Treating Hyperlipidemias in Adults

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Disclosures

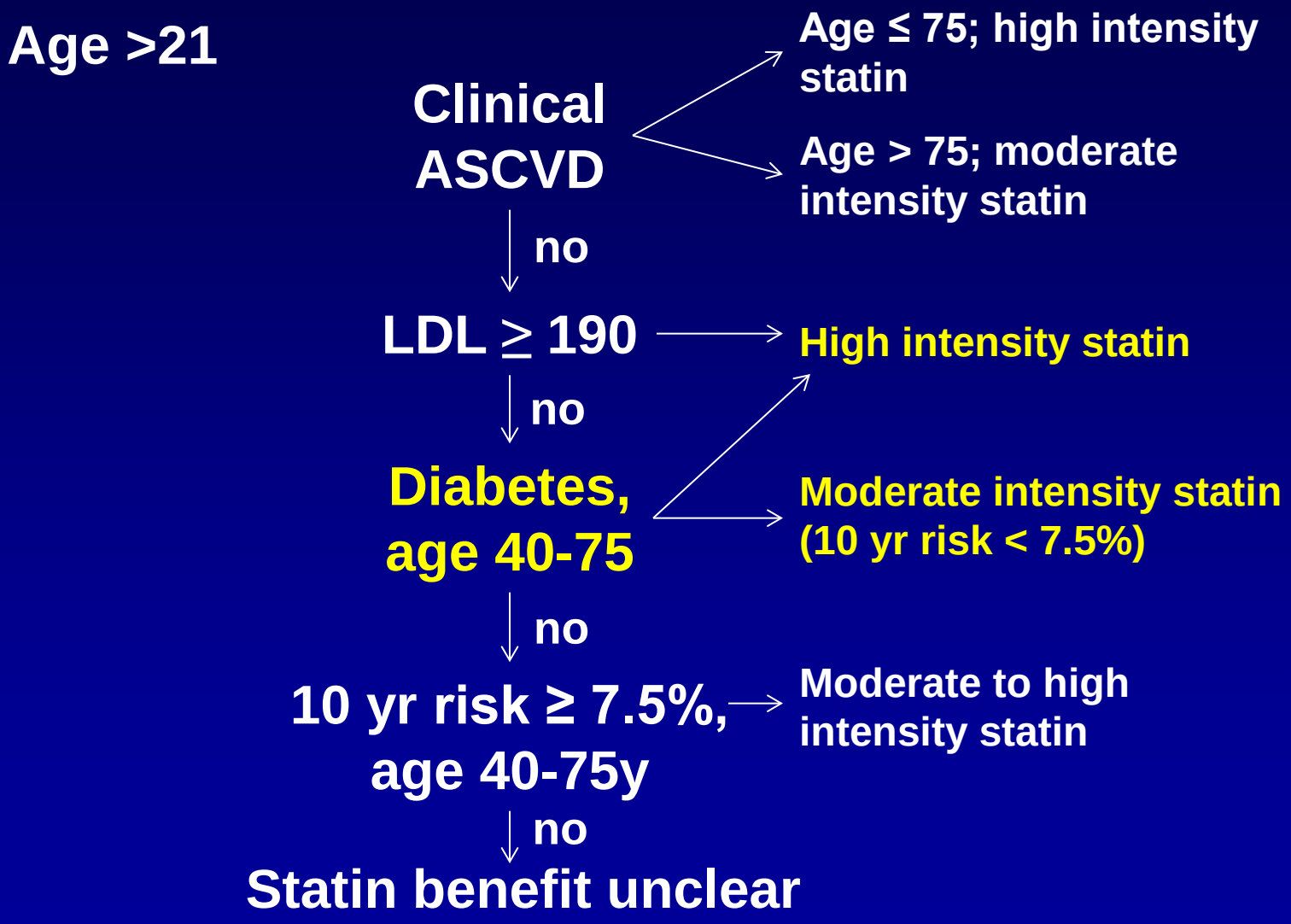
- **Conflicts: None**
- **Talk will address off-label use of statins (alternate day dosing)**

Objectives

Upon completion of this activity, participants will be able to:

- **Explain the primary role of statins in cardiovascular risk reduction**
- **Discuss approaches to managing lipids in statin intolerant patients**
- **Identify when and how to use the new PCSK9 inhibitors**

ASCVD Statin benefit groups



Statin Intensity

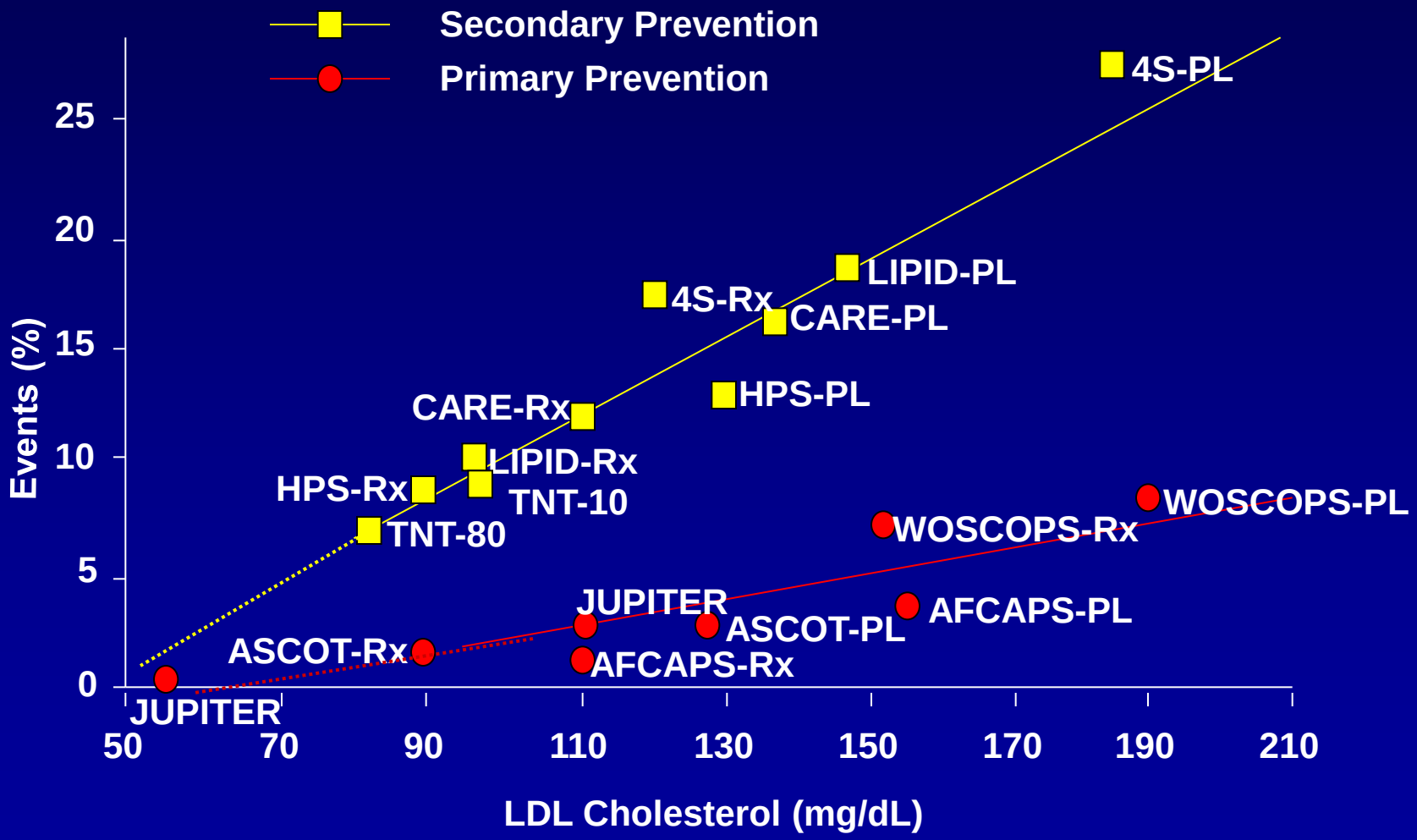
High intensity statin

- ↓LDL >50%
- Atorva 40, 80
- Rosuva 20, 40

Moderate intensity statin

- ↓LDL 30-50%
- Atorva 10, 20
- Fluva 80
- Lova 40
- Pitava 2, 4
- Prava 40, 80
- Rosuva 5, 10
- Simva 20, 40

CHD Events Reduced with LDL Lowering (Statin Trial Data)



Adapted from Illingworth DR. *Med Clin North Am*. 2000;84:23-42.

Case

52 ♂ type 2 DM with known CVD

- MI and CABG 3 years ago
- DM2 x 8 years, HbA1c ranges 7.5-8.1%
- Nonsmoker, BP controlled

Meds:

- Insulin
- Metformin
- Gabapentin
- Lisinopril
- ASA
- Pravastatin 20mg/d
- ("intolerant" of higher doses)

Labs

- TC 173
- HDL-c 28
- LDL-c 109
- TG 180
- HbA1c 7.7%
- TSH 1.2

What is the most appropriate management?

A. Change to a more potent statin
B. Add co-Q-10 and a more potent statin
C. Add a PCSK9 inhibitor
D. Add ezetimibe
E. Add empagliflozin

Terminology to Describe Statin Associated Muscle Symptoms (SAMS)

Condition	Definition
Myalgia	muscle ache or weakness *without* creatine kinase (CK) elevation[1]
Myopathy	muscle symptoms *with* increased CK levels (concern if CK>10 x ULN[2])
Rhabdomyolysis	muscle symptoms with marked CK elevation (typically >10 x ULN) and with creatinine elevation (usually with brown urine and urinary myoglobin)[1]

1. Pasternak et al. *Circulation*. 2002;106:1024-1028.
2. Evans et al. *Drug Saf*. 2002;25:649-663.

Prevalence of SAMS

- In clinical practice 10-25% of patients report statin intolerance
  - In trials, similar reports of muscle complaints between statin and placebo groups

Factors That Increase the Risk of Statin-Induced Myopathy

Patient Characteristics
Increasing age
Female sex
Renal insufficiency
Hepatic dysfunction
Hypothyroidism
Diet (ie, grapefruit juice)
Polypharmacy

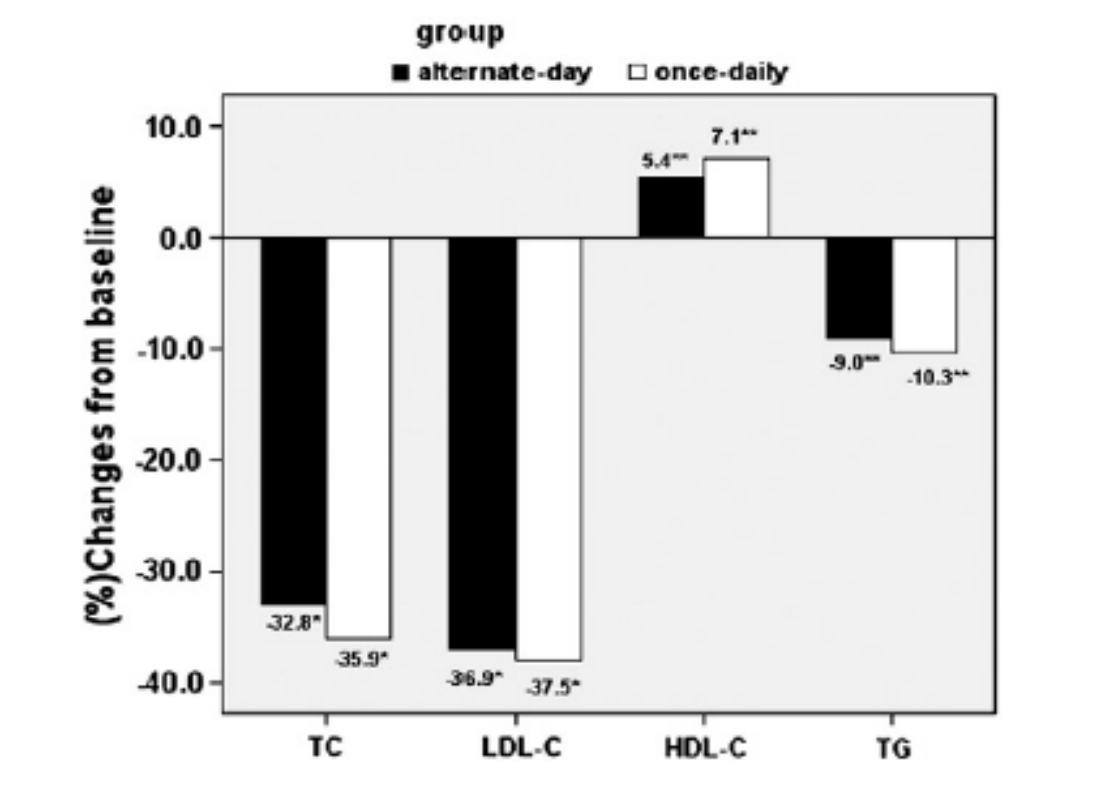
Statin Properties
High systemic exposure
Lipophilicity
High bioavailability
Limited protein binding
Potential for drug-drug interactions metabolized by CYP pathways (particularly CYP450 3A4)

Try another statin?

EAS Panel Recommendations for SAMS

- Discontinue then re-try
- Try at least 3 different statins
- Use max tolerated statin dose combined with non-statin lipid therapies

Alternate Day Statin Dosing



37 patients randomly assigned to rosuvastatin 10 mg daily or rosuvastatin 10 mg every other day, x 6 weeks

Similar results seen in a study comparing atorvastatin 10 mg daily vs 10 mg every other day; ↓LDL 38% vs 35% (Matalka, Am J Heart 2002)

Li et al, Clin Chim Acta 2012, 413:139-42

< Alternate Day Statin Dosing

- **10 patients with statin intolerance (myalgias, ↑LFTs or GI distress) were treated with rosuvastatin 5-20 mg once weekly; ↓LDL 29% at 4 months, 8 tolerated once weekly dosing (Backes et al, Am J Cardiol 2007; 100:554-5)**

Try Alternate Day Statin Dosing?

- *Off label use*
- No CVD outcomes data
- Would theoretically be better with atorvastatin or rosuvastatin which have relatively long half lives
- A reasonable option, may lead to greater ↓LDL and ↓CHD than ezetimibe monotherapy

Statin + CoQ10?

Statin + CoQ10

- **RCT of CoQ10 in patients with confirmed statin myopathy**
  - **Cross-over run in on simvastatin or placebo; only subjects who had muscle pain on statin but not placebo, and no pain in washout phase were enrolled**
  - ***Only 38.5% of pts with prior statin myalgia met this criteria***
- **Subjects then randomized to statin + placebo or statin + CoQ10, for 8 weeks, then 4 week washout, then other treatment for 8 weeks**

Taylor et al, Atherosclerosis 2015; 238:329-35

Statin + CoQ10 Results

- Pain scores increased with statin Rx in both groups with no difference between CoQ10 or placebo
- # subjects with muscle pain was higher in CoQ10 group than placebo group (P=0.05)
- No effect of CoQ10 on lipid lowering efficacy of statin

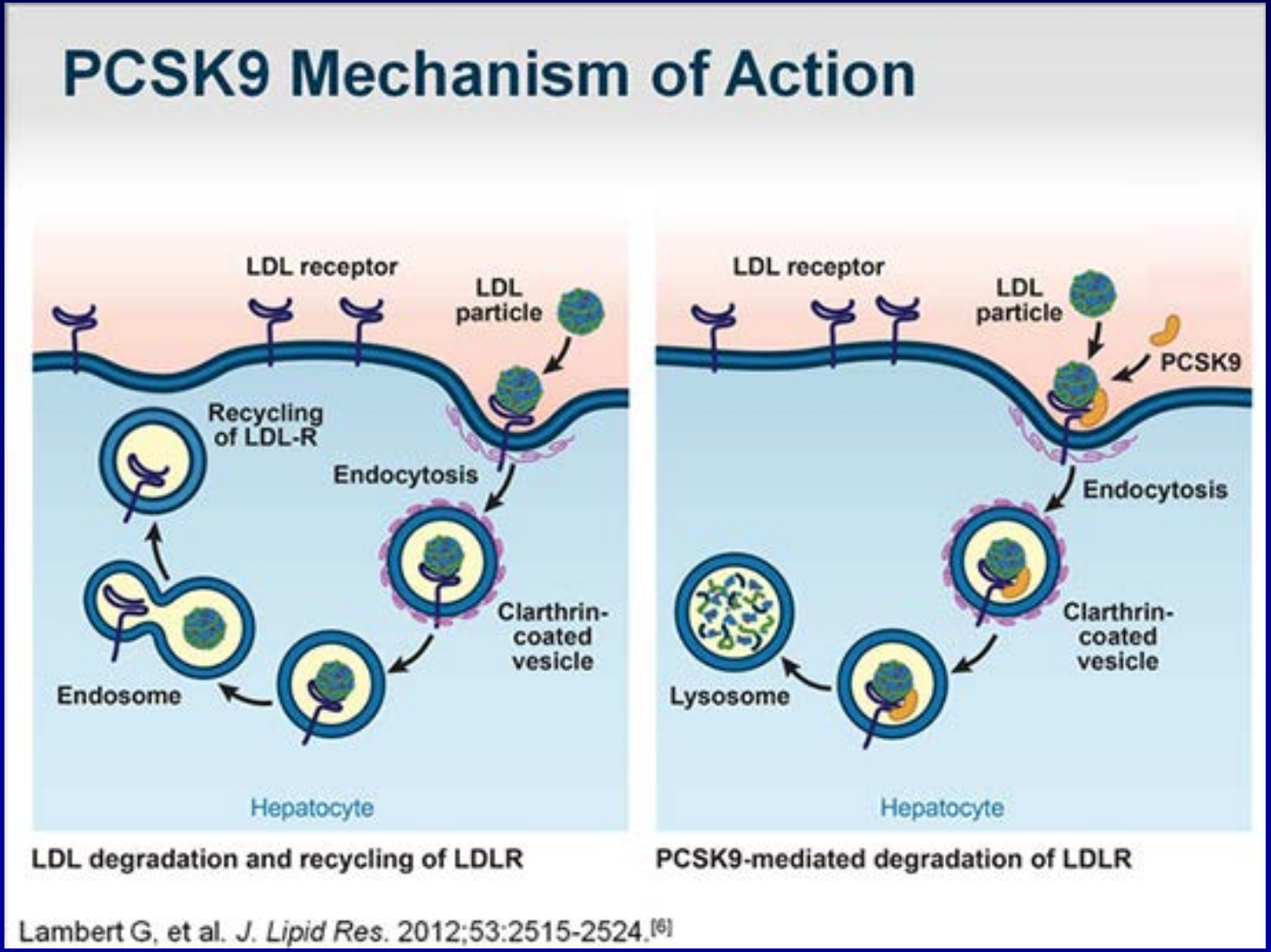
Taylor et al, Atherosclerosis 2015; 238:329-35

Statin + Co-Q10?

- Not likely to benefit
- Most muscle complaints on statins are not due to statins

Add a PCSK9 Inhibitor?

New drugs: PCSK9 Inhibitors



Lambert G, et al. *J. Lipid Res.* 2012;53:2515-2524.[6]

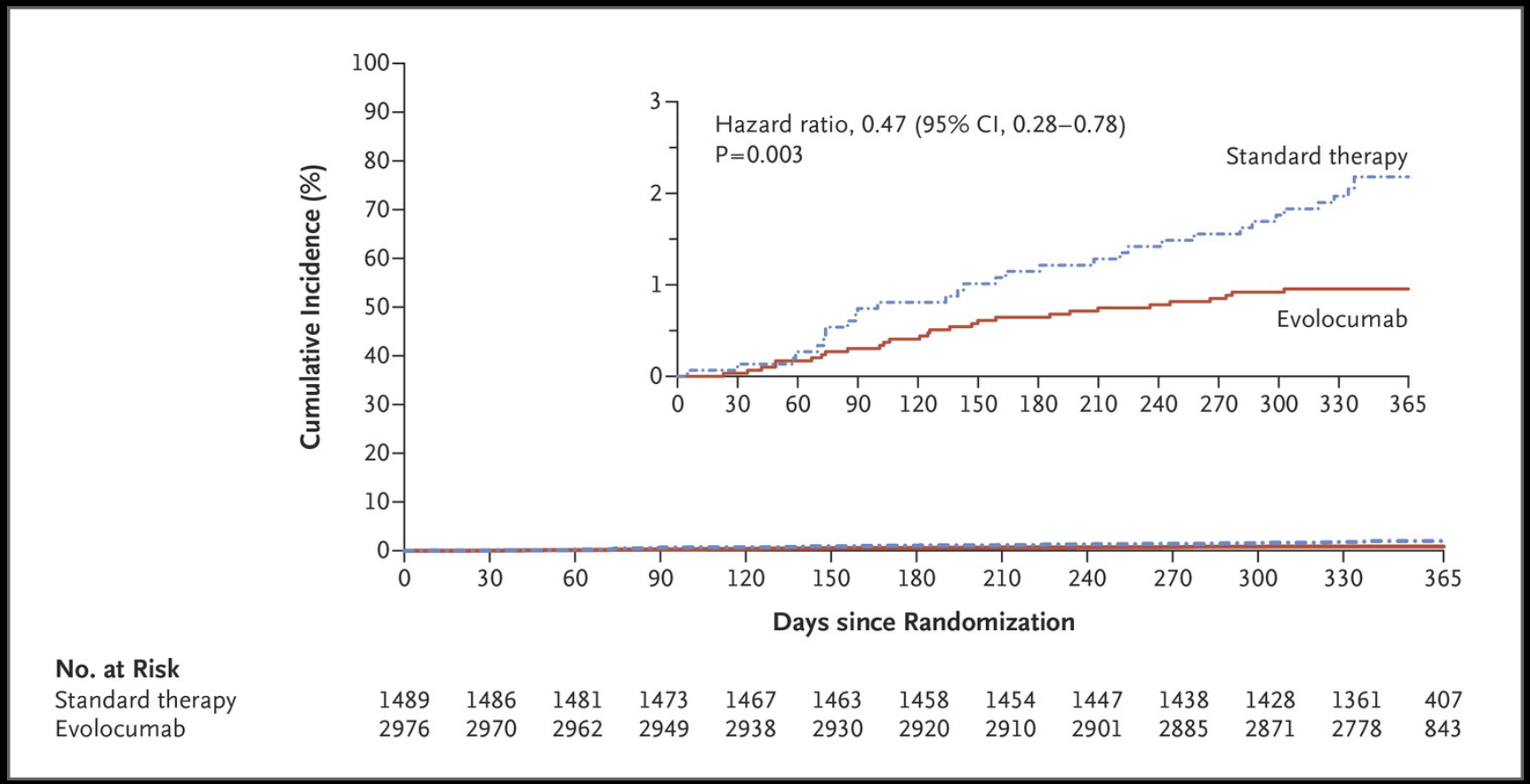
PCSK9 Mechanisms

- **Gain of function mutations in PCSK9 are associated with autosomal dominant hypercholesterolemia (resembles FH)**
  - **PCSK9 continually directs LDL-R to lysosome, leading to decreased LDL-R on cell surface, and decreased clearance of LDL**
- **Loss of function mutations in PCSK9 are associated with low LDL and low CVD**
  - **LDL-R is recycled to cell surface and clears LDL from circulation**

PCSK9 inhibitors

- Monoclonal antibodies to PCSK9
- Prevent PCSK9 from directing the LDL-R for degradation, so there is increased recycling of LDL-R to hepatocyte surface and increased clearance of LDL from circulation

Cumulative Incidence of Cardiovascular Events.



Sabatine MS et al. N Engl J Med 2015;372:1500-1509.

The NEW ENGLAND JOURNAL of MEDICINE

PCSK9 Inhibitors

- CKD/Liver disease – no data in severe; no dose adjustment in mild/mod
- Pregnancy/ lactation – no data
  - Animal studies: likely crossed placenta in T2/T3
  - No fetal development issues
- Pediatrics – Evolucumab ok in 10 teens with HoFH
- Geriatrics - ok

Add a PCSK9 Inhibitor?

- **Yes – if patient can afford and can tolerate it**

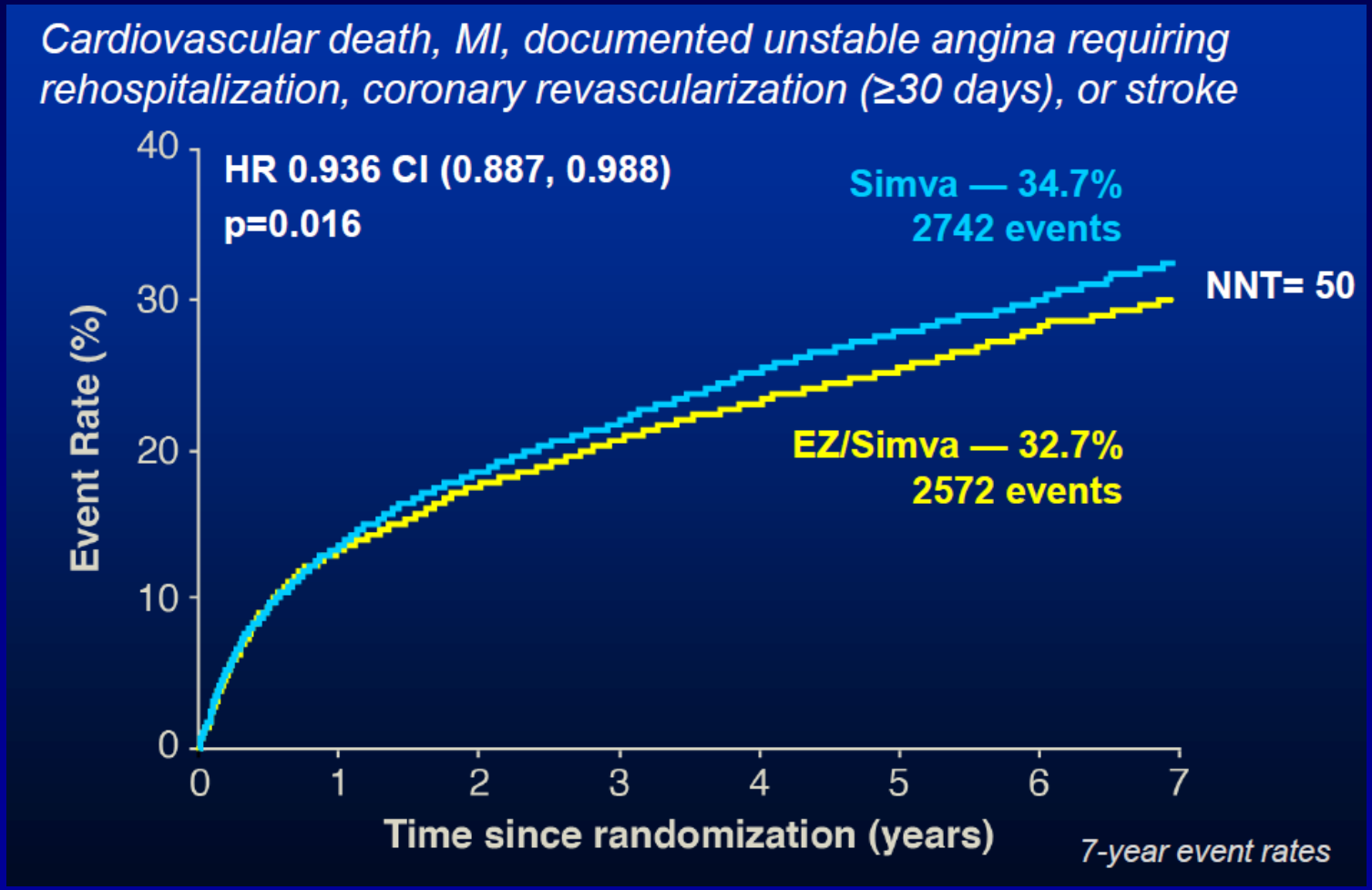
- **Unknowns:**
  - **CV outcomes,**
  - **long term safety,**
  - **long term efficacy (so far no anti-drug antibodies appear to be neutralizing)**

Add Ezetimibe?

Ezetimibe

- As monotherapy expect ↓LDL ~ 18%
  - When added to statin expect ↓LDL ~ 25%
- No CVD outcomes data for ezetimibe monotherapy available

Add Ezetimibe? IMPROVE-IT



http://www.eas-society.org/fileArchive/IMPROVE%20IT%20-%20PRESENTATION%202014-11-17.pdf

Add Ezetimibe?

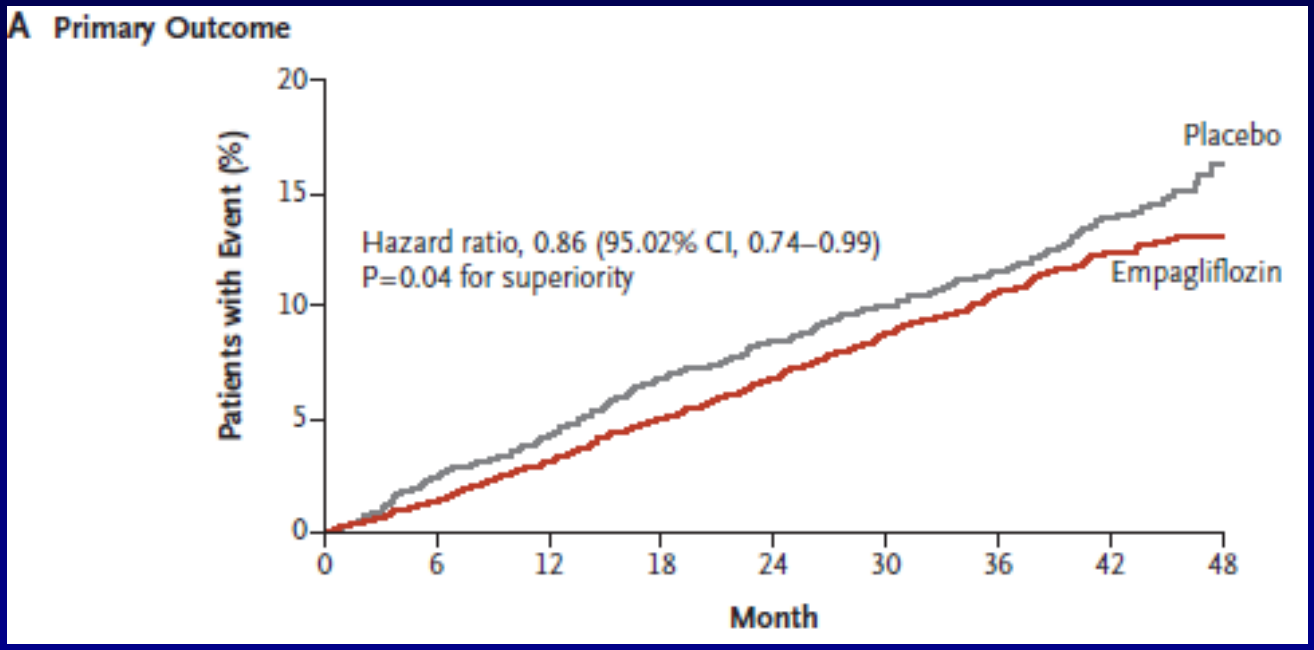
- **Yes – is safe and efficacious**
- **Improved CV outcomes shown**
- **Adding ezetimibe is an option**

Add Empagliflozin?

SGLT2 inhibition

- **EMPA-REG OUTCOME study**
- **7020 type 2 diabetics (HbA1c 8.0%) with known CVD randomized to empagliflozin (10 or 25mg/d) or placebo**
- **77% on statins**
- **80% on ACE inhibitors/ARBs**

Add SGLT2i? EMPA-REG OUTCOME



Primary outcome: CVD death, nonfatal MI, nonfatal stroke;

Significant benefits also seen in all cause mortality (P<0.001) and CHF hospitalization (P=0.002)

LDL actually *increased* on EMPA (~87 in placebo, ~90 on EMPA)

Zinman et al, NEJM 2015

Add Empagliflozin?

- Maybe
- Further CVD benefit shown

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