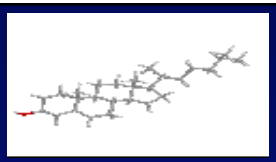
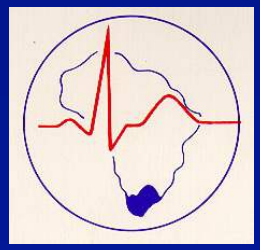


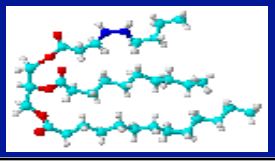
# Dyslipidaemia in Diabetes

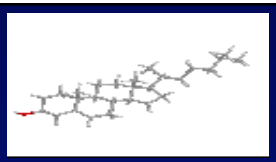
## Managing Lipid Abnormalities



Dirk Blom
UCT Cape Heart Centre
Lipid Clinic - Groote Schuur Hospital



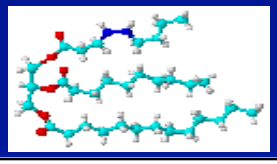


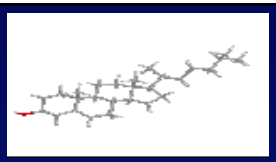


# Disclosures



- Honoraria for presentations
  - AstraZeneca, MSD, Novartis, Pfizer, Chiesi, Cipla
- Clinical trial payments: Novartis, LIB Therapeutics, IONIS, Verve, Arrowhead
- Advisory board: Chiesi, Novartis, MSD

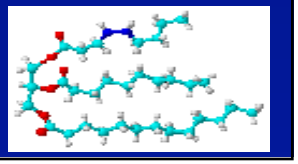


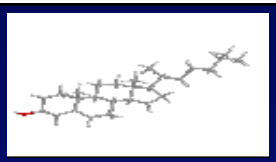


# Topics

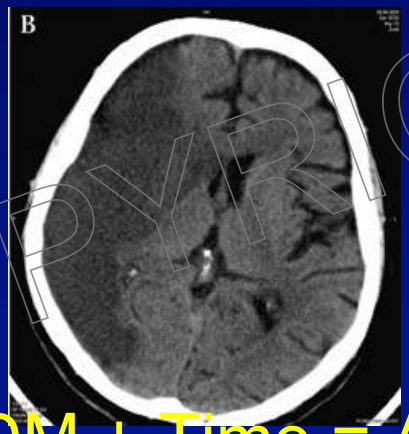


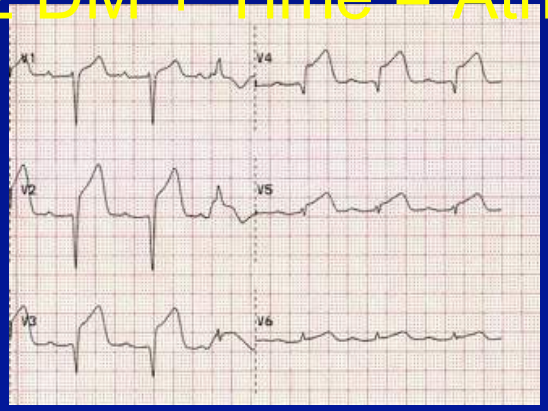
- Cardiovascular disease in DM
- Lipids
  - LDL lowering
  - Remnant lipoproteins – moderate hypertriglyceridaemia
  - Severe Hypertriglyceridaemia
- Not covered today
  - HDL – the highly difficult lipoprotein
  - Lp(a)
  - Anti-inflammatory therapies





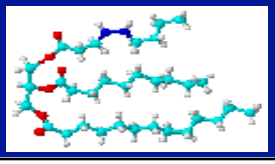
# The Sad Reality

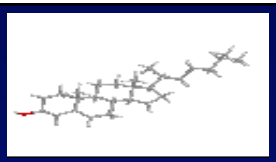



Type 2 DM + Time = Atherosclerosis



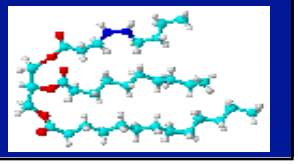




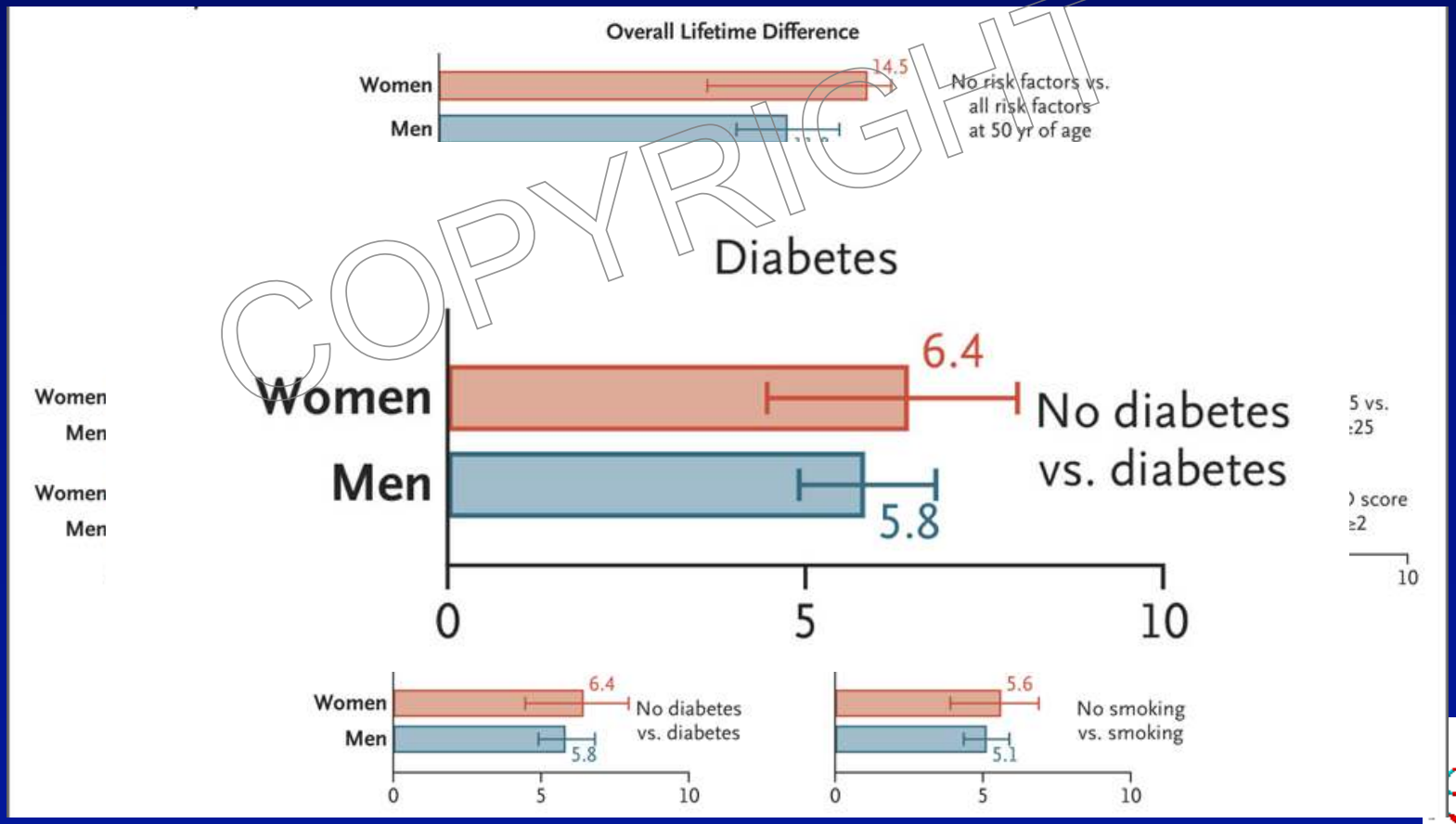
# Type 2 Diabetes and CVD



- 50-75% of deaths in patients with DM are CVD related
- Very high rates of PVD
- Atherosclerosis often ‘diffuse’
  - ↑Mortality post MI
  - ↑ Mortality + morbidity following vascular interventions
  - Higher rates of graft failure or stent blockage



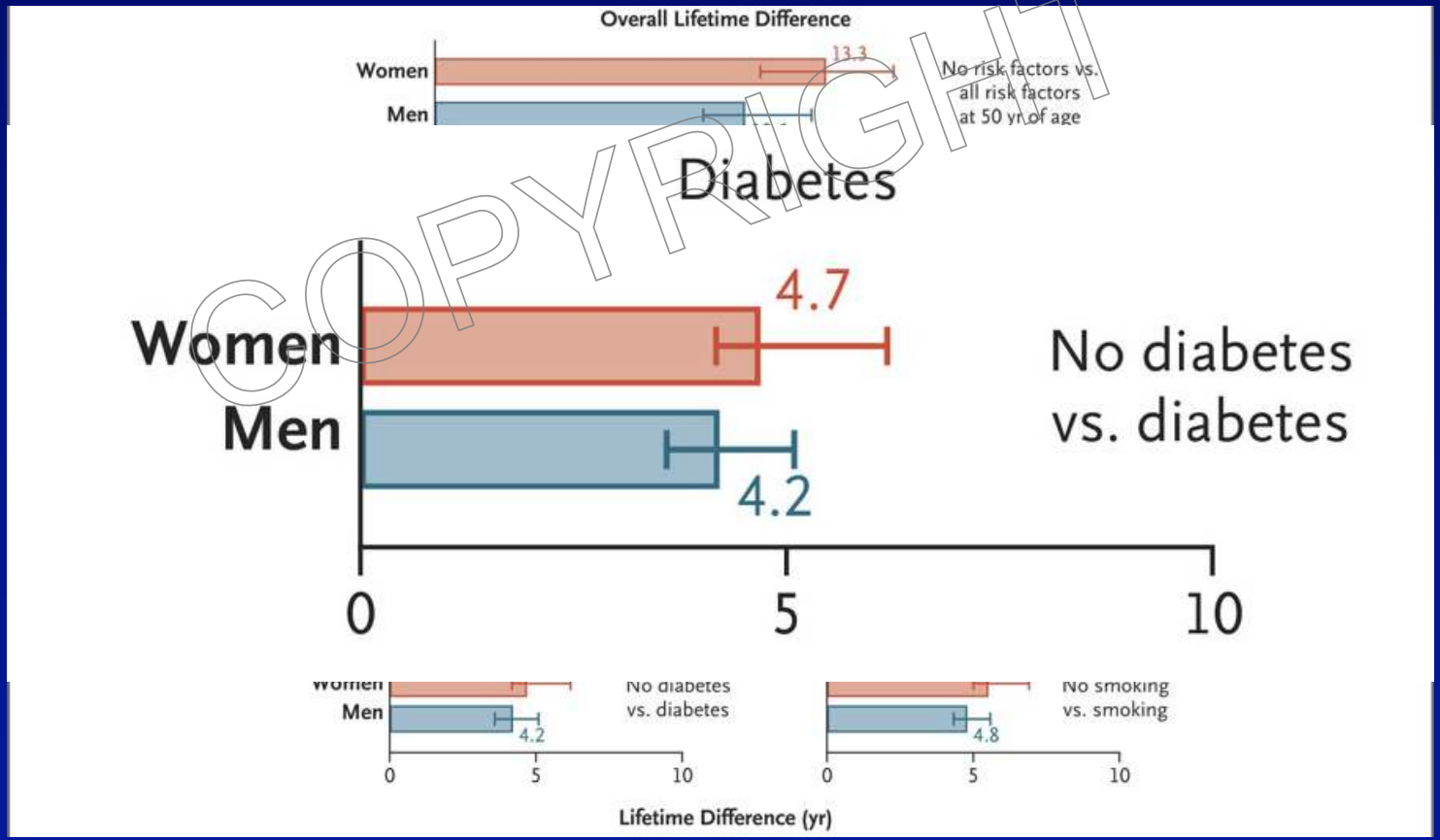
# Total Years of Life Lost






DOI: 10.1056/NEJMoa2415879

# Year of life Lost – CV Death



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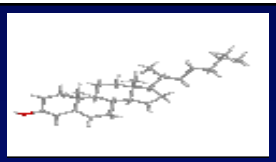
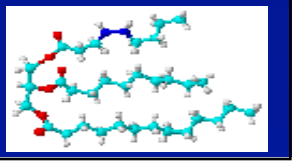
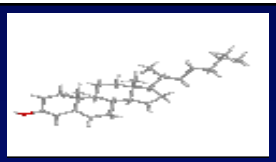


# Driving Atherosclerotic Risk





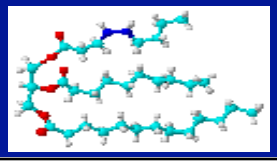
# Atherogenic Factors in DM

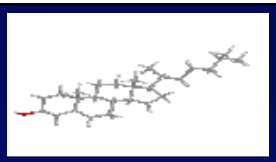
- Dysglycaemia
- Hypertension
- Abdominal obesity
- Procoagulant state
- Inflammation
- Oxidative stress
- NAFLD
- Renal dysfunction



<u>Dyslipidaemia</u>

- Increased TGRL
- Increased remnants
- Small dense LDL particles
- Increased oxidised lipoproteins
- Low HDL
- Dysfunctional HDL



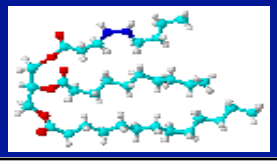


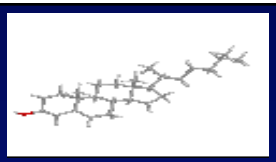
# Major Modifiable Risk Factors

- Smoking
- Glycaemia
- Blood pressure
- **Lipids**

- Sedentary lifestyle
- Diet
- Obesity…



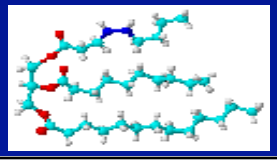


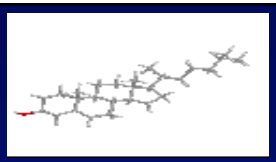


# Choose Your Target



- Non-fatal MI prevention
- 200 individuals treated for 5 years
  - Glycaemia ↓ HbA1C by 1%: 2 events prevented
  - LDLC ↓ by 1 mmol/L : 8.2 events prevented
  - BP systolic ↓ 4 mm Hg: 12.5 events prevented



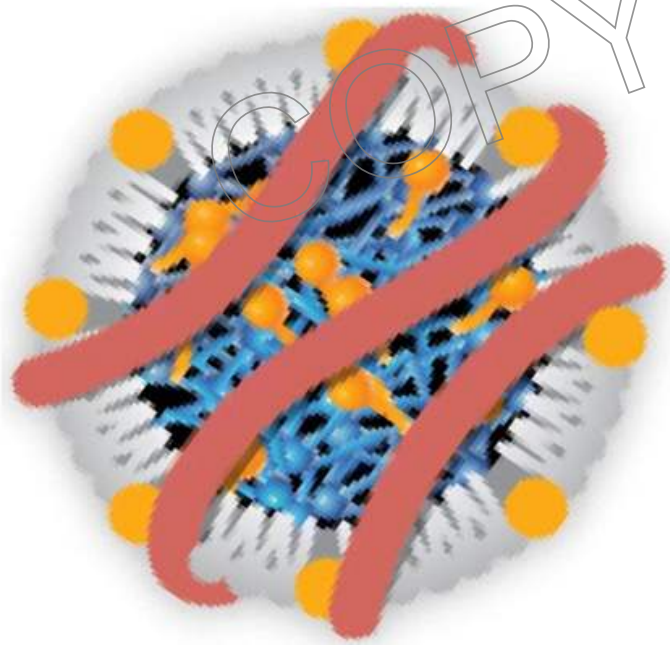


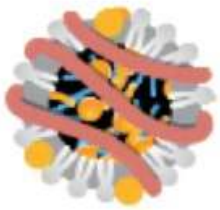
# Lipoproteins in DM

Increased TG-rich large VLDL

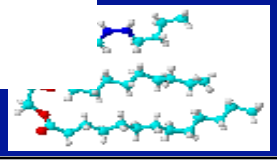
small dense LDL

low HDL





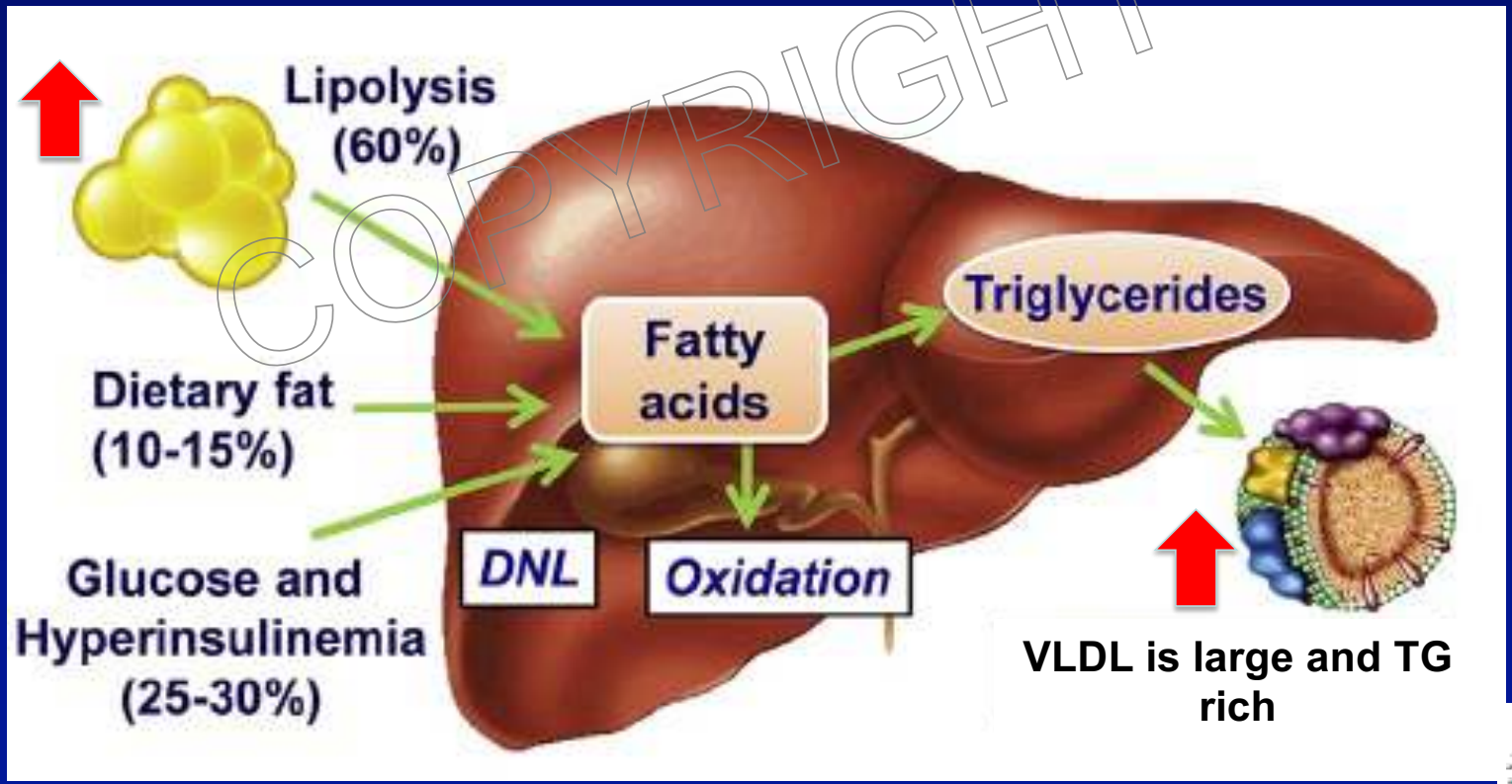




https://doi-org.ezproxy.uct.ac.za/10.1007/s11886-021-01450-1

# Pathophysiology

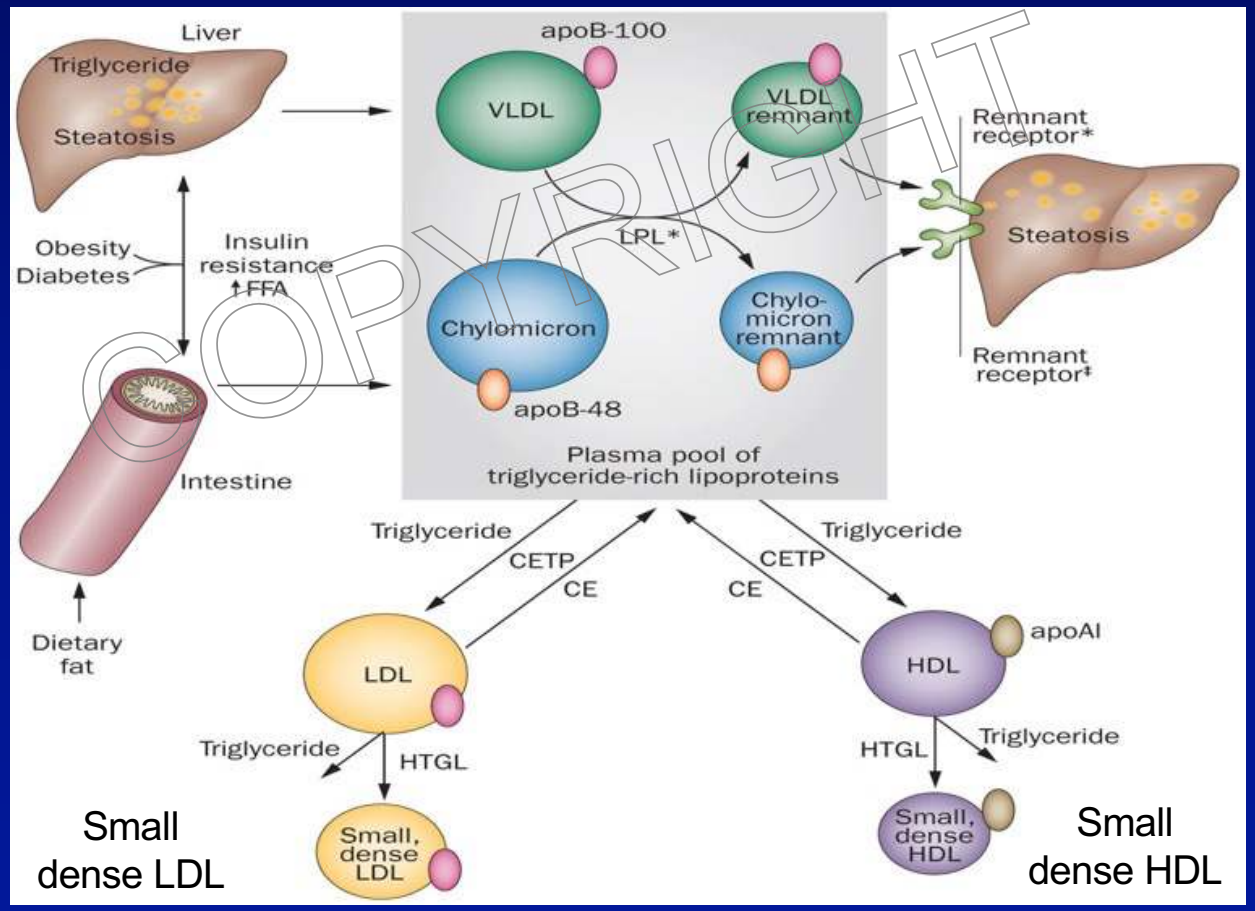
Increased fat mass/ upper body





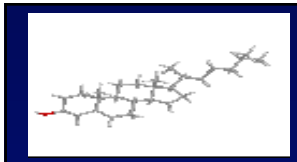

*Atherosclerosis 2015; 239:483-495*

# Lipoprotein Remodeling

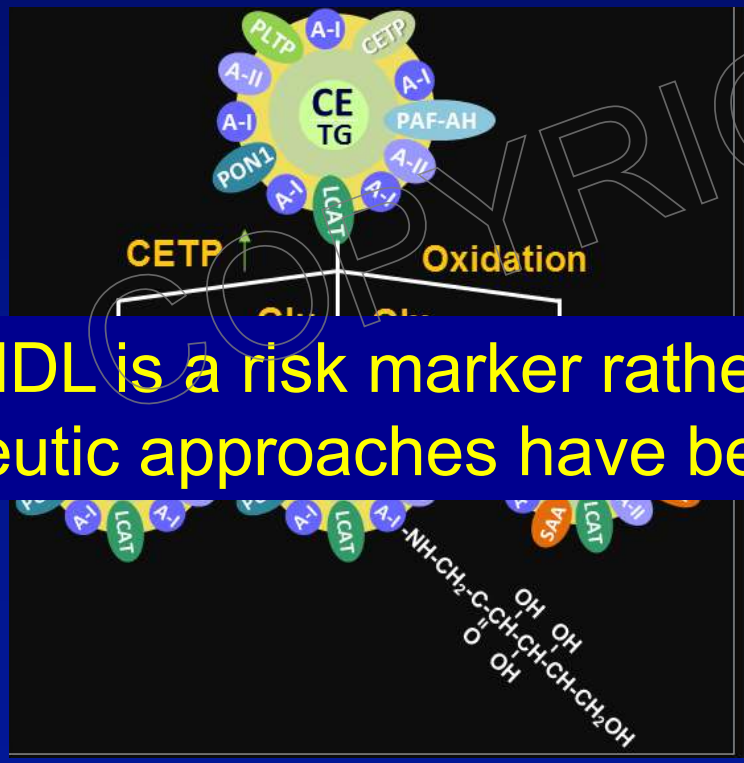





*Nat. Rev. Cardiol. doi:10.1038/nrcardio.2013.140*



# Dysfunctional HDL in DM

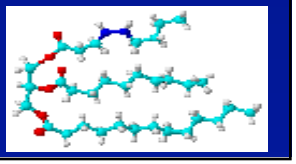



- ABCA1-mediated cholesterol efflux ↓
- LCAT activation ↓
- PON1 ↓
- Anti-oxidative activity ↓
- Protection against ICAM-1 expression ↓
- Inhibition of neutrophil infiltration ↓
- Stimulation of re-endothelialization ↓

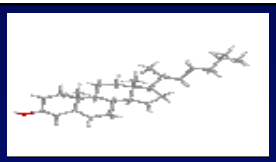


HDL is a risk marker rather than a risk factor

Therapeutic approaches have been disappointing thus far

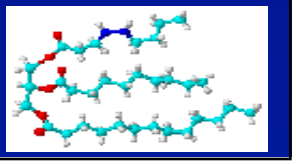


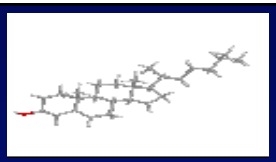
https://www.medscape.org/noscan/slideshow/760297#32



# Therapeutic Approaches



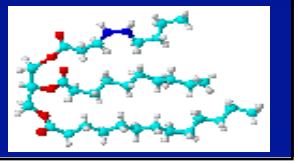



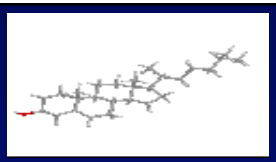




# LDLC

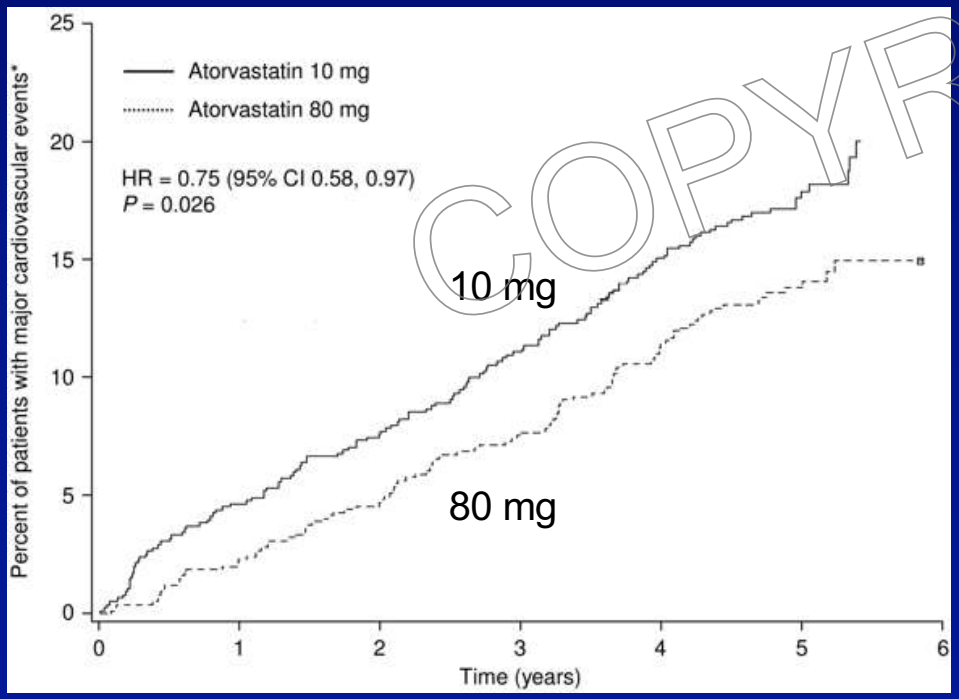
Tried and Trusted Target

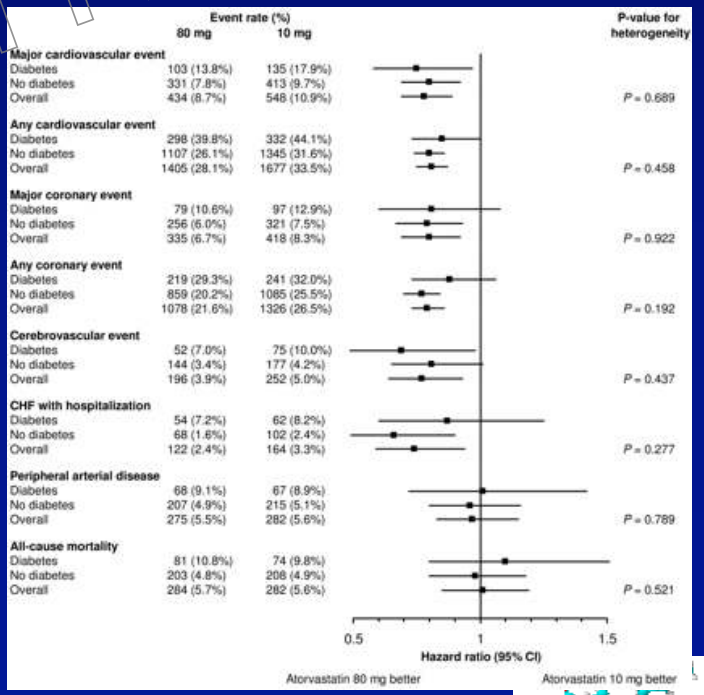




# Statins: TNT Study

## Participants with DM: Increased event rates compared to non-diabetics

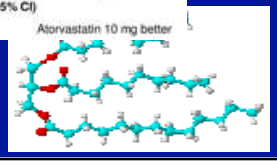


| | Event rate (%) 80 mg | 10 mg | P-value for heterogeneity |
|---|---|---|---|
| **Major cardiovascular event** | | | |
| Diabetes | 103 (13.8%) | 135 (17.9%) | |
| No diabetes | 331 (7.8%) | 413 (9.7%) | |
| Overall | 434 (8.7%) | 548 (10.9%) | P = 0.689 |
| **Any cardiovascular event** | | | |
| Diabetes | 298 (39.8%) | 332 (44.1%) | |
| No diabetes | 1107 (26.1%) | 1345 (31.6%) | |
| Overall | 1405 (28.1%) | 1677 (33.5%) | P = 0.458 |
| **Major coronary event** | | | |
| Diabetes | 79 (10.6%) | 97 (12.9%) | |
| No diabetes | 256 (6.0%) | 321 (7.5%) | |
| Overall | 335 (6.7%) | 418 (8.3%) | P = 0.922 |
| **Any coronary event** | | | |
| Diabetes | 219 (29.3%) | 241 (32.0%) | |
| No diabetes | 859 (20.2%) | 1085 (25.5%) | |
| Overall | 1078 (21.6%) | 1326 (26.5%) | P = 0.192 |
| **Cerebrovascular event** | | | |
| Diabetes | 52 (7.0%) | 75 (10.0%) | |
| No diabetes | 144 (3.4%) | 177 (4.2%) | |
| Overall | 196 (3.9%) | 252 (5.0%) | P = 0.437 |
| **CHF with hospitalization** | | | |
| Diabetes | 54 (7.2%) | 62 (8.2%) | |
| No diabetes | 68 (1.6%) | 102 (2.4%) | |
| Overall | 122 (2.4%) | 164 (3.3%) | P = 0.277 |
| **Peripheral arterial disease** | | | |
| Diabetes | 68 (9.1%) | 67 (8.9%) | |
| No diabetes | 207 (4.9%) | 215 (5.1%) | |
| Overall | 275 (5.5%) | 282 (5.6%) | P = 0.789 |
| **All-cause mortality** | | | |
| Diabetes | 81 (10.8%) | 74 (9.8%) | |
| No diabetes | 203 (4.8%) | 208 (4.9%) | |
| Overall | 284 (5.7%) | 282 (5.6%) | P = 0.521 |

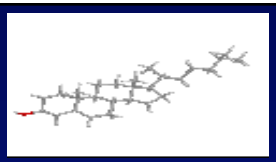


No heterogeneity

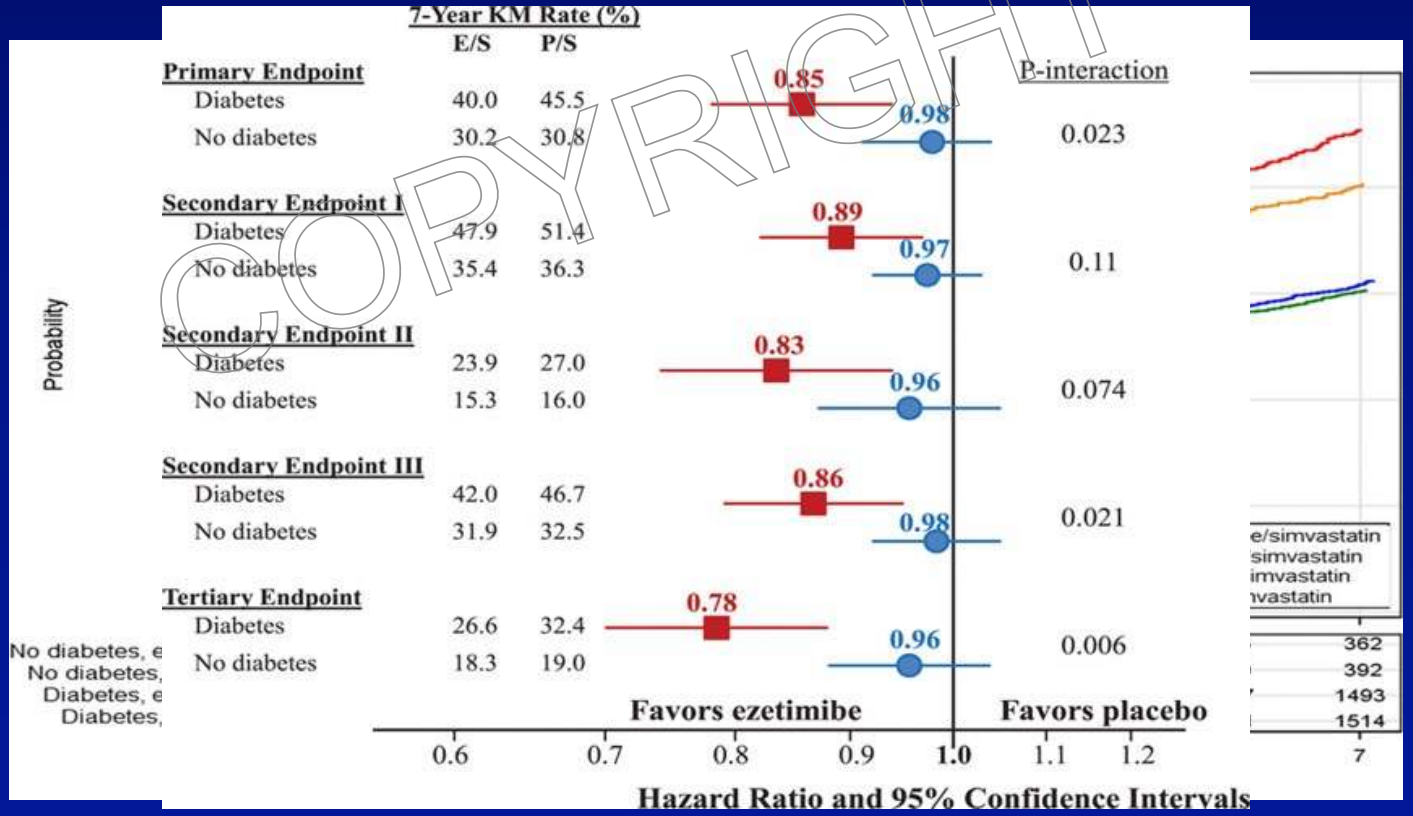




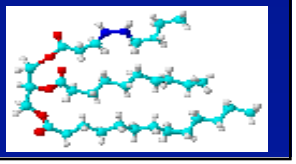
*Diabetes Care. 2006;29(6):1220-1226. doi:10.2337/dc05-2465*



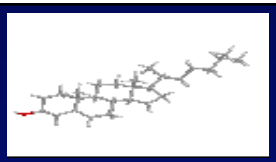
# Ezetimibe: IMPROVE-IT





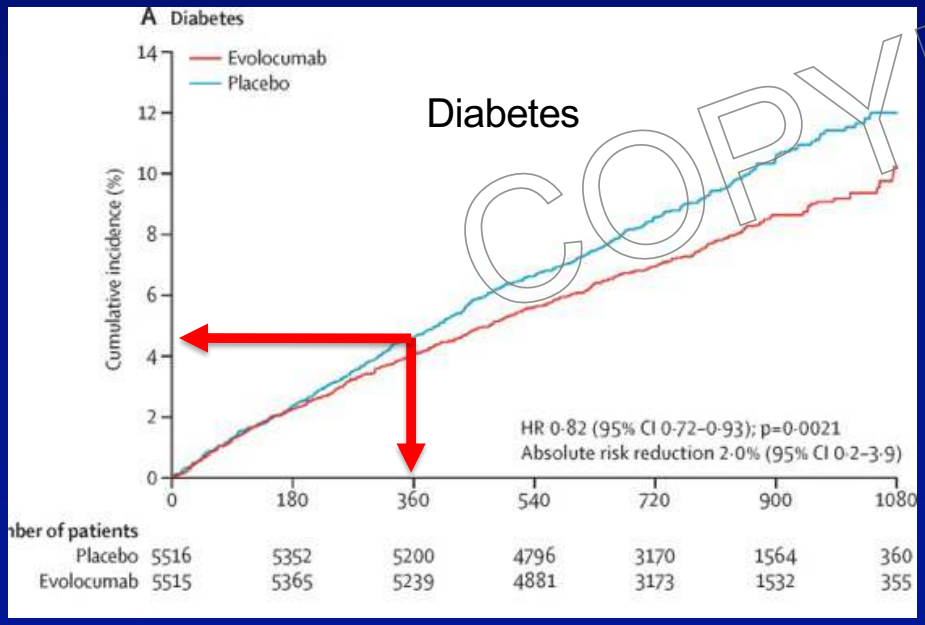



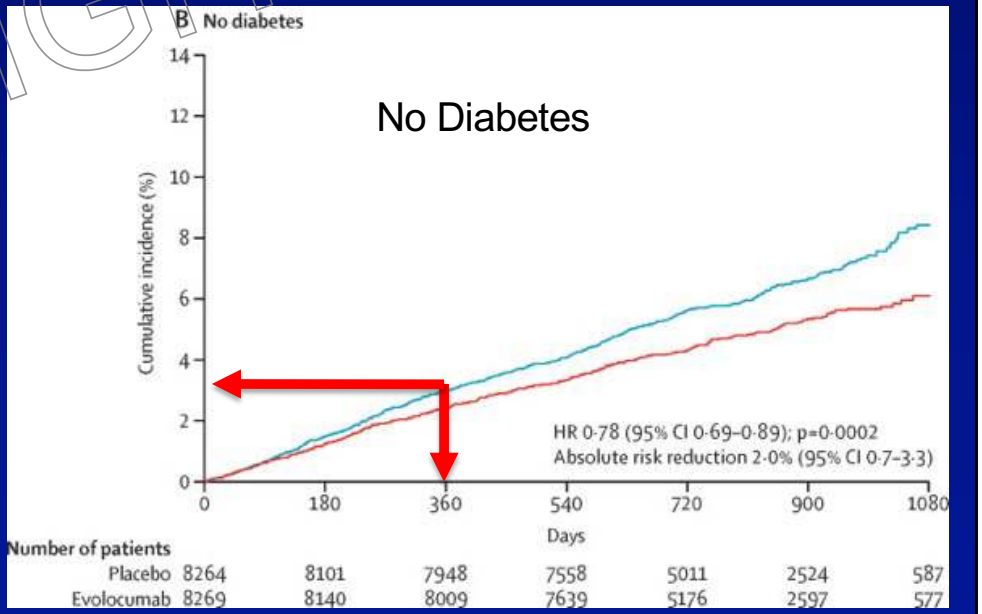
DOI: (10.1161/CIRCULATIONAHA.117.030950)

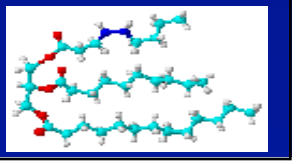


# PCSK9 Inhibitors: Evolocumab

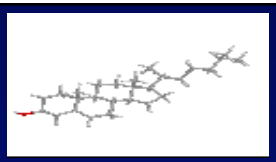




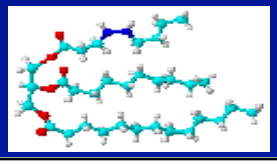
*Lancet Diabetes & Endocrinology, The, 2017-12-01, Volume 5, Issue 12, Pages 941-950,*



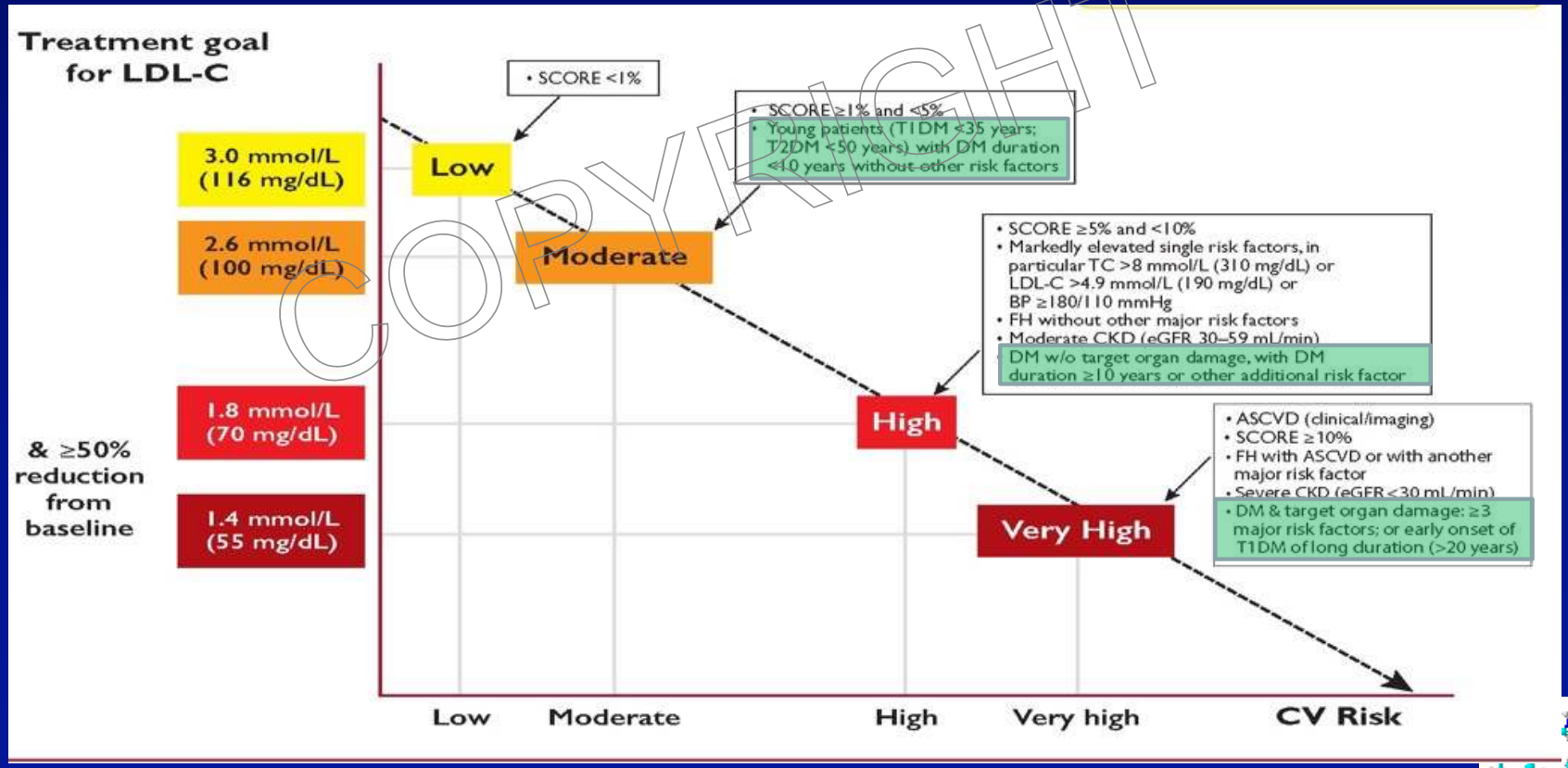
# LDLC Summary

- Remains the primary target
- Goals
  - <1.4 mmol/L for very high risk
  - <1.8 mmol/L for high risk
  - At least 50% reduction from baseline
- Statins
  - Ezetimibe
  - PCSK9 inhibition
  - Others (bempedoic acid…)





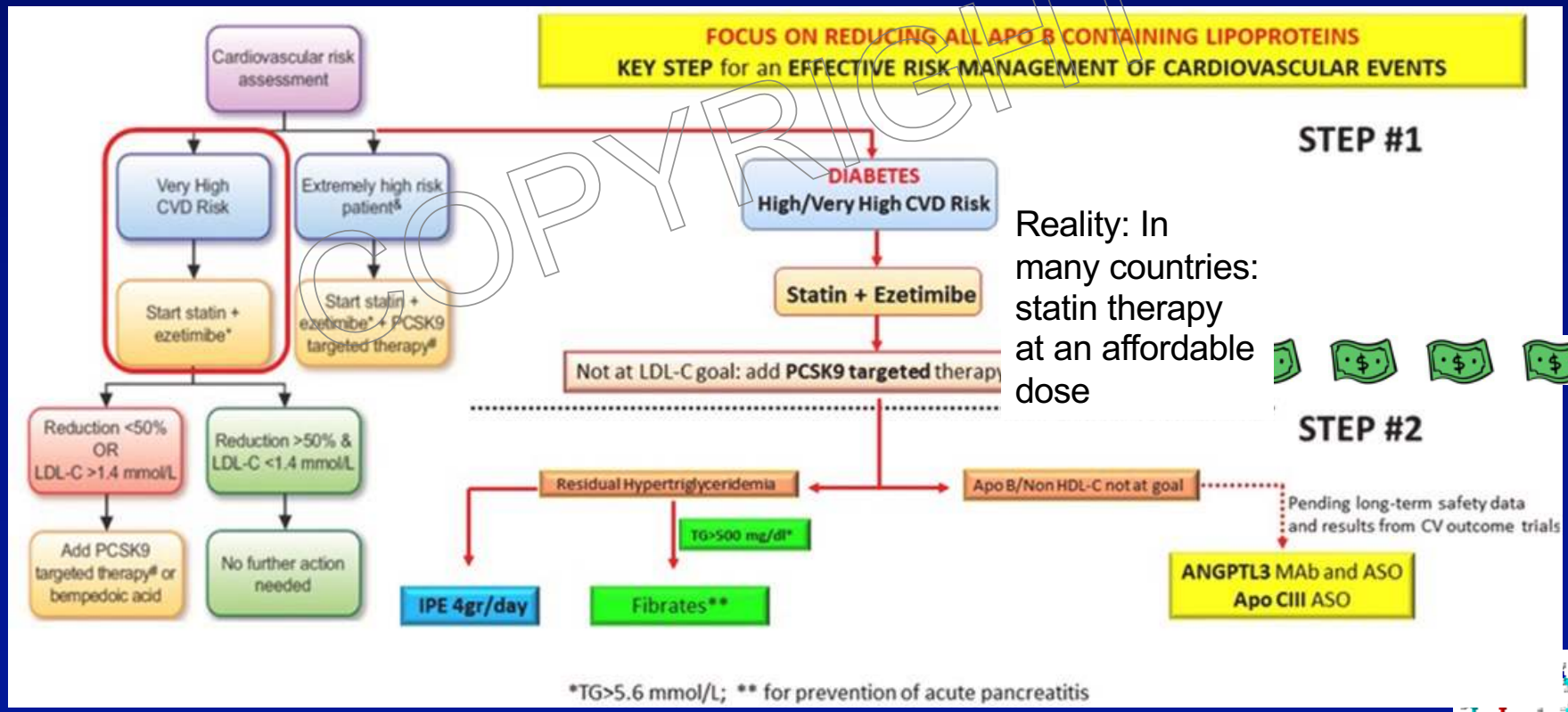
# Lipid Guidelines






*Eur Heart J, Volume 41, Issue 1, 1 January 2020, Pages 111–188, https://doi.org/10.1093/eurheartj/ehz455*

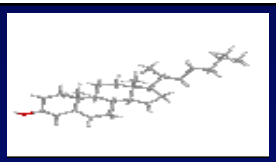
# Getting to Target



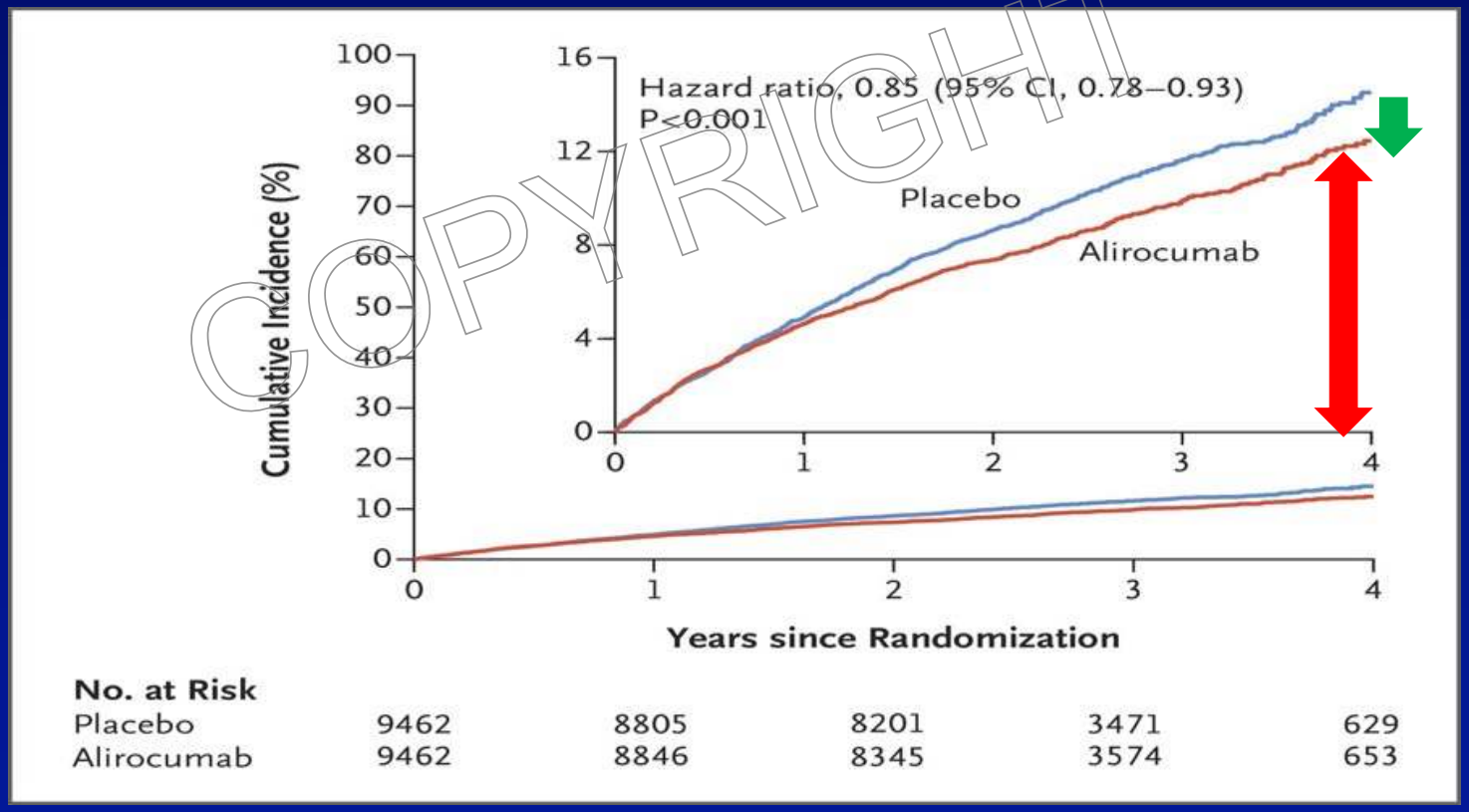

Reality: In many countries: statin therapy at an affordable dose



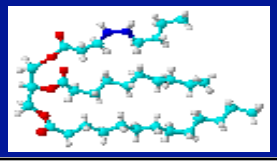
doi: 10.1016/j.atherosclerosis.2023.117313.



# Residual Risk

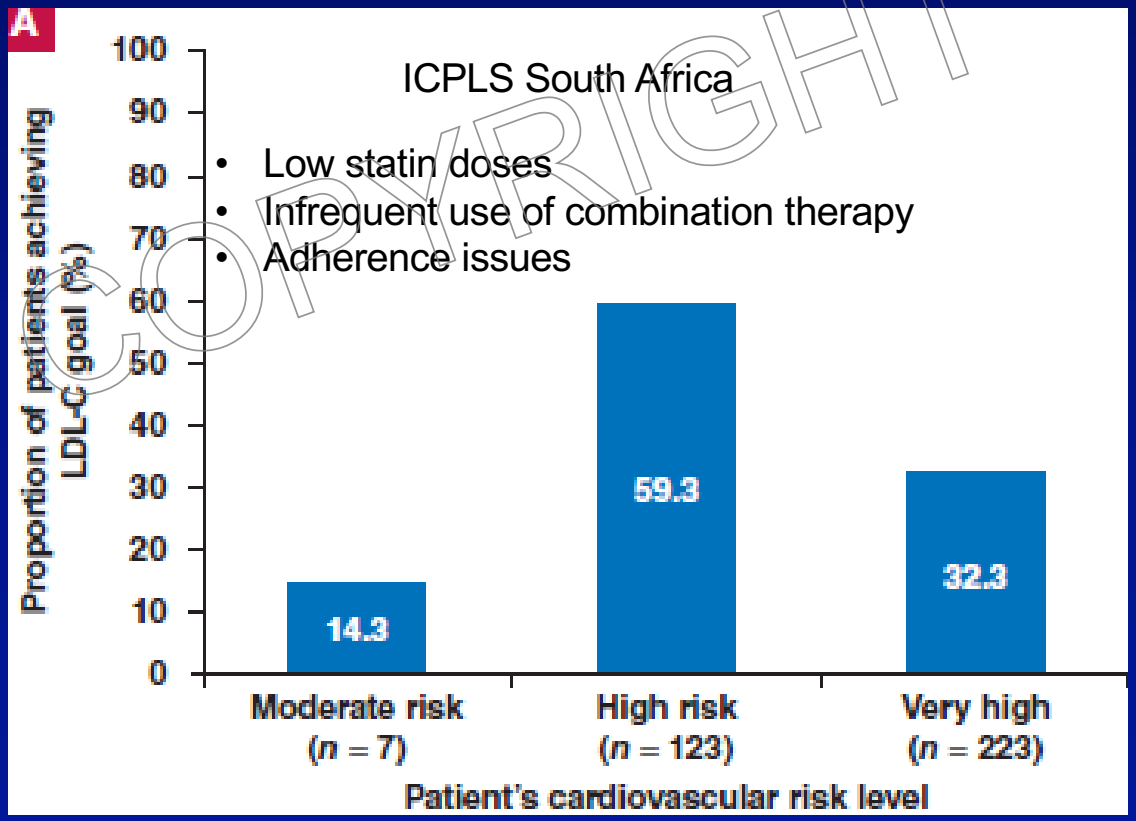




*GG Schwartz et al. N Engl J Med 2018;379:2097-2107.*

# ‘Too Little’

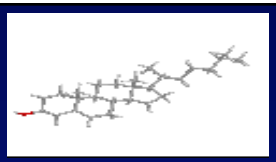



ICPLS South Africa

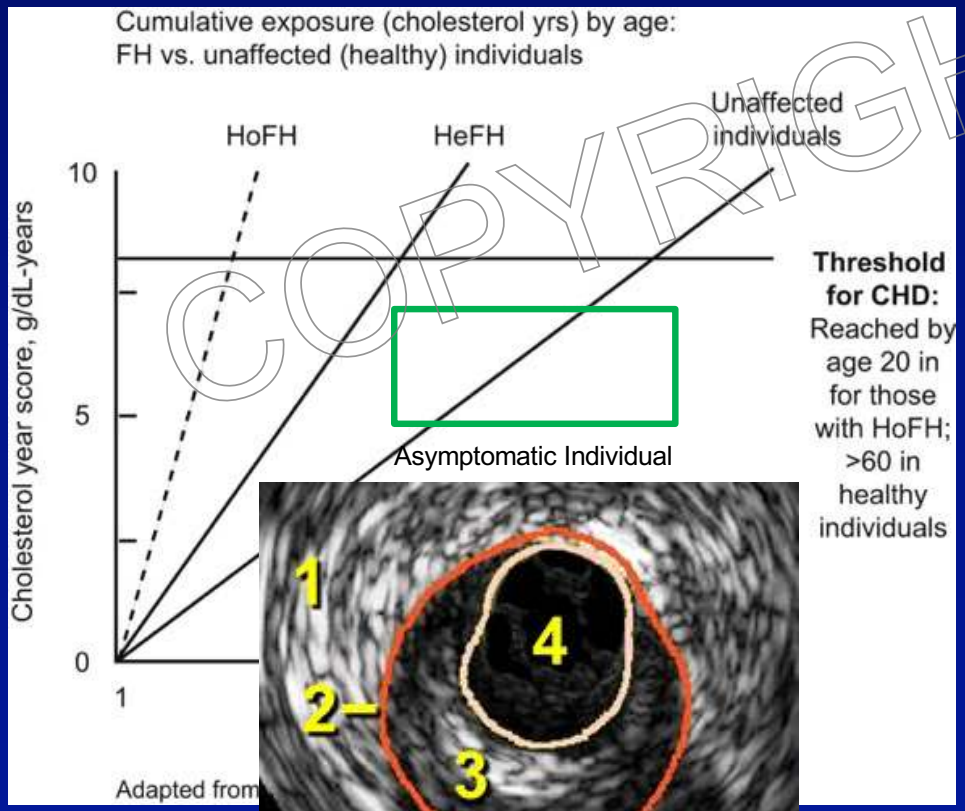
- Low statin doses
- Infrequent use of combination therapy
- Adherence issues



*Cardiovascular Journal of Africa, Volume 30 Number 1, Jan / Feb 2019, p. 15 - 23*



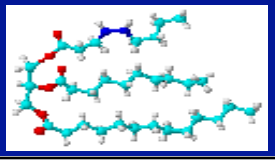
# ‘Too Late’



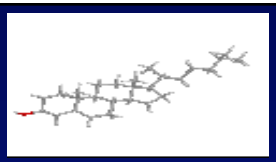



Modified by

- Diabetes
- Smoking
- HT
- Inflammation
- ..



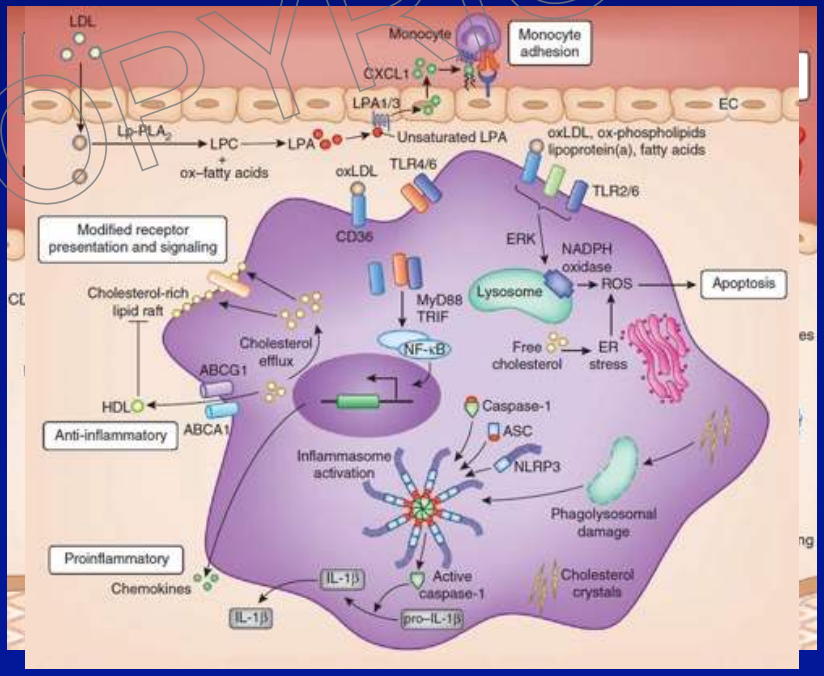
*Atherosclerosis. 2012 Aug;223(2):262-8*

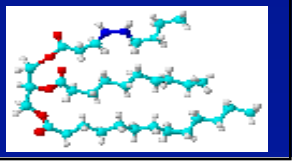


# ‘Too Simplistic’

- Multifactorial and complex pathogenesis

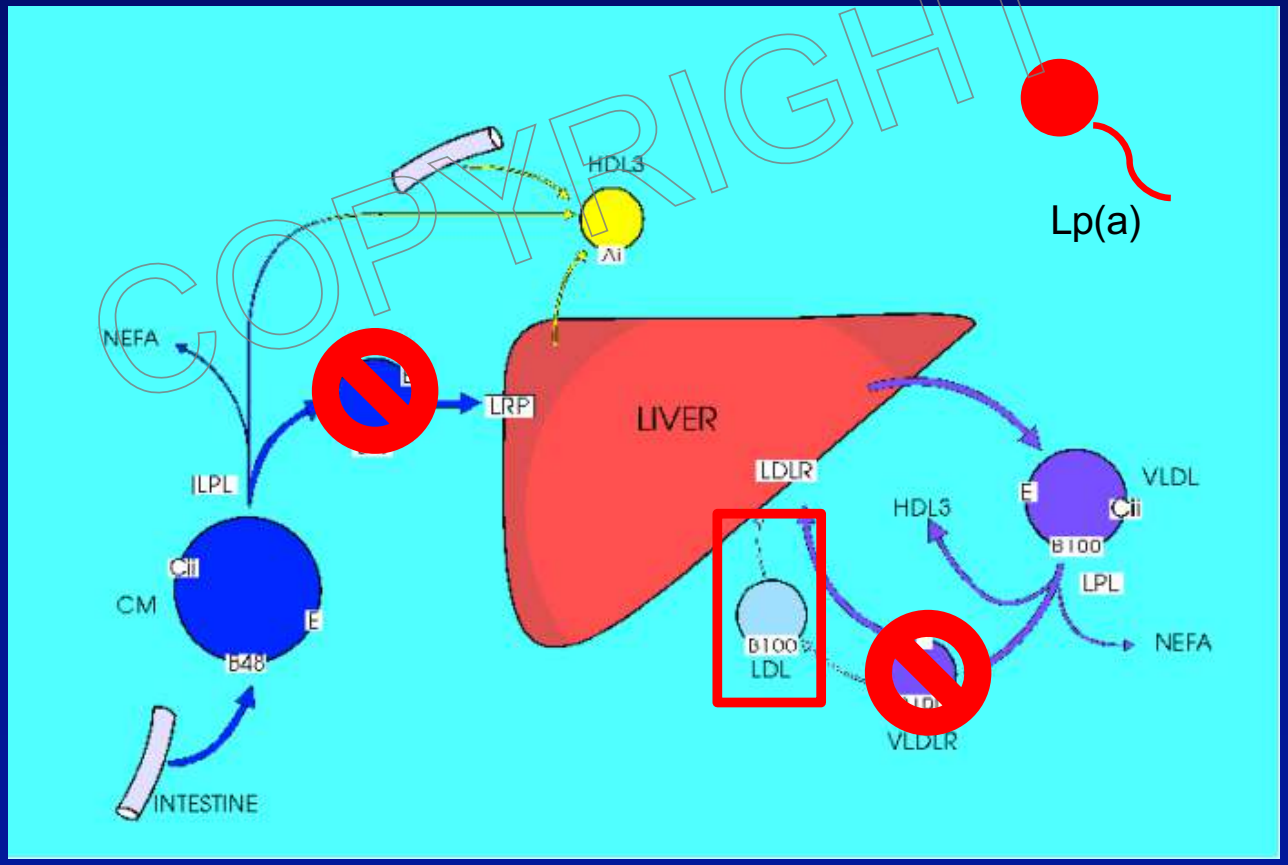


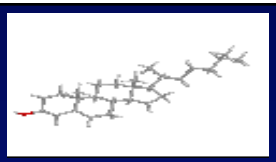


*Nature Medicine 17, 1410–1422 (2011)*

# ‘More than LDL’



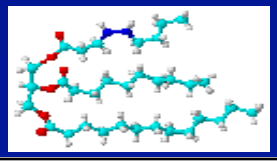


# Beyond LDL

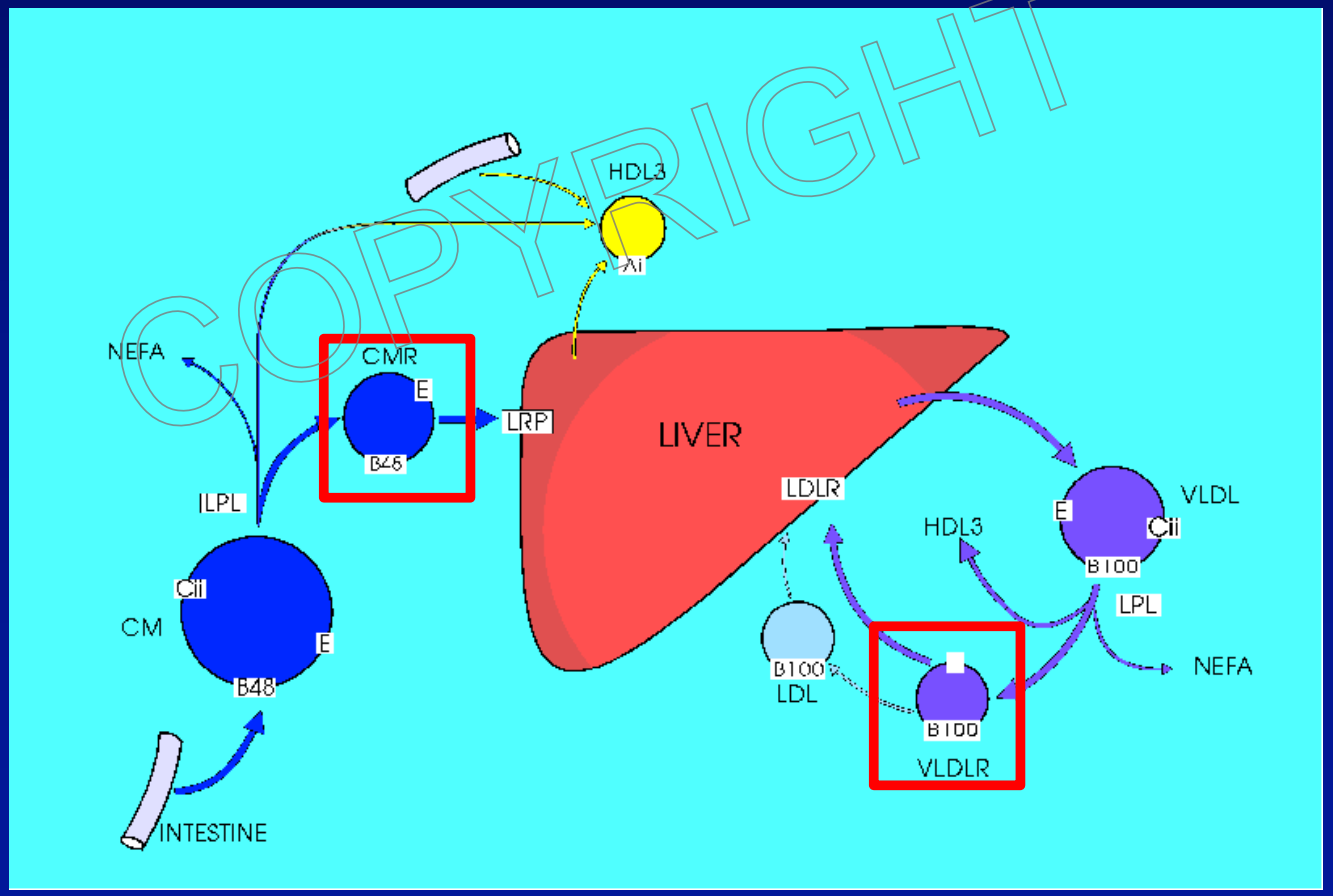
- Lp(a)
  - Limited data from small apheresis studies
  - Novel therapeutics in clinical trials
- HDL
  - Evidence suggests HDL is more of a risk marker than a risk factor
- Remnant lipoproteins

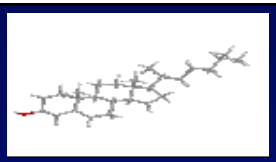
The HbA1C of TGRL metabolism





# TGRL Metabolism

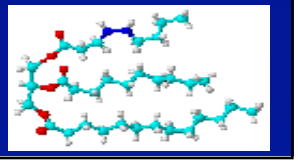


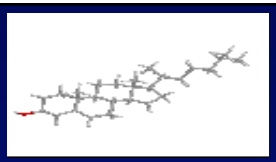


# Moderate HyperTG and CVD

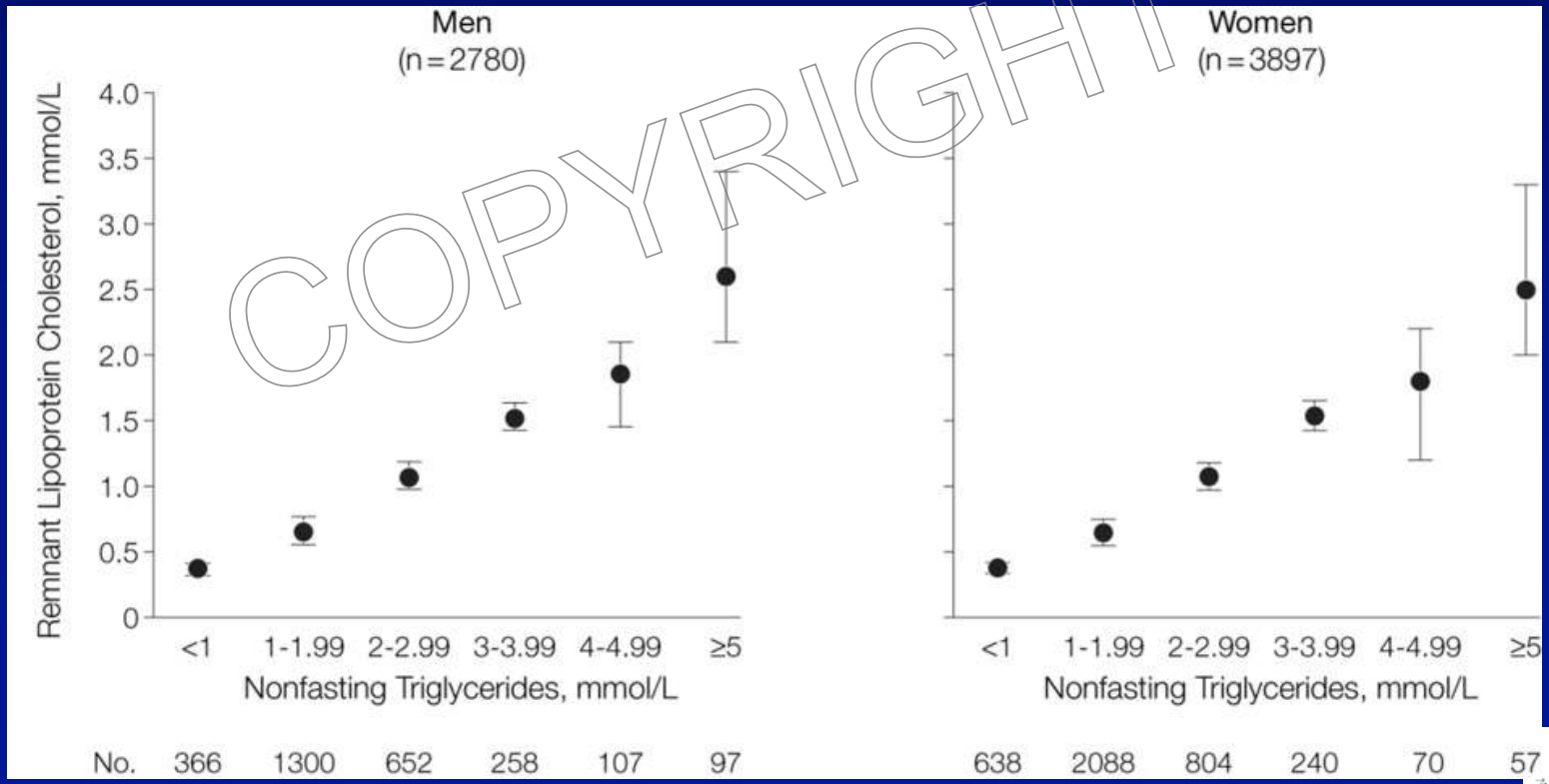


- Remnant particles are TG-rich compared to HDL and LDL
- Generally fasting samples do not contain chylomicrons and nascent VLDL is low
- Moderate (2-5 mmol/L) hypertriglyceridaemia therefore marks increased remnants
- In severe hyperTG chylomicrons and large VLDL dominate

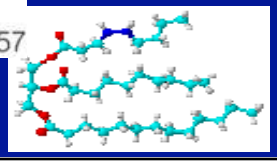




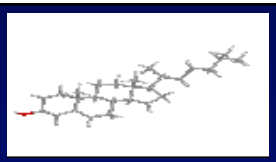
# Remnant Cholesterol





*JAMA. 2007;298(3):299-308. doi:10.1001/jama.298.3.299*

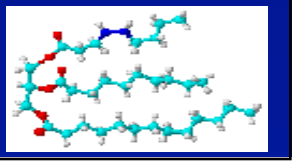


# Cholesterol in Lipoproteins

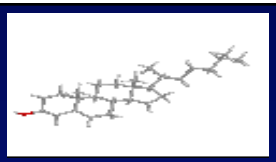
| R<br>p-value | Remnant cholesterol | HDL cholesterol | LDL cholesterol | Triglycerides |
|---|---|---|---|---|
| Remnant cholesterol | | -0.45 | 0.12 | 0.96 |
| HDL cholesterol | p<0.001 | | -0.12 | -0.42 |
| LDL cholesterol | p<0.001 | p<0.001 | | 0.12 |
| Triglycerides | p<0.001 | p<0.001 | p<0.001 | |
| Number | 14,906 | 28,041 | 10,722 | 3,826 | 1,418 | 982 |

7.0



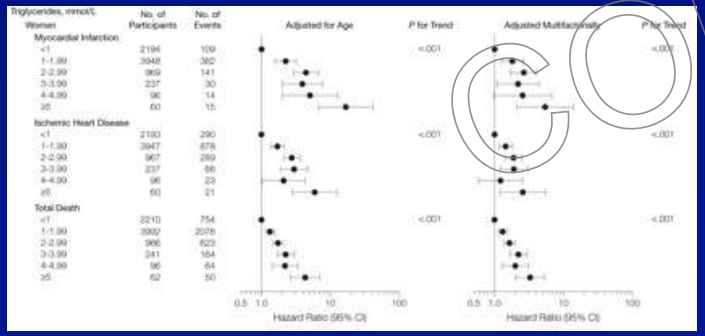


https://doi.org/10.1016/j.jacc.2012.08.1026

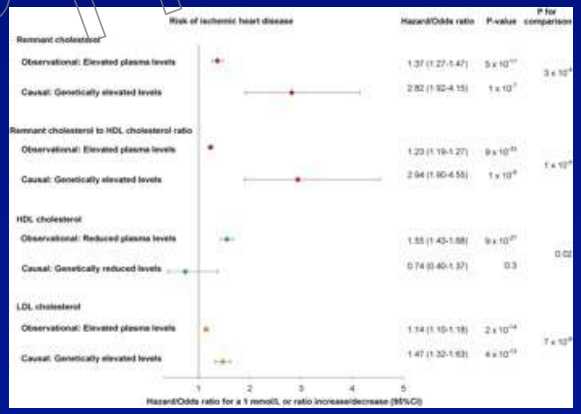


# Evidence

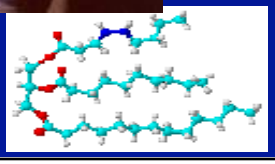
## Copenhagen Heart Study Epidemiology




## Mendelian Randomization



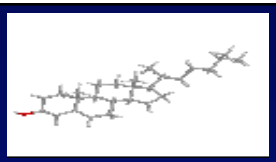

## Monogenic Disorder



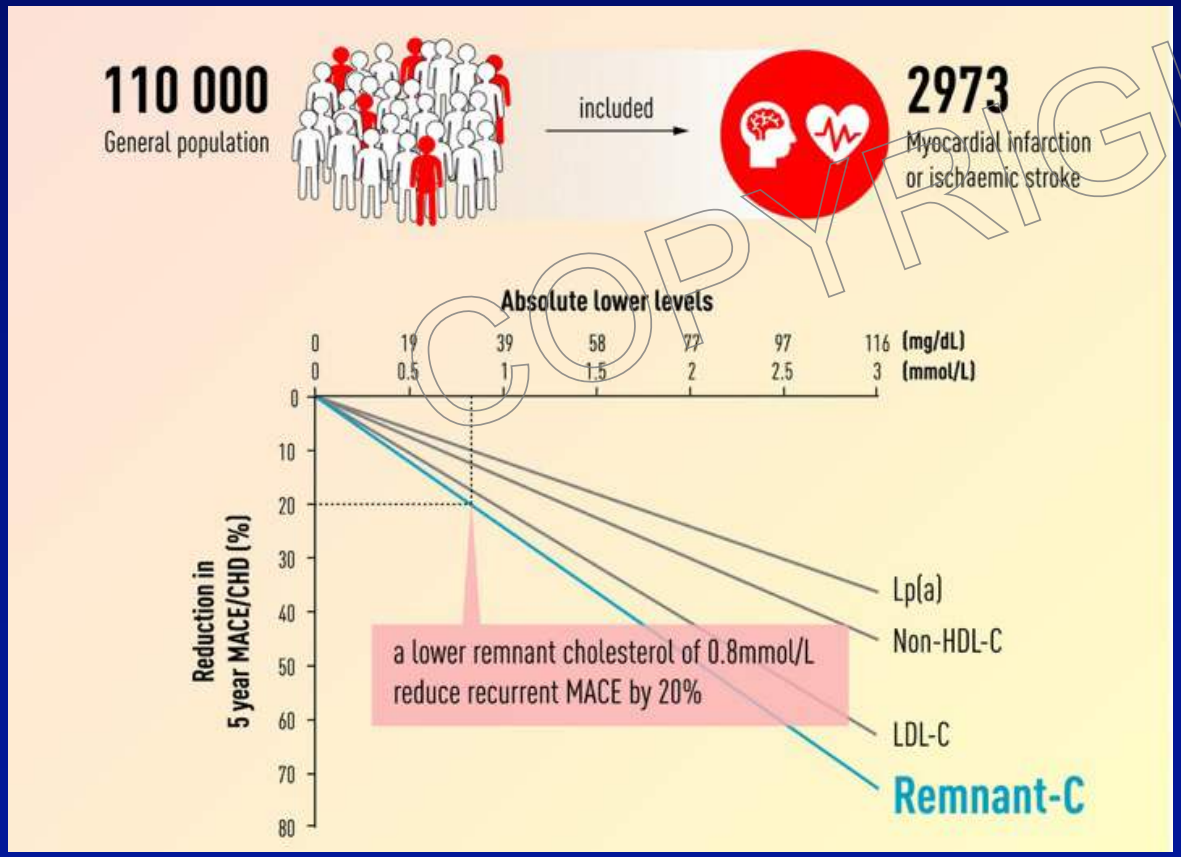


*JAMA. 2007;298(3):299-308. doi:10.1001/jama.298.3.299*

*https://doi.org/10.1016/j.jacc.2012.08.1026*

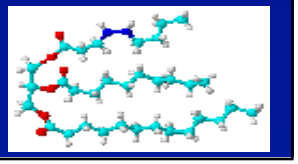


# Magnitude of Effect



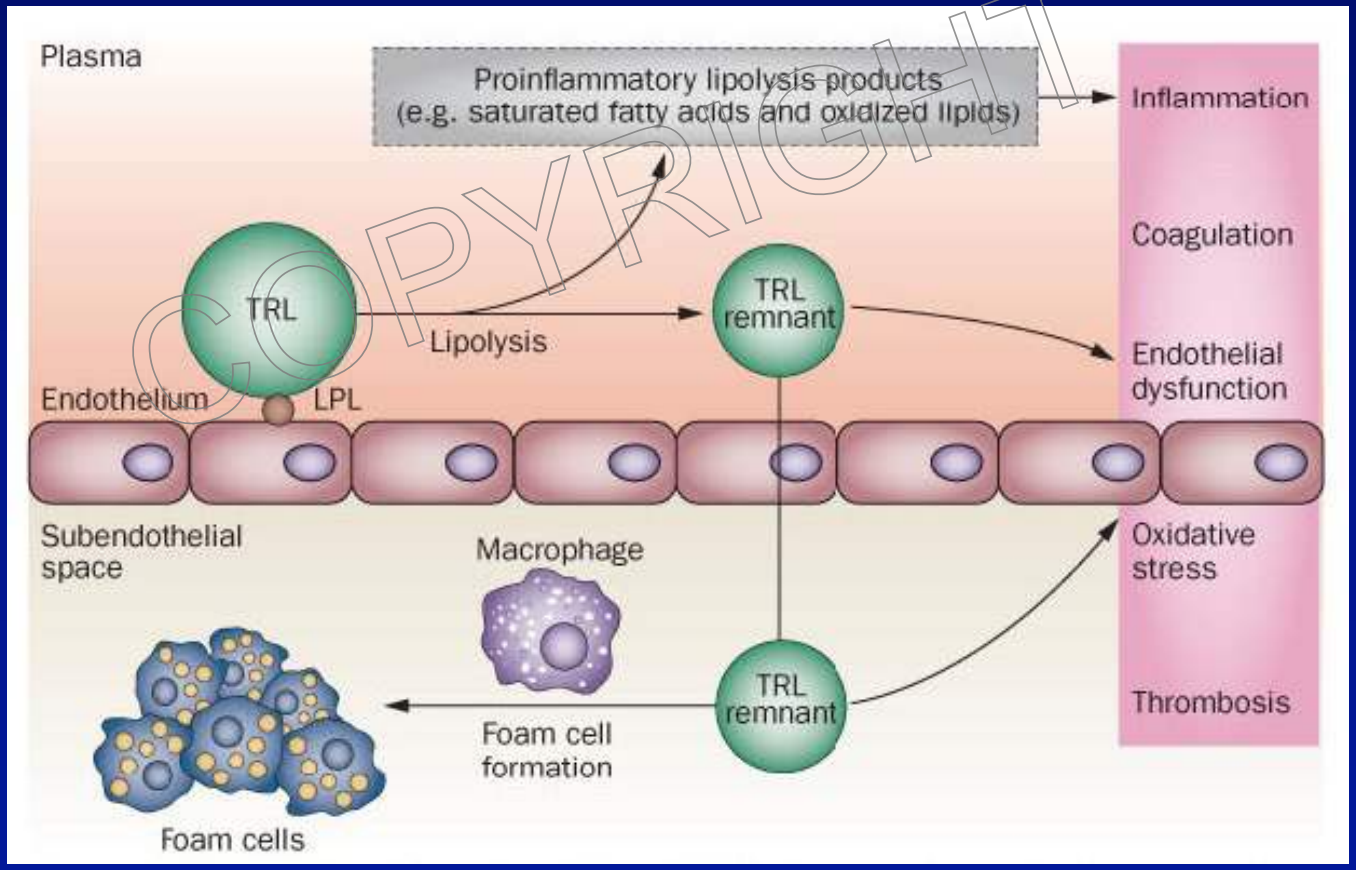



Reducing remnant cholesterol by 0.8 mmol/L is expected to reduce MACE by 20%



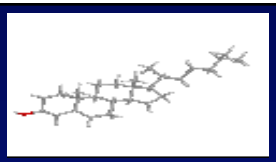
https://doi.org/10.1111/joim.13059

# Pathophysiology



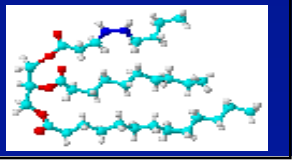


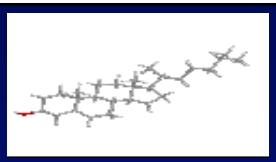

*Nat Rev Cardiol. 2013 Nov;10(11):648-61.*



# Drug Management



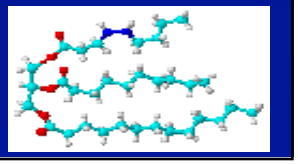



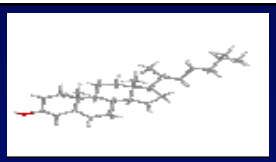


# Statin + X ?



Does adding a second agent to patients treated with aggressive statin therapy further reduce CV disease?



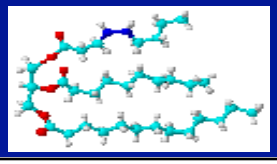


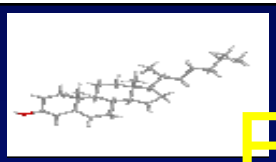
# X

- Fibrates
- Niacin
- Omega-3

- ApoC3 inhibition
- ANGPTL3 inhibition
- FGF21 analogues



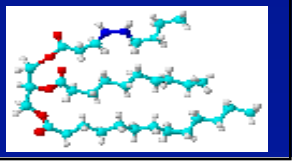




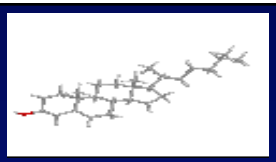
# Fibrates: Reanalysis of Older Studies

| | Study type | Population | No. | Study drug | Comparator | Primary outcome | Results | Additional findings |
|---|---|---|---|---|---|---|---|---|
| HHS (1987) | RCT | Dyslipidemia | 4,081 | Gemfibrozil 1,200 mg/day | Placebo | Fatal and non-fatal MI or cardiac death | 34%* reduction | |
| VA-HIT (1999) | RCT | CHD | 2,531 | Gemfibrozil 1,200 mg/day | Placebo | Non-fatal MI or coronary death | 22%* reduction | |
| BIP (2000) | RCT | CHD | 3,090 | Bezafibrate 400 mg/day | Placebo | Fatal or nonfatal MI or sudden death | 9.4% reduction (NS) | 41.8% reduction in subgroup (HDL-C <35 mg/dL, TG ≥200 mg/dL) |
| LEADER (2002) | RCT | Lower PAD | 1,568 | Bezafibrate 400 mg/day | Placebo | CHD or stroke | 4% reduction (NS) | 40% reduction of non-fatal CHD |
| FIELD (2005) | RCT | T2DM | 9,795 | Fenofibrate 200 mg/day | Placebo | CHD death or non-fatal MI | 11% reduction (NS) | 24% reduction of non-fatal MI |
| ACCORD-Lipid (2010) | RCT | T2DM | 5,518 | Simvastatin plus fenofibrate 160 mg/day | Simvastatin | Non-fatal MI, non-fatal stroke, cardiovascular death | 8% reduction (NS) | 28.6% reduction in subgroup (HDL-C ≤34 mg/dL, TG ≥204 mg/dL) |
| ACCORDION (2017) | Post-trial f/u | T2DM | 4,644 | Simvastatin plus fenofibrate 160 mg/day | Simvastatin | Non-fatal MI, non-fatal stroke, cardiovascular death | 7% reduction (NS) | 27% reduction in subgroup (HDL-C ≤34 mg/dL, TG ≥204 mg/dL) |
| Three City Study (2015) | Cohort | Elderly without CVD | 7,484 | Statins or fibrates | No lipid lowering drugs | CHD or stroke | Fibrates: 34%* reduction of stroke, 12% increase in CHD (NS) | |
| ECLIPSE-REAL (2019) | Cohort | Metabolic syndrome | 10,705 | Statin plus fenofibrate 160 mg/day | Statin monotherapy | CHD, stroke, cardiovascular death | 26%* reduction | 36% reduction in subgroup (HDL-C <34 mg/dL, TG ≥204 mg/dL) |



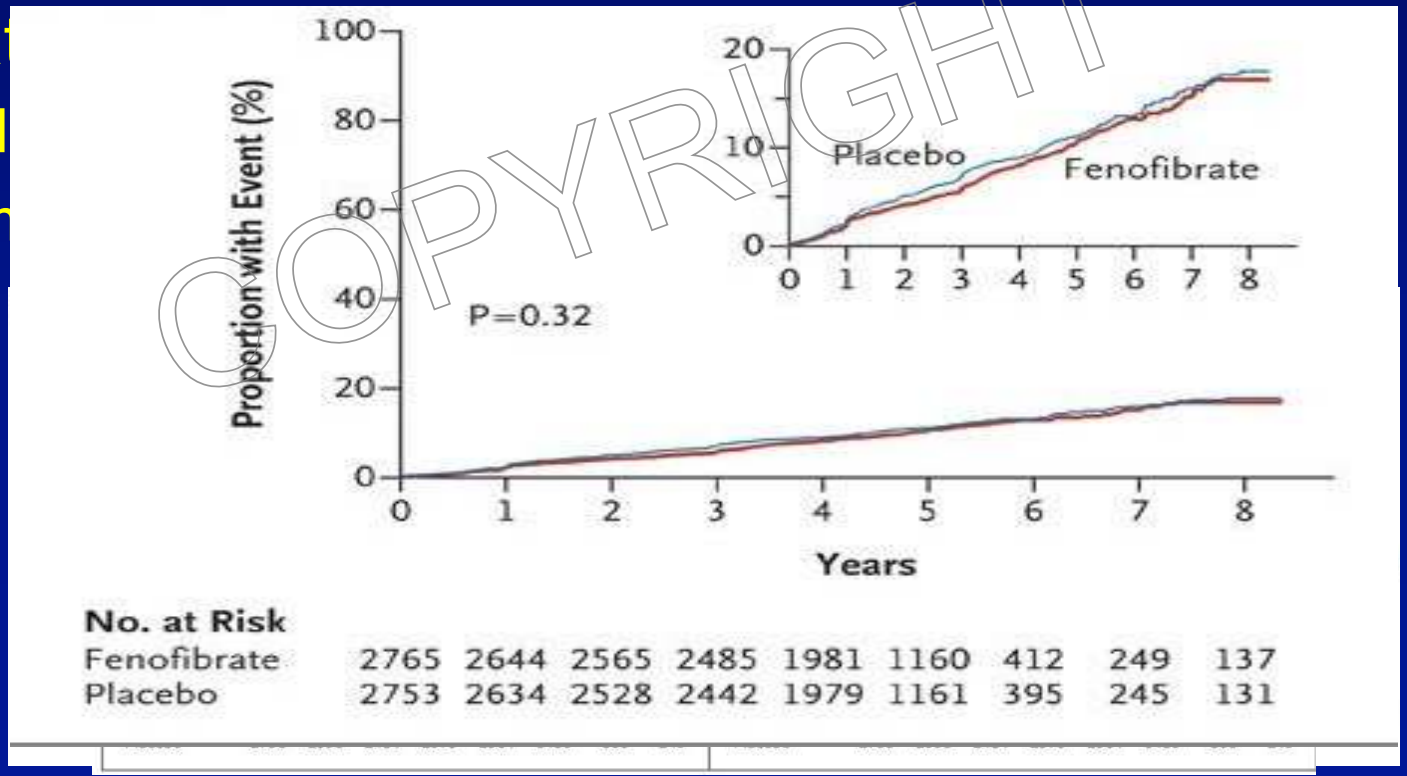


*Diabetes Metab J. 2020 Apr; 44(2): 213–221.*



# Fibrates

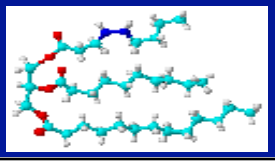
- Fibrat
  - DM
  - Sim





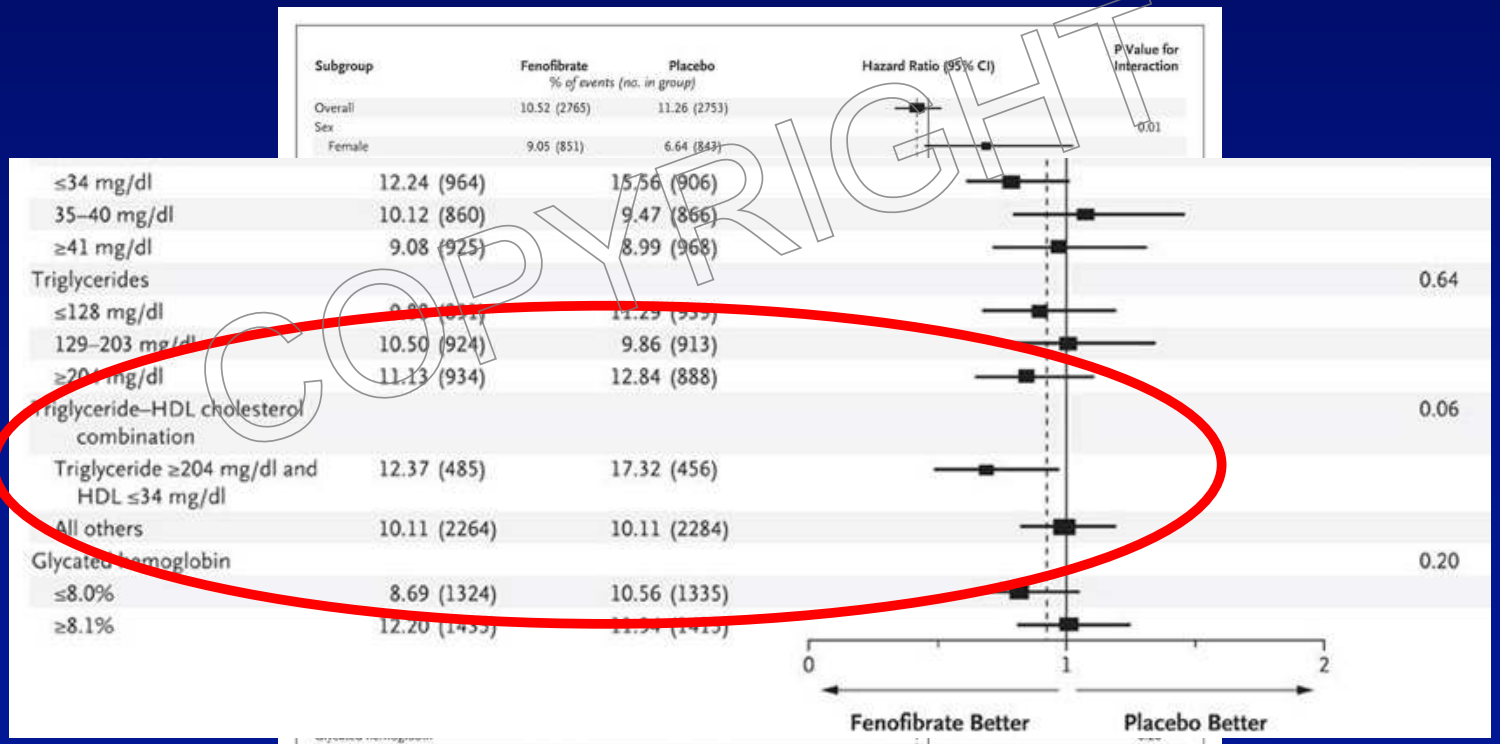

Fenofibrate 1.07 mmol/L
Placebo 1.05 mmol/L

Fenofibrate 2.07 mmol/L
Placebo 2.10 mmol/L



*N Engl J Med 2010:10.1056/NEJMoa1001282*

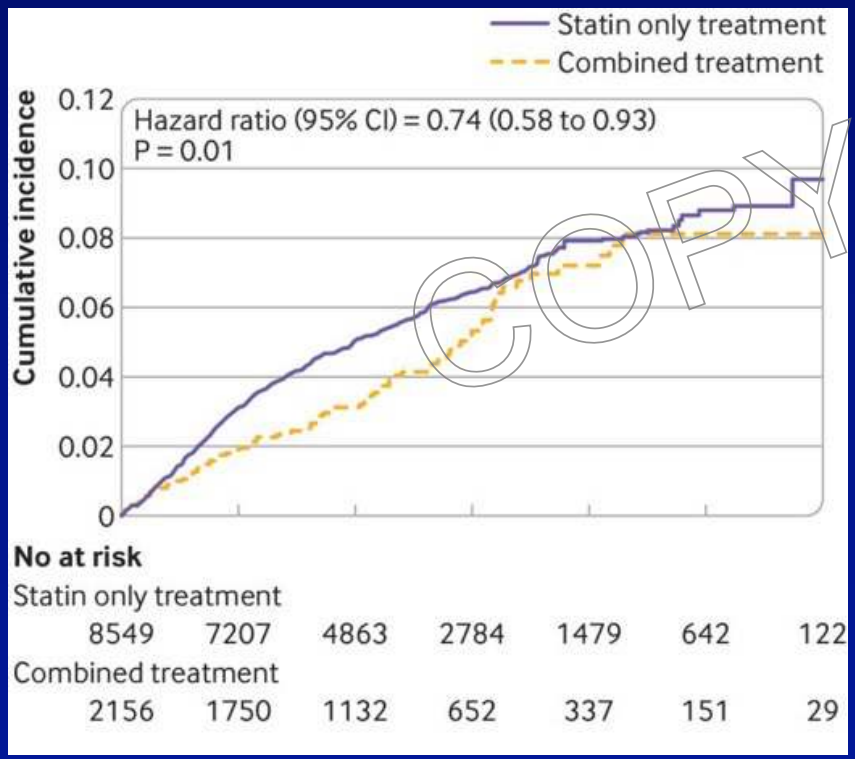
# Subgroups






*The ACCORD Study Group. N Engl J Med 2010;362:1563-1574.*

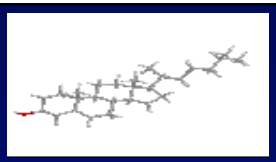
# Observational Data






- Korean patients with metabolic syndrome
- Statin vs. statin + fibrate
- Propensity weighted analysis

*BMJ 2019;366:l5125*



# Prominent Study

The NEW ENGLAND JOURNAL of MEDICINE

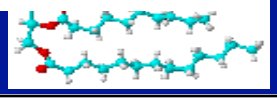


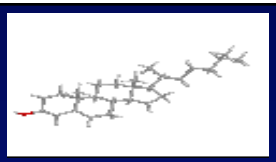
EDITORIALS

N Engl J Med 2022; 387:1923-1934

## The Fibrates Story — A Tepid End to a PROMINENT Drug

Salim S. Virani, M.D., Ph.D.





# 'Correct Population'



- High risk
- Elevated TG
- Low HDLC
- High-intensity statin therapy

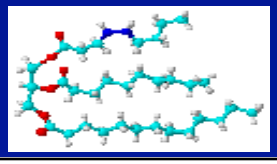
2/3 secondary prevention

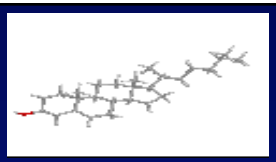
Median baseline 3.06 mmol/L

Median baseline 0.85 mmol/L

2/3 on high intensity statin

LDLC 2.04 mmol/L

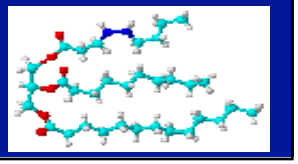


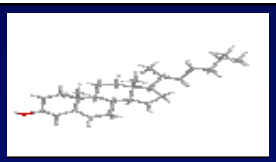


# Lipid Treatment Effects

| | |
|---|---|
| Triglycerides | -26.2% |
| Remnant cholesterol | -25.6% |
| VLDL-C | -25.2% |
| HDL-C | +5.1% |
| LDL-C | +12.3% |
| Non HDLC | -0.2% |
| apoB | +4.8% |

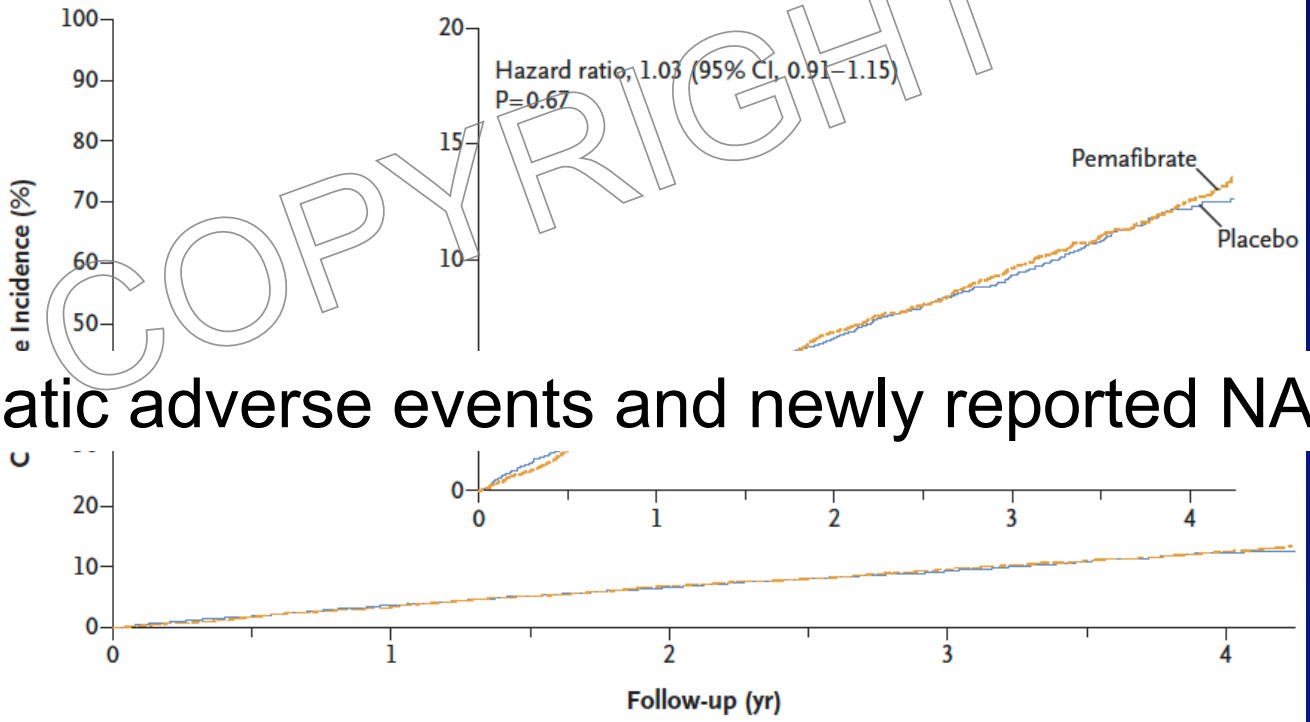




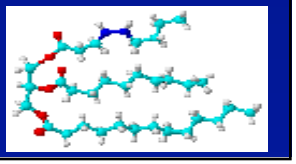


# Outcomes

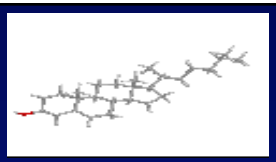





Less hepatic adverse events and newly reported NAFLD



*N Engl J Med 2022; 387:1923-1934*

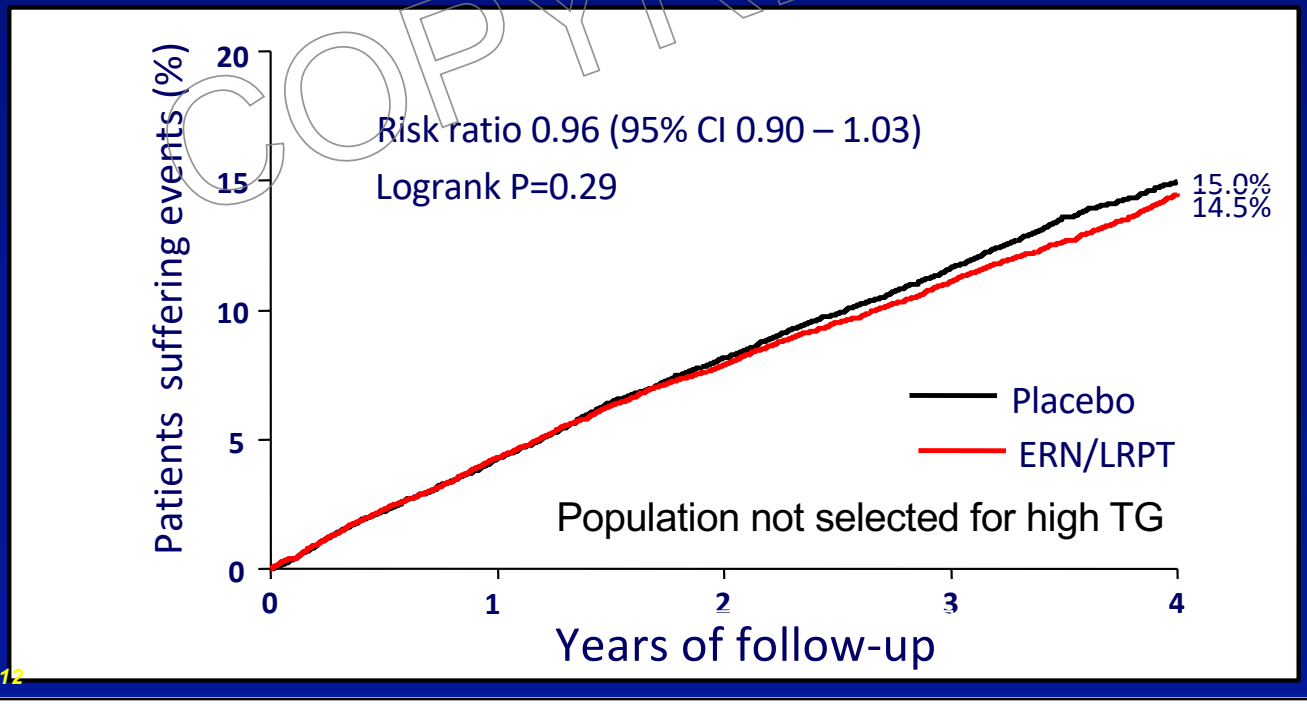


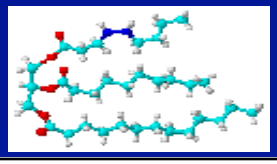
# Niacin: HPS II –THRIVE

– Simvastatin ± extended-release niacin

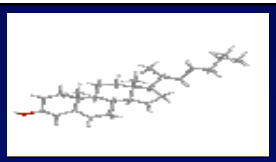
No subgroups with benefit





N Engl J Med 2014;371:203-212



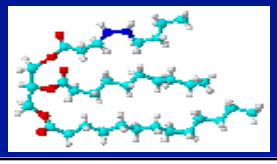
# Omega-3 Fatty Acids

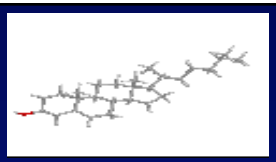
- Epidemiological observations of populations with a high marine fish intake

- GISSI Prevenzione HF
- JELIS

- Multiple subsequent studies

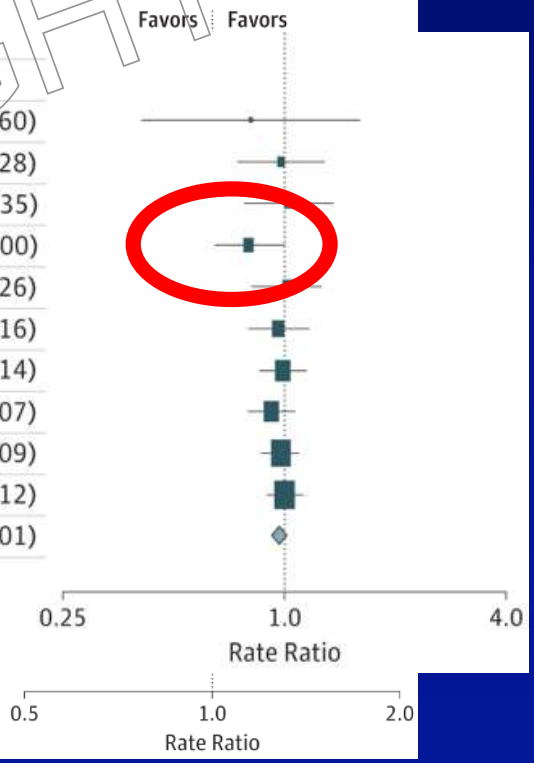




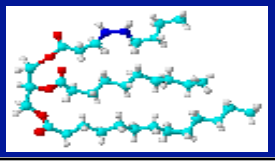


# Omega-3 Meta-Analysis

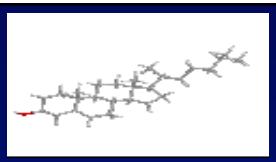
| | No. of Events (%) | | |
|---|---|---|---|
| Major vascular events | | | |
| DOIT | 29 (10.3) | 35 (12.5) | 0.81 (0.41-1.60) |
| AREDS-2 | 213 (9.9) | 208 (10.1) | 0.98 (0.75-1.28) |
| SU.FOL.OM3 | 216 (17.2) | 211 (16.9) | 1.02 (0.78-1.35) |
| JELIS | 262 (2.8) | 324 (3.5) | 0.80 (0.65-1.00) |
| Alpha Omega | 332 (13.8) | 331 (13.6) | 1.02 (0.82-1.26) |
| OMEGA | 534 (27.7) | 541 (28.6) | 0.96 (0.80-1.16) |
| R&P | 733 (11.7) | 745 (11.9) | 0.99 (0.86-1.14) |
| GISSI-HF | 783 (22.4) | 831 (23.9) | 0.92 (0.80-1.07) |
| ORIGIN | 1276 (20.3) | 1295 (20.7) | 0.98 (0.87-1.09) |
| GISSI-P | 1552 (27.4) | 1550 (27.3) | 1.00 (0.90-1.12) |
| All | 5930 (15.2) | 6071 (15.6) | 0.97 (0.93-1.01) |
| | | | P=.10 |





*JAMA Cardiol. 2018;3(3):225-233. doi:10.1001/jamacardio.2017.5205*



# REDUCE-IT



The NEW ENGLAND JOURNAL of MEDICINE

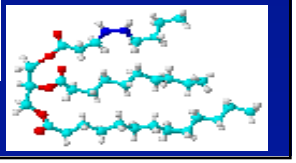
ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

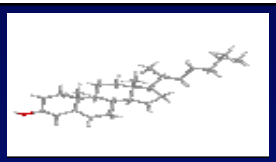
## Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael
Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doy
Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D.,
for the REDUCE-IT Investigators*

4 g per day
Purified ethyl ester of EPA

ABSTRACT

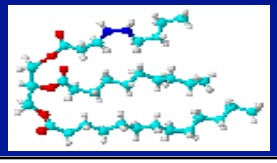


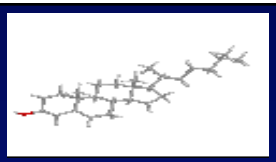


# Inclusion Criteria



- Risk
  - 45 years or older with CVD
  - 50 years or older with DM + one further risk factor
- Lipids
  - TG 1.69 to 5.63 mmol/L
    - Subsequent amendment to > 2.26 mmol/L
  - LDLC between 1 – 2.5 mmol/L on statins

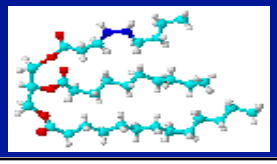




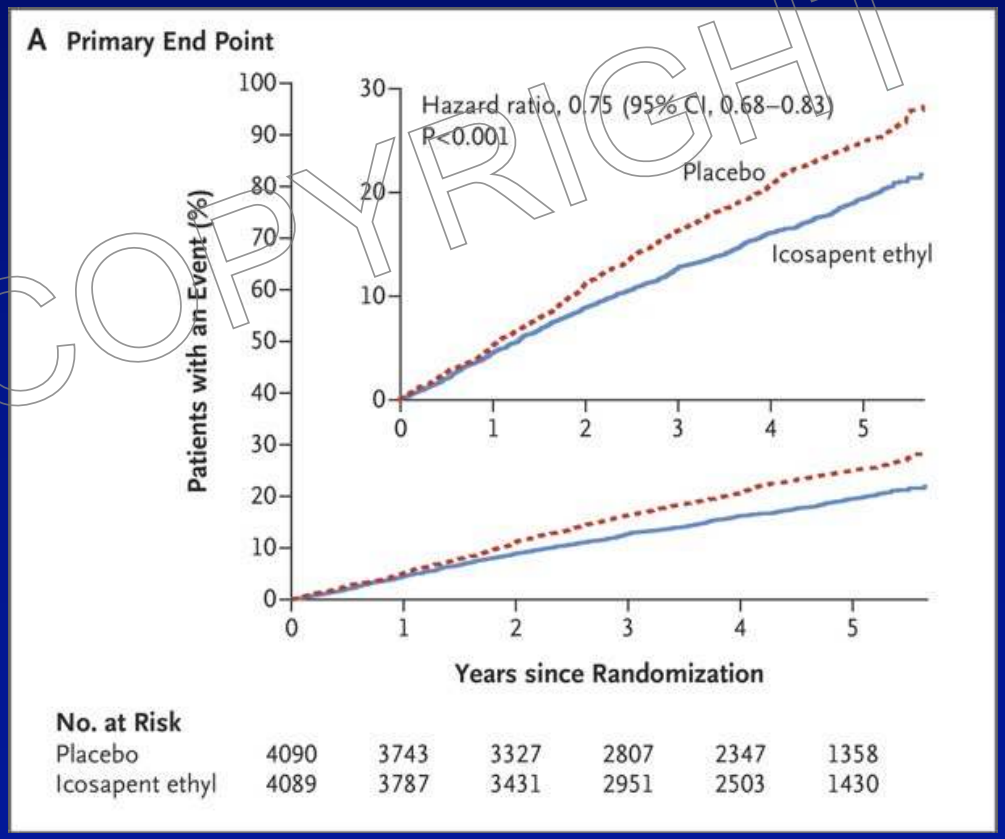
# Lipid Changes



- TG decreased by 0.44 mmol/L
- LDLC increased by 0.05 mmol/L
  - Increase with placebo was 0.18 mmol/L
- HDLC increased by 0.03 mmol/L

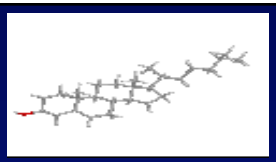


# CV Endpoints



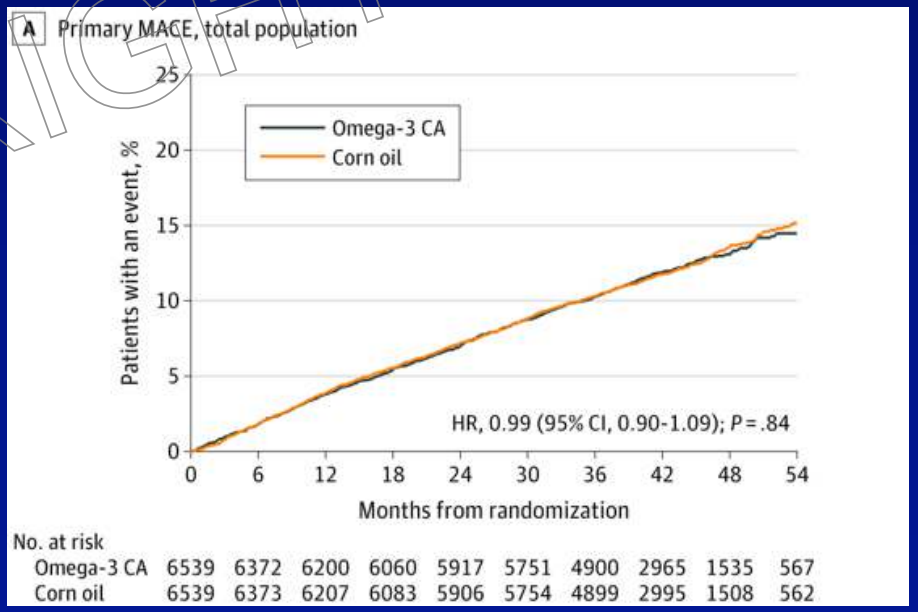



*N Engl J Med 2019; 380:11-22*

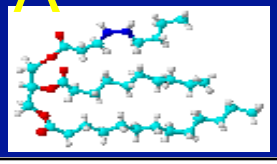


# Strength Study

- High CV risk population
  - Not exclusively diabetics
- Adequate statin dose
- High TG  (2.0-5.6 mmol/L)
- Low HDL (sex specific)

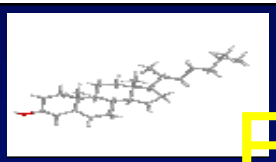



- Epanova 4 g/d: omega-3 carboxylic acids (mainly EPA and DHA)

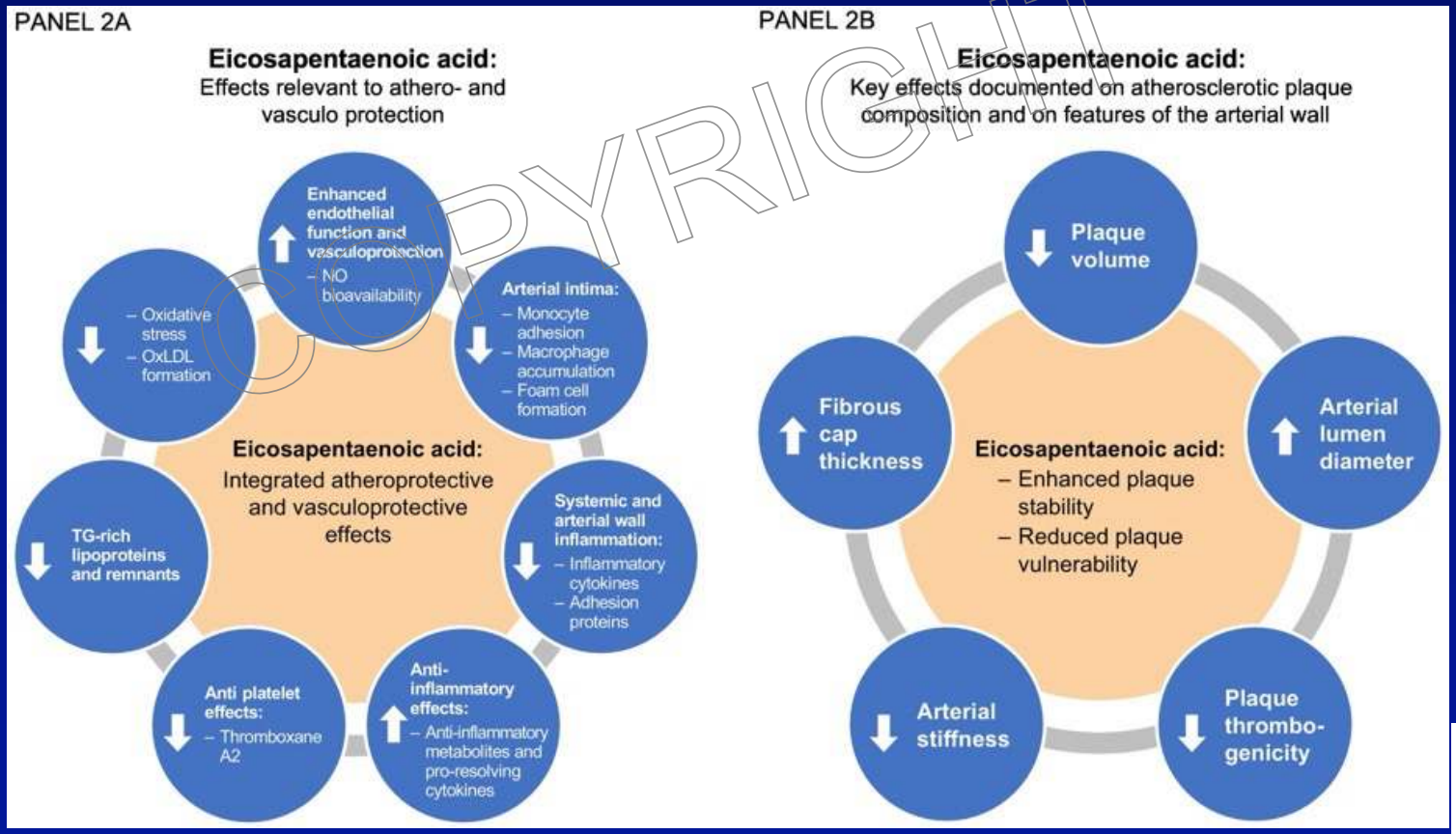




*JAMA. 2020;324(22):2268-2280. doi:10.1001/jama.2020.22258*

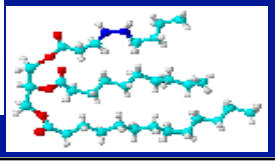


# EPA: Potential Mechanisms of Action



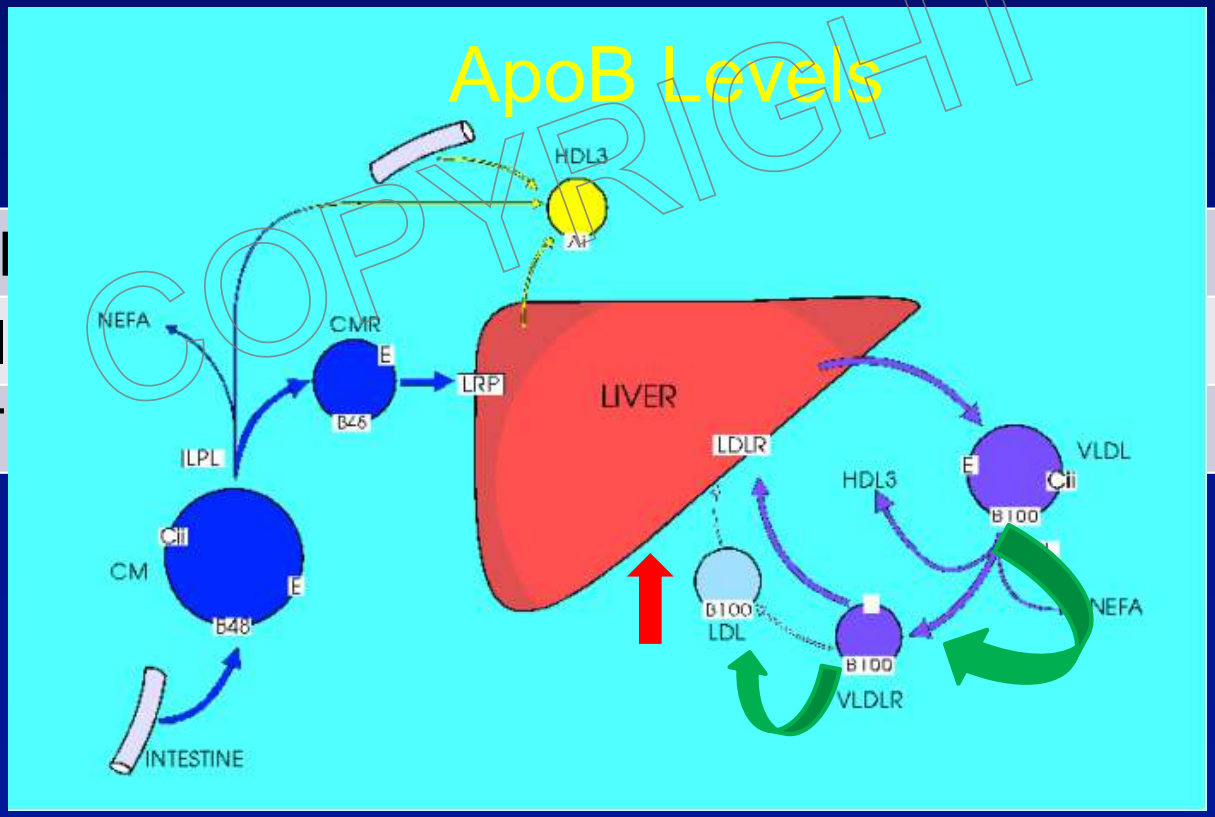


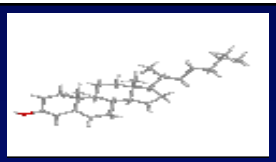

https://doi.org/10.1016/j.pharmthera.2022.108172



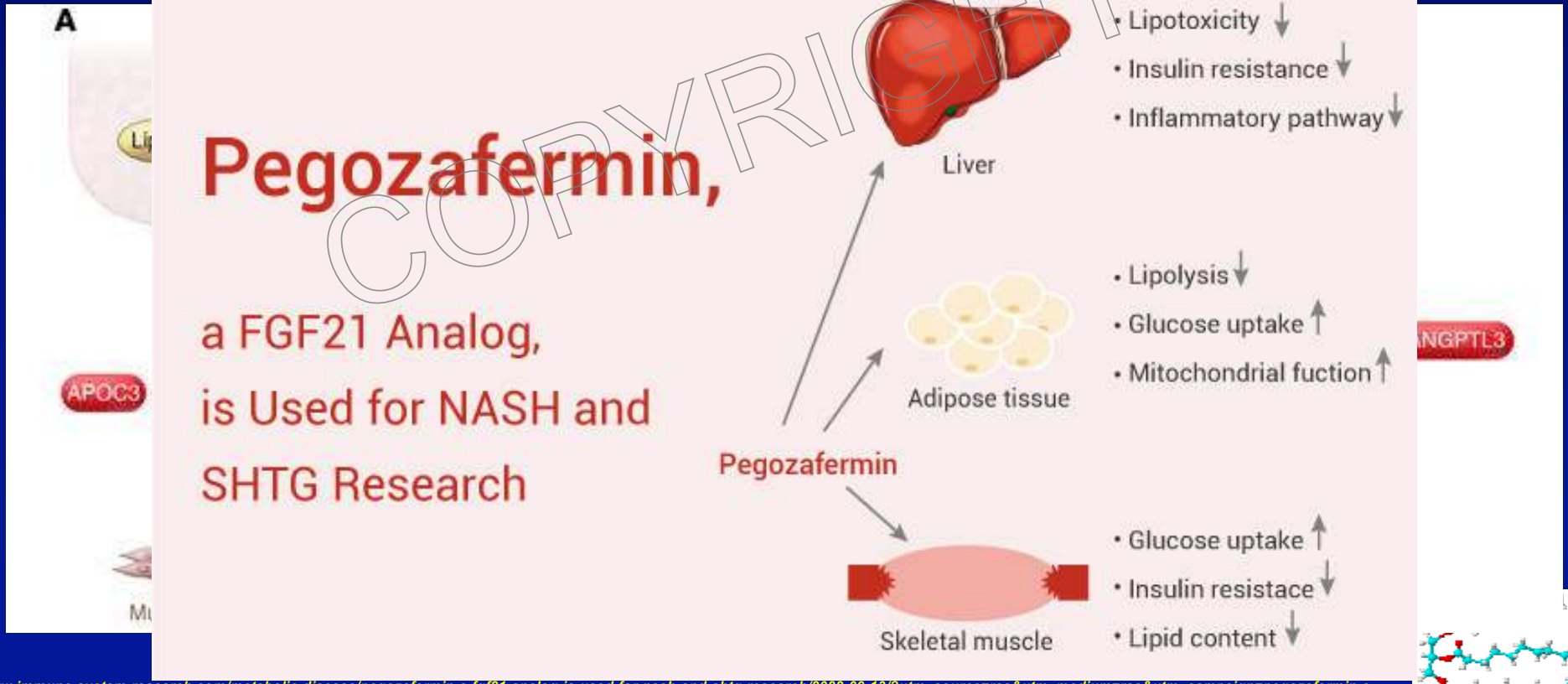
# Shifting The Burden

| |
|---|
| PROMINEI |
| REDUCE-I |
| STRENGT |

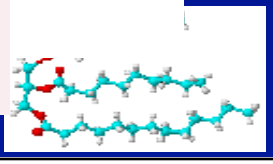




# Novel Approaches

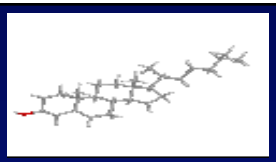




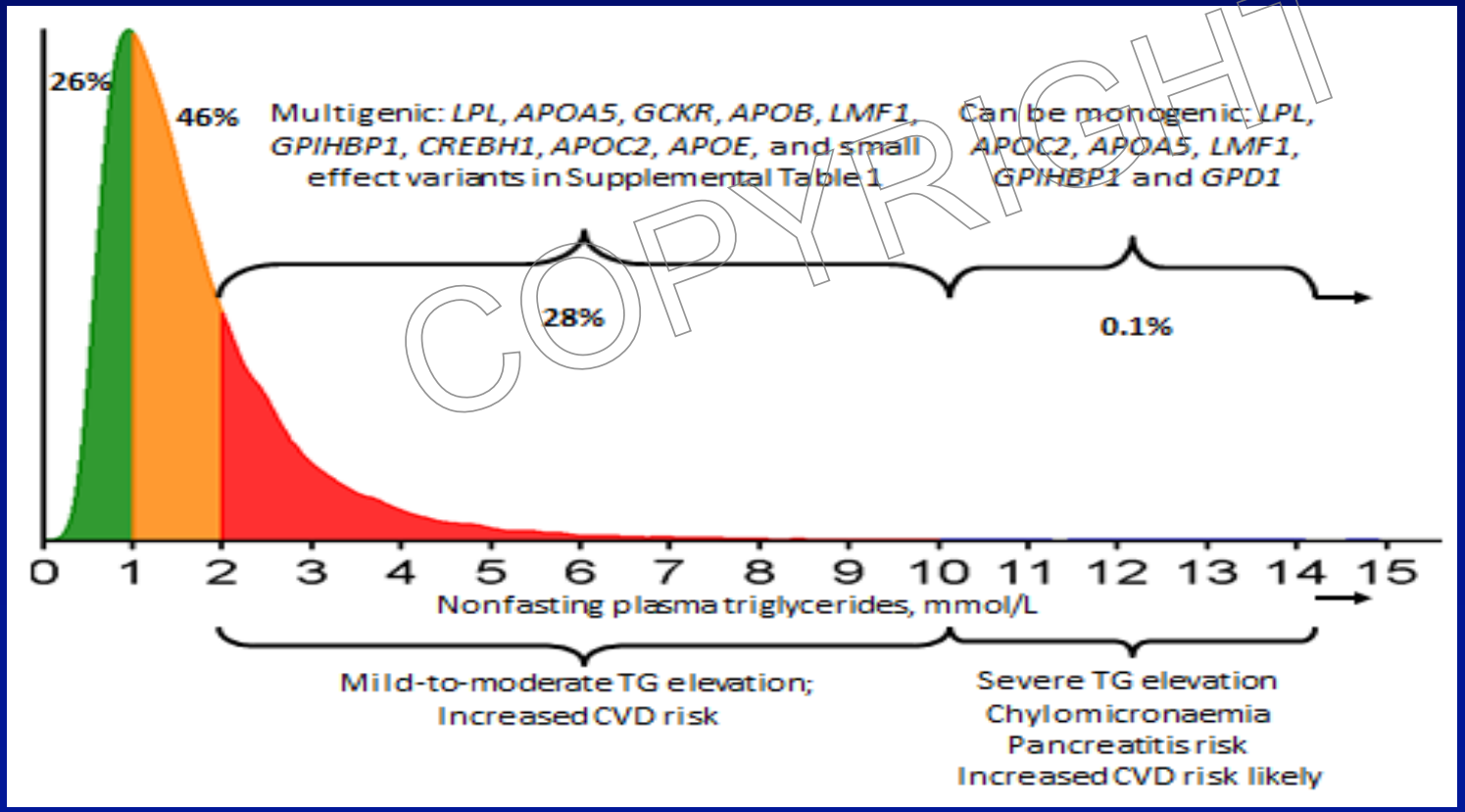



https://www.immune-system-research.com/metabolic-disease/pegozafermin-a-fgf21-analog-is-used-for-nash-and-shtg-research/2022-09-13/?utm_source=rss&utm_medium=rss&utm_campaign=pegozafermin-a-fgf21-analog-is-used-for-nash-and-shtg-research

J Clin Invest. 2022;132(11):e148559.



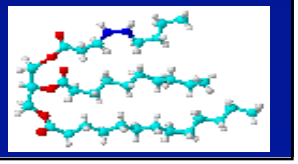
# Severe Hypertriglyceridaemia





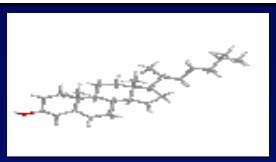

Diabetes

- Multifactorial chylomicronaemia
- Polygenic



*Lancet Diabetes Endocrinol 2013.* Published Online December 23, 2013. http://dx.doi.org/10.1016/S2213-8587(13)70191-8

# Eruptive Xanthomata



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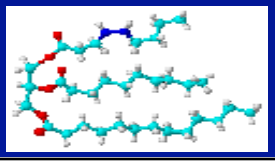
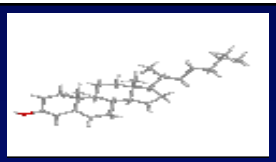
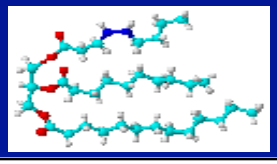


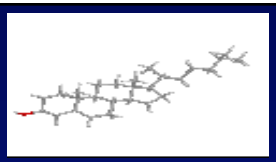


# Pancreatitis



- TG > 10-15 mmol/L associated with risk
- Poorly predictable
- Pathogenesis
  - Local generation of free fatty acids with detergent effect?
  - Impaired capillary circulation?
- Potentially fatal





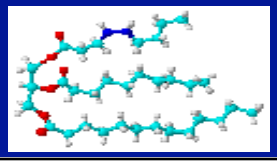
# Prevention

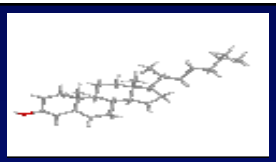
- TG> 10-15 mmol/L: Initial primary therapeutic aim is panc
- Iden
- Rem
  - **Di**
  - Ins
- Rest
- Fibra

This is the one indication for a fibrate that everybody agrees on

on







# McDonalds Meal

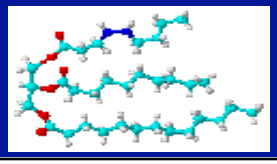
- Complete digestion and absorption of dietary fat
- Clearance is zero (e.g. LPL deficiency)
- Ignore VLDL production
- Fasting triglycerides are 4 mmol/L
- Plasma volume of 3 L
- 1 mol triglycerides ≈ 885 g

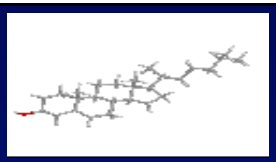
Double Hamburger with cheese 42 g
French fries (large) 30 g
Chocolate triple thick shake (Supersize) 28 g

Total meal is 100g of triglyceride → 113 mmol
Change in triglycerides: 113 mmol of triglyceride / 3 L
plasma volume = 37.66 mmol/L
Triglycerides can rise from 4 mmol/L to over 40 mmol/L

Cholesterol consumed: 255 mg (≈ 0.7 mmol)







# Known Knowns



- Treat LDLC (or apoB/ non-HDLC) aggressively
- Lower  LDLC is better – less than 1.4 mmol/L with very high risk
  - Statin therapy ± ezetimibe ± PCSK9i
- Severe hypertriglyceridaemia (TG >10 mmol/L)
  - Fibrates to prevent pancreatitis
- Normal TG (<1.5-2.3 mmol/L) , normal HDLC
  - No fibrates/omega-3 for atherosclerosis prevention
- Consider icosapent ethyl/$_{\text{fibrate (?)}}$ with high risk and TG 1.5-5.6 mmol/L