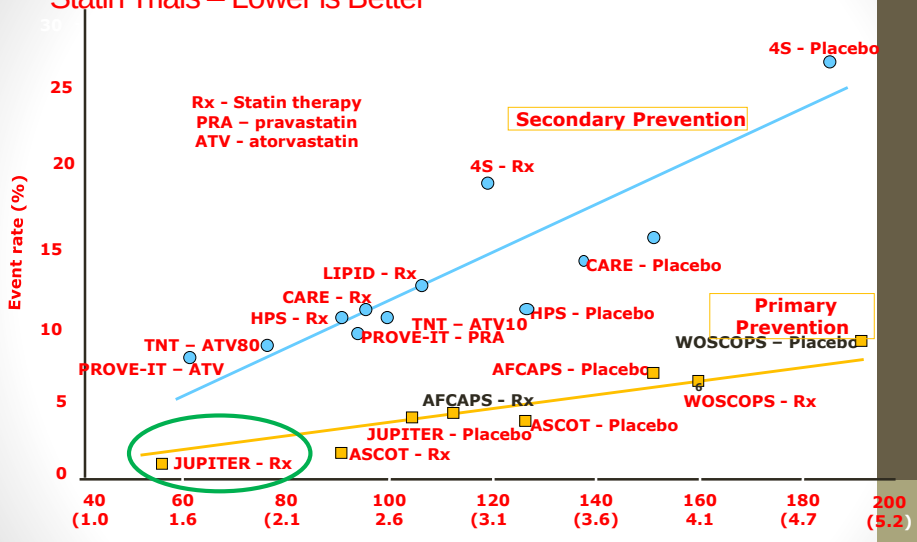
Statin claims

MAHMOUD SOLIMAN,MD

2018

On-Treatment LDL-C is Closely Related to CHD Events in Statin Trials – Lower is Better



Relationship Between Changes in LDL-C and HDL-C Levels and CHD Risk

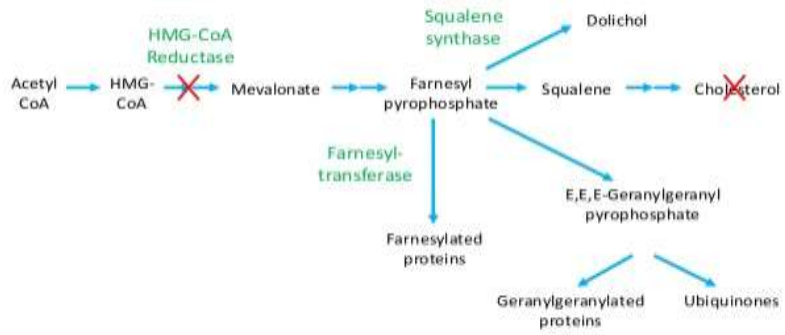
1% decrease in LDL-C reduces CHD risk by 1%[1]

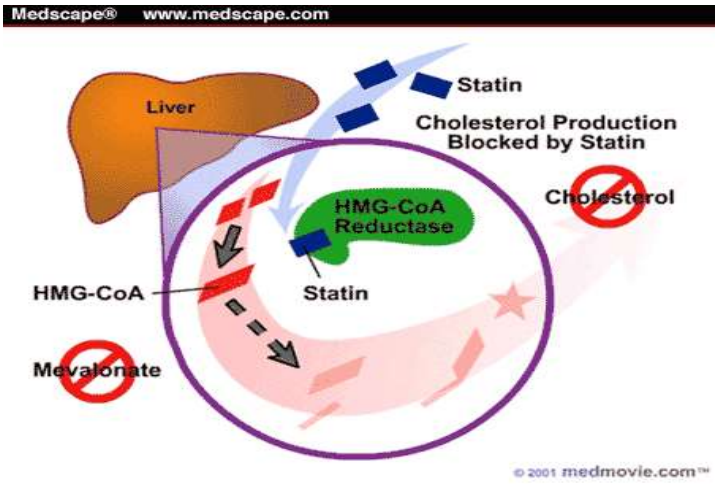
1% change in HDL-C associated with 1–3% reduction in CHD risk[2–5]

1.Grundy SM et al. *Circulation*. 2004; 110: 227–39
2.Gordon DJ et al. *Circulation* 1989; 79: 8–15
3.Boden W. *American Journal of Cardiology* 2000; 86 (Suppl): 19L–2L
4.Manninen V et al. *JAMA* 1988; 260: 641–651
5.Rubins HB et al. *N Engl J Med* 1999; 341: 410–418

Mechanism of Action

Inhibition of the Cholesterol Biosynthetic Pathway





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Pharmacological treatment of hypercholesterolaemia

Recommendations	Class	Level
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

EAS

www.escardio.org/guidelines

European Heart Journal 2016 – doi:10.1093/eurheartj/ehv272

ESC/EAS GUIDELINES 2016

Treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class	Level
In patients at VERY HIGH CV risk, an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk, an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In subjects at LOW or MODERATE risk an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

EAS

www.escardio.org/guidelines

European Heart Journal 2016 - doi:10.1093/eurheartj/ehv272

AACE 2017 Guidelines

Table 6
Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10-20% – Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Statin mania

What about the other side

The moon has another face

Muscle symptoms

Muscle pain and damage

- Many people who start taking statins report muscle pain and many discontinue statins because of it. Many of these people do well when they are switched to a different variety of statin.

- **Rhabdomyolysis :** can cause severe muscle pain, liver damage, kidney failure and death. The risk effects is extremely low, and calculated in a few cases per million of patients taking statins.

Liver affection

- Occasionally, statin use could cause an increase in the level of enzymes that signal liver inflammation.
- It may be suspected when there is unusual fatigue or weakness, loss of appetite, pain in your upper abdomen, dark-colored urine, or jaundice

Monitoring lipids and enzymes in patients on lipid-lowering therapy (2)

Monitoring liver and muscle enzymes (Cont'd)
What if liver enzymes become elevated in a person taking lipid-lowering drugs? If ALT <3x ULN: • Continue therapy. • Recheck liver enzymes in 4–6 weeks. If value rises to ≥3x ULN • Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4–6 weeks. • Cautious reintroduction of therapy may be considered after ALT has returned to normal. • If ALT remains elevated check for the other reasons.
How often should CK be measured in patients taking lipid-lowering drugs? *Pre-treatment* • Before starting therapy. • If baseline CK is 4x ULN, do not start drug therapy; recheck. *Monitoring* • Routine monitoring of CK is not necessary. • Check CK if patient develops myalgia. Be alert regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease or sport athletes.

Monitoring liver and muscle enzymes (Cont'd)

What if CK becomes elevated in a person taking lipid-lowering drugs?
Re-evaluate indication for statin treatment.

If ≥4 x ULN:
- If CK >10x ULN: stop treatment, check renal function and monitor CK every 2 weeks.
- If CK <10x ULN: if no symptoms, continue lipid lowering therapy while monitoring CK.
- If CK <10x ULN: if symptoms present, stop statin and monitor normalization of CK, before re-challenge with a lower statin dose.
- Consider the possibility of transient CK elevation for other reasons such as exertion.
- Consider myopathy if CK remains elevated.
- Consider combination therapy or an alternative drug.

If <4 x ULN:
- If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK).
- If muscle symptoms, monitor symptoms and CK regularly.
- If symptoms persist, stop statin and re-evaluate symptoms after 6 weeks; re-evaluate indication for statin treatment.
- Consider re-challenge with the same or another statin.
- Consider low-dose statin, alternate day or once/twice weekly dosing regimen or combination therapy.

STATIN & DIABETES

- Association????????????

- Causality ??????????????

Evidence from clinical trials

- ,**In 2008, (JUPITER) trial :**
- **showed 26% higher incidence of diabetes in the rosuvastatin group.**

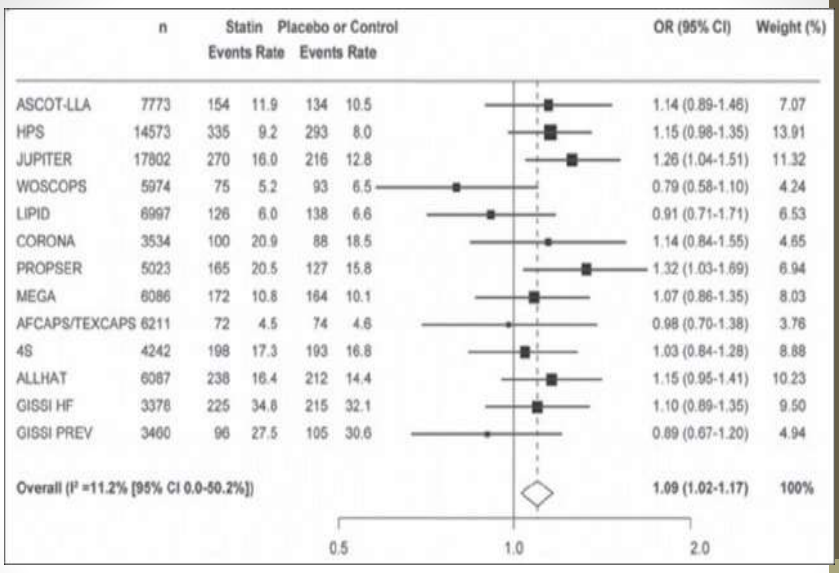
In, 2012, the FDA added new safety label changes for the statin class of cholesterol-lowering drugs regarding the potential for **increased (HbA1c) and fasting plasma glucose.**

Use of statins increases risk of developing diabetes

Date:March 4, 2015

Source:Diabetologia

Summary: Statin therapy was associated with a 46% increased risk of type 2 diabetes after adjustment for confounding factors, suggesting a higher risk of diabetes in the general population than previously reported.



Lancet, Vol. 375, Sattar *et al*. Statins and risk of incident

Statins and New-Onset Diabetes Mellitus:

LDL Receptor May Provide a Key Link

2017 •

Qi Yu[1,2,3*], Ying Chen[1,4] and Cang-Bao Xu[1,2] •

AACE 2017

- **R57.** For clinical decision-making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction **(Grade A, BEL 1)**.

Statin & grapefruit

Mechanism of interaction

- Grapefruit contains a compound called bergamottin that interacts cytochrome P-450 and P-glycoprotein.
- These enzyme system responsible for statin breakdown leading its accumulation

- Not all statins are incompatible with grapefruit, but the ones that are, include:
  - atorvastatin
  - Lovastatin
  - Simvastatin
- Other statins do not interact with grapefruit including:
  - rosuvastatin
  - pravastatin
  - fluvastatin
  - pitavastatin

Statin and Alezhiemer

- Zissimopoulos et al tracked almost 400,000 statin users, all aged 65 or older, who took the medications between 2006 and 2013.
- The researchers linked high use of statins to a 15 percent lower risk of Alzheimer's in women and a 12 percent lower risk in men compared to those who had low use.

Statin and cancer

- Many researchers believe statin therapy may raise the risk of developing cancer or worsen existing cancer. Other studies, though, suggest that the cholesterol-lowering drugs may actually offer some cancer protection.

Statin and Coenzyme Q10

- coenzyme Q10 deficiency may be one mechanism for statin-induced myopathies. However, coenzyme Q10 supplements have not been shown to routinely improve muscle function. Additional research in this area is warranted

Statins are smart drugs ???

Who's at risk of developing statin side effects?

- Taking multiple medications to lower your cholesterol
- Female sex
- Low body weight
- Age 65 or older
- Drinking too much alcohol
- kidney or liver disease

Drugs and food that interact with statins

- Grapefruit
- Some drugs :
- Amiodarone,
- Gemfibrozil
- Protease inhibitors, such as saquinavir and ritonavir
- Some antibiotic and antifungal medications, such as clarithromycin and itraconazole)
- Some immunosuppressant medications, such as cyclosporine

conclusion

Statins trials enriched the science of lipidology by a wealth
Of data through the last decades

However ,we must care about

LIVER
MUSCLE SYMPTOMS
DIABETES
DRUG INTERACTIONS
PREDISPOSED PATIENTS

THANK YOU