Discussant of the IMPROVE IT Trial: Presented at AHA Scientific Sessions Nov. 2014

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Disclosures

No disclosures

I do not accept honoraria from pharmaceutical companies.

I served as the chair of the **2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults**

PROVE-IT TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2004 VOL. 350 NO. 15

Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

CONCLUSIONS

Among patients who have recently had an acute coronary syndrome, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen. These findings indicate that such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels.

Atorvastatin 80 mg/d v. Pravastatin 40 mg/d

N ENGL J MED 350;15 WWW.NEJM.ORG APRIL 8, 2004

IMPROVE-IT

- A large scale (18,144 participants), multi-center RCT of high risk post Acute Coronary Syndrome (ACS) patients
- Intervention: ezetimibe 10 mg added to simvastatin 40*
- Comparator: simvastatin 40*
  Both groups achieved a mean LDL-C < 70 mg/dl
- Study took 9 years; f/u was 7 years
- No increase in side effects with the intervention

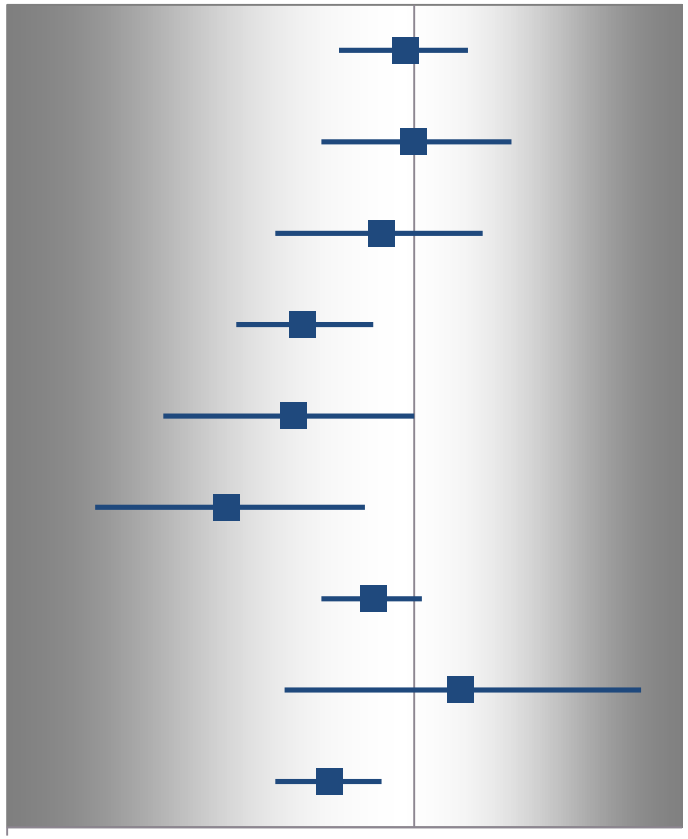
*some uptitration allowed.

LDL-C and Lipid Changes in IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	**69.9**	145.1	137.1	48.1	3.8
EZ/Simva	**53.2**	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5

IMPROVE-IT slide set with permission

Individual Cardiovascular Endpoints and CVD/MI/Stroke



	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

**7-year event rates (%)*

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View from 35,000 Feet:

1) Study reaffirms the central role of intensive LDL reduction in the prevention of recurrent cardiac events (heart attack and stroke)

2) Results expand the options for additional "proven" * lipid lowering therapies

   *Shown to add incremental benefit and are safe when taken as directed

What The RCT Data Suggests:

3) Perhaps we have not yet established a lower boundary of the benefits of lowering LDL-C in this highest risk group (if we can do it safely)

Does This Change the Guidelines?

2013 ACC-AHA Guidelines recommended high-intensity statin therapy for those with ACS, but expressly stated:

"Clinicians treating high risk patients who have a less than anticipated response to statins, who are unable to tolerate a less than recommended intensity of a statin or who are completely statin intolerant, may consider the addition of non-statin cholesterol lowering therapy"

Does This Change the Guidelines?

… In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects, drug-drug interactions and consider patient preferences.”

Stone NJ et al. 2013 ACC-AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risks in adults: J Am Coll Cardiol 2014;63:2889–934.

Clinical principles

(adapted from Dr. Oliver Wendell Holmes)*

1) **Not to guess when you can know**

-Seek high level evidence to guide decisions

2) **Not to take authority when you can have facts**

-Headlines can be misleading; consider evidence quality, see if results are biologically plausible

3) **Don't prescribe just because the patient is ill; consider net benefit**

--use best data to inform clinician judgment

*Neuheuser D. Qual Saf Health Care 2006;15:302–304.

"NOT TO GUESS WHEN YOU CAN KNOW"

Look to RCTs --when appropriately designed, conducted, and reported, represent the "gold standard"

Recent large-scale RCTs didn't prove "lower is better"

--**HERS**: Estrogen-progestin of no benefit in women with coronary disease

--**ILLUMINATE**: Torcetrapib study terminated abruptly and prematurely after excess deaths

--**AIM-HIGH/HPS2-THRIVE** – no support for niacin added to a statin

"Not to Take Authority When You Can Have Facts"

Does the mechanism of action of ezetemibe make these results biologically plausible?

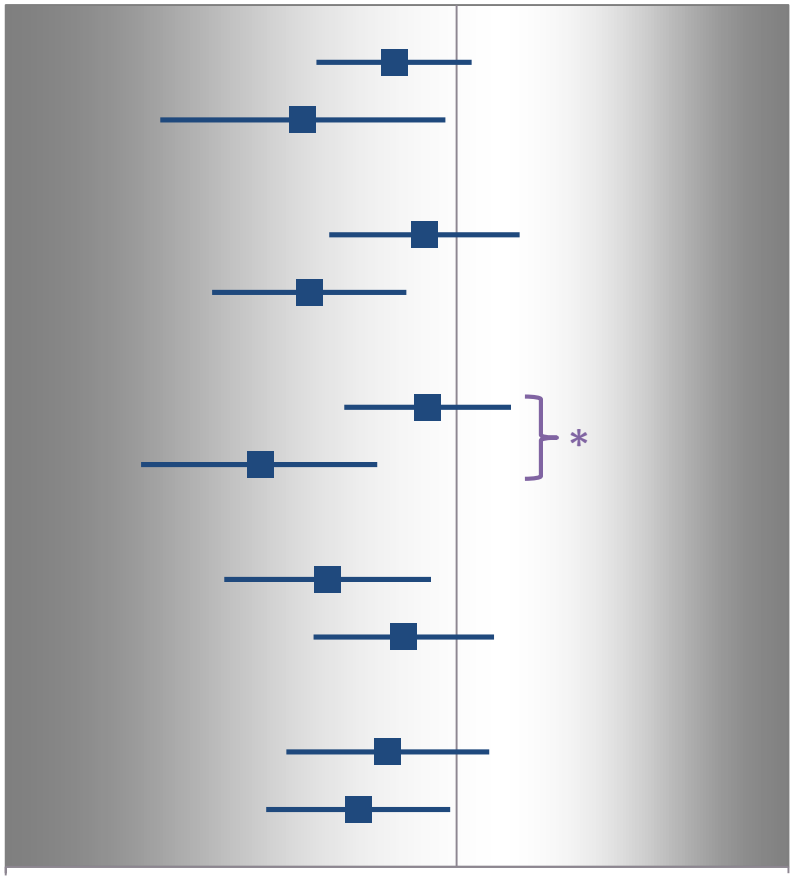
Ezetemibe inhibits the function of the protein encoded by the Niemann-Pick C1-like 1 gene (NPC1L1) to transport cholesterol at the intestinal level.

Ezetemibe blocks sterol absorption by 50% and LDL-C by about 15-20%.

Naturally occurring mutations that disrupt NPC1L1 function have lower LDL-C and reduced risk of CHD significantly over a lifetime.
This supports lifestyle change at an early age.

*Myocardial Infarction Genetics Consortium Investigators NEJM Nov 2014.

Major Pre-specified Subgroups



	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age < 65 years	30.8	29.9
Age ≥ 65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C > 95	31.2	29.6
LDL-C ≤ 95	38.4	36.0

†*7-year event rates*

Simva Better **p-interaction = 0.023, otherwise > 0.05*

Safety

No statistically significant differences in cancer or muscle- or gallbladder-related events

% = n/N for the trial duration	Simva n=9077 %	EZ/Simva n=9067 %	p
ALT and/or AST≥3x ULN	2.3	2.5	0.43
Cholecystectomy	1.5	1.5	0.96
Gallbladder-related AEs	3.5	3.1	0.10
Rhabdomyolysis*	0.2	0.1	0.37
Myopathy*	0.1	0.2	0.32
Rhabdo, myopathy, myalgia with CK elevation*	0.6	0.6	0.64
Cancer* (7-yr KM %)	10.2	10.2	0.57

** Adjudicated by Clinical Events Committee*

“Consider net benefit”

Guidelines: Still strong evidence for high intensity statin therapy in secondary prevention

Use high intensity statin and lifestyle to achieve lowest LDL level that a safe and tolerated regimen can provide.

1) If high intensity statin not tolerated or response to therapy not adequate, the data support using a moderate intensity statin to which a non-statin such as ezetemibe can be added
2) These data do not speak to use of ezetemibe in patients with low risk primary prevention