 mg/dL) was associated with 40% higher risk of cardiovascular (CV) events. In contrast, patients with low on-treatment TG (<1.7 mmol/L) were at lower risk.

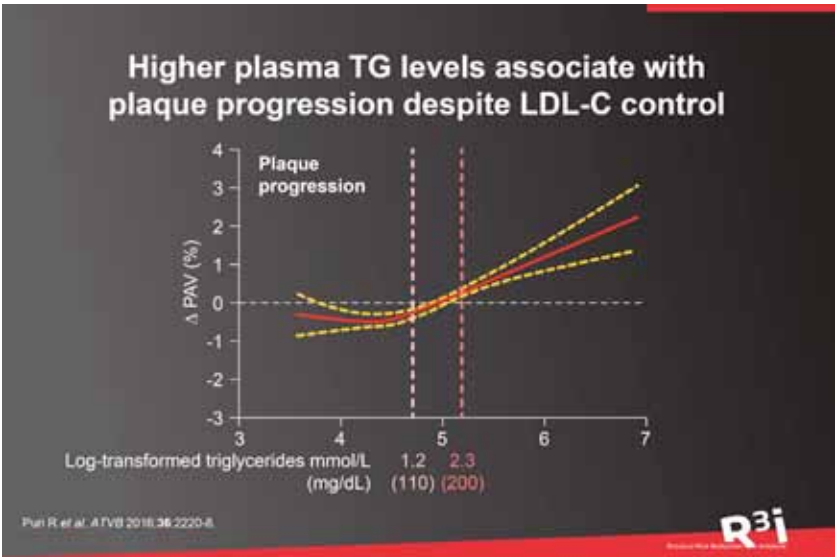
Miller M *et al. J Am Coll Cardiol* 2008;**51**:724-30.



Fasting TG predict short- and long-term risk of recurrent CV events in ACS patients

In the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial, higher baseline plasma TG were associated with a greater short-term risk of recurrent events. The dal-OUTCOMES study with dalcetrapib also showed that elevated plasma TG at baseline increased the long-term risk of recurrent CV events.

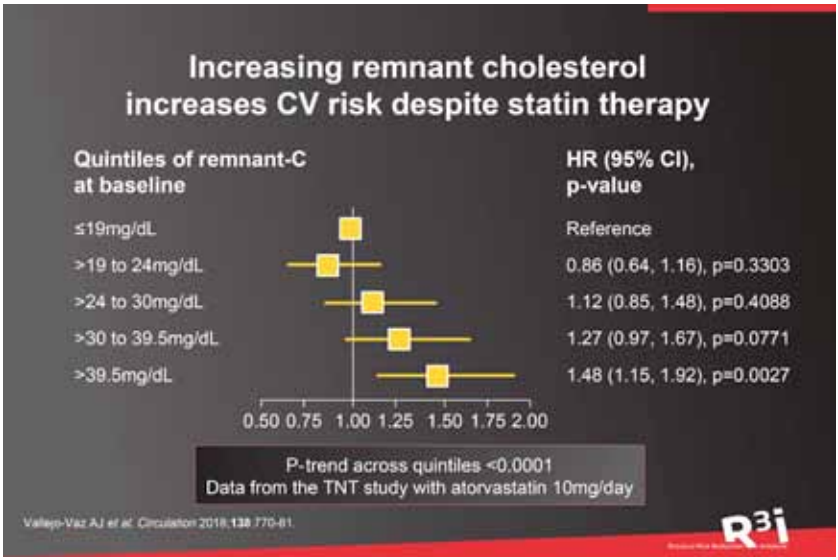
Schwartz GG *et al. JAMA* 2001;**285**:1711-8; Schwartz GG *et al. N Engl J Med* 2012;**367**:2089-99.



Higher plasma TG levels associate with plaque progression despite LDL-C control

In an analysis of 4,957 patients with coronary disease (96% on statin) undergoing serial intravascular ultrasonography, atheroma volume increased at plasma TG levels >1.2 mmol/L (>110 mg/dL). Disease progression, defined by percent atheroma volume (PAV) >0, was evident at TG levels >2.3 mmol/L (>200 mg/dL). Even among patients with LDL-C levels <1.8 mmol/L (<70 mg/dL) on statin, plasma TG >2.3 mmol/L was associated with plaque progression.

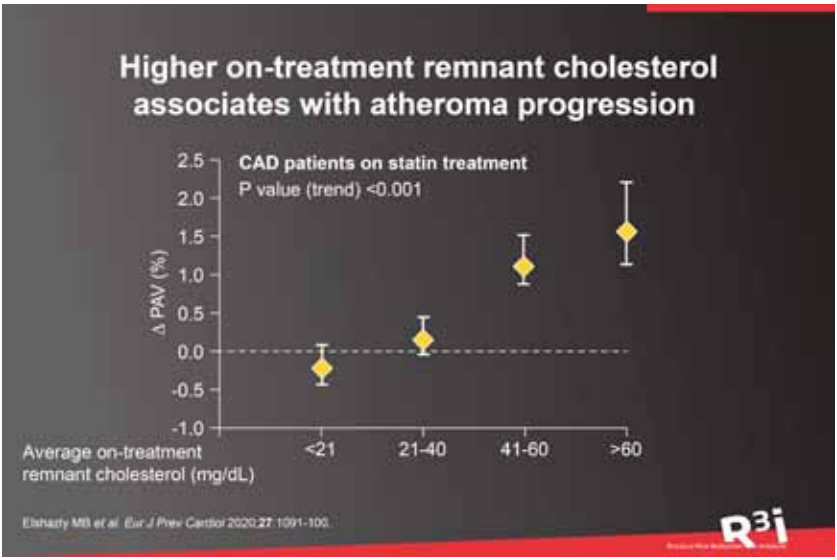
Puri R *et al. ATVB* 2016;**36**:2220-8.



Increasing remnant cholesterol increases CV risk despite statin therapy

Analysis of the TNT (Treating to New Targets) trial showed that higher remnant cholesterol levels were associated with increased cardiovascular risk. Patients in the highest quintile for remnant cholesterol (>39.5 mg/dL) had a 48% increase in the risk of major adverse cardiovascular events (MACE) compared with those in the lowest quintile (≤19 mg/dL).

Vallejo-Vaz AJ *et al. Circulation* 2018;**138**:770-81.

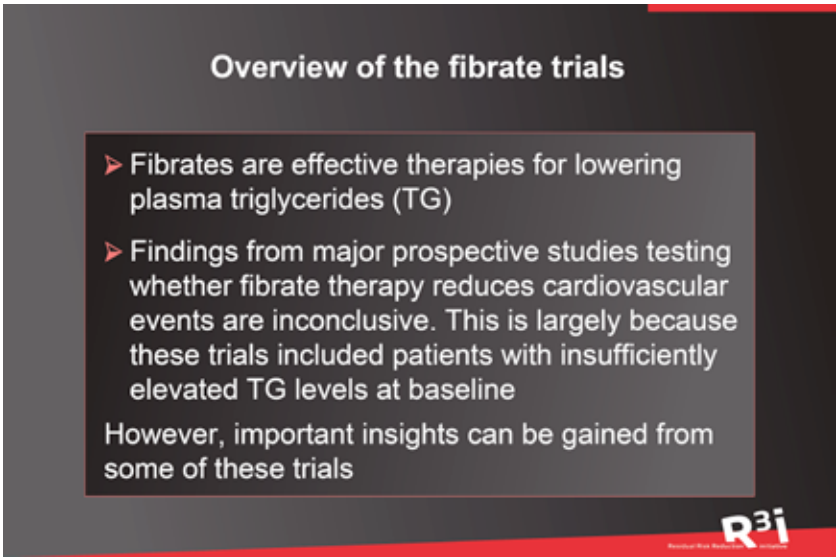


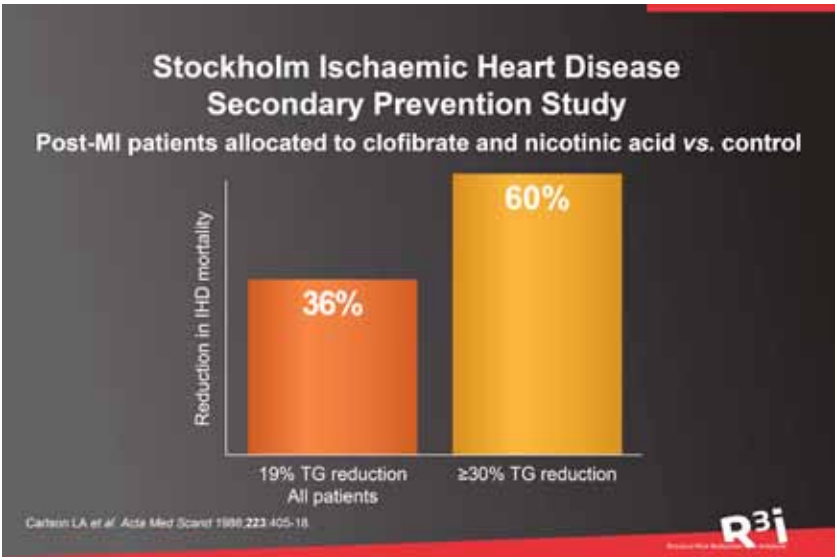
Higher on-treatment remnant cholesterol associates with atheroma progression

This study analyzed data from 10 trials including 5,754 patients with coronary artery disease (CAD) undergoing serial intravascular ultrasonography. Almost all were on a statin. On-treatment remnant cholesterol (defined as non-HDL-C – LDL-C) ≥25 mg/dL was associated with coronary atheroma progression. Patients in the highest on-treatment remnant cholesterol quartile (>60 mg/dL) had more atheroma progression ($p<0.001$) and higher 2-year MACE rates (23% *vs.* 14%, $p<0.001$) compared with those in the lowest quartile (<21 mg/dL).

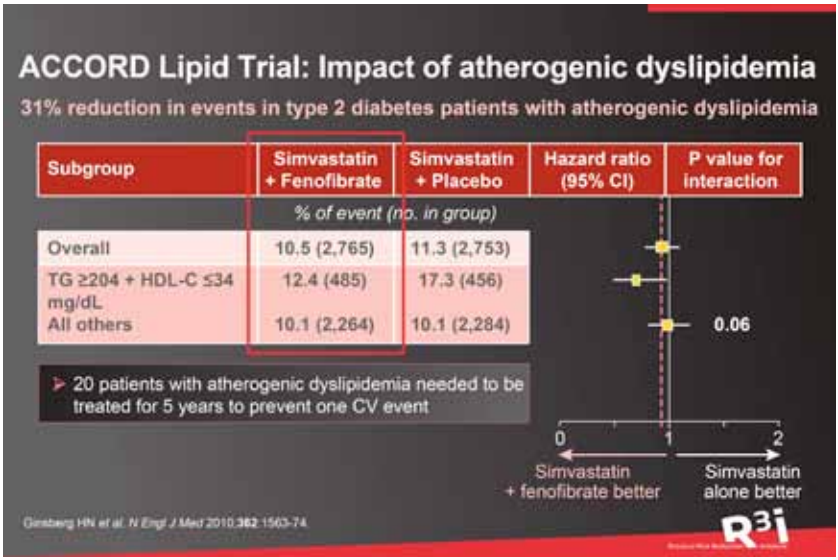
Elshazly MB *et al. Eur J Prev Cardiol* 2020;**27**:1091-100.


Fibrate trials
R3i


Overview of the fibrate trials
Fibrates are effective therapies for lowering plasma triglycerides (TG)
Findings from major prospective studies testing whether fibrate therapy reduces cardiovascular events are inconclusive. This is largely because these trials included patients with insufficiently elevated TG levels at baseline
However, important insights can be gained from some of these trials
R3i



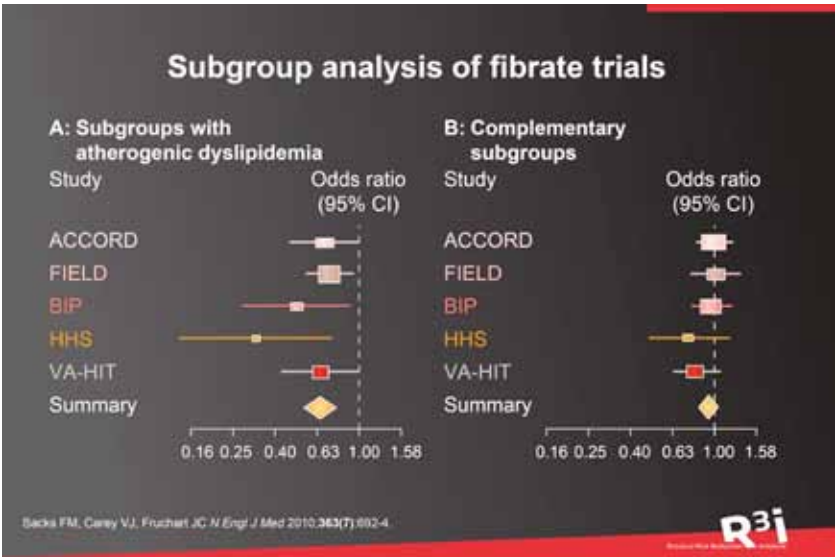
Stockholm Ischemic Heart Disease Secondary Prevention Study
This study randomized post-MI patients to treatment with clofibrate and nicotinic acid (n = 279) or control (n = 276). Treatment with clofibrate and nicotinic acid reduced plasma TG by 19% and was associated with 36% reduction in IHD mortality at 5 years versus control. For patients attaining ≥30% reduction in plasma TG levels, the 5-year reduction in IHD mortality was more pronounced, at 60%.
Carlson LA *et al. Acta Med Scand* 1988;**223**:405-18.



ACCORD Lipid Trial: Impact of atherogenic dyslipidemia

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid study investigated the effect of fenofibrate treatment on MACE in type 2 diabetes patients treated with simvastatin. There was no benefit from fenofibrate in the total study population. This was not surprising as median plasma TG at entry were only 1.8 mmol/L (interquartile range 1.3 to 2.6 mmol/L). However, the subgroup of patients defined a priori with elevated plasma TG and low HDL-C at baseline did derive a 31% relative reduction in MACE.

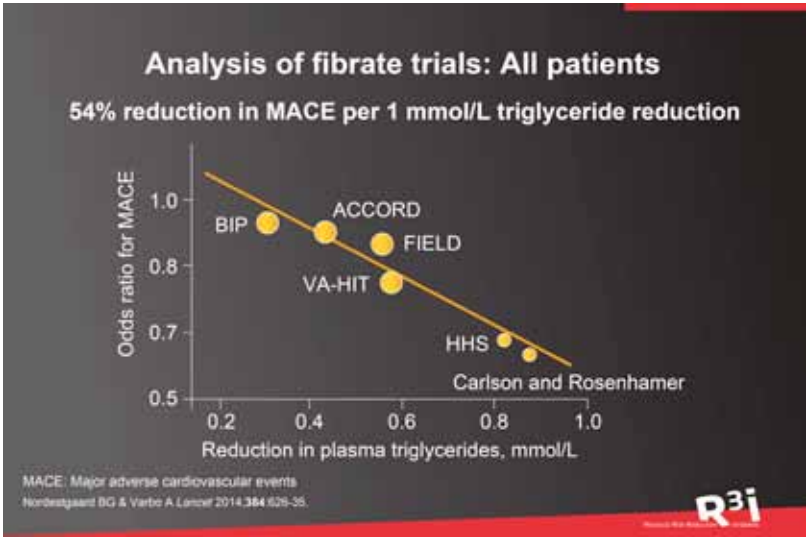
Ginsberg HN *et al. N Engl J Med* 2010;**362**:1563-74.



Subgroup analysis of fibrate trials

A post hoc analysis of the major fibrate trials in patients with atherogenic dyslipidemia, defined as for the ACCORD Lipid trial, showed a similar result. There was 35% reduction in cardiovascular events in patients with atherogenic dyslipidemia compared with only 6% reduction in risk in patients without this dyslipidemic profile.

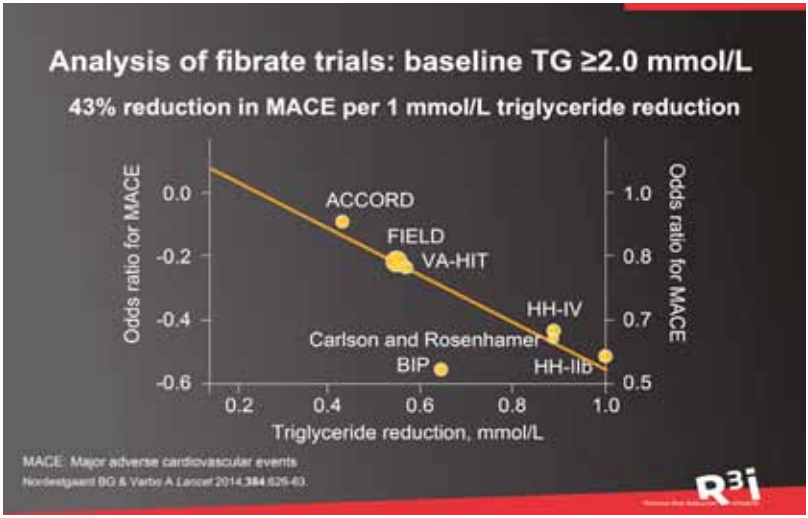
Sacks FM, Carey VJ, Fruchart JC. *N Engl J Med* 2010;**363(7)**:692-4



Analysis of fibrate trials: All patients

Among fibrate trials that included post-hoc subgroup analyses for patients with baseline TG ≥2.0 mmol/L (≥178 mmol/L), 1 mmol/L reduction in plasma TG reduced MACE by 54%.

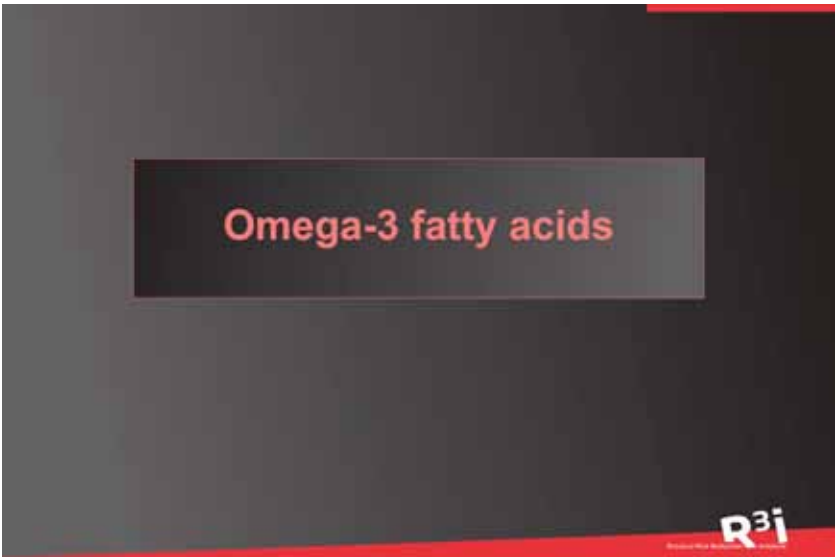
Nordestgaard BG, Varbo A. *Lancet* 2014;**384**:626-35.

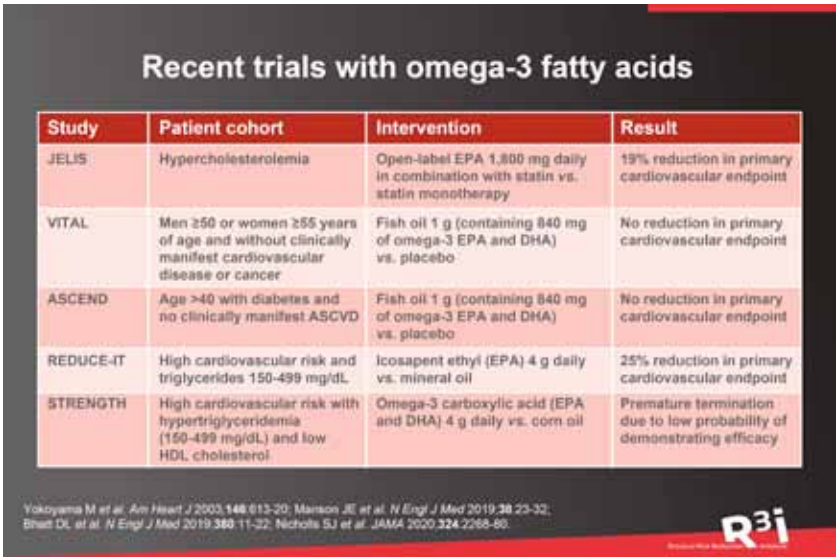


Analysis of fibrate trials: baseline TG ≥2.0 mmol/L

In the same analysis, patients with high baseline TG, ≥2.0 mmol/L or ≥178 mmol/L, derived a similar clinical benefit with a 43% (45% to 78%) reduction in risk of MACE.

Nordestgaard BG, Varbo A. *Lancet* 2014;**384**:626-35.

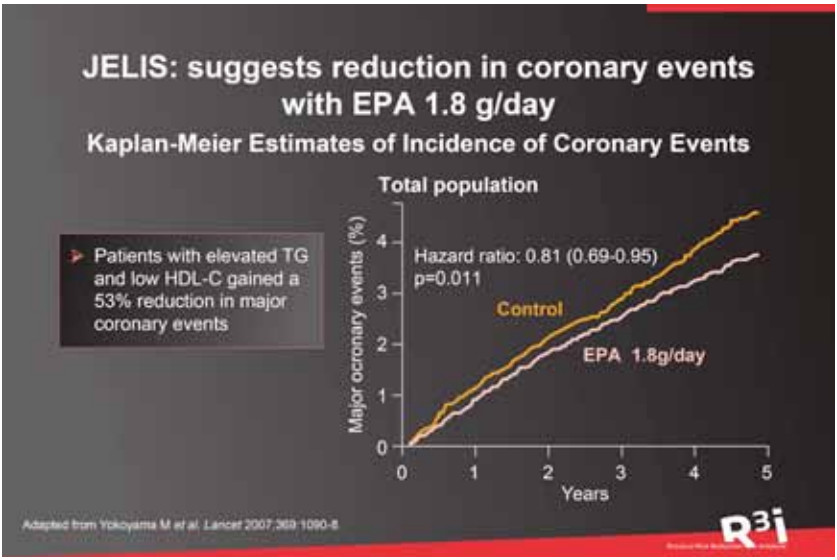

Omega-3 fatty acids
R3i



Recent trials with omega-3 fatty acids

Omega-3 fatty acids are another class of medication recommended by guidelines for lowering plasma TG. The results of cardiovascular outcomes studies, however, have been variable. There was no evidence of benefit in either ASCEND or VITAL, both of which used a 1 g daily dose of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

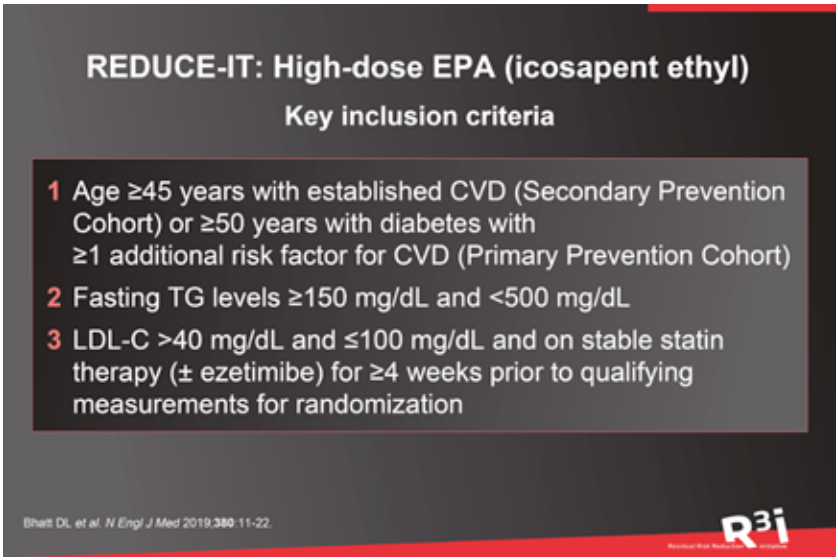
Yokoyama M *et al. Am Heart J* 2003;**146**:613-20; Manson JE *et al. N Engl J Med* 2019;**38:23-32**; Bhatt DL *et al. N Engl J Med* 2019;**380**:11-22; Nicholls SJ *et al. JAMA* 2020;**324**:2268-80.



JELIS: suggests reduction in coronary events with EPA 1.8 g/day

JELIS (Japan EPA Lipid Intervention Study) was an open-label randomized study comparing treatment with 1.8 g/day of EPA and a statin (pravastatin 10 mg or simvastatin 5 mg) *vs.* statin alone in patients with hypercholesterolemia. Treatment with EPA on top of statin reduced major coronary events by 19% (p = 0.01) versus statin alone. In a further subgroup analysis, patients with baseline TG >1.7 mmol/L (>150 mg/dL) and low plasma concentration of HDL-C gained 53% reduction in major coronary events.

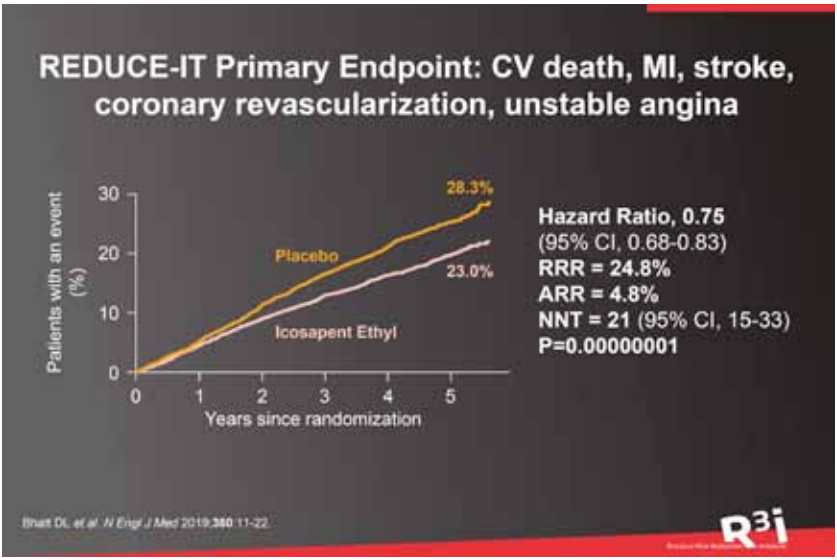
Yokoyama M *et al. Am Heart J* 2003;**146**:613-20.



REDUCE-IT: High-dose (4 g/day) EPA (icosapent ethyl)

REDUCE-IT (Reduction of Cardiovascular Events With EPA–Intervention Trial) enrolled patients with established ASCVD or diabetes with other risk factors. All patients were on background statin therapy and had fasting baseline TG between 1.5 and 5.6 mmol/L (135 to 499 mg/dL) and LDL-C levels between 1.0 and 2.6 mmol/L (41 to 100 mg/dL). Patients were randomized to high-dose EPA (icosapent ethyl 4 g daily) or a mineral oil placebo.

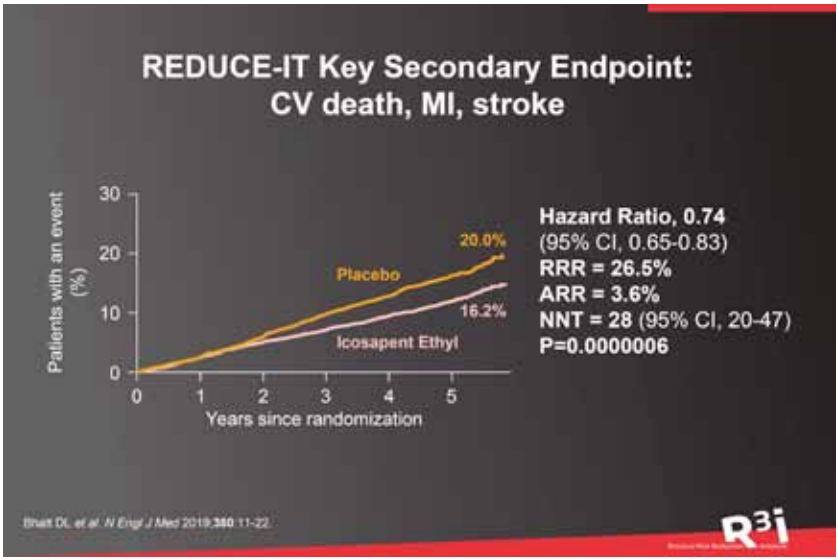
Bhatt DL *et al. N Engl J Med* 2019;**380**:11-22.



REDUCE-IT Primary Endpoint

High-dose EPA (icosapent ethyl) was associated with 25% relative risk reduction in the primary composite endpoint: Hazard ratio 0.75, 95% CI 0.68 to 0.83. This was despite only a modest decrease in plasma TG (median 18.3%, 39 mg/dL).

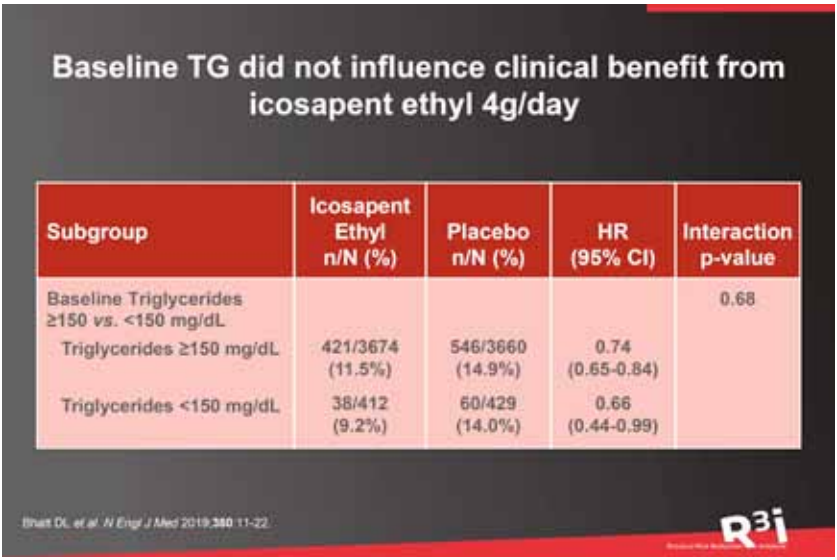
Bhatt DL *et al. N Engl J Med* 2019;**380**:11-22.



REDUCE-IT Key Secondary Endpoint

High-dose EPA (icosapent ethyl) also reduced the key secondary endpoint: Hazard ratio 0.74, 95% CI 0.65 to 0.83.

Bhatt DL *et al. N Engl J Med* 2019;**380**:11-22.

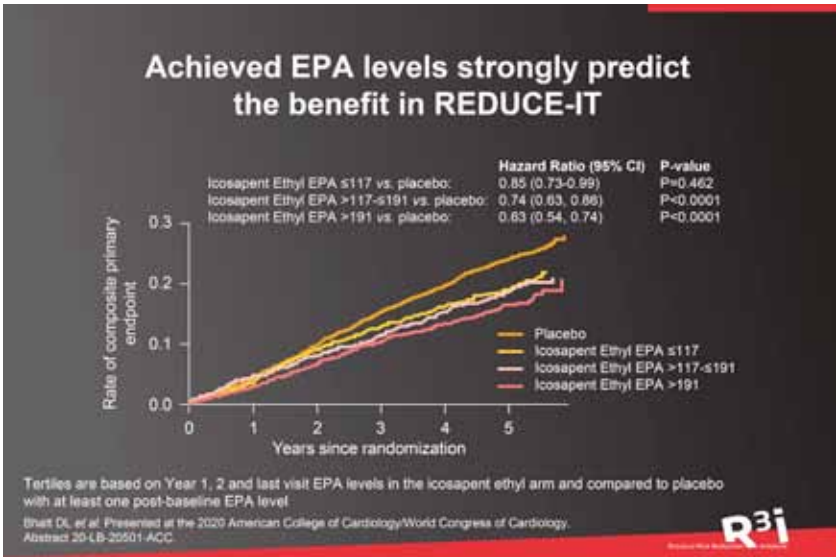


Baseline TG did not influence the clinical benefit from icosapent ethyl 4 g/day

The modest reduction in plasma TG with high-dose EPA (icosapent ethyl) suggests that it is unlikely that TG reduction alone accounted for the substantial clinical benefit observed in REDUCE-IT. Additionally, cardiovascular risk reduction was not influenced by baseline TG levels above or below 1.7 mmol/L (150 mg/dL), or by achievement of TG levels below 1.7 mmol/L at one year.

It should also be noted that levels of high-sensitivity CRP, a systemic marker of inflammation, were 38% lower in the intervention arm than in the placebo arm at 2 years. This difference was partly due to an increase in CRP in the placebo (mineral oil) arm.

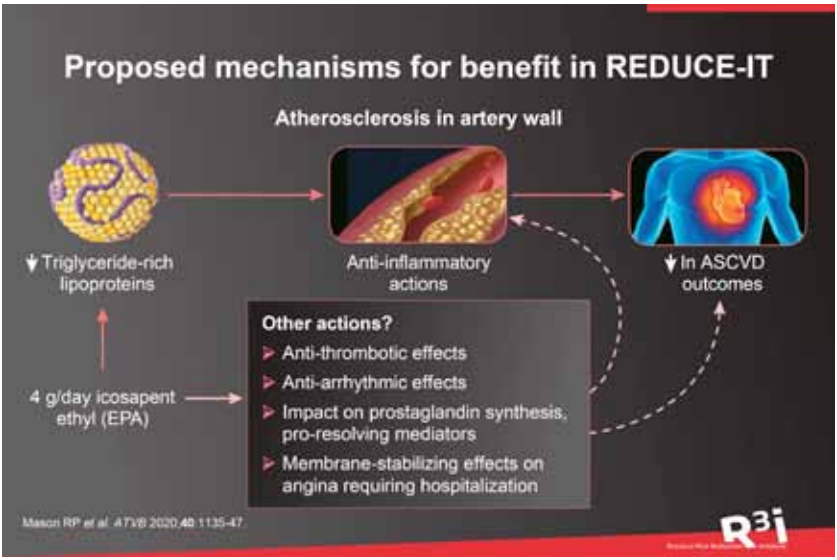
Bhatt DL *et al. J Am Coll Cardiol* 2019;**74**:1849-50; Bhatt DL *et al. N Engl J Med* 2019;**380**:11-22.



Achieved EPA levels strongly predict the benefit in REDUCE-IT

In REDUCE-IT, serum EPA levels increased 3.6-fold from a median baseline level of 26.1 to 144.0 mg/mL at year 1 of follow-up ($p<0.001$). Subsequent analysis indicated that the achieved EPA level was a predictor of the clinical benefit from high-dose EPA.

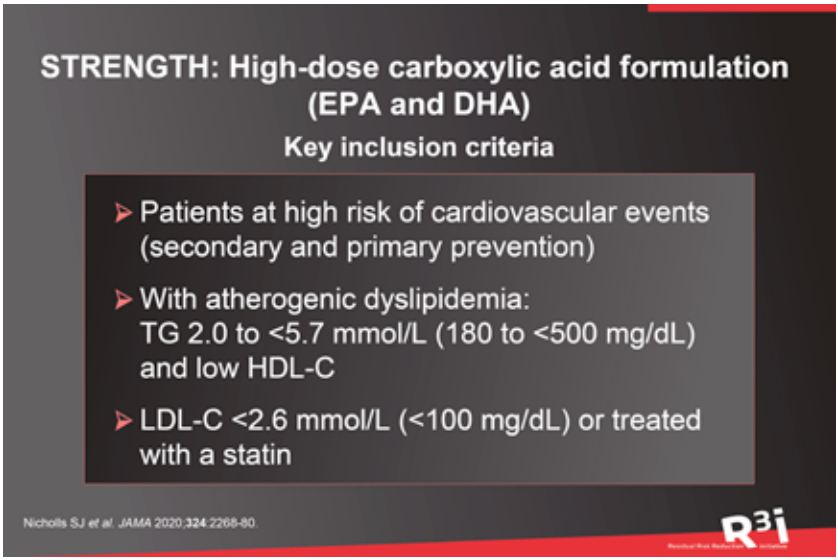
Bhatt DL *et al.* Presented at the 2020 American College of Cardiology/World Congress of Cardiology. Abstract 20-LB-20501-ACC.



Proposed mechanisms for benefit in REDUCE-IT

The benefit from high-dose EPA in REDUCE-IT may be attributable to effects on several different mechanisms. Lowering of TG-rich lipoproteins may account for some but certainly not all of the observed benefit. Other biological actions of omega-3 fatty acids that may be implicated include anti-thrombotic, anti-arrhythmic, membrane-stabilizing or anti-inflammatory (direct or indirect) effects.

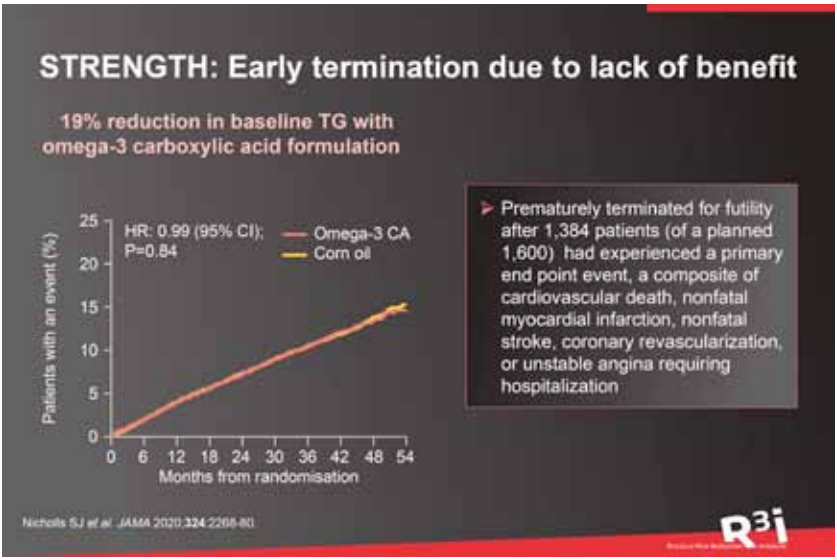
Mason RP *et al. ATVB* 2020;**40**:1135-47.



STRENGTH: High-dose carboxylic acid formulation (EPA and DHA)

STRENGTH (Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia) investigated the effects of a carboxylic acid formulation of EPA/DHA compared with placebo (corn oil) among patients with dyslipidemia and high cardiovascular risk.

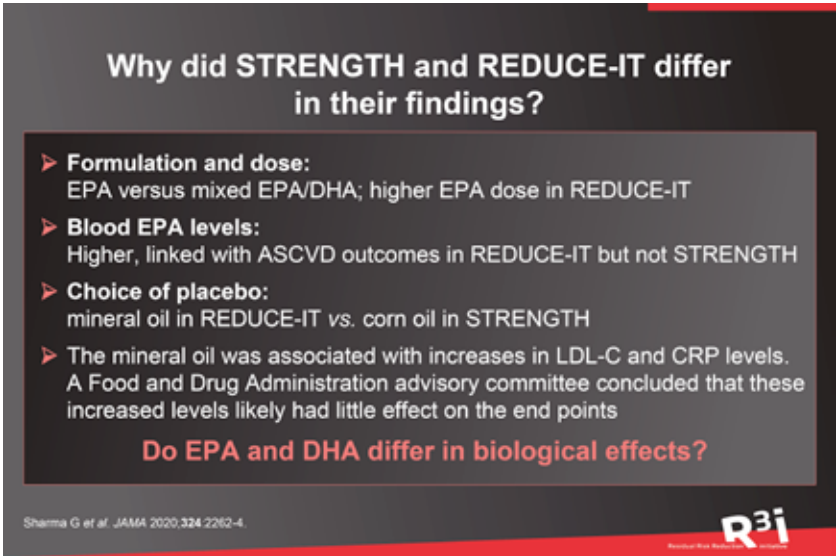
Nicholls SJ *et al. JAMA* 2020;**324**:2268-80.



STRENGTH: Early termination due to lack of benefit

The trial was terminated early following an interim analysis which showed a low probability for benefit with this mixed omega-3 fatty acid formulation. At this time, 1384 primary endpoints had been recorded in 13,078 randomized patients (6539 allocated to each treatment). The primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization occurred in 12.0% of the omega-3 treatment group compared with 12.2% of the placebo group (p = 0.84). The magnitude of TG lowering in STRENGTH was similar to that observed in REDUCE-IT.

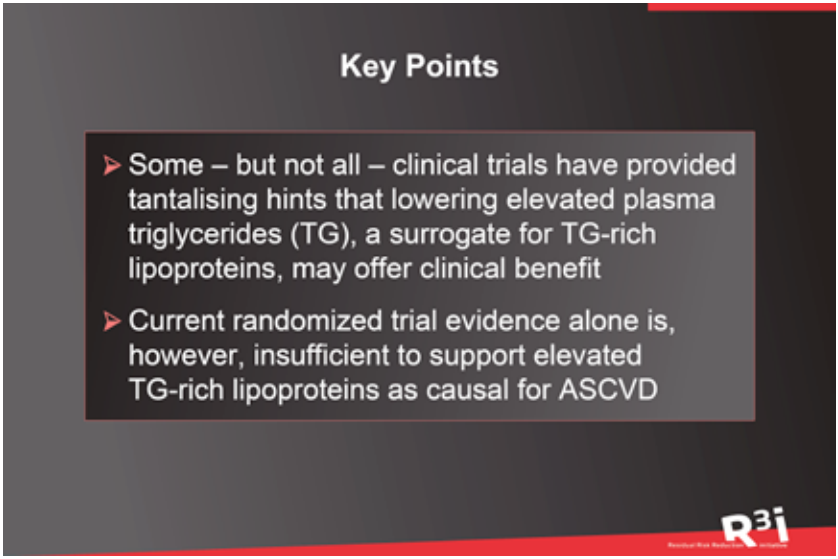
Nicholls SJ *et al. JAMA* 2020;**324**:2268-80.



Why did STRENGTH and REDUCE-IT differ in their findings?

A number of reasons have been proposed to explain the discrepant findings of STRENGTH and REDUCE-IT. Differences in the characteristics of the study patient populations may be also relevant. REDUCE-IT enrolled a higher proportion of patients with coronary artery disease (71% versus 56% in STRENGTH). Explanation of the different results of these two trials remains unresolved.

Sharma G *et al. JAMA* 2020;**324**:2262-64.

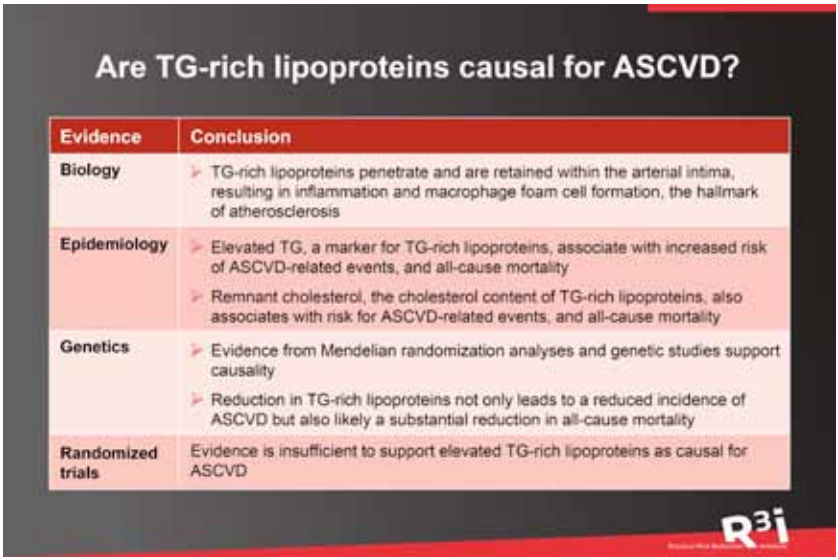


Triglyceride-rich lipoproteins and ASCVD – looking to the future

SECTION

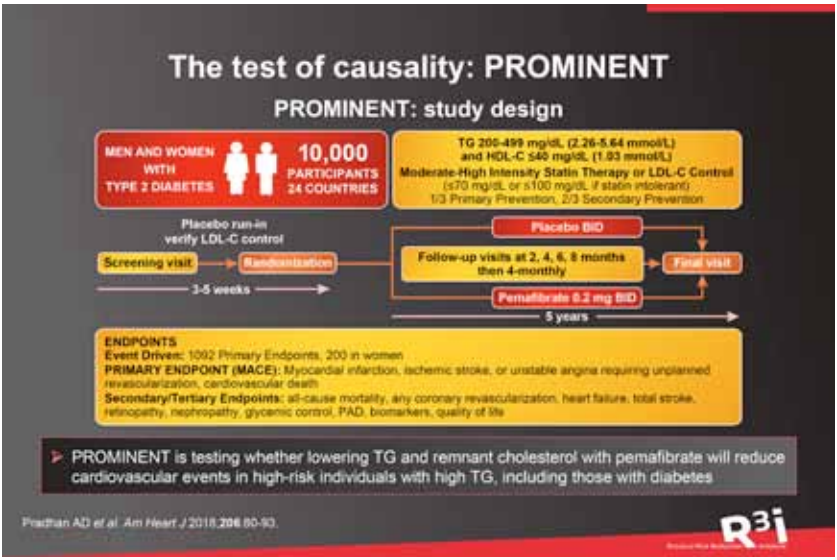
5

Residual Risk Reduction initiative



Are TG-rich lipoproteins causal for ASCVD?

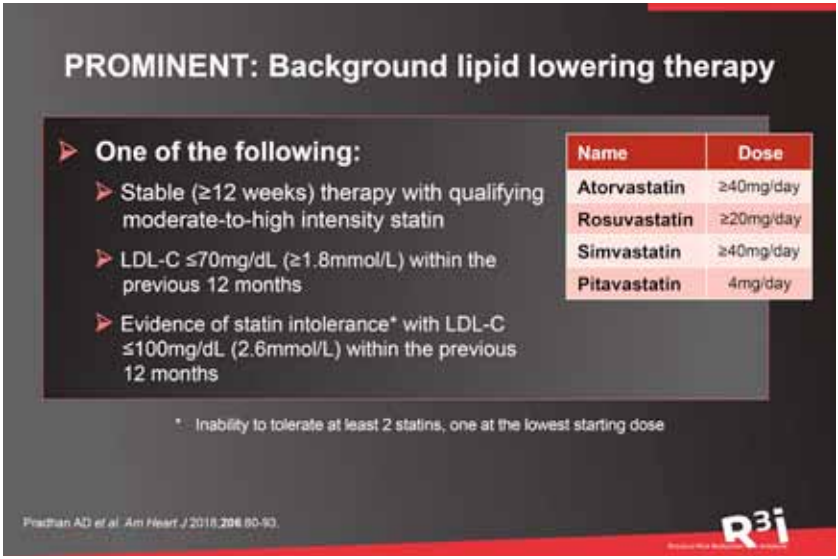
Observational, genetic, and experimental studies indicate that TG-rich lipoproteins, represented by plasma TG or remnant cholesterol, are an additional causal risk factor for ASCVD. However, randomized intervention trial evidence is urgently needed to show that TG-lowering reduces cardiovascular events in patients with raised TG.



The test of causality: PROMINENT

The PROMINENT (Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabetes) trial is critical to establishing the causality of elevated TG-rich lipoproteins for ASCVD. The trial will investigate whether lowering TG and remnant cholesterol using pemafibrate, a novel selective peroxisome proliferator-activated alpha modulator (SPPARMα), will reduce cardiovascular events in high-risk individuals with type 2 diabetes and high TG.

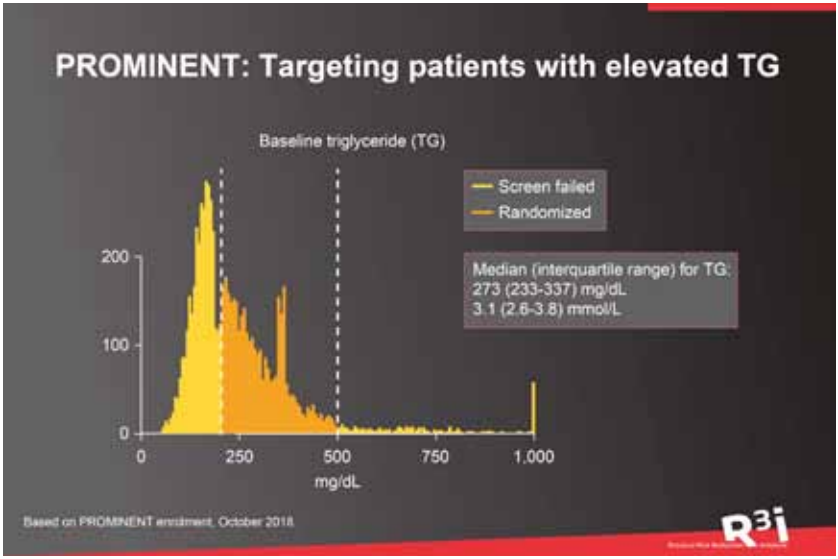
Pradhan AD *et al. Am Heart J* 2018;**206**:80-93.



PROMINENT: Background lipid-lowering therapy

Low-density lipoprotein cholesterol was well controlled in patients enrolled in PROMINENT.

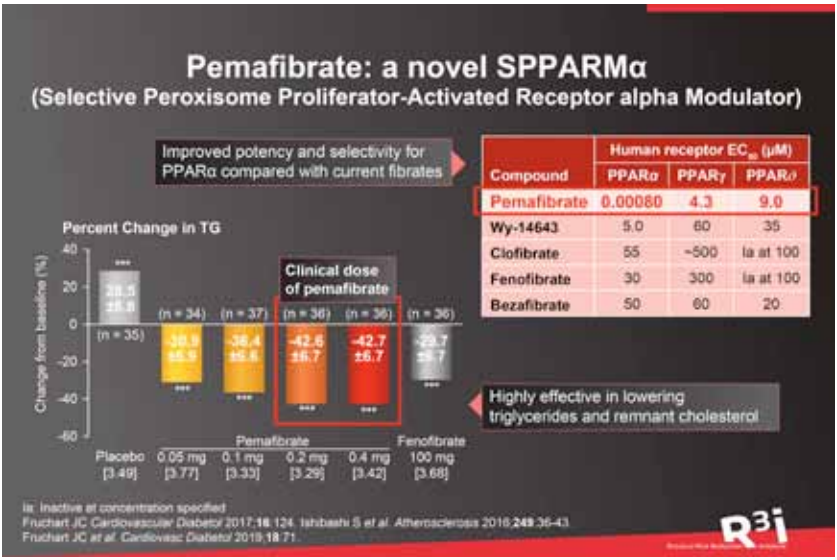
Pradhan AD *et al. Am Heart J* 2018;**206**:80-93.



PROMINENT: Targeting patients with elevated TG

Unlike the fibrate trials, PROMINENT has enrolled patients with sufficiently elevated TG levels, with evidence suggesting a median baseline TG of 3.1 mmol/L (273 mg/dL).

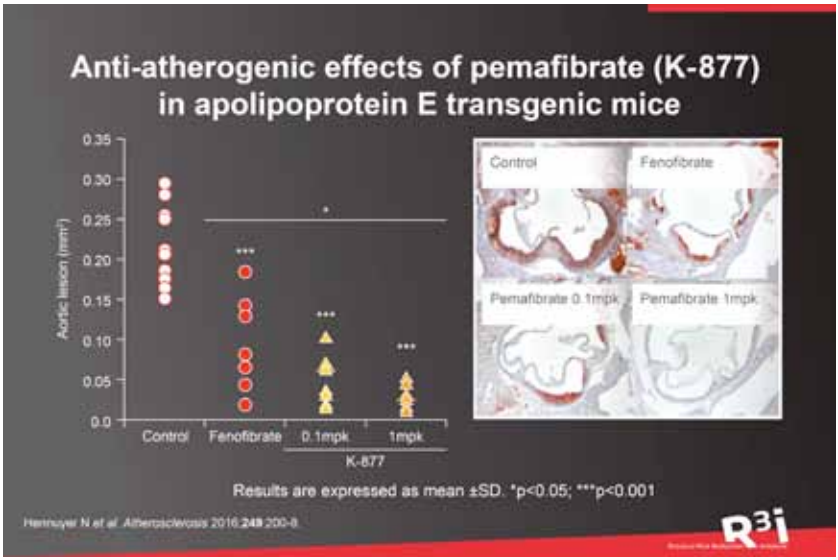
Based on PROMINENT enrolment, October 2018.



Pemafibrate: a novel SPPARMα

Pemafibrate is a SPPARMα which offers advantages over current fibrates. Cell-based transactivation assays demonstrated greatly enhanced potency and selectivity for PPARα compared with fenofibric acid (the active metabolite of fenofibrate). Clinical trials also demonstrated efficacy in lowering plasma TG and remnant cholesterol (by more than 40% and 50%, respectively).

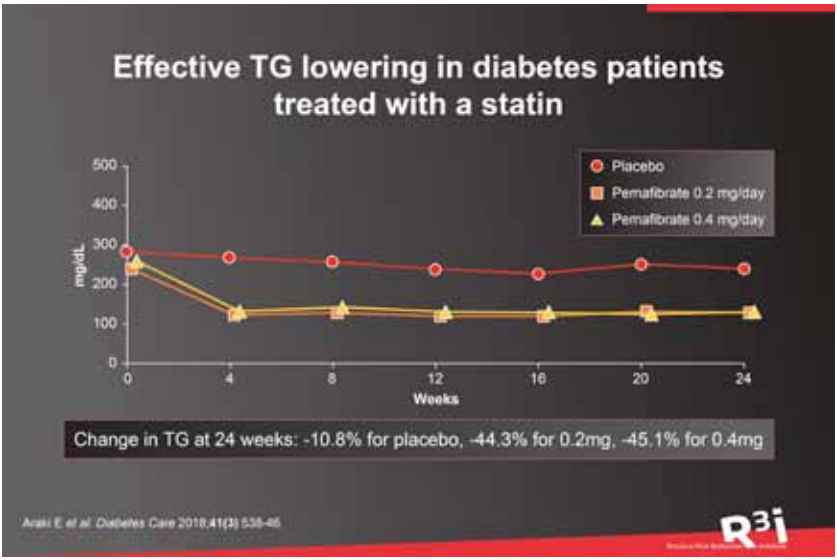
Fruchart JC *Cardiovasc Diabetol* 2017;**16**:124; Ishibashi S *et al. Atherosclerosis* 2016;**249**:36-43. Fruchart JC *et al. Cardiovasc Diabetol* 2019;**18**:71.



Anti-atherogenic effects of pemafibrate in an animal model

In an animal model of atherosclerosis (transgenic apolipoprotein E2KI mice fed a Western diet), pemafibrate (0.1mpk and 1mpk) reduced markers of inflammation and macrophages in the aorta, as well as aortic atherosclerotic lesion burden. These findings suggest that pemafibrate exerts protective anti-atherogenic properties in mice associated with lowering plasma TG and remnant lipoproteins.

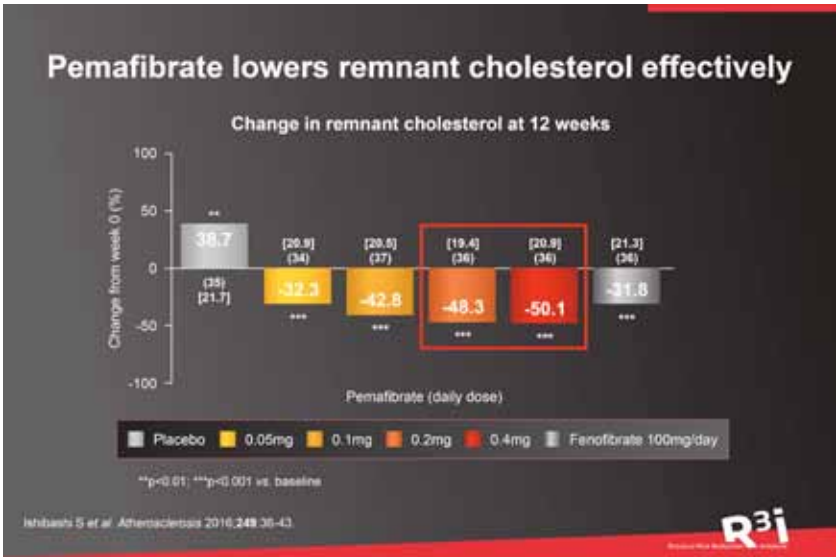
Hennuyer N *et al. Atherosclerosis* 2016;**249**:200-8.



Effective lowering of TG in diabetes patients treated with a statin

In type 2 diabetes patients treated with a statin, pemafibrate 0.2 mg or 0.4 mg daily resulted in sustained lowering of serum TG levels by ~45% compared with placebo. Pemafibrate also decreased other atherogenic lipoproteins including apolipoproteins B100, B48, and CIII levels.

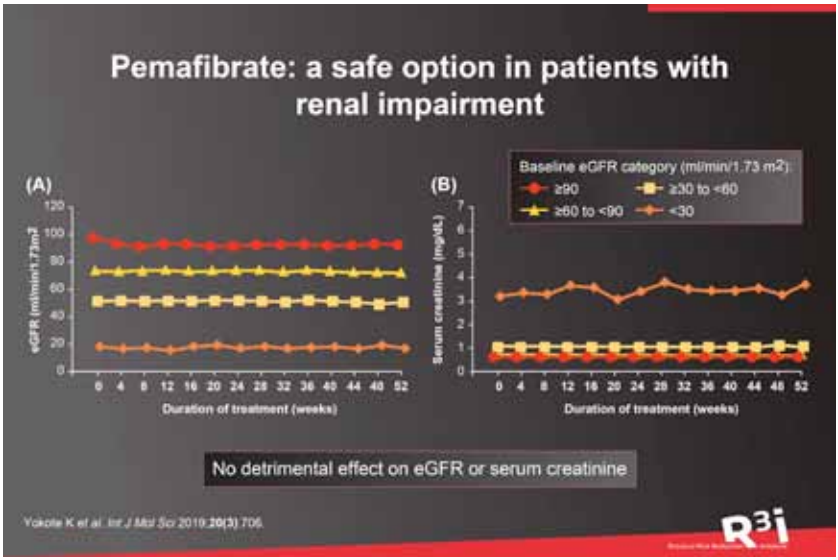
Araki E *et al. Diabetes Care* 2018;**41**:538-46.



Pemafibrate lowers remnant cholesterol effectively

Pemafibrate 0.2 mg and 0.4 mg daily also substantially reduced plasma levels of remnant cholesterol by up to 50%.

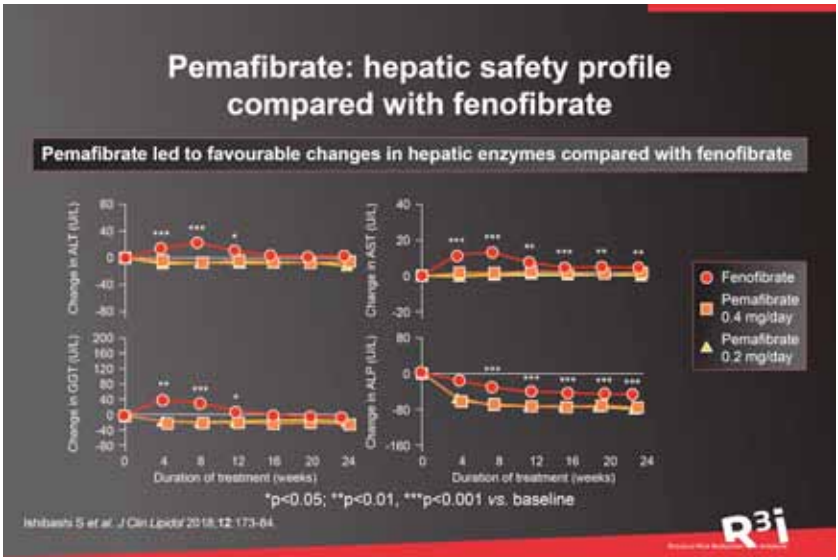
Ishibashi S *et al. Atherosclerosis* 2016;**249**:36-43.



Pemafibrate: a safe option in patients with renal impairment

Pemafibrate (0.2 mg or 0.4 mg daily) was investigated in a study in dyslipidemic patients with estimated glomerular filtration rate (eGFR) ranging from normal, i.e. >90 mL/min/1.73 m^2 to <30 mL/min/1.73 m^2. After 52 weeks treatment, there was no difference in efficacy between patients with normal renal function or those with renal impairment. Additionally, renal function, assessed by eGFR and serum creatinine, did not worsen in patients with renal impairment over 52 weeks treatment.

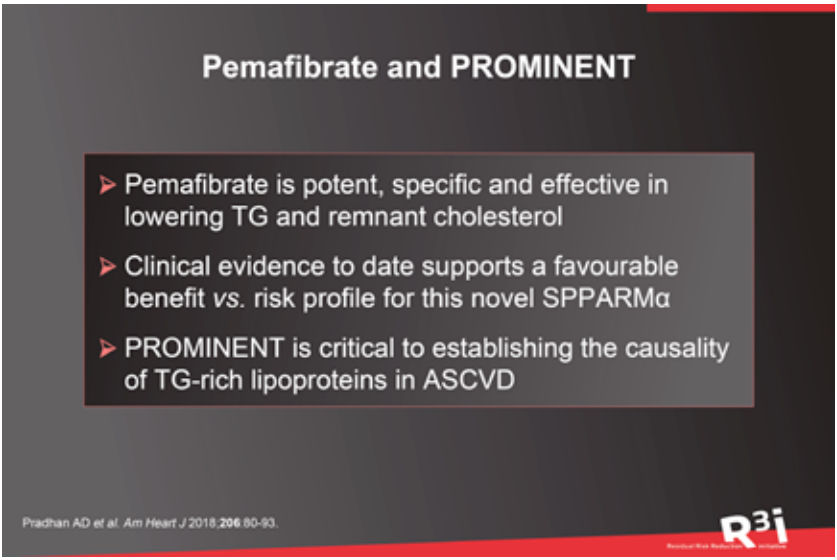
Yokote K *et al. Int J Mol Sci* 2019;**20(3)**:706.



Pemafibrate: a safe hepatic profile compared with fenofibrate

Pemafibrate showed a favourable hepatic safety profile in clinical trials. In one study, pemafibrate significantly decreased alanine aminotransferase and gamma-glutamyl transferase levels, whereas both increased during fenofibrate treatment.

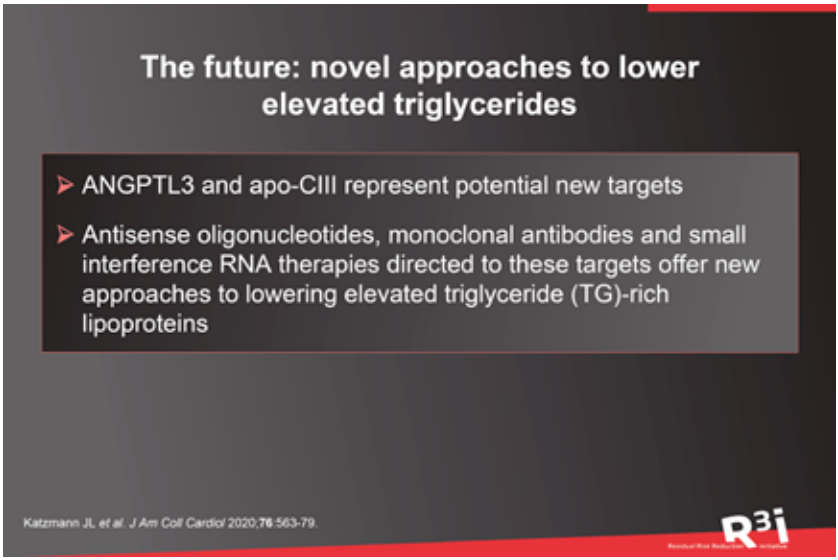
Ishibashi S *et al. J Clin Lipidol* 2018;**12**:173-84.



Pemafibrate and PROMINENT

Based on a favourable efficacy and safety profile, pemafibrate is an ideal tool to test whether lowering plasma TG and remnant cholesterol (representative of TG-rich lipoproteins), reduces cardiovascular events.

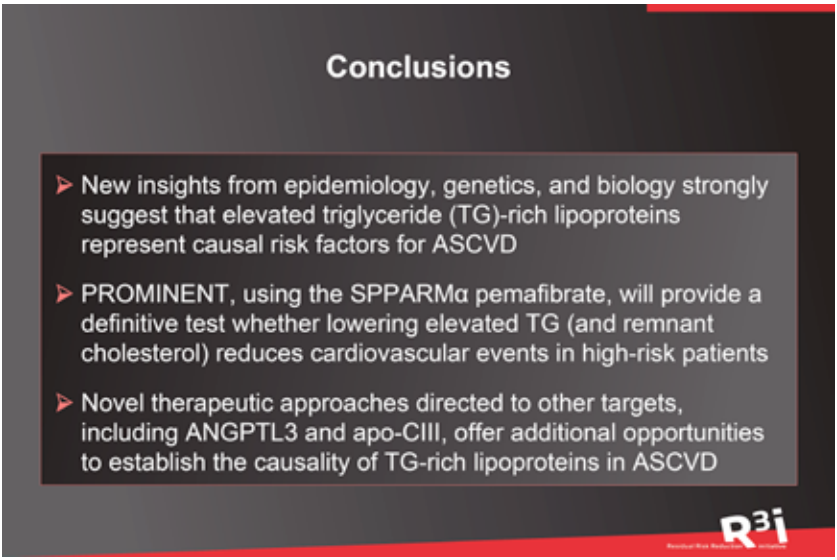
Pradhan AD *et al. Am Heart J* 2018;**206**:80-93.



The future: novel approaches to lower elevated triglycerides

ANGPTL3 and apo-CIII represent potential new targets for therapeutic intervention to lower plasma TG-rich lipoproteins.

Katzmann JL et al. J Am Coll Cardiol 2020:76:563-79.


Conclusions
New insights from epidemiology, genetics, and biology strongly suggest that elevated triglyceride (TG)-rich lipoproteins represent causal risk factors for ASCVD
PROMINENT, using the SPPARMα pemafibrate, will provide a definitive test whether lowering elevated TG (and remnant cholesterol) reduces cardiovascular events in high-risk patients
Novel therapeutic approaches directed to other targets, including ANGPTL3 and apo-CIII, offer additional opportunities to establish the causality of TG-rich lipoproteins in ASCVD
R3i

Abbreviations

ACS	Acute coronary syndrome
ALT	Alanine aminotransferase
ANGPTL3, 4 and 8	Angiopoietin-like proteins 3,4 and 8
apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
CAD	Coronary artery disease
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic acid
GGT	Gamma-glutamyl transferase
GPIHBP1	Glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1
HDL-C	High-density lipoprotein cholesterol
HL	Hepatic lipase
IDL	Intermediate-density lipoproteins
IHD	Ischemic heart disease

IL	Interleukin
IQR	Interquartile range
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LOF	Loss-of-function
Lp(a)	Lipoprotein(a)
LpL	Lipoprotein lipase
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NMR	Nuclear magnetic resonance
PAV	Percent atheroma volume
PPARα	Peroxisome Proliferator-Activated Receptor alpha
SPPARMα	Selective Peroxisome Proliferator-Activated Receptor alpha Modulator
TG	Triglycerides
VCAM-1	Vascular cell adhesion molecule-1
VLDL	Very low-density lipoproteins

Trials

ACCORD	Action to Control Cardiovascular Risk in Diabetes trial
ASCEND	A Study of Cardiovascular Events iN Diabetes
JELIS	Japan EPA Lipid Intervention Study
MIRACL	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial
PROMINENT	Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabetes
PROVE IT-TIMI 22	Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 trial
STRENGTH	Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia
TNT	Treating to New Targets trial
VITAL	VITamin D and OmegA-3 TriaL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Residual Risk Reduction initiativ