Statins resistance

By

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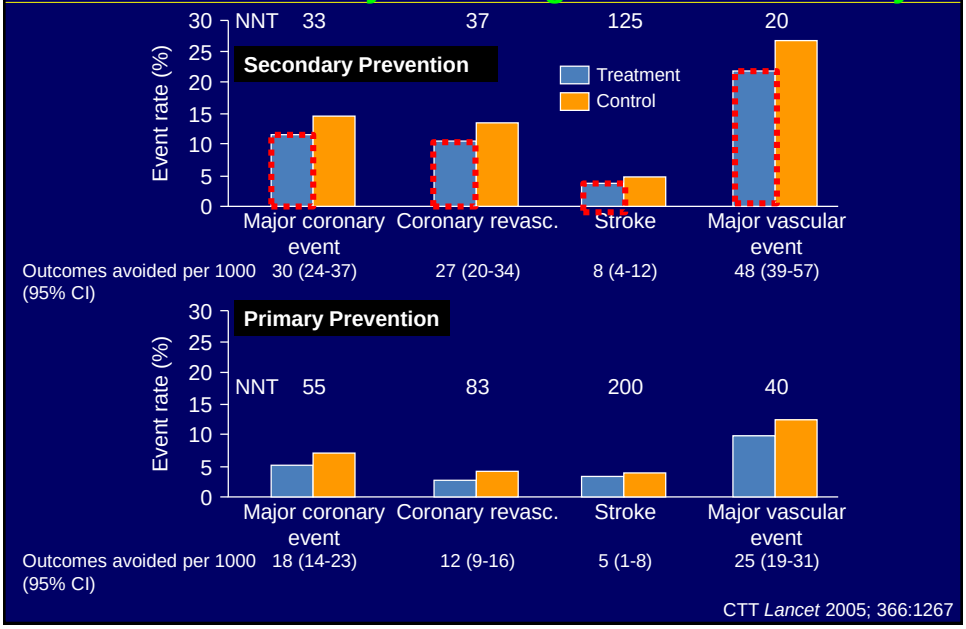
Absolute Benefit of Statins

Events Prevented by Reducing LDL 1 mmol for 5 yrs



CTT *Lancet* 2005; 366:1267

Prospective meta-analysis: 90,056 participants in 14 randomized statin trials

For each 1 mmol/L LDL-C lowering

- **12% reduction in all-cause mortality (*P*<0.0001)**
- **19% reduction in coronary mortality (*P*<0.0001)**
- **23% reduction in MI and coronary death (*P*<0.0001)**
- **24% reduction in revascularizations (*P*<0.0001)**
- **17% reduction in fatal or non-fatal stroke (*P*<0.0001)**
- **21% reduction in any major vascular event (*P*<0.0001)**
- **No increase in non-vascular mortality or cancers**

Adapted from Baigent C et al. Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet* 2005; 366:1267-78

Risk Factors for Statin Induced Myopathy Patient Characteristics

- ***Demographics***
  - Older Age,
  - Female gender
  - Asian race
- ***Genetic Predisposition***
  - CYP isoenzymes
  - FH of statin intolerance
- ***Comorbidities***
  - Hypothyroidism
  - Systemic disease
  - Alcoholism / drugs
  - Major surgery
  - Myopathy
    - Hereditary (PYGM, CTP II, AMPD)
    - Acquired

Medication Interactions as Cause of Statin-Induced Muscle-Related Side Effects

- **Fibrates** -
  - **Avoid statin + gemfibrozil**
  - **Statin + fenofibrate or bezafibrate can be used cautiously**
- **Anti-rejection drugs**
  - **Cyclosporine, tacrolimus, sirolimus mycophenylate, rapamycin, 3T3**
  - **Limit statin doses to rosuvastatin 5 mg, atorvastatin 10 mg**
- **Antifungals**
- **Macrolide antibiotics**
- **HIV protease inhibitors**
  - **Avoid lovastatin and simvastatin**
  - **Initiate atorvastatin at 10mg**

Discontinue statin during treatment

- **Amiodarone**
- **Diltiazem**

Rare cause of statin myopathy
Initiate lower doses of statin

statin resistant and intolerant

IS THERE A DIFFERENCS BETWEEN

- **statin resistant**
- **statin-intolerant**

Facts

- the reduction of LDL-C in response to statin therapy can vary by as much as 5-70% from person to person, even when compliance is taken into account, with many individuals not reaching LDL-C target values .
- LDL-C response can be influenced by racial factors, , whereas response attenuated in blacks compared with whites.
- there are almost no studies which compared statin resistant patients with statin nonresistant patients.

There is impact of genetic factors on statin action

It has been mentioned already that

- the same dose of the same statin in different individuals produces different LDLC decreases,
- time to reach maximum LDL-C decrease differs significantly between individuals
- There are studies have identified numerous candidate genes (>50) and dozens of single-nucleotide polymorphisms (SNPs) that have been reported to be associated with differing aspects of response to statin

when

in some individuals statins are unable to prevent atherosclerotic changes and/ or reduce clinical outcomes . This individual called to have

"statin resistance,"

Resistance to statins

Resistance to statins can be related to the differences in

I. drug absorption,
II. drug transport,
III. intrahepatic drug metabolism,
IV. drug metabolism within other organs,
V. Difference in drug excretion mechanisms

What is statin resistance and what is statin intolerance?

- **According to the National Library of Medicine**

Statin resistance :

- Although the definition of resistance seems to be quite clear, but it is very difficult to determine what really statin resistance is
- **It can be defined as** it is **diminished** or **failed response** of an individual to the intended effectiveness of a statin To reach LDL-C target values **despite**
  - best available therapy,
  - mostly a highest tolerable dose
  - of a more potent statin,

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The resistance to statins has been associated with

A. polymorphisms in the 3-hydroxy-3- methylglutaryl coenzyme A reductase (HMG-CoA-R), P-glycoprotein (Pg-P/ABCB1),
B. breast cancer
C. resistance protein (BCRP/ABCG2),
D. multidrug resistance-associated proteins (MRP1/ABCC1
E. cholesteryl ester transfer protein (CETP)
F. tumor necrosis factor a (TNF-a) genes.

When discussing guidelines the problem of resistance as an inability to reach the LDL-C target values is a reality ,but in none of them, the term "statin resistance" is mentioned

Statin intolerance is

the progressive diminution of the susceptibility of a patient to the effects of a statin, as a result of continued administration, or excess of adverse effects which prevent the patient from further treatment or using the adequate drug doses.

- Millions of statin-treated patients are considered statin intolerant because they are unable to tolerate statin therapy at all or, much more often, they may not tolerate a full therapeutic statin dose ,or having adverse effects, mostly myopathy and increased activity of liver enzymes.
- The adverse effects influencing intolerance include myopathy ranging in severity from asymptomatic increases in creatine kinase to muscle aches or weakness even in the absence of blood creatine kinase elevation.

Reported Adverse Effects of Statins

- Muscle-related symptoms
- Elevated hepato-cellular enzymes
- Cancer
- New diabetes
- Hemorrhagic stroke
- Fatigue
- Neuro-psychiatric effects and insomnia
- Proteinuria / hematuria
- Erectile dysfunction

Treatment possibilities for patients with statin resistance or intolerance

Prevention of Statin Intolerance

- **Pre-treatment assessment**
  - Assess risk (e.g. elderly, prior muscle pains, FH of myopathy, renal disease, DM, hypothyroidism)
  - Consider exogenous factors (e.g. statin dose, alcohol use, drug-drug interactions, excessive grapefruit juice use)
  - Measure baseline CK, ALT, TSH, creatinine
- **Counseling**
  - Inform that statins are very well tolerated in most people
  - Inform about muscular symptoms and when to discontinue
- **Monitoring**
  - Check CK / ALT when monitoring lipid lowering efficacy
    - At 6-8 weeks after starting or with dose increase and then every 6-12 m
    - Avoid severe exercise for several days prior to testing

Non-Statin Lipid Lowering Strategies

Ezetimibe
- Lowers LDL 15-20%
- Well tolerated
- May be added to low dose statin

Bile acid sequestrants
- Lowers LDL 15%
- May prevent diabetes
- Colesevalam better tolerated

Fibrates
- ↓ TG LDL little change
- ? Benefit when HDL low

Niacin
- Flushing/pruritus may limit tolerance
- Lowers LDL 20%
- TG ↓40%, HDL ↑30%

Ezetimibe + Bile acid sequestrant
- 40-45% LDL reduction

Future Non-Statin Strategies to Reduce LDL Cholesterol

- **CETP inhibitor**
  - Torcetrapib (increased mortality) and Dalcetrapib (no benefit)
  - Anacetrapib results awaited (↑ HDL 138%, ↓ LDL 40%)
  - Evacetrapib Phase 2 study presented 2010

- **Mipomersen**
  - Inhibits protein synthesis of apoB
  - Reduces LDL ~30%
  - Injected weekly
  - No outcomes trials

PCSK9 inhibitors
- Reduce LDL 50-60 %,
- Injected q 2 weeks
- No outcomes trials

Take home message

We have to differentiate between statin resistance and intolerance

Adverse Effects of Statin Treatment

- **More common than clinical trials suggest**
- **Probably more frequent at higher doses**

❖ **Important cause of poor adherence to treatment**

- **Manage adverse events**
  - **Use alternative statin**
  - **Reduce frequency of statin**
  - **Use non-statin agents as monotherapy or together with reduced dose or frequency statin**

Thank You