Controversial Issues on New Guideline

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

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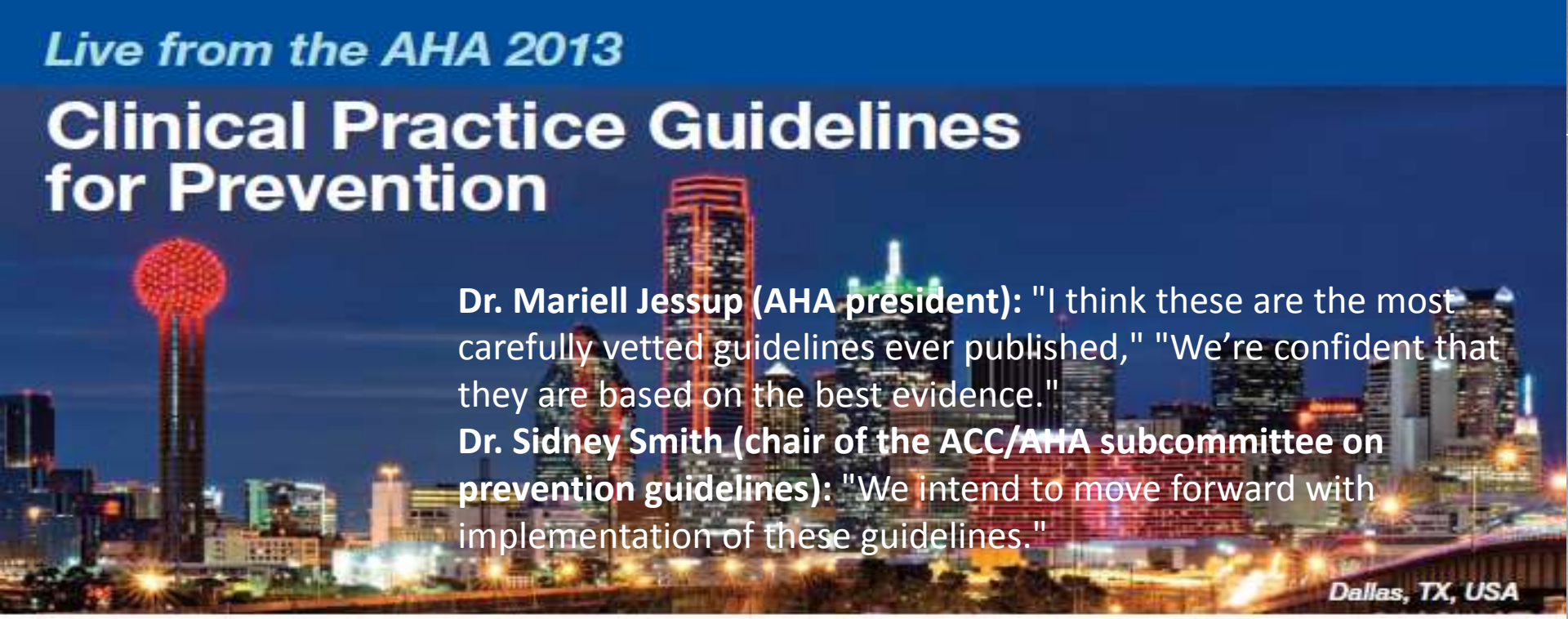
Live from the AHA 2013

Clinical Practice Guidelines for Prevention



Dr. Mariell Jessup (AHA president): "I think these are the most carefully vetted guidelines ever published," "We're confident that they are based on the best evidence."

Dr. Sidney Smith (chair of the ACC/AHA subcommittee on prevention guidelines): "We intend to move forward with implementation of these guidelines."

Session chairs: Dr Mariell Jessup, University of Pennsylvania and President of the AHA
Professor John Harold, Cedars-Sinai Heart Institute and President of the ACC

In November 2013 the American Heart Association (AHA) and the American College of Cardiology (ACC) published joint guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) risk.[1] On November 20, 2013 the Chair of the guidelines committee, Professor Neil Stone, presented on the new guidelines during the late-breaker session at the AHA. The session also included Professor Donald Lloyd-Jones presenting the new AHA and ACC guideline on the assessment of cardiovascular risk,[2] an important component of the new cholesterol guidelines.

Some Issues raised over new anti-cholesterol guidelines

Family Practice News | digital network

News and Views that Matter to Family Physicians

Guideline authors, AHA-ACC leaders confident in risk calculator

The New York Times

Risk Calculator for Cholesterol Appears Flawed

By GINA KOLATA

Published: November 17, 2013 | 794 Comments

Controversy, confusion over new cardiovascular-risk guidelines

By Susan Perry | 11/19/13

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Donald Lloyd-Jones, MD, ScM, FAHA

"I think these are these are the most carefully vetted guidelines ever published," said Dr. Mariell Jessup, AHA president. "We're confident that they are based on the best evidence."

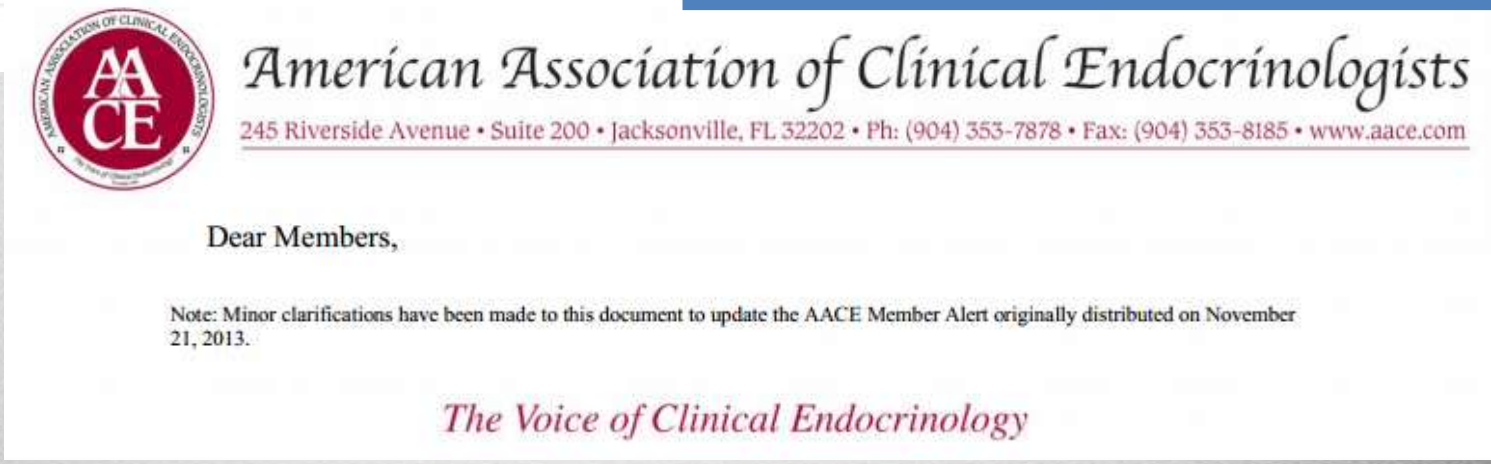
Some Doctors Challenge New Statin Guidelines

They say too many people would get the cholesterol-lowering drugs; heart groups defend the recommendations

November 18, 2013 | RSS Feed | Print

The EAS/ESC guidelines have worked well in Europe. They have been widely accepted and adopted and, based on the discussion above, we recommend the EAS/ESC guidelines as more fitting for Europe.

We recommend that AACE members continue to refer to AACE guidelines and position statements on Lipids and Obesity to assist decision making in their practices.



What ISSUEs?

1. New risk calculator?
2. Non-statin, is it available?
3. No LDL treatment target and instead focus on the intensity of statin?
4. Efficacy and Safety of high intensity statin therapy in Asian population?
5. Statin therapy on CKD patients?
6. Other new emerging risk factors?

What ISSUEs?

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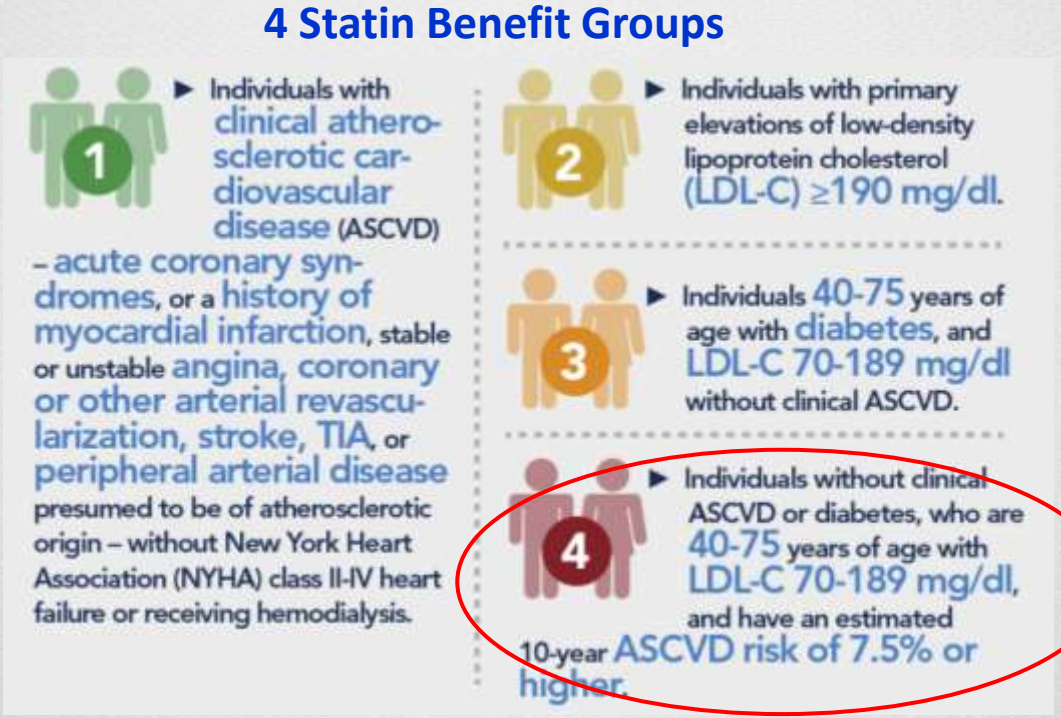
Through a rigorous process, **4 groups** of individuals were identified for whom an extensive body of RCT evidence demonstrated a reduction in atherosclerotic cardiovascular disease (ASCVD) events (including coronary heart disease [CHD], cardiovascular deaths, and fatal and nonfatal strokes) with a good margin of safety from statin therapy:



Stone NJ, et al. published online November 12, 2013 Circulation.

New risk calculator: Pooled Cohort Equations

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
1. The race- and sex-specific Pooled Cohort Equations* to predict 10-year risk for a first hard ASCVD event should be used in nonHispanic African Americans and nonHispanic Whites, 40 to 79 years of age.	B (Moderate)	N/A	I	B (4-8)

- To evaluate ASCVD risk the patients who are not currently treated with statins
- To help assess whether an individual patient may benefit from statin therapy.

stone NJ, et al. published online November 12, 2013 Circulation.

Characteristics of new risk calculator: CVD events

Risk Score				CVD Events			
Study Group	**Study and Region**	**Data Source**	**Publication Year**	**MI**	**CHD death**	**Stroke**	**Stroke death**
ATP 3	**Framing-ham** MA, USA	EAF, EAM	2001	√	√		
EURO SCORE	12 cohorts Europe	EF, EM	2003		√		√
QRISK*	QRESE ARCH, United Kingdom	EF, EM	2007	√	√	√	√
Pooled Cohort Equations	CARDIA, Framing-ham, ARIC, CHS, USA	EAF, EAM AAF, AAM	2013	√	√	√	√

stone NJ, et al. published online November 12, 2013 Circulation.

Characteristics of new risk calculator: Risk factors

Risk Score	Risk Factors/covariates included											
	Age	Sex	TC	HDL-C	SBP	BP Rx	Diabetes	Smoking	Family hx CVD	BMI	Social	Region
ATP 3	√	√	√	√	√	√		√				
EURO SCORE	√	√	√	√	√			√				√
QRISK*	√	√	√	√	√	√		√	√	√	√	√
Pooled Cohort Equations	√	√	√	√	√	√	√	√				

*QRISK also assess risk of coronary revasc, angina pectoris, unstable angina, and TIA.

stone NJ, et al. published online November 12, 2013 Circulation.

Characteristics of new risk calculator: race, sex

56.4%

17.4%

	Caucasian Women	African-American Women	Caucasian Men	African-American Men
N	11,240	2641	9098	1647
Age range, y	40–79	40–79	40–79	40–79
C statistic	0.81	0.82	0.75	0.71
Calibration χ^2	6.43	7.25	4.86	6.71

- Based on evidence from broad populations of Caucasian and African-American patients
- First risk calculator to include female sex and African-American race

Not included Hispanic, Asian and Native American

stone NJ, et al. published online November 12, 2013 Circulation.

The New York Times

Health

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Risk Calculator for Cholesterol Appears Flawed

By GINA KOLATA
Published: November 17, 2013 | 794 Comments

Dr. Nancy Cook and Dr. Paul M. Ridker of Harvard Medical School found that a new online calculator used to assess heart treatment options overestimated the risks that many people face.

Issues of New Risk Calculator

Dr. Ridker and Cook of Harvard Medical School

The problems were identified by two Harvard Medical School professors whose findings will be published Tuesday in a commentary in The Lancet, a major medical journal. The professors, Dr. Paul M. Ridker and Dr. Nancy Cook, had pointed out the problems a year earlier when the National Institutes of Health's National Heart, Lung, and Blood Institute, which originally was developing the guidelines, sent a draft to each professor independently to review. Both reported back that the calculator was not working among the populations it was tested on by the guideline makers.

Dr. Blaha and Blumenthal of Johns Hopkins University

The new ACC/AHA cardiovascular-risk guidelines feature updated equations for women, distinct equations for African–American individuals, and include stroke prediction. However, the equations rely on the same traditional risk factors as previous versions, are driven predominantly by age, and curtail the intermediate-risk group, in which personalized risk assessment is recommended.

Dr. Nissen of Cleveland Clinic

Dr Steven Nissen (Cleveland Clinic, OH) said he has long been an advocate of using intensive doses of statins in high-risk patients, so the question for him is not about the efficacy of the drugs for reducing morbidity and mortality. "But we have to treat the right patients, and the problem is that the risk calculator in the guidelines has never been previously published and therefore could not be independently verified," he told **heart *wire*** .

And this is problematic because there are some instances where the risk-assessment algorithm is not consistent with best medical practice.

Risk calculator overestimate risk!

Dr. Paul M. Ridker and Dr. Nancy Cook


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The Lancet, Volume 382, Issue 9906, Page 1680, 23 November 2013
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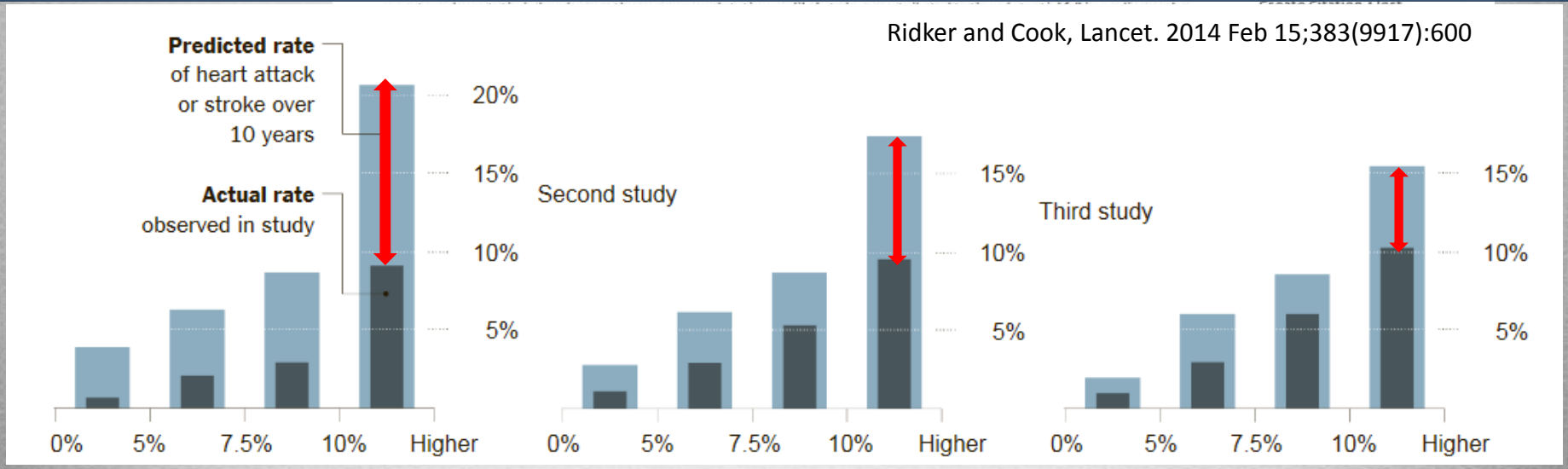
Statins: new US guideline sparks controversy

New calculator overestimates CV risk with 75 to 150%

Ridker and Cook, Lancet. 2014 Feb 15;383(9917):600



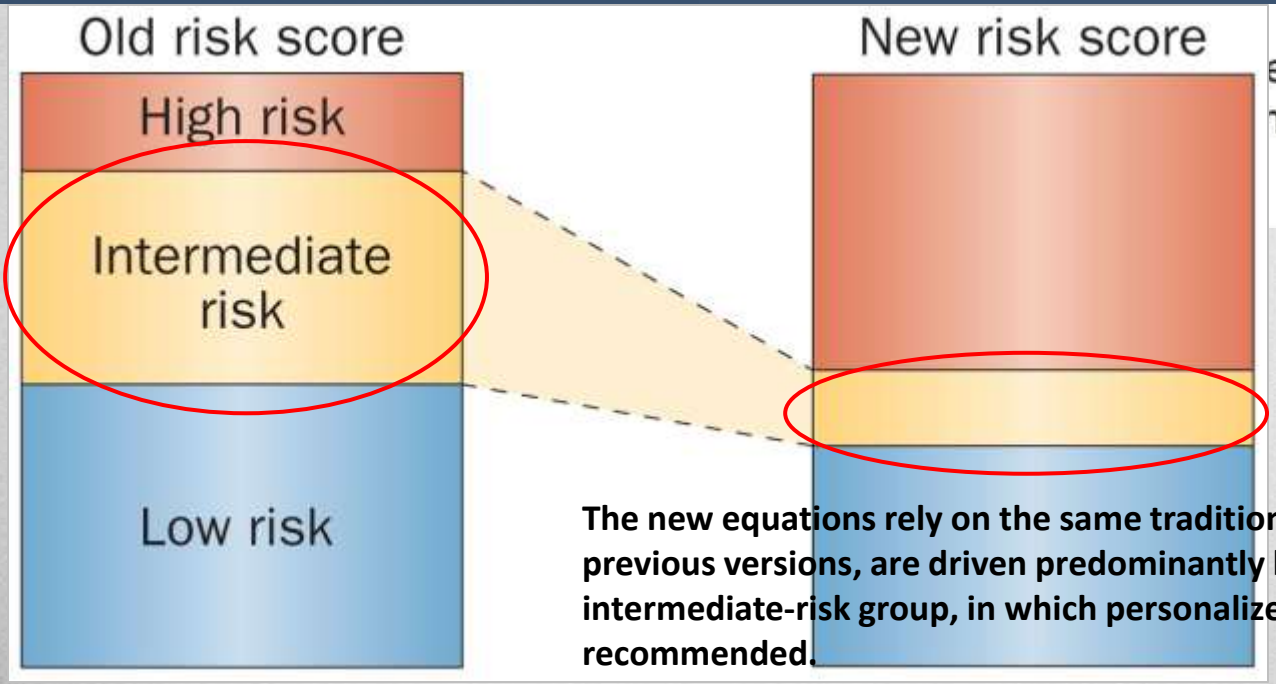
Women's Health Study | **Women's Health Initiative** | **Physician's Health Study**

More or less personalized?

Dr. Michael Blaha and
Dr. Roger Blumenthal

nature REVIEWS CARDIOLOGY

Curtailed the intermediate-risk group



The new equations rely on the same traditional risk factors as previous versions, are driven predominantly by age, and curtail the intermediate-risk group, in which personalized risk assessment is recommended.

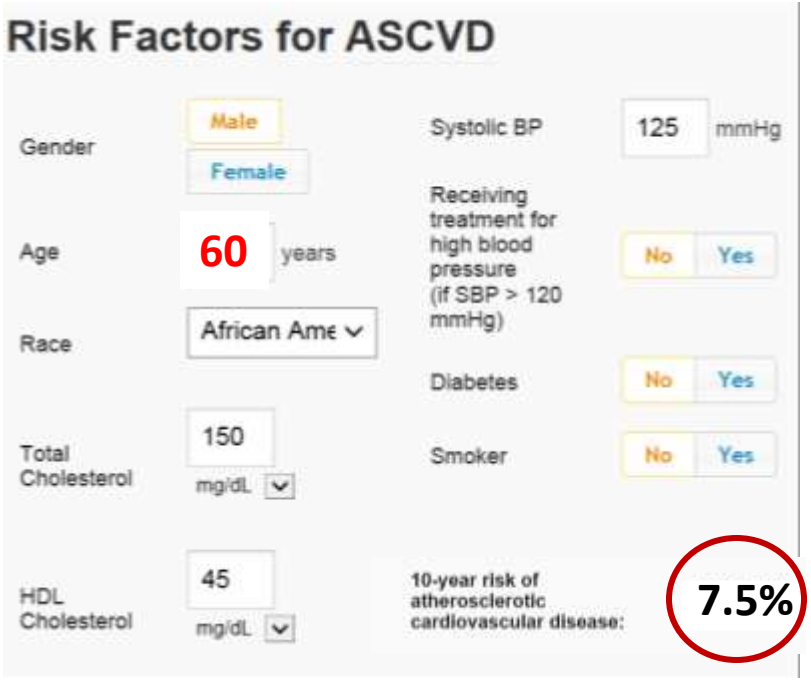
Blaha and Blumenthal, Nature Reviews Cardiology 2014;11:136

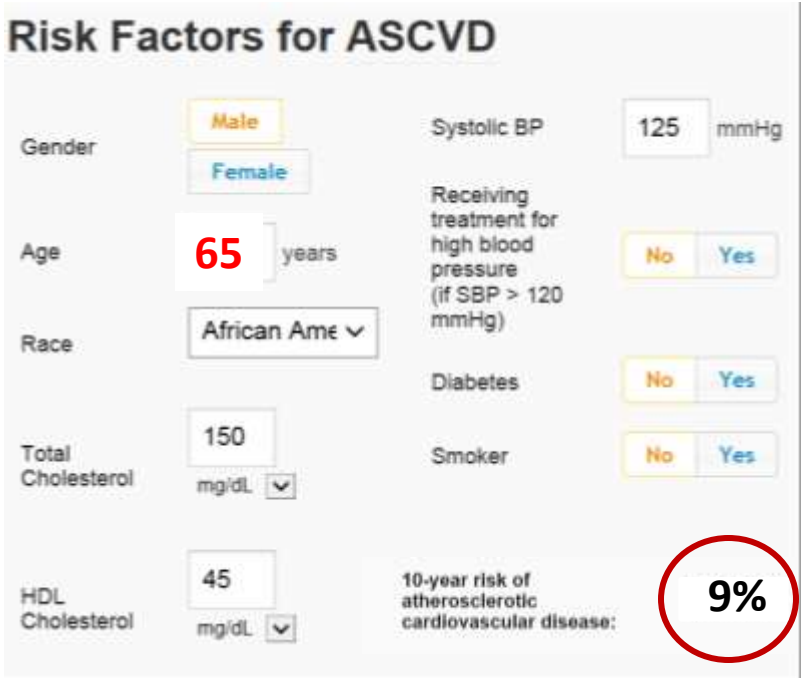
Dr. Steven Nissen

"Age and race seem to drive it a lot"

<hypothetical case>

	Age	Sex	Race	Total cholesterol	HDL cholesterol	Systolic BP	BP Rx	Diabetes	Smoking
case 1	60	male	Black	150	45	125	No	No	No
case 2	65	male	Black	150	45	125	No	No	No





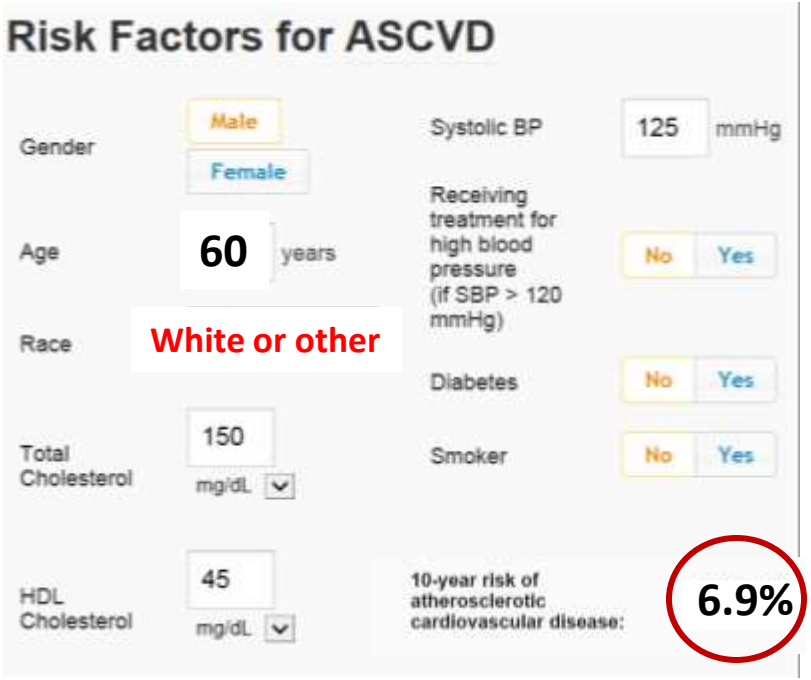
Accessed at http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx

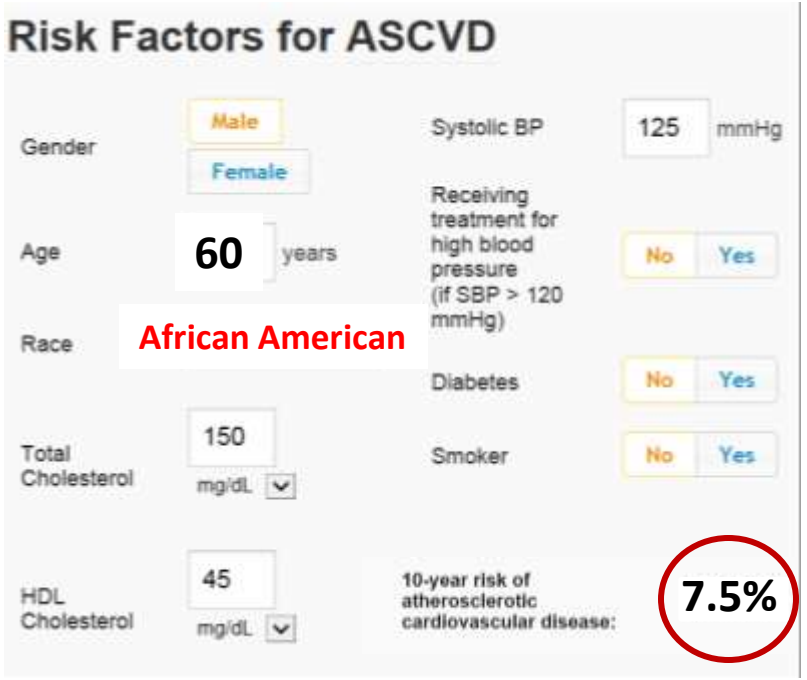
Dr. Steven Nissen

"Age and race seem to drive it a lot"

<hypothetical case>

	Age	Sex	Race	Total cholesterol	HDL cholesterol	Systolic BP	BP Rx	Diabetes	Smoking
case 1	60	male	White	150	45	125	No	No	No
case 2	60	male	Black	150	45	125	No	No	No

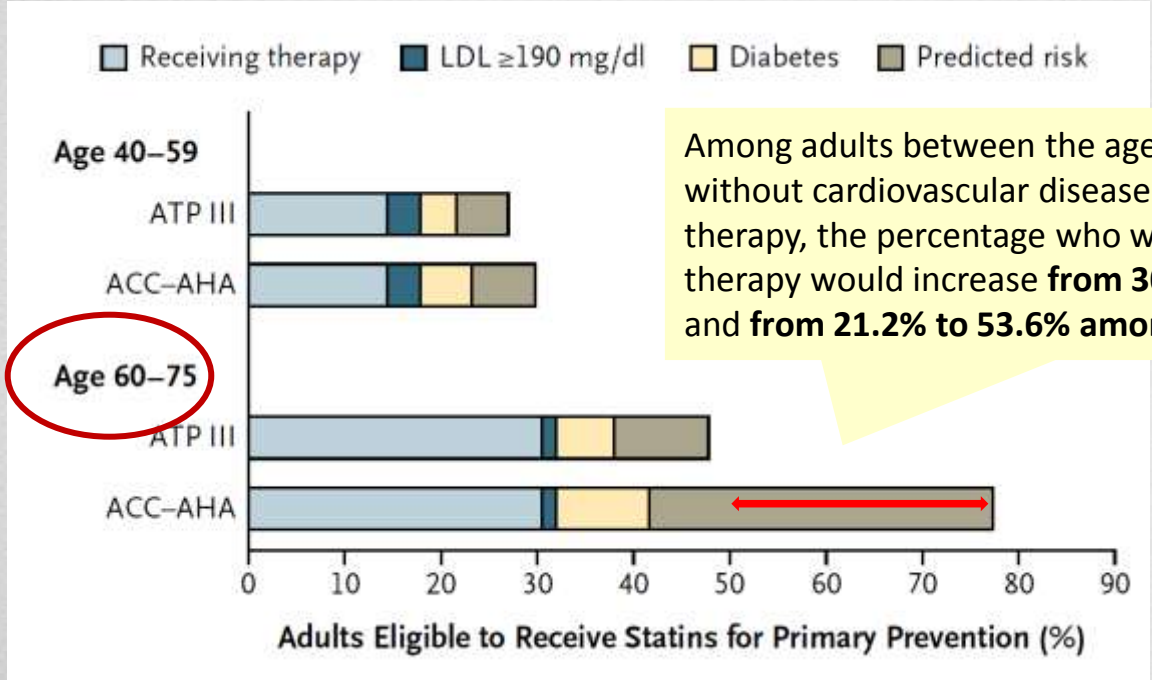




Accessed at http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx

Percent of U.S. Adults Who Would Be Eligible for Statin Therapy for Primary Prevention, According to Set of Guidelines and Age Group

Using data from the National Health and Nutrition Examination Surveys of 2005 to 2010



Among adults between the ages of 60 and 75 years without cardiovascular disease who are not receiving statin therapy, the percentage who would be eligible for such therapy would increase **from 30.4% to 87.4% among men** and **from 21.2% to 53.6% among women.**

MJ Pencina et al. N Engl J Med 2014;370:1422-31

Opinions to support new calculator

Refining the American guidelines for prevention of cardiovascular disease

If people took blood pressure and cholesterol lowering
medicines from age 60 years without previous risk factor measurement, one third would benefit and they would, on average, gain 7 years of life without a heart attack or stroke.

Nicholas Wald, Joan Morris st al. Lancet 2014;383

Overall agreement with other risk calculators

	Non-diabetic patients (n=64)	Diabetic patients (n=64)
ACC/AHA calculator *vs* other calculators[3]	64·4% (65·6)	65·2% (60·2)
Overall agreement among 25 calculators (18 for diabetics) excluding the ACC/AHA calculator[3]	64·3% (64)	72·6% (73)
Calculators with >75% categorisation agreement in either non-diabetics or diabetics with the ACC/AHA calculator		
Reynold's Risk Score	82·8%	N/A
UK Prospective Diabetes Study	71·9%	81·3%
QRISK2-2011	78·1%	87·5%
Australian Absolute CVD Risk	79·7%	76·6%
New Zealand CV Risk Charts	81·3%	78·1%
Australian Risk Charts	87·5%	73·4%
New Zealand Know Your Numbers	79·7%	57·8%
PROCAM (Health Check)	65·6%	79·7%

Data are average (median) or average. ACC/AHA=American College of Cardiology/American Heart Association.

Table: Agreement of the ACC/AHA risk calculator with a sample of other commonly used risk calculators

It seems that the ACC/AHA risk calculator categorises patients in a similar way to many of the other available calculators. Any risk estimate should only be used as a tool to facilitate the initial discussion of benefits and harms of treatments as part of shared decision making.

McCormack et al. Nat Rev Cardiol 2014;3:136-7

Response of AHA.

American Heart Association/American College of Cardiology Media Alert

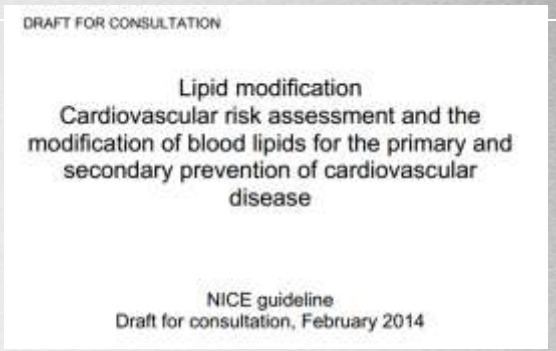
November 18, 2013

DALLAS – Nov. 18, 2013 – The American Heart Association and American College of Cardiology vigorously defend the recently published risk assessment and cholesterol guidelines despite recent media reports critical of the risk assessment calculator tool.

"We stand behind our guidelines, the process that was used to create them and the degree to which they were rigorously reviewed by experts," said Mariell Jessup, M.D., president of the American Heart Association.

The risk calculator provides an estimate of a patient's ten year risk of having a heart attack or stroke, and is one component that healthcare providers should use as they discuss whether or not a patient would benefit from a statin drug, a type of medication that lowers artery-clogging LDL cholesterol. The guidelines and risk assessment tool are developed from, and based on, the best evidence available as determined by the expert panel. Authors say the risk assessment tool is intended to spark a conversation between patients and their physician to help drive individualized care based on that patient's health profile.

"Clinical practice guidelines such as these should not take the place of sound clinical judgment. These guidelines should enable a discussion between a patient and their healthcare provider about the best way to prevent a heart attack or stroke, based on the patient's personal health profile and their preferences. The risk calculator score is part of that discussion, because it provides specific information to the patient about their personal health. A high score does not automatically mean a patient should be taking a statin drug" said John Gordon Harold, M.D, president of the American College of Cardiology.



NICE, an agency that provides guidance for the **National Health Service** (NHS), is calling for **primary-prevention** patients with 10-year risk of cardiovascular disease (**QRISK2)** that exceeds **10%** to be treated with **high-intensity statin therapy.**

- For pts with type 2 diabetes + 10-year risk of CVD of >10% (**United Kingdom Prospective Diabetes Study** [UKPDS] tool)➔High intensive statin (atorva 80mg)
- For pts with stage 1 or 2 CKD + 10-year risk of CVD of >10% (QRISK2 tool)➔ moderate intensity statin (atorvastatin 20 mg)

NICE does not recommend prescribing fibrates, niacin, bile-acid sequestrants, omega-3 fatty acids, or plant sterols for the primary and secondary prevention of CVD or in those with CKD and diabetes.

Unsolved issues in new calculator: Pooled Cohort Equations

- New risk calculator overestimate risk then it is possible that as many as 40 to 50 percent of the 333 million middle-aged Americans targeted by new guideline.

- From the available documents it cannot be evaluated how this would work in relation to other scoring models and other race (Hispanic, Asian, native American) or other countries.

- Treatment strategies based on lifetime ASCVD risk are problematic because of the lack of data on the long-term follow-up of RCTs >15 years, the safety and ASCVD event reduction when statins are used for periods >10 years, and treatment of individuals <40 years of age.

What ISSUEs?

1. New risk calculator
2. **Non-statin, is it available?**
3. No LDL treatment target and instead focus on the intensity of statin
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6. Other new emerging risk factors

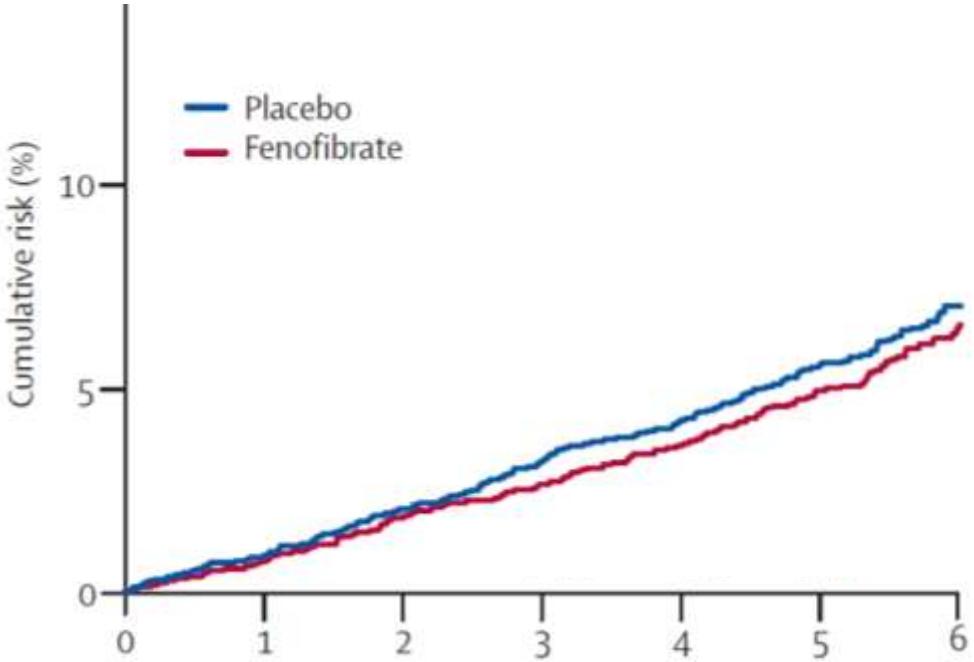
Evidence of non-statin therapy

	Trial	Agent	Risk reduction for CHD/CVD
Fibrate	FIELD	Fenofibrate vs placebo	no reduction of primary outcomes 11% reduction of total CVD risk
	ACCORD	Fenofibrate + simvastatin vs simvastatin	No reduction of primary outcomes compared with simvastatin alone
Niacin	AIM-HIGH	niacin or placebo	No reduction of primary outcomes
	HPS2-THRIVE	niacin/laropiprant+simve or simva	No reduction of primary outcomes
Apo-A1	Apo-A1 Milano	Apo-A1 vs placebo	Decrease in coronary AS progression (change of %AV=
Omega-3	ALPHA-OMEGA	EPA-DHA vs placebo and ALA	No reduction of primary outcomes
ACAT inhibitor	Nissen et al	Pactimibe vs placebo	No decrease in coronary AS progression
CETP inhibitor	ILUMINATE	Torcetrapib+atorva vs atorva	No decrease in coronary AS progression
	dal-OUTCOMES	dalcetrapib or placebo	No reduction of primary outcomes
Phospholipase A2 Inhibitor	Serruys et al.	Darapladib vs placebo	Reduction of coronary NC in plaque
	VISTA-16	Varespladib or placebo	No reduction of primary outcomes significantly increased the risk of MI
Ezetimibe	IMPROVE-IT	Ezetimibe+simvastatin vs simvastatin	Pending

FIELD: Effects of fenofibrate-Simvastatin in Type 2 DM

N=9,795 pts with type 2 DM
randomized to placebo or fenofibrate

[Cumulative risk curves of time to first events]



Primary End Point
: CHD death or non-fatal MI

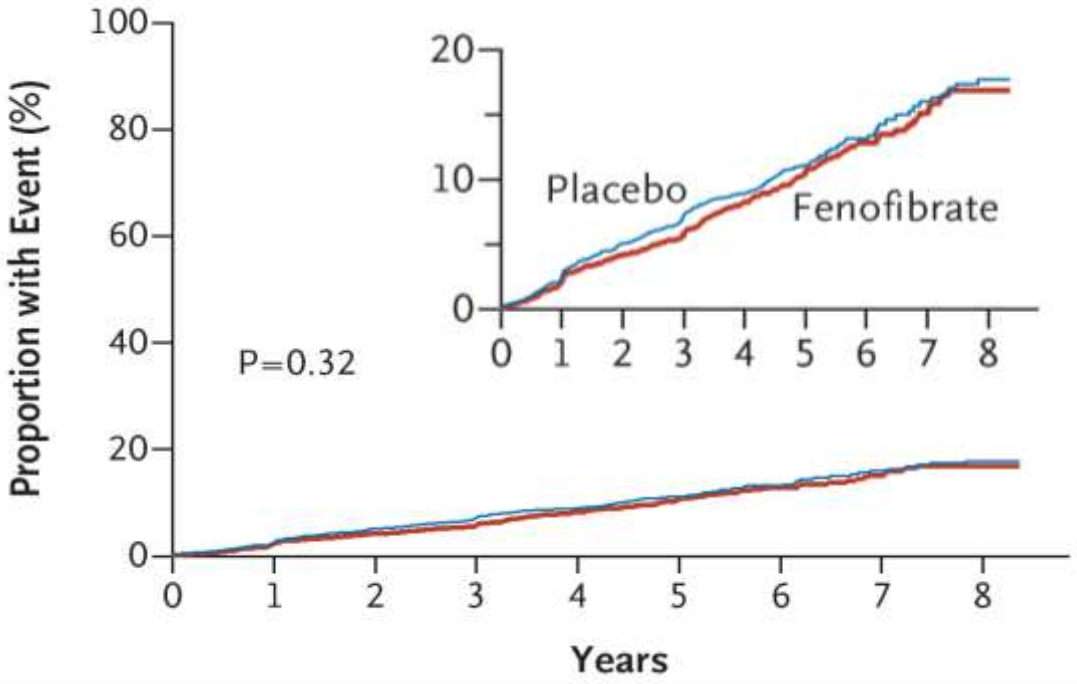
HR 0.89, (0.79-1.08), P = 0.16

Keech A, et la. Lancet 2005;366:1849–61.

ACCORD : Effects of fenofibrate in Type 2 DM

N=5,518 pts with type 2 DM
randomized to statin or fenofibrate+ statin

[Kaplan-Meier Analysus of the primary outcome]



Primary End Point
: nonfatal MI, nonfatal stroke, or CV death.

The annual rate of the primary outcome 2.2% vs 2.4% (0.92; 0.79-1.08; P = 0.32).

The ACCORD Study Group, et la. N Engl J Med 2010;362:1563–74.

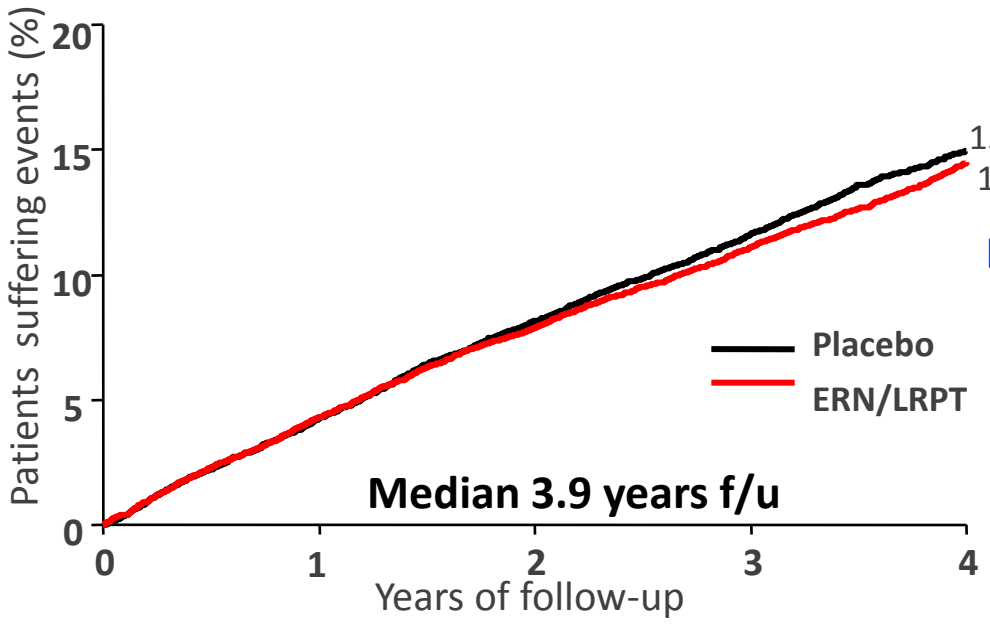
ER niacin and laropiprant (secondary prevention)

HPS2-THRIVE

N=25,673 pts with ACS

randomized to niacin/laropiprant+simva or placebo (simva 40mg c/s ezetimibe 10mg)

Effect of ERN/LRPT on MAJOR VASCULAR EVENTS



Primary End Point

: **Coronary deaths, nonfatal heart attack, strokes, and coronary revascularizations**

RR 0.96, (0.70-1.03), P = 0.29

Patient Characteristics

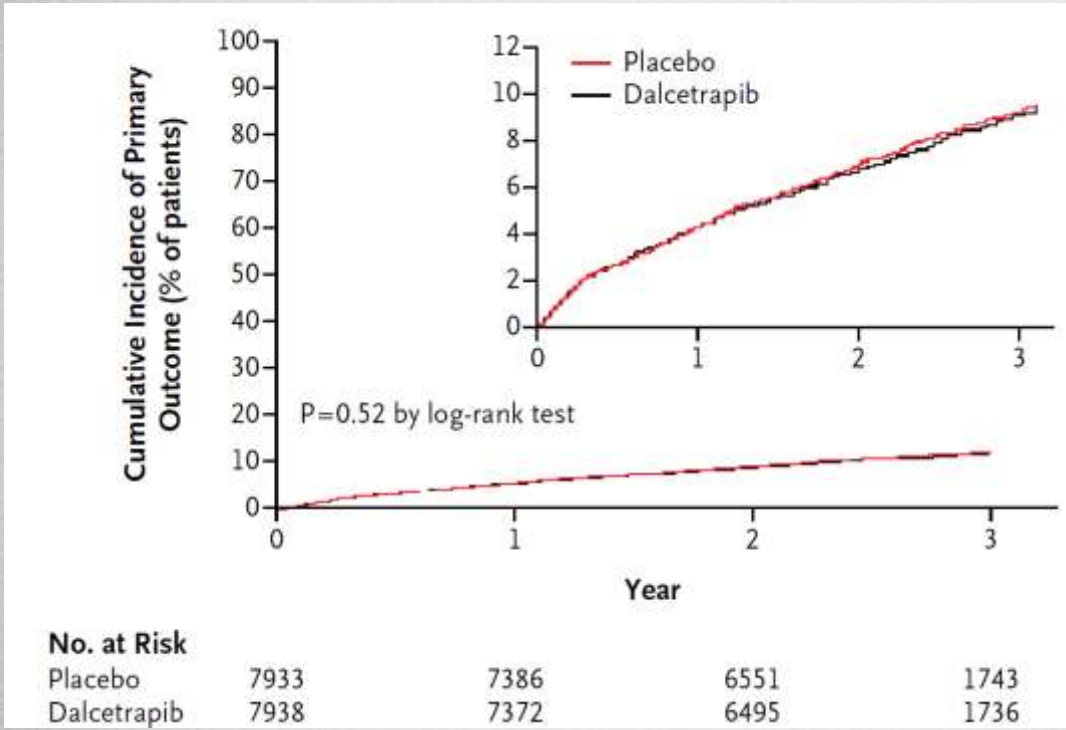
: Age 50-80, History of MI, ischaemic stroke or TIA, PAD or DM with other CHD

HPS2-THRIVE Collaborative Group, et al. Eur Heart J. 2013;34(17):1279-91.

CETP Inhibitor (secondary prevention)

dal-OUTCOMES

N=15,8711 pts with ACS
randomized to dalcetrapib or placebo



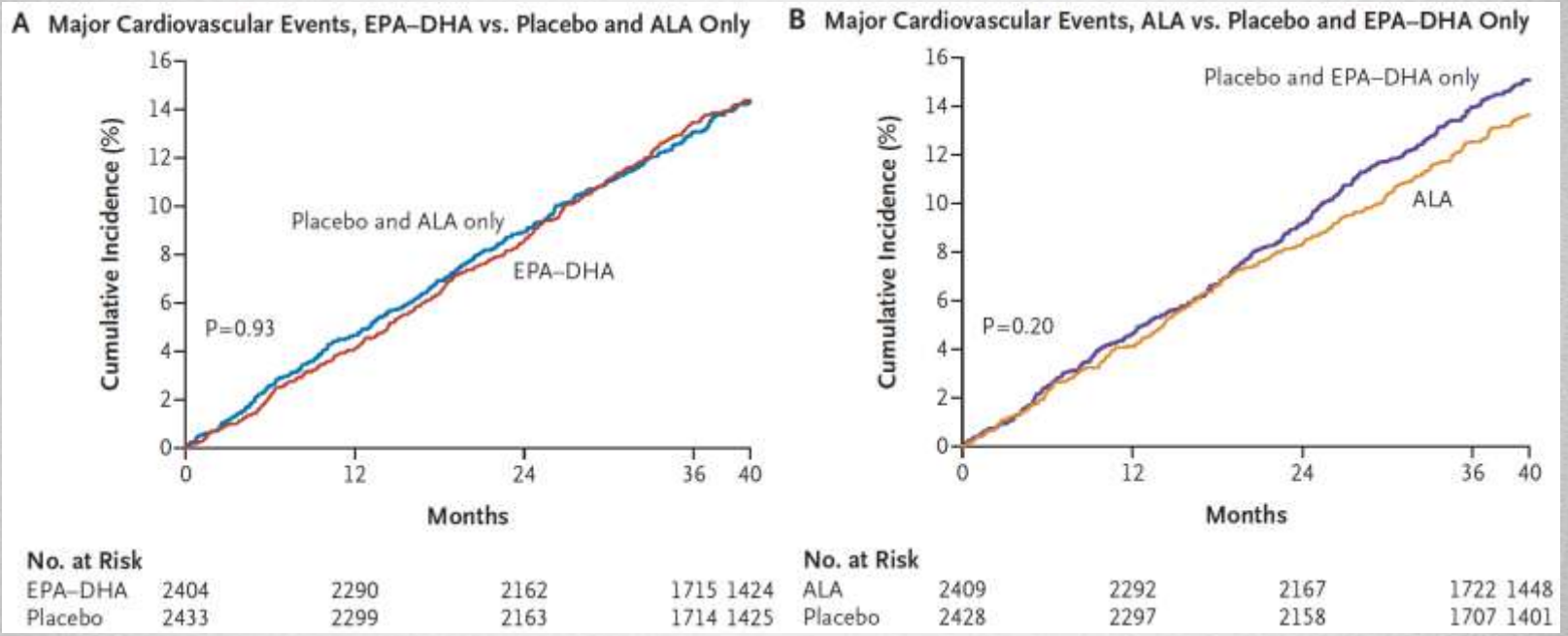
Primary End Point
:death from CHD, nonfatal MI, ischemic stroke, UA, or cardiac arrest with resuscitation

Schwartz et al. N Engl J Med 2012;367:2089-99.

Omega-3 (secondary prevention)

ALPHA-OMEGA

N=4837 with myocardial infarction
randomized to eicosapentaenoic acid(EPA) and docosahexaenoic acid(DHA)
or alpha-linolenic acid(ALA) or EPA-DHA and ALA or placebo



Primary End Point :fatal and nonfatal cardiovascular events and cardiac interventions

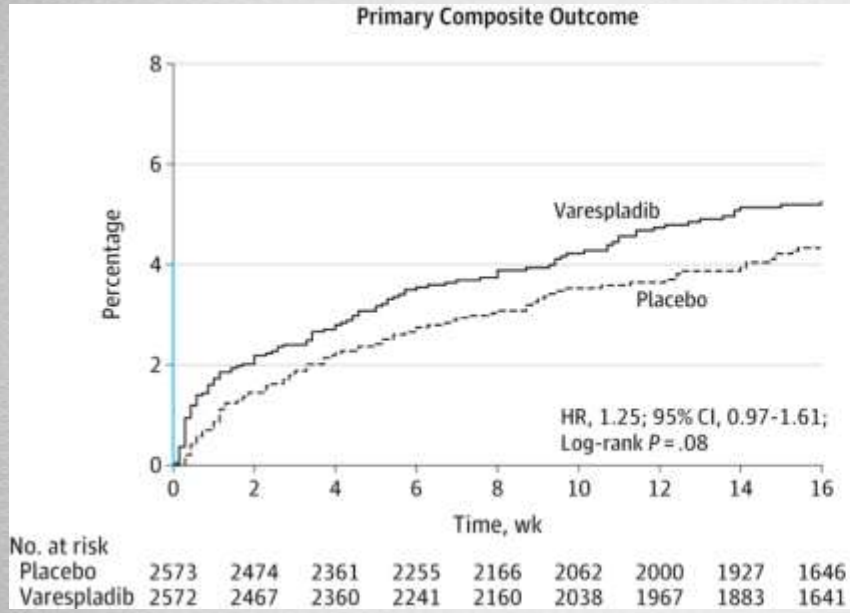
Kromhout D et al. N Engl J Med 2010:363:2015

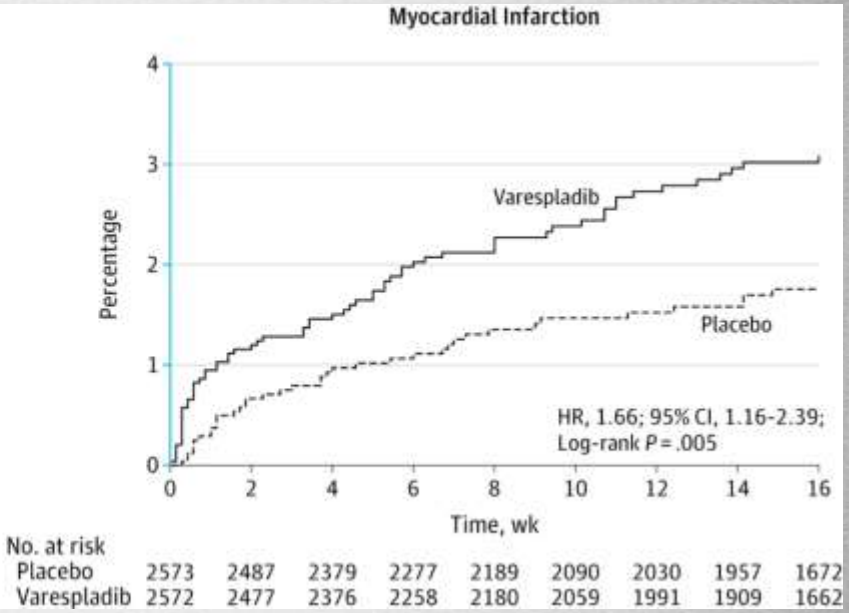
Phospholipase A2 Inhibitor (secondary prevention)

VISTA-16

N=5145 with ACS

Randomized to varespladib or placebo





Primary End Point : CV mortality, nonfatal MI, nonfatal stroke, or UA with evidence of ischemia requiring hospitalization

Nicholls et al. JAMA. 2014 Jan 15;311(3):252-62.

Nonstatin therapy recommendation.

- Non-statin drugs are **not recommended for first-line treatment.**
- No data supporting the routine use of non-statin drugs combined with statin therapy.
- Non-statin drugs combined with statin therapy may consider
  - High-risk patients *who have a less-than-anticipated response to statins*
  - High-risk patients *who are unable to tolerate a less-than-recommended intensity of a statin*
  - High-risk patients *who are completely statin intolerant*
    - *High-risk patients* : ASCVD, LDL–C ≥190 mg/dL, Diabetes

Ref. stone NJ, et al. published online November 12, 2013 Circulation.

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Major Recommendation for Statin

Adults age >21 y and a candidate for statin therapy

secondary prevention

Clinical ASCVD

Yes → **Age <75 y**
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

Yes → Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin

primary prevention

LDL–C ≥190 mg/dL

Yes → **High-intensity statin**
(Moderate-intensity statin if not candidate for high-intensity statin)

No

Diabetes Type 1 or 2 Age 40-75 y

Yes → Moderate-intensity statin

Yes → DM with age <75y+ Estimated 10-y ASCVD risk ≥7.5%*
High-intensity statin

No

Estimate 10-y ASCVD Risk with Pooled Cohort Equations*

≥7.5%
Estimated 10-y ASCVD risk and age 40-75 y

Yes → Moderate-intensity statin

Stone NJ, et al. published online November 12, 2013 Circulation.

Intensity of Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose **lowers LDL-C** on average, by approximately **≥ 50%**	Daily dose lowers LDL-C on average, by approximately **30% to < 50%**	Daily dose lowers LDL-C on average, by **< 30%**
Atorvastatin(40)-80 mg **Rosuvastatin 20** (40) **mg**	**Atorvastatin 10** (20) **mg** **Rosuvastatin** (5) **10 mg** **Simvastatin 20-40 mg** **Pravastatin 40** (80) **mg** **Lovastatin 40 mg** Fluvastatin XL 80 **mg** **Fluvastatin 40 mg bid** Pitavastatin 2-4 **mg**	Simvastatin 10 **mg** **Pravastatin 10-20 mg** **Lovastatin 20 mg** Fluvastatin 20-40 **mg** Pitavastatin 1 **mg**

*** Specific statins and doses are noted in bold that were evaluated in RCTs**

Stone NJ, et al. published online November 12, 2013 Circulation.

No LDL Target
We lost our road map?

- The final choice of strategy is often left to the doctor's clinical judgment.
- No treatment goals in LDL-C can certainly be argued because it can be that treatment goals are arbitrary.
- Treatment goals are widely used in different clinical settings
- Targets are a most important tool in daily practice, aiding patient-to-doctor communications and optimizing compliance.

No LDL Target

Go straight! **Lower is best!**

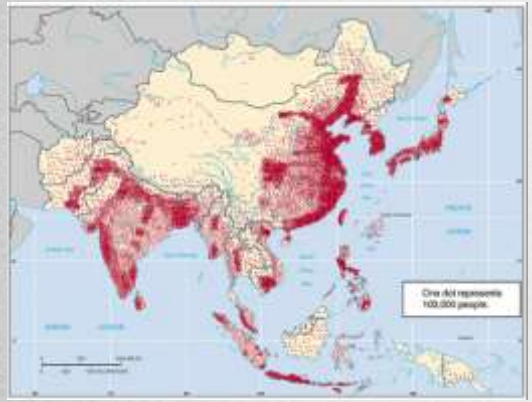
1. Current clinical trial data do not indicate what the target should be.
2. We do not know the magnitude of additional ASCVD risk reduction that would be achieved with one target lower than another.
3. It does not take into account potential adverse effects from multidrug therapy that might be needed to achieve a specific goal.

*Use of LDL–C targets may result in **under-treatment** with evidence-based statin therapy or **overtreatment with nonstatin drugs** that have not been shown to reduce ASCVD events in RCTs.*

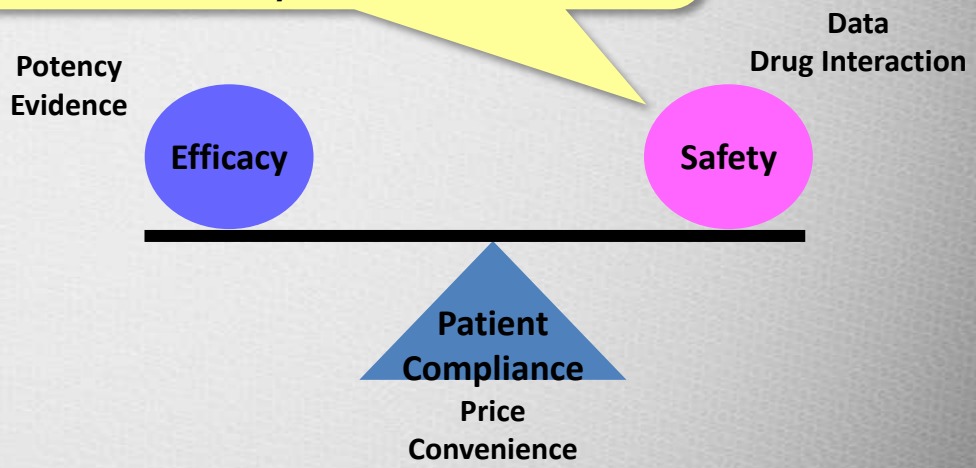
Efficacy and Safety Issues

Especially for Asian population

- Do we need high intensive statin?
- Is high intensive statin safe for Asian?



"Statin benefit is indisputable, but they need to be taken with care and knowledge of their side effects."
from FDA, Feb 2012



Statin studies regarding plaque regression from Asian populations

Study	Methods	Design	FU
• **ESTABLISH** Okazaki S et al. Circulation 2004;110;1061-1068	Coronary, IVUS	ACS, **Atorva 20mg** (n=35) vs control (n=35)	6m
• **REACH** Yamada T et al. Circ J 2007;71:1845–1850	Coronary, IVUS	CAD with hyperchol, **Atorva 10-20mg** (n=26) vs usual care? (n=32)	12m
• **JAPAN-ACS** Hiro T et al. J Am Coll Cardiol 2009;54:293–302	Coronary, IVUS	RCT, open labeled, ACS c PCI, **Atorva 20mg** (n=127) vs **Pitava 4mg** (n=125)	8-12m
• **COSMOS** Takayama T et al. Circ J 2009;73:2110-7	Coronary, IVUS	Multicenter open-label trial, **Rosuva 2.5-20mg** (n=125), incremental dose	18m
• **ARTMAP** Lee et al. Am J Card... 2012;109:1700			6m
• Kawasaki et al. J Am C... 2005;45:1946 –1953			6m
• Yokoyama M et al. Am Heart J 2005;150:287	Coronary, RF-IVUS	PCI, **Atorva 10mg** (n=25) vs control (n=25)	6m
• Hong et al. JACC Cardiovasc Interv 2009;2:679–688	Coronary, RF-IVUS	CAD, Simva 20mg (n=50) vs **Rosuva 10mg** (n=50)	12m
• Takarada et al. Atherosclerosis 2009;202:491-497	Coronary, OCT	AMI c PCI, **Statin** (**simva 20mg** or **Rosuva 10mg** (n=23) vs control (n=17)	9m

No RCT data regarding clinical outcomes of statin in Asian populations!

Statins safety recommendation

Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:

- **History of hemorrhagic stroke**
- **Asian ancestry**

Table 8. Summary of Statin Safety Recommendations

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Safety				
1. To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD* risk, and potential for adverse effects. Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present. Characteristics predisposing individuals to statin adverse effects include, but are not limited to: • Multiple or serious comorbidities, including impaired renal or hepatic function. • History of previous statin intolerance or muscle disorders. • Unexplained ALT elevations >3 times ULN. • Patient characteristics or concomitant use of drugs affecting statin metabolism. • >75 years of age. Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: • History of hemorrhagic stroke. • Asian ancestry.	A (Strong)	46-55	I	B

Stone NJ, et al. published online November 12, 2013 Circulation.

Similar incidence of adverse events across dose range

*Data from **2006 safety meta-analysis** involving **14,236 patients from 49 trials***

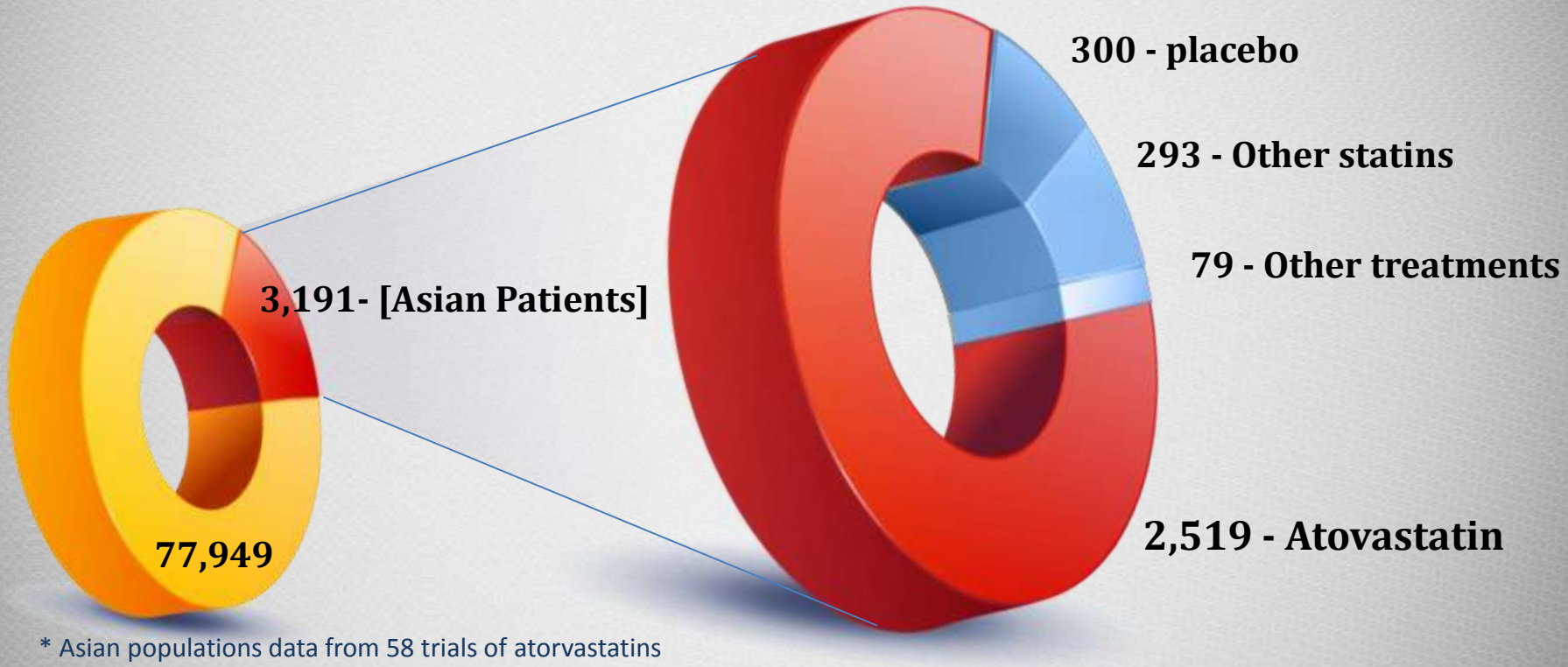
	Number of patients (%)		
	Placebo (n=2180)	Atorvastatin 10 mg (n=7258)	Atorvastatin 80 mg (n=4798)
Patients with ≥1 AE			
All	768 (35.2)	3870 (53.3)	2285 (47.6)
Treatment-associated	270 (12.4)	983 (13.5)	699 (14.6)
Withdrawals due to AEs			
All	51 (2.3)	251 (3.5)	136 (2.8)
Treatment-associated	27 (1.2)	171 (2.4)	84 (1.8)
Serious nonfatal AEs			
All	122 (5.6)	453 (6.2)	385 (8.0)
Treatment-associated	92 (4.2)	12 (0.2)	25 (0.5)
Deaths	2 (0.09)	29 (0.40)	17 (0.35)

Newman C et al. Am J Cardiol. 2006;97:61-67.

Comparison between Total and Asian populations

[Total Number of Patients]

[Asian Patients]



* Asian populations data from 58 trials of atorvastatins
Asion population : Asian, Oriental, South Asian, Indian and Pacific Islanders.

Ref. GWICC 2012.GW23-e2689.

Similar safety profile of Atorvastatin in Asian patients

Liver Safety

ALT >3xULN

- Long-term trials : 2.1% vs 2.8% → Similar
- Short-term trials : 2.4% vs 3.0% → Similar

* **Long-term trials : median** 3.1 - 4.9 years/ **Short-term trials : median** 4 - 72 weeks

Musculoskeletal Safety

Rhabdomyolysis : None

Myalgia : Lower in Asian patients than in all patients (6.7% vs 8%)

* Asian populations data from 58 trials of atorvastatins
Asion population : Asian, Oriental, South Asian, Indian and Pacific Islanders.

GWICC 2012.GW23-e2689.

Similar safety profile of Lipitor in Korea patients

Single-step titration, open-label study

425 pts with atorvastatin starting doses of 10 - 40 mg depended on CV risk and LDL-C levels

Comparison of the geographic variations among three similar AT GOAL trials

	Korea study		Thai study		US study
Sample size(n)	425		242		1,295
Risk category(%)					
Low	7		22		26
Intermediate	10		11		20
High	**83**	≫	**67**	≫	**54**
LDL-C goal achievement at 4 week(%)	81.9		87.1		84.2
LDL-C goal achievement at 8 week(%)	86		89		85
LDL-C reduction(%)	42		46		42
Treatment-related AEs(%)	5.6		14.9		17.4
Serious AE(%)	0.7		0.8		1.7

Lee CW, et al. Cardiovasc Drugs Ther. 2010;24:181-88

What ISSUEs?

1. New risk calculator
2. Non-statin, is it available?
3. No LDL treatment target and instead focus on the intensity of statin
4. Efficacy and Safety of high intensity statin therapy in Asian population
5. **Statin therapy on CKD patients**
6. Other new emerging risk factors

2013 ACC/AHA guideline

- **In adults with *CKD and CHD/CVD* (excluding hemodialysis)**

  Atorvastatin 80 mg reduced CHD/CVD events more than fixed lower-dose statin treatment.

- **In adults aged >40 with *CKD without CVD* (excluding hemodialysis)**

  Simvastatin 20 mg plus ezetimibe 10 mg reduced CVD event

  but modestly increased the risk for muscle symptoms requiring discontinuation of treatment.

Stone NJ, et al. published online November 12, 2013 Circulation.

2013 KDIGO Lipid management guideline

❖ **In adults aged ≥ 50 years with eGFR<60 ml/min/1.73㎡ without dialysis or transplantation,**

- recommend treatment with a statin or statin/ezetimibe combination. (1A)

❖ **In adults aged 50 ≥ years with CKD and eGFR ≥ 60 ml/min/1.73㎡**

- recommend treatment with a statin. (1B)

❖ **In adults aged *18–49 years with CKD* without dialysis or transplantation,**

- suggest statin treatment in people ***with CVD or CVD risk.*** (2A)

: known coronary disease (MI or coronary revascularization), DM, prior ischemic stroke and estimated 10-year incidence of coronary death or non-fatal MI >10%

***KDIGO, Kidney Disease Improving Global Outcomes**

KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease 2013

2013 KDIGO Lipid management guideline

- **At the time of *dialysis initiation***

  in patients already receiving statins or statin/ezetimibe combination,

  - suggest that statins or statin/ezetimibe combination not be initiated. (2A))

- **In adults with *dialysis-dependent CKD*,**

  - suggest that these agents be continued. (2C)

- **In adult with *kidney transplant recipients*,**

  - suggest treatment with a statin. (2B)

KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease 2013

What ISSUEs?

1. New risk calculator
2. Non-statin, is it available?
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4. Efficacy and Safety of high intensity statin therapy in Asian population
5. Statin therapy on CKD patients
6. **Other new emerging risk factors**

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association.

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

David C. Goff, Jr, Donald M. Lloyd-Jones, Glen Bennett, Sean Coady, Ralph B. D'Agostino, Sr, Raymond Gibbons, Philip Greenland, Daniel T. Lackland, Daniel Levy, Christopher J. O'Donnell, Jennifer Robinson, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Paul Sorlie, Neil J. Stone and Peter W. F. Wilson

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Role of Biomarkers and Noninvasive Tests

< Summary of Recommendations for Risk Assessment >

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
3. If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following—family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making.	E (Expert Opinion)	Appendix 1	IIb†	B (9-17)
4. The contribution to risk assessment for a first ASCVD event using ApoB, CKD, albuminuria, or cardiorespiratory fitness is uncertain at present.	N (No Recommendation For or Against)	Appendix 1	N/A	N/A
5. CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event.	N (No Recommendation For or Against)	Appendix 1	III: No Benefit†	B (12,16,18)

stone NJ, et al. published online November 12, 2013 Circulation.

Future Update

- Treatment of TG/non HDL-C?
- Apo B, Lp(a), or LD L particles are useful for decision?
- Non-invasive imaging
- Lifetime ASCVD risk should be used?
- Paatients with heart failure or undergoging hemodialysis that might benefit from statin therapy?
- Statin-associated new onset diabetes and management

“New American guidelines are a brave and wise departure from current practice!”

Harlan M Krumholz, Harold H Hines Jr professor of medicine
Yale University School of Medicine, New Haven, USA

Krumholz et al. BMJ 2013; 347 doi: http://dx.doi.org/10.1136/bmj.f7110 (Published 27 November 2013)