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Statins, Ezetimibe, and Proprotein Convertase Subtilisin–kexin Type 9 (PCSK9) inhibitors to Reduce Low-Density Lipoprotein-Cholesterol and Cardiovascular Events

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Abstract:

Multiple lines of evidence suggest that the physiologically normal levels of low-density lipoprotein cholesterol (LDL-C) and the thresholds for development of atherosclerosis and adverse coronary events are in the 30 to 70 mg/dL range. More patients have been studied in randomized controlled trials assessing the effects of statins on outcomes than any other drug class in the history of medicine. This cumulative body of evidence documents that atherosclerosis progression is halted and coronary heart disease (CHD) events are minimized when statin therapy with or without ezetimibe and, possibly proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors, are utilized to drive down the LDL-C to a range of about 30 to 50 mg/dL. Thus far, these agents appear to be safe even when LDL-C is lowered to about 50 mg/dL; although more robust outcome and safety data are required, particularly for the PCSK9 inhibitors and very low LDL-C levels (e.g. down to 25 mg/dL). In conclusion, the current national guidelines specifying only the use of a high-potency statin without specific LDL-C goals may lead to substantial under treatment of high-risk individuals, leaving them vulnerable to future adverse cardiovascular (CV) events.

Key Words: cholesterol, LDL, atherosclerosis, coronary disease, PCSK9 inhibitors, statins, ezetimibe, evolocumab, alirocumab.

Introduction:

Forty percent of Americans show evidence for arterial plaque development by 50 years of age.[1] Despite cholesterol levels trending down in recent decades atherosclerosis remains endemic in part because about one-third, or 73 million adults in the US still have low-density lipoprotein cholesterol (LDL-C) levels above ideal.[2,3] Although LDL-C levels of about 30 to 70 mg/dL may seem unreasonably low by modern US standards, they are squarely in normal range for humans and other mammals eating the diet and living the lifestyle for which we are genetically adapted (**Figure 1**).[2,3] Indeed, even among those who are heterozygotes for two inactivating mutations in the proprotein convertase subtilisin–kexin type 9 (PCSK9) gene, causing strikingly low levels of LDL-C (mean = 14 mg/dL) there appears to be no harmful effects.[4] Furthermore, mendelian randomization analysis indicates having a lifelong very low LDL-C is associated with a very low risk of coronary heart disease (CHD).[5] Thus, it appears that having very low LDL-C levels throughout life markedly reduces atherosclerosis development is compatible with otherwise normal health. Furthermore, there is good evidence that dramatic LDL-C lowering via lipoprotein apheresis improves cardiovascular (CV) morbidity and life expectancy in familial hypercholesterolemia.[6]

LDL-C: Obligate Precursor to Atherosclerosis

Among the myriad CV risk factors that contribute to the genesis and progression

of arterial atherosclerosis, the LDL-C level is among the most critical. LDL-C penetrates the intima whereby Apo B binds to proteoglycans leading to oxidized LDL-C, which incites inflammation, endothelial dysfunction, and atherosclerosis.[7] Severe elevations of LDL-C levels (> 190 mg/dL) are strongly associated with CHD risk; however atherosclerosis and its complications are common even for those with LDL-C levels of 90 to 130 mg/dL.[8] Furthermore, individuals in the top decile of LDL-C levels account for just 20% of the CHD events.[8] Thus, restricting therapy to only on those with severely elevated LDL-C levels will ignore about 4 out of every 5 people destined to suffer an adverse CV event.[2,8]

The numerous randomized controlled trials using statins have documented significant reductions in CHD events and all-cause mortality, especially among secondary prevention populations.[2,8-10] Most individuals in these trials had baseline LDL-C levels from 110 to 180 mg/dL, with on-treatment LDL-C levels ranging between 55 and 120 mg/dL.[2,9] Statin-induced LDL-C reductions of 25 to 50% caused corresponding drops in adverse CV events of about 20 to 44%.[2,8-10] Despite these impressive reductions in risk, the majority of CHD events continued to occur. High-risk individuals such as those with established CV disease, diabetes or familial hypercholesterolemia may have a substantial residual risk for future adverse CV events even while being treated with a high-potency statin. Theoretically, this residual risk in secondary prevention may be significantly attenuated by therapies that can safely and effectively drive LDL-C levels down into the 30-to 70-mg/dL range. Indeed, newer agents such as the PCSK9 inhibitors and ezetimibe, when added to baseline statin

therapy impart more robust reductions in LDL-C, and may possibly further improve CV outcomes.[11-14] A very large meta-analysis of RCTs reported that using statins to drive LDL-C down to very low levels is safe and effective, with further CV risk reduction beyond the benefits noted with moderate LDL-C lowering (**Figure 2**).[11]

Current Guidelines' Recommendations

The most recent iteration of the ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic CV Risk in Adults eliminated specific treatment goals[15] stating there was no evidence of CV benefit in treating to a specific LDL-C target. Unfortunately, this statement ignores the fact that hundreds of thousands of patients have been studied in randomized controlled trials showing that statins with or without ezetimibe lower risk of CHD events in proportion to their ability to lower LDL-C, particularly in the setting of secondary prevention. Although the current AHA/ACC guidelines are practical and more affordable from a public health standpoint, other consensus expert guidelines including the National Lipid Association, the European Society of Cardiology, and the European Atherosclerosis Society guidelines have continued to re-affirm the importance of LDL-C as the primary target for treatment, citing goals of < 100 mg/dL for high-risk individuals, with an option to treat very high-risk patients to less than 70 mg/dL.[16]

High-density lipoprotein cholesterol (HDL-C) is not recommended as a target for treatment.[16] Although HDL-C is an important risk factor and should be used in risk calculation, it has not been found to be useful as a target for pharmacological therapy.[16] Multiple large and definitive studies show that despite significant improvement in HDL-C levels, niacin, fibrates and the cholesterol ester transfer protein inhibitors do not significantly reduce adverse outcomes (and on the balance may cause more harm than benefit).[17,18] Non-HDL cholesterol , and/or Apo B levels are considered as important lipid targets by many lipid experts; and these parameters may be particularly relevant for individuals with elevated triglycerides, diabetes, metabolic syndrome, or chronic kidney disease.[16]

Preventing Atherosclerosis and Adverse Coronary Events

When examined in aggregate, the randomized trials using statins reveal a continuous direct association between on-treatment LDL-C and risk of CHD events, without any specific threshold where lower LDL-C levels are not correlated with lower risk.[19] Both primary prevention and secondary prevention trials show this relationship, though it is much stronger in the setting of secondary prevention where event rates are much higher (**Figure 3a and 3b**).[16] Of particular interest, the LDL-C threshold at which the CV event rate is extrapolated to approach zero is about 55 mg/dL for primary prevention and 30 mg/dL for secondary prevention. This massive body of evidence based on very high quality data from randomized controlled trials implicates LDL-C as

the requisite catalyst in the atherosclerosis process wherein very low LDL-C levels may minimize the rate of CHD events despite an otherwise ominous CV risk factor profile.

Evidence from randomized controlled trials also clearly documents a highly significant direct relationship between on-treatment LDL-C level and atherosclerotic progression rate.[2] The cumulative body of data indicates that when patients are on therapy with a statin, ezetimibe, and/or a PCSK9 inhibitor, the atherosclerosis progression/regression rate as quantified by the intravascular coronary ultrasound is closely related to the chronic LDL-C level (**Figure 4**).[20,21]

LDL-lowering Drugs: Which Ones Improve Cardiovascular Outcomes?

Throughout the entire history of medicine and pharmacology, no drug class has been so thoroughly tested in large randomized controlled trials as have the statins. As outlined above, in aggregate this database of statin trials reveals highly significant inverse relationships between on-statin LDL-C levels and: a) progression coronary atherosclerosis, and b) risk of major adverse CV events. Despite the availability of high-potency statins (most of which are now available as inexpensive generics), up to half of patients with CHD or at high risk due to issues such as diabetes, subclinical CHD (documented by asymptomatic coronary artery calcification) and familial hypercholesterolemia are not treated to an LDL-C of 70 mg/dL.[11,22] A substantial portion

of this ongoing future risk of CV events might be mitigated by more aggressive LDL-C reduction. Ezetimibe, a cholesterol-absorption inhibitor, has recently also proven to be effective for lowering LDL-C and modestly reducing major CV events.[12] The IMPROVE-IT was a large randomized trial in which ezetimibe when added to a statin significantly lowered on-treatment LDL-C from 70 to 54 mg/dL, with a concomitant statistically significant reduction in adverse CV events compared to the statin alone.[23]

Several large randomized controlled trials using drugs such as high-dose oral equine estrogens, niacin, fibrates, and CETP inhibitors have each lowered LDL-C levels but failed to improve CV outcomes in randomized controlled trials.[24] These agents not coincidentally have common serious adverse effects, in addition to their LDL-lowering actions. Lipid modifying drugs are medications that must be taken for years to decades; serious off-target adverse effects can tilt the risk/benefit ratio so that on the balance the agents do not improve prognosis despite improving the lipid profile.

PCSK9 Inhibitors

Evolocumab and alirocumab are monoclonal antibodies that inhibit PCSK9. These two PCSK9 inhibitors are both administered via subcutaneous injections twice per month. Evolocumab and alirocumab each reduce LDL levels approximately 45 to 70% beyond what can be achieved with maximally tolerated statin +/- ezetimibe

therapy.[25,26] When PCSK9 inhibitors are used with statins +/- ezetimibe for baseline therapy, about 90% of individuals are able to achieve LDL levels under 70 mg/dL; compared to only 50% of individuals on high-potency statin +/- ezetimibe.[12-14]

These PCSK9 inhibitors share with statins the ability to increase LDL receptor activity on the surface of the hepatocyte. However, because statins markedly up-regulate the production of PCSK9, the use of a PCSK9 inhibitor with a statin will provide synergistic reductions in LDL-C.[12-14,27] Support for the premise that PCSK9 inhibition may reduce improve outcomes comes from the observation that loss-of-function genetic variants leading to reductions in PCSK9 activity have been linked to a significantly reduced lifetime risk for adverse CV events.[5,22] Two recently published post hoc analyses, which comprise only preliminary and exploratory data, suggest that PCSK9 inhibitors may have the potential to reduce adverse CV events (**Figure 5 and Figure 6**).[13,14] Both evolocumab and alirocumab lowered LDL-C levels by approximately 61%, from baseline on-statin levels of about 120 mg/dL down to 48 mg/dL.

In their pre-release development programs, evolocumab and alirocumab were able to drive LDL-C levels below 25 mg/dL in 37% and 24% of patients respectively. Thus, we will have soon have unprecedented data regarding the potential benefits versus harms of treating to very low LDL-C levels. Evolocumab and alirocumab are both being studied in very large clinical CV event reduction trials, which are expected to report results in 2017.[28]

The recently published Glascov trial randomized 968 patients with coronary disease to evolocumab + statin versus placebo + statin. Intravascular ultrasound of the coronary arteries was performed at baseline and 18 months later at study end. The course of evolocumab therapy met both its primary endpoint (change in percent atheroma volume (PAV) compared with placebo, and the secondary endpoint—atheroma regression compared to placebo.[21]

Potential Dangers of Very Low LDL-C

Cholesterol is an obligate precursor for synthesis of steroid hormones, vitamin D, and bile acids, and is also an essential component of all cell membranes. Accordingly, it is probable that an ideal range of blood cholesterol exists above and below which adverse health consequences might be anticipated. Chronic serious illnesses, including cancer, gastrointestinal diseases, infections and neurological/psychological disorders are often associated with depressed LDL-C levels as a result of malnutrition and/or cachexia. Although low cholesterol levels are often correlated with increased morbidity and mortality, especially among the elderly, the reduced lipid levels among these cohorts may occur as a result of, not the cause of disease.

Epidemiologic studies show that people with lifelong low levels of LDL-C tend to

have excellent life expectancy.[5,29] The cumulative body of data with statins indicates substantial CV benefits that are directly proportional to LDL-C lowering with no increase in adverse events such as cancer or non-CV mortality.[2,9] The incidence of the two most frequently reported adverse effects attributed to statins—muscle/joint pain, and abnormal liver function tests—rise modestly as a function of statin doses but are unrelated to the on-treatment LDL-C levels achieved.[9] Although subjective statin-related side effects such as myalgias, fatigue, and loss of mental acuity are common, statin intolerance is markedly over-diagnosed both by patients (via the nocebo effect) and physicians. For example, in blinded alirocumab studies, 60 to 70% of patients previously considered statin-intolerant were able to tolerate 20 mg of atorvastatin.[13,24]

Individuals with heterozygous hypobetalipoproteinemia have lifelong total cholesterol levels in the range of 80 to 130 mg/dl with LDL-C levels of as low as 30 mg/dL. This heritable condition is generally characterized by excellent overall general health and above average life expectancy, owing to the absence of atherosclerosis and its complications. A recently published study performed a series of meta-analyses involving over 300,000 people with nine polymorphisms in 6 different genes to evaluate the effects of genetically induced lifelong lower LDL-C levels on risk of CHD.[5] This "Mendelian Randomization" natural experiment reported that LDL-C levels were strongly correlated with risk of CHD, suggesting that safe and effective LDL-lowering therapies are likely to be highly efficacious for the improving long term CV prognosis. (**Figure 7**).[5]

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Figure Legends

Figure 1: Comparative total cholesterol levels among various populations of humans and wild animals.[2]

Figure 2: *The x-axis represents achieved on-statin LDL-C levels. LDL C = low-density lipoprotein cholesterol; HR = hazard ratio.*

Statin LDL-C Levels and Risk for Major Cardiovascular Events. Distribution of achieved on-statin LDL-C levels (dark blue curve; right y-axis) and the risk of major cardiovascular events (light blue line; left y-axis).[11]

Figure 3a: Relationship between on-treatment LDL-C levels and CHD events in studies of primary prevention. Pl = placebo; Rx = treatment.[16]

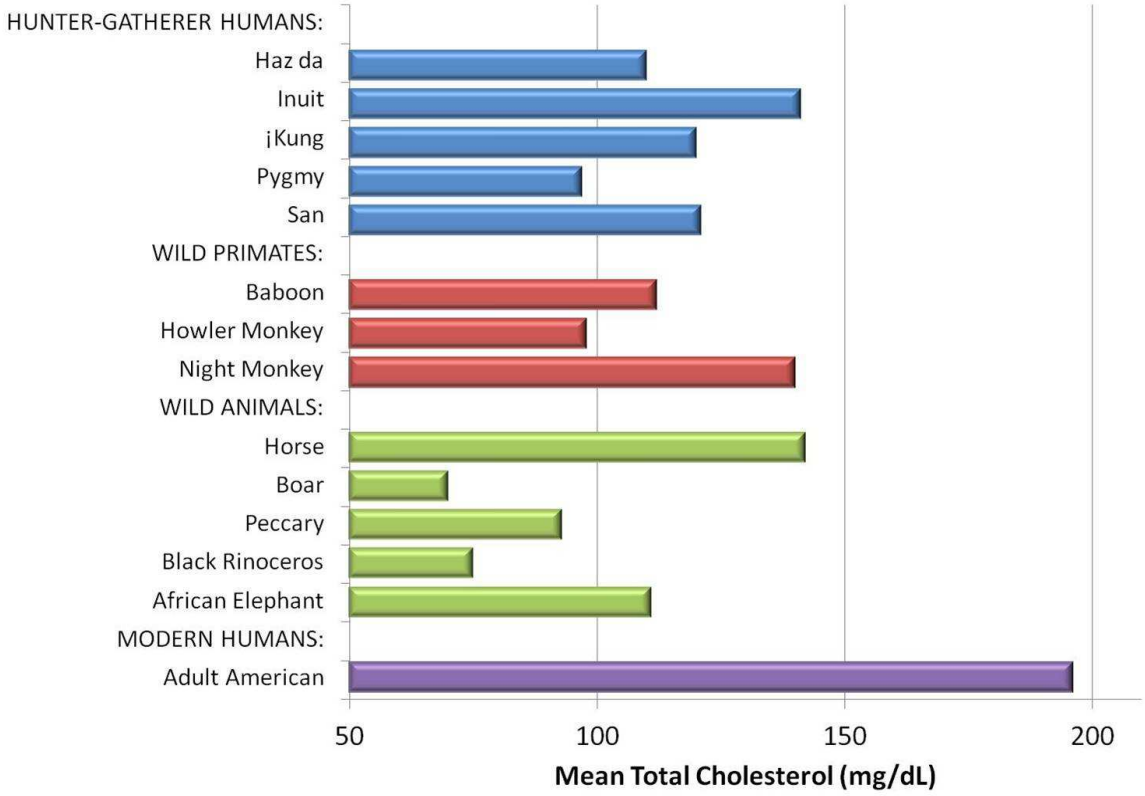
Figure 3b: Relationship between on-treatment LDL-C levels and CHD events in studies of secondary prevention.[16]

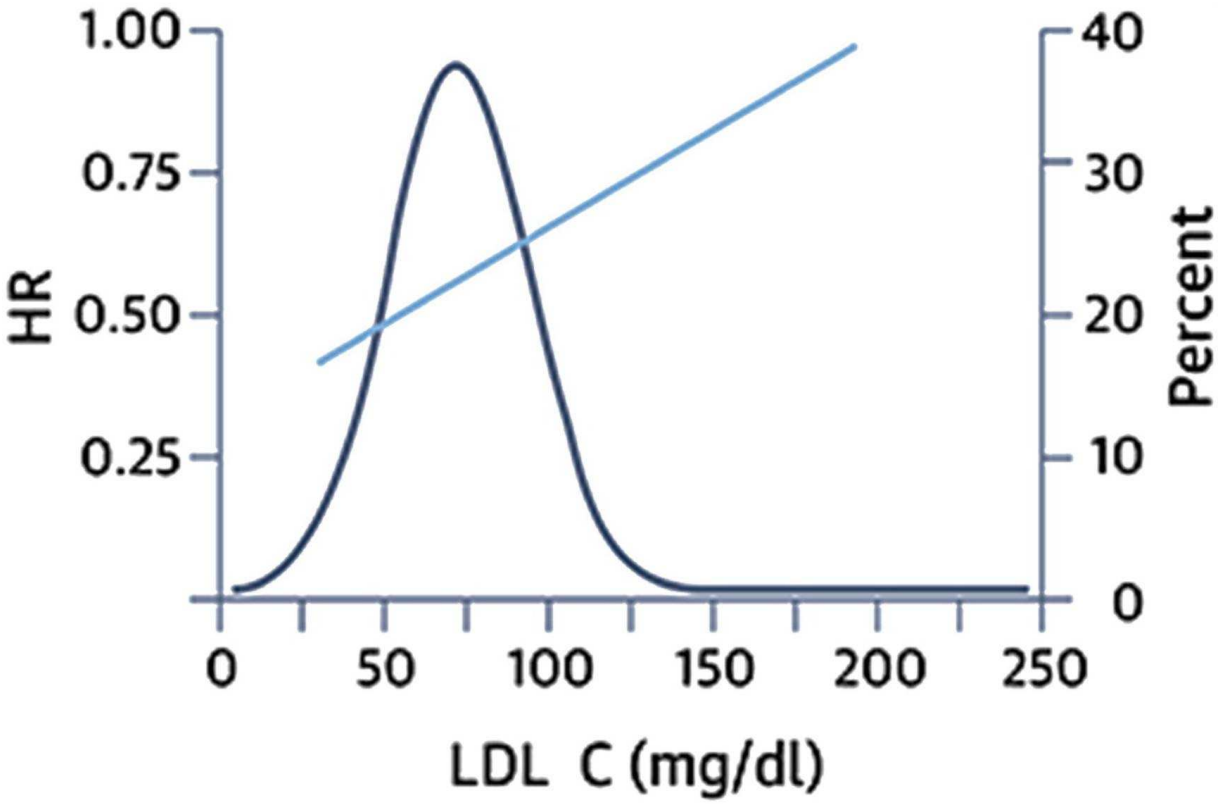
Figure 4: Relationship Between Achieved LDL-C Levels and the Median Change in Percent Atheroma Volume as documented by Intravascular Ultrasound Trials.[20]

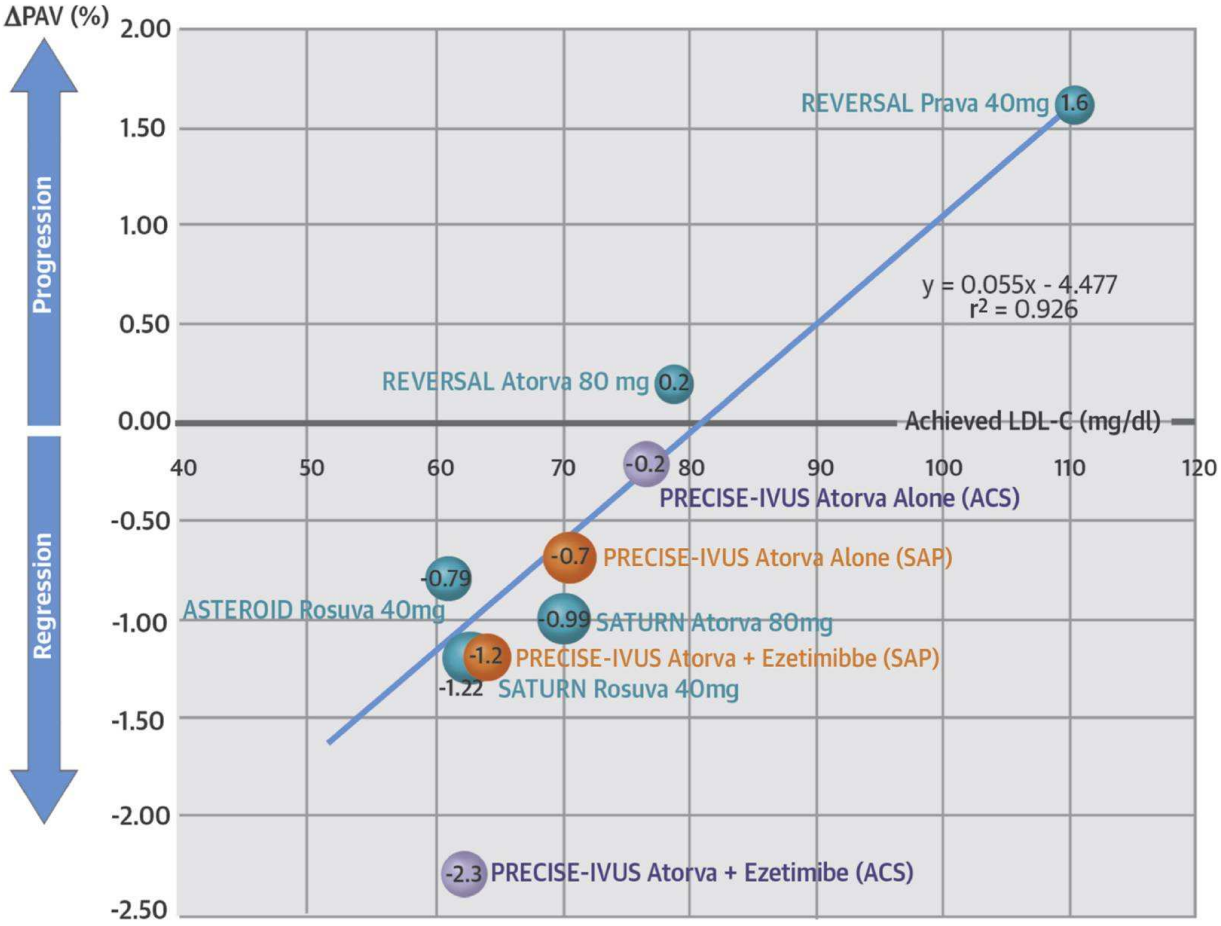
Figure 5: Cumulative Incidence of Cardiovascular Events Evolocumab vs standard therapy.[14]

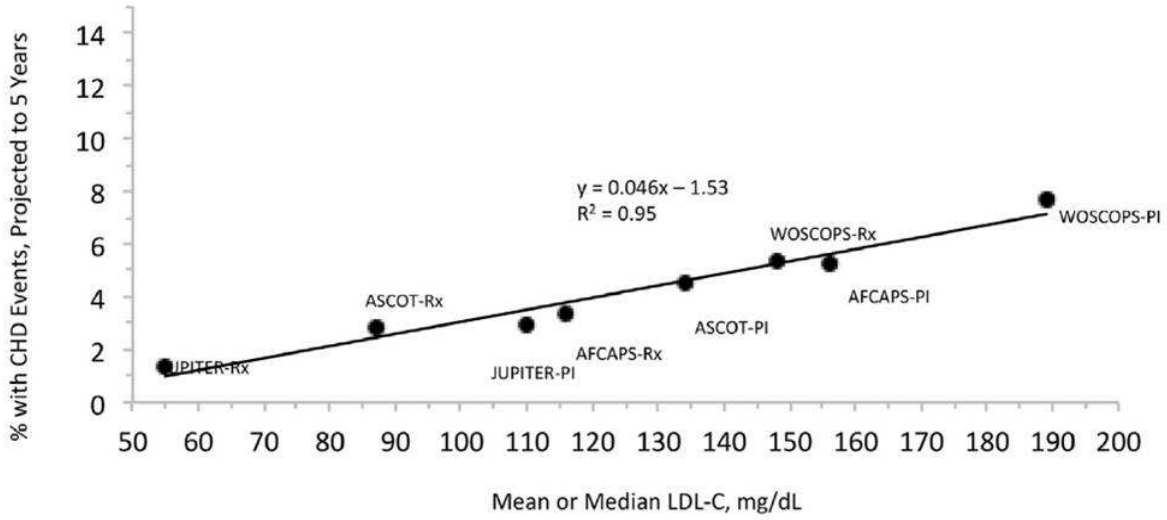
Figure 6: Cumulative Incidence of Cardiovascular Events Alirocumab vs placebo therapy.[13]

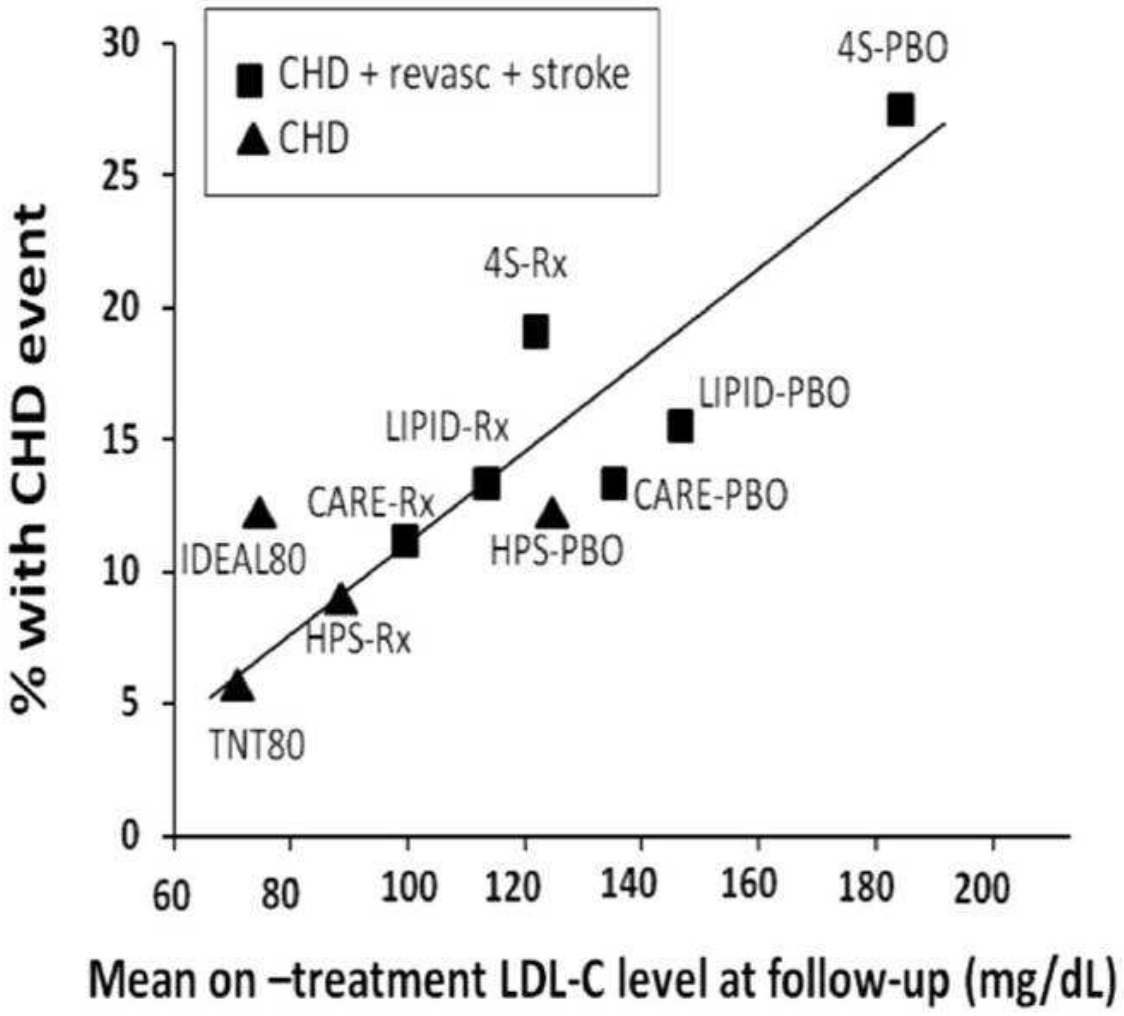
Figure 7: Boxes represent the proportional risk reduction (1 − OR) of CHD for each exposure allele plotted against the absolute magnitude of lower LDL-C associated with that allele (measured in mg/dl).[5]

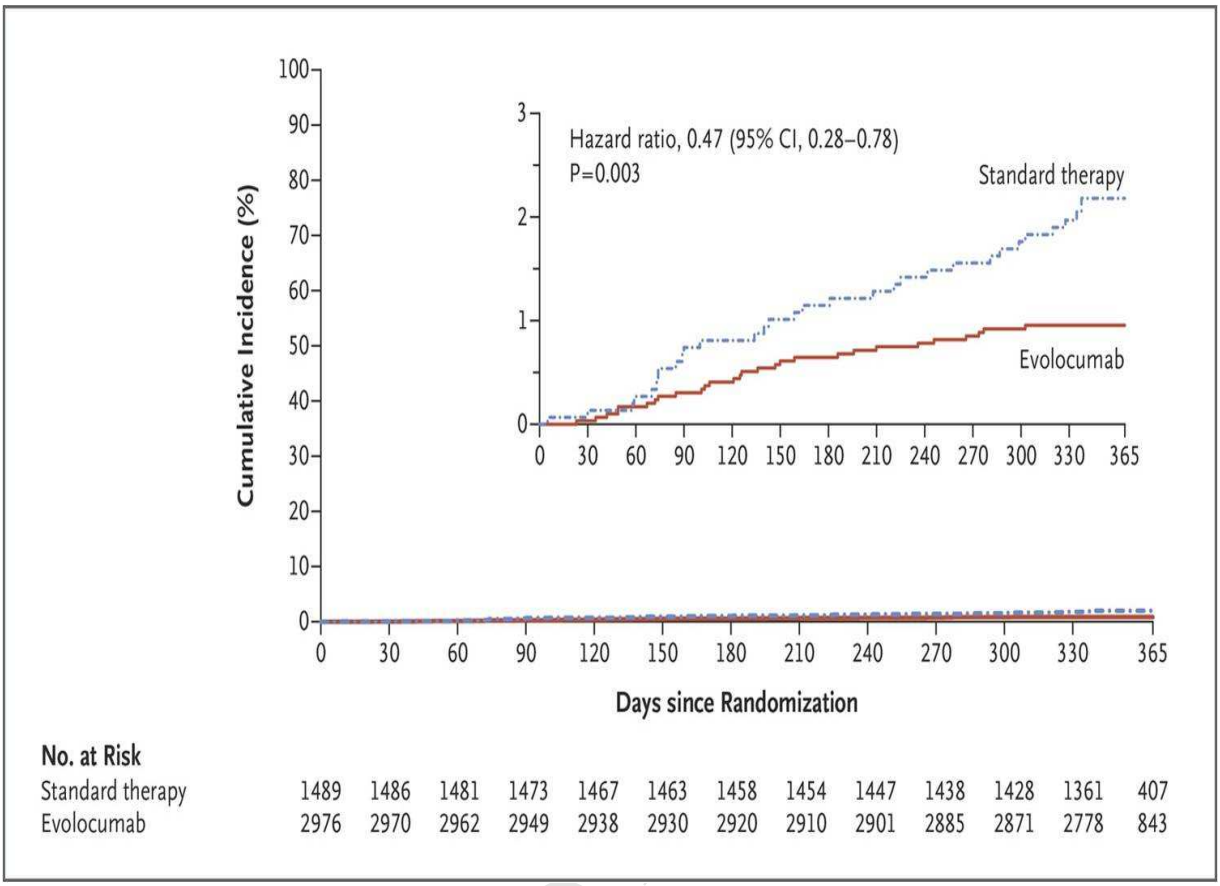





ΔPAV (%)
Progression
Regression
2.00
1.50
1.00
0.50
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
40
50
60
70
80
90
100
110
120
Achieved LDL-C (mg/dl)
y = 0.055x - 4.477
r2 = 0.926
REVERSAL Prava 40mg 1.6
REVERSAL Atorva 80 mg 0.2
-0.2 PRECISE-IVUS Atorva Alone (ACS)
-0.7 PRECISE-IVUS Atorva Alone (SAP)
-0.79
ASTEROID Rosuva 40mg
-0.99 SATURN Atorva 80mg
-1.2 PRECISE-IVUS Atorva + Ezetimibbe (SAP)
-1.22 SATURN Rosuva 40mg
-2.3 PRECISE-IVUS Atorva + Ezetimibe (ACS)

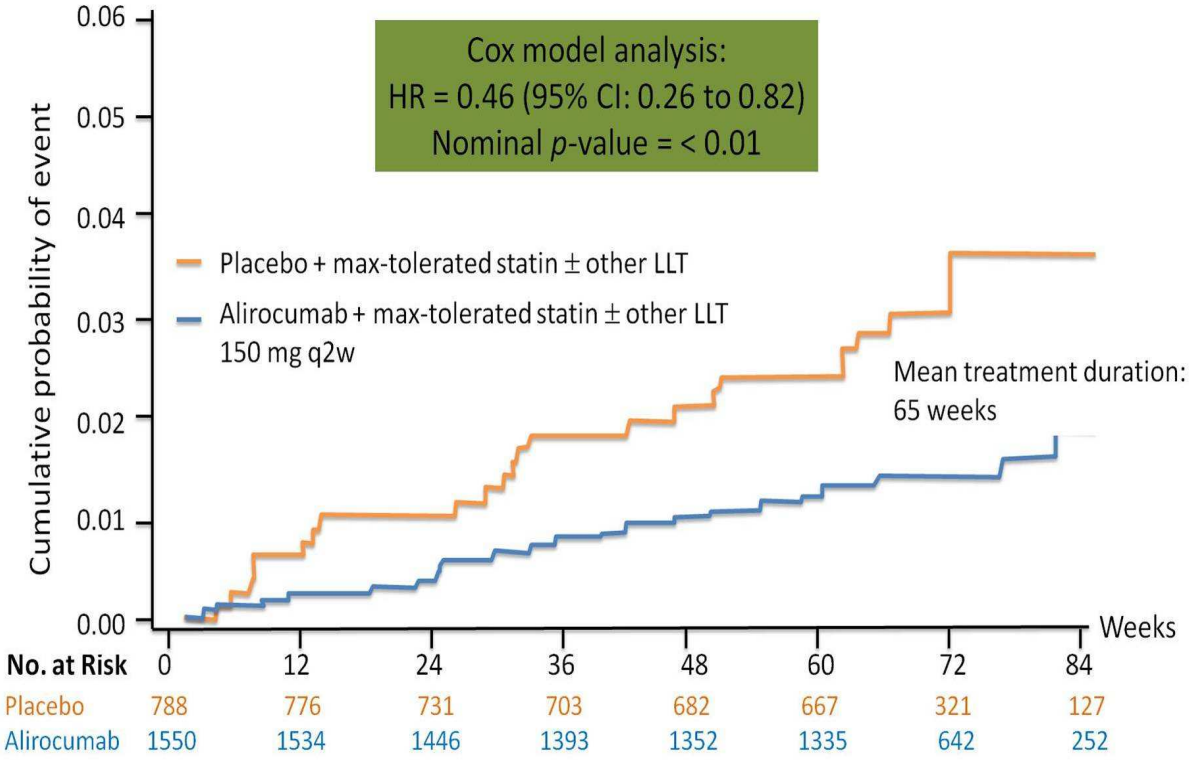


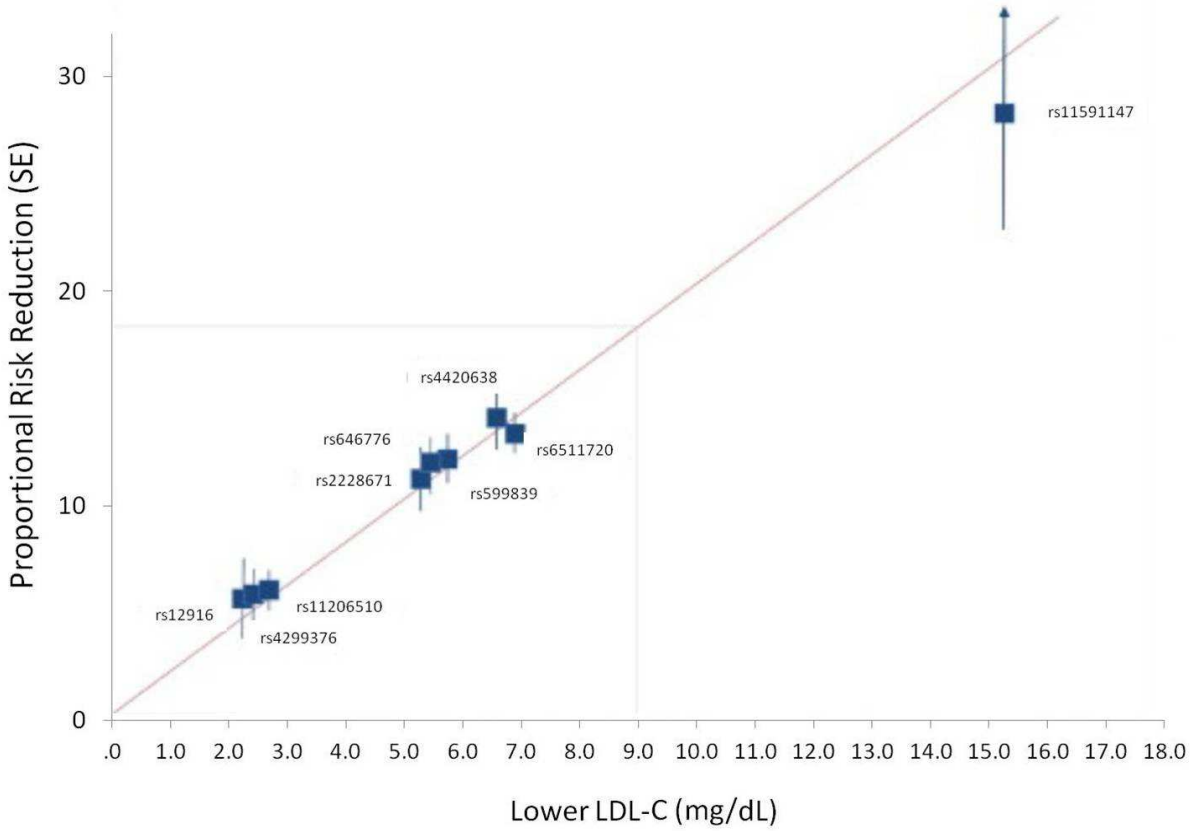

CHD + revasc + stroke
CHD
4S-PBO
4S-Rx
LIPID-PBO
LIPID-Rx
CARE-Rx
CARE-PBO
IDEAL80
HPS-PBO
HPS-Rx
TNT80
% with CHD event
Mean on –treatment LDL-C level at follow-up (mg/dL)
0
5
10
15
20
25
30
60
80
100
120
140
160
180
200



No. at Risk

Standard therapy	1489	1486	1481	1473	1467	1463	1458	1454	1447	1438	1428	1361	407
Evolocumab	2976	2970	2962	2949	2938	2930	2920	2910	2901	2885	2871	2778	843




Proportional Risk Reduction (SE)
30
20
10
0
.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
14.0
15.0
16.0
17.0
18.0
Lower LDL-C (mg/dL)
rs11591147
rs4420638
rs646776
rs6511720
rs2228671
rs599839
rs12916
rs11206510
rs4299376