Joint Meeting of Coronary Revascularization

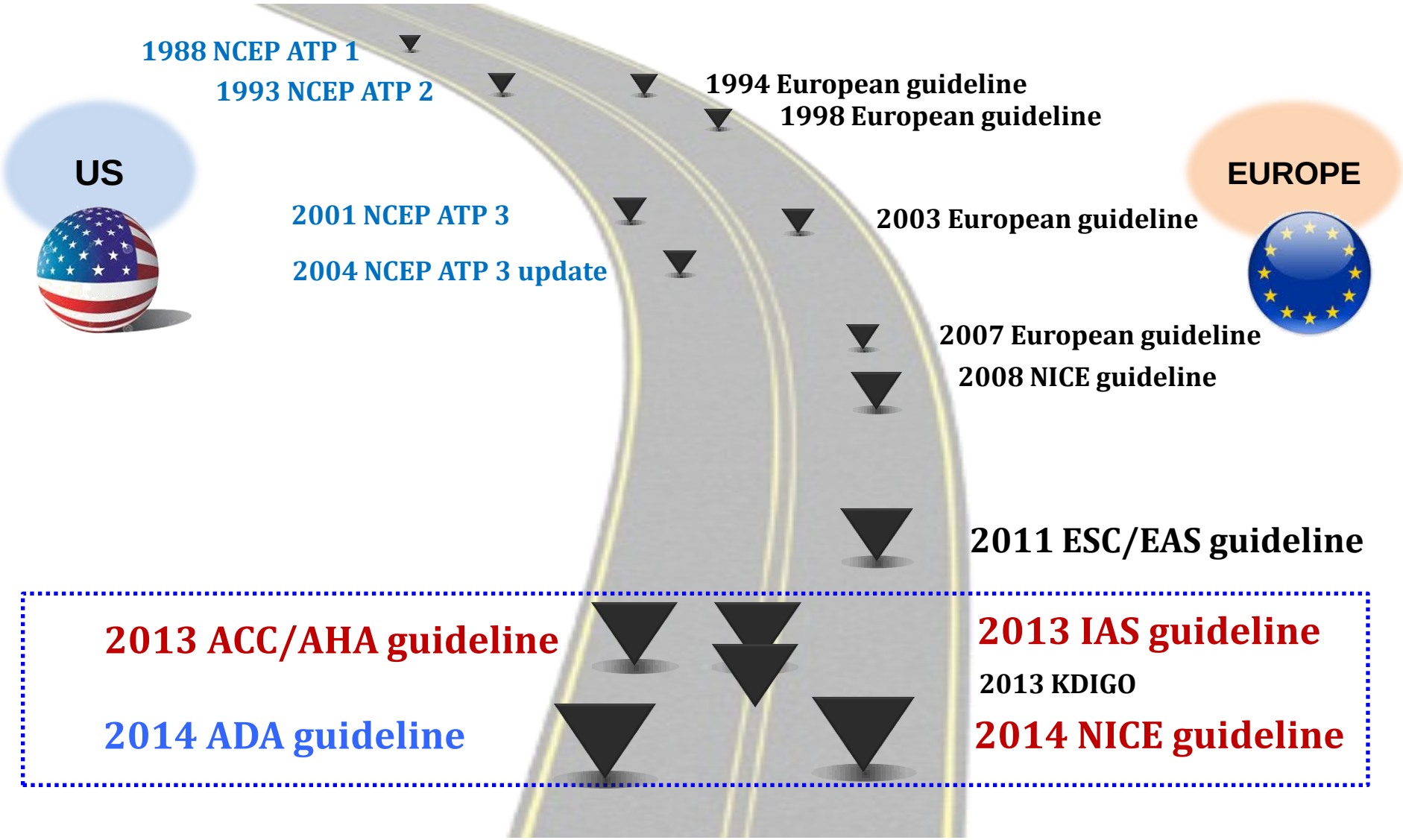
Current Guidelines in Lipid Management and Controversies

Seung-Ho Hur, MD, PhD, FACC

Keimyung University
Dongsan Medical Center,
Daegu, Korea

계명대학교 동산의료원
Keimyung University Dongsan Medical Center

From cumulating of evidence from RCTs
Evolution of Lipid guideline is continued



Current Guidelines - Based on High Quality of Evidences

2013 IAS guideline

The International Atherosclerosis Society (IAS) has developed a guide for dyslipidemia intervention. This guide is based on deliberations of an IAS committee with international representation. Its recommendations are based on an interpretation of available data from a majority of the panel members. The Position Paper was developed as follows. Fifteen committee members were nominated by the IAS Executive Committee and were invited to participate on the writing panel. They were both experts and representative of different regions of the world. Timely questions relating to lifestyle and drug management of dyslipidemia were selected and shared with the panel. Responses were organized as IAS panel deliberations.

The recommendations are based on international consensus. Three major lines of evidence underpinned the recommendations: epidemiological studies, genetic studies, and clinical trials. Where appropriate, the recommendations were further informed by pathological studies, pharmacology, metabolic studies, smaller clinical trials, meta-analyses of clinical trials, animal studies, and the basic sciences. Each line of evidence contains strengths and weakness.

1. Based on international consensus
2. Based the major line evidence

- **Epidemiological studies**
- **Genetic studies**
- **Clinical trials.**

2013 ACC/AHA guideline

Table 1b. Quality Rating the Strength of Evidence

Type of Evidence	Quality Rating*
• Well-designed, well-executed† RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes. • MAs of such studies. Highly certain about the estimate of effect. Further research is unlikely to change our confidence in the estimate of effect.	High
• RCTs with minor limitations‡ affecting confidence in, or applicability of, the results. • Well-designed, well-executed nonrandomized controlled studies§ or well-designed, well-executed observational studies‖. • MAs of such studies. Moderately certain about the estimate of effect. Further research may on our confidence in the estimate of effect and may change the estima	Moderate
• RCTs with major limitations. • Nonrandomized controlled studies and observational studies with limitations affecting confidence in, or applicability of, the results. • Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). • Physiological studies in humans. • MAs of such studies. Low certainty about the estimate of effect. Further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate.	

The highest quality evidence derived from

- **RCTs with ASCVD outcomes**
- **Systematic reviews RCTs with ASCVD**
- **Meta-analyses of RCTs with ASCVD outcomes**

2014 NICE guideline

Grading the quality of clinical evidence

1. A quality rating was assigned, based on the study design. RCTs start as High and observational studies as Low, uncontrolled case series as Low or Very low.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated at 1 or2 points respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for down

1. Evidence reviews included

- **Parallel randomised trials**
- **Non-randomised trials**
- **Observational studies (including prognostic studies)**

2. RCTs assigned as high quality evidence.

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Purpose of Lipid Management

2013 ACC/AHA guideline

AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

American Heart Association. Learn and Live

The Expert Panel was charged with updating the clinical practice recommendations for the treatment of blood cholesterol levels to reduce atherosclerotic cardiovascular disease (ASCVD) risk using data from randomized controlled trials (RCTs) and systematic reviews and meta-analyses of RCTs. For this

2013 IAS guideline

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

The International Atherosclerosis Society (IAS) here updates its recommendations on treatment of high level of blood cholesterol and dyslipidemia for the purpose of reducing risk for atherosclerotic cardiovascular disease (ASCVD). This summary highlights the major conclusions of the full report. The latter provides background rationale, panel deliberations,

2014 NICE guideline

NICE
National Institute for Health and Care Excellence

These programmes include lipid modification as part of the strategy for CVD risk management. Though many lipid-lowering therapies have been developed,[249,249] the singular successes achieved with statin therapy mean that these agents form the first-line therapy for pharmacological intervention on lipid profiles.[249,250] The action of statins highlights the key nature of reductions in

Evolution of Risk Assessment Algorithm

	Before	Present
ACC/AHA guideline	ATP III, 2001 Framingham risk score	2013, Pooled cohort risk equation
IAS guideline	IAS, 2003 Framingham risk score & PROCAM risk score	2014, Lloyd-Jones/Framingham algorithm
NICE guideline	NICE, 2008 Framingham risk score	2014, QRISK 2 risk calculator

Comparison with Framingham Risk Tool

[Risk factors and variables]													
	Race	Age	Sex	Chol	SBP	BP Rx	Smok-ing	DM	AF	RA, CKD	BMI	Family hx	Social†
ATP III Framingham (MI, CHD death)	X	O	O	TC, HDL	O	O	O	X					
Pooled Cohort Equations	O	O	O	TC, HDL	O	O	O	O					
Lloyd-Jones Framingham	O		O	TC	O		O	O					
QRISK2	O	O	O	TC/ HDL	O	O	O	O	O	O	O	O	O

*BP, blood pressure; CVD, cardiovascular disease; Hx, history; AF, atrial fibrillation; RA, rheumatoid arthritis , CKD, chronic kidney disease.
† Townsend deprivation score

Comparison of Clinical Guidelines

	2013 ACC/AHA guideline	2013 IAS guideline	2014 NICE guideline
Risk Assessment Algorithm	Pooled Cohort risk equation	Lloyd-Jones/Framingham algorithm	QRISK 2 risk calculator
Outcome	10-year risk of ASCVD (MI, CHD death, stroke, stroke death)	Lifetime risk of ASCVD (MI, coronary insufficiency, CHD death, angina, atherothrombotic stroke, IC, or CV death)	10-year risk of CVD (CHD, stroke, and TIA)
Population	w/o CVD Aged 40-79	w/o CVD Aged 50-80	w/o CVD Aged 25-84
Ethnicity	Caucasian and African Americans	Re-calibrated for each country	UK & non UK
Risk factor	Age Sex Cholesterol BP Smoking Diabetes Race	Age Sex Cholesterol BP Smoking Diabetes	Age Sex Cholesterol BP Smoking Diabetes Race AF RA CKD BMI Family History CVD Social status

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Summary of Target Patient Group

	2013 ACC/AHA guideline	2013 IAS guideline	2014 NICE guideline	2014 ADA guideline
Secondary prevention	With ASCVD		With CVD	DM with CVD
Primary prevention	• **LDL–C≥190 mg/dL** aged ≥ 21 y • **with DM** aged 40-75 y • **estimated 10-y ASCVD risk≥7.5%** aged 40-75 y	Risk level ≤ 80 y • **Moderately High** • **High** (Based on re-calibrated Framingham score for each country) **Moderate (15-24%) ⇨ optional** **- Moderately High (25-40%) ⇨ consideration** **- High (> 40%) ⇨ indicated**	• **Type 1 DM*** • **Type 2 DM with estimated 10-y CVD risk ≥ 10 % (QRISK2)** •**estimated 10-y ASCVD risk≥ 10 % (QRISK2)** • **Individuals aged ≥ 85 yrs** • **with CKD**	• **DM aged ≥ 40 y with risk factors** (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria).

* Type 1 DM who are older than 40 years **or** have had diabetes for more than 10 years **or** have established nephropathy **or** have other CVD risk factors.

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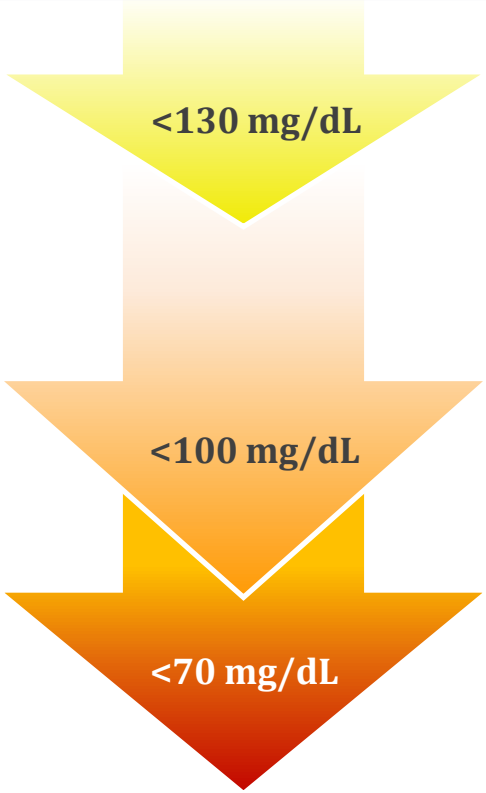
Change of Target Lipid Level

- **LDL was the primary target of lipid management.**
- **Treat to goal was more aggressive.**

Recommended LDL-C treatment goals



ATP I 1988
< 130 mg/dL
: Patients ≥ 2 risk factors or with CHD

ATP II 1993
< 100 mg/dL
: Patients with CHD

ATP III 2001
ATP III Update 2004
<100 mg/dL
: Patients with CHD or CHD risk equivalents (10 year risk > 20%)

ATP III Update 2004
<70 mg/dL
: Therapeutic option for very high risk patients

2003 ESC/EAS guideline
< 115 mg/dL
: For general patients

2003 ESC/EAS guideline
2007 ESC/EAS guideline
<100 mg/dL
: Patients with CVD or DM

2007 ESC/EAS guideline
< 80 mg/dL
: Patients with CVD or DM if feasible

2011 ESC/EAS guideline
<70 mg/dL
: Therapeutic option for very high risk patients

No recommendation for treat-to target approach

2013 ACC/AHA guideline

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Treatment Targets				
1. The panel makes no recommendations for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD.	N (No recommendation)	1-4	N/A	N/A

1. Current RCT data do not indicate what the target should be
2. Unknown magnitude of additional ASCVD risk reduction with one target compared to another
3. Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal
4. Therefore, **unknown net benefit from treat-to target approach**

No recommendation for treat-to target approach

2014 NICE guideline

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	2008 NICE guideline	2014 NICE guideline
Secondary prevention	• A target for TC or LDL-C **is not recommended** • Statins titration if not reach TC <4.0 and LDL-C <2.0 mmol/L on the initial dose	**Use the proportion of people taking high intensity statins** for secondary prevention rather than cholesterol levels
Primary prevention	• A target for TC or LDL –C **not recommended**	**Deleted as no longer** relevant given cost effectiveness of using different statins

Optimal levels, *NOT treatment goal*, of atherogenic cholesterol

2013 IAS guideline

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

- Atherogenic cholesterol : either LDL-C or Non-HDL-C.
- Non-HDL-C
  - includes cholesterol in all atherogenic lipoproteins
  - is more reflective of atherogenicity in persons with elevated triglycerides.
  - can be accurately measured in non-fasting serum.

Secondary prevention	• LDL-C < 70 or non-HDL-C < 100 mg/dL
Primary prevention	• **High-risk** LDL-C < 100 or non-HDL-C < 130 mg/dL • **Low-risk** LDL-C 100–129 or non-HDL-C 130 -159 mg/dL

The IAS makes an important distinction between optimal levels of atherogenic lipoproteins and goals of therapy. The IAS does not specifically prescribe "treatment goals" for atherogenic lipoproteins for different circumstances. Instead it identifies optimal levels of atherogenic cholesterol and makes the general statement that the intensity of cholesterol-lowering therapy should be adjusted to long-term risk. Potency of cholesterol-lowering therapy relative to optimal levels must be left to clinical judgment.

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Evidences of Statin and Nonstatin Therapy

Statin Tx

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials (≥1,000 patients, ≥ 2.0 years treatment periods)

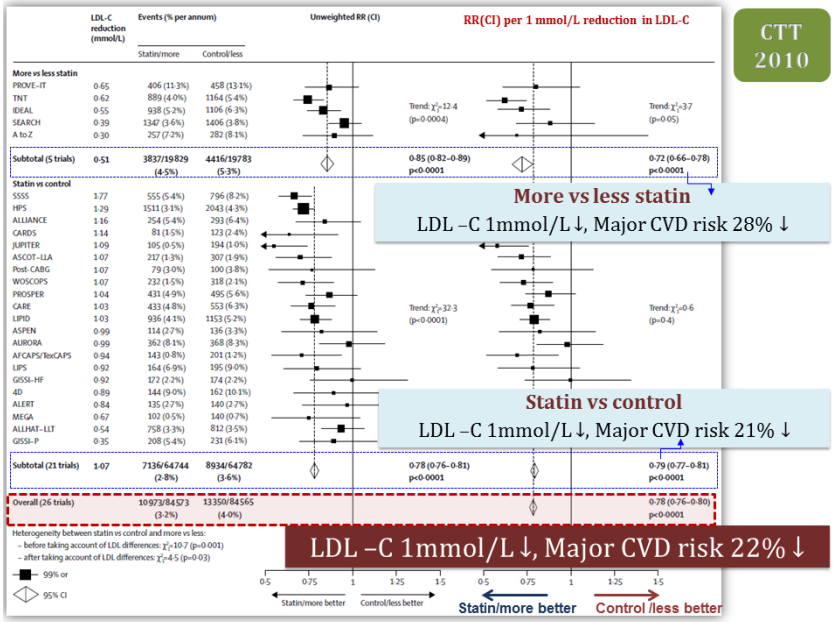
CTT 2010

	Number of patients	Treatment comparison (mg per day)	Median follow-up in survivors (years)*	Baseline LDL-C (mmol/L)	LDL-C difference at 1 year (mmol/L)	Women (%)	Diabetes (%)	Prior CHD (%)	Other vascular disease (%)†	No prior vascular disease (%)‡
More versus less statin										
PROVE-IT	4162	A80 vs P40	2·1	2·625	−0·65	911 (22%)	734 (18%)	4162 (100%)	328 (8%)	0
A to Z	4497	S40 then S80 vs placebo then S20	2·0	2·095	−0·30	1100 (24%)	1059 (24%)	4497 (100%)	479 (11%)	0
TNT	10001	A80 vs A10	5·0	2·52	−0·62	1902 (19%)	1501 (15%)	10001 (100%)	1537 (15%)	0
IDEAL	8888	A40–80 vs S20–40	4·8	2·645	−0·55	1702 (19%)	1069 (12%)	8888 (100%)	971 (11%)	0
SEARCH	12064	S80 vs S20	7·0	2·50	−0·39	2052 (17%)	1267 (11%)	12064 (100%)	1062 (9%)	0
Subtotal (5 trials)	39612	NA	5·1‖	2·53‖	−0·51‖	7667 (19%)	5630 (14%)	39612 (100%)	4377 (11%)	0
Statin versus control										
4S§§	4444	S20–40 vs placebo	5·4	4·88	−1·77	827 (19%)	202 (5%)	4444 (100%)	126 (3%)	0
WOSCOPS	6595	P40 vs placebo	4·8	4·96	−1·07	0	76 (1%)	338 (5%)	193 (3%)	6096 (92%)
CARE	4159	P40 vs placebo	5·0	3·58	−1·03	576 (14%)	586 (14%)	4159 (100%)	0	0
Post-CABG	1351	L40–80 vs L2·5–5	4·3	4·02	−1·07	102 (8%)	116 (9%)	1351 (100%)	37 (3%)	0
AFCAPS/TexCAPS	6605	L20–40 vs placebo	5·2	3·89	−0·94	997 (15%)	155 (2%)	10 (<1%)	9 (<1%)	6586 (>99%)
LIPID	9014	P40 vs placebo	6·0	3·88	−1·03	1516 (17%)	782 (9%)	9014 (100%)	905 (10%)	0
GISSI-P	4271	P20 vs no treatment	2·0	3·92	−0·35	587 (14%)	582 (14%)	4271 (100%)	179 (4%)	0
LIPS	1677	F80 vs placebo	3·9	3·42	−0·92	271 (16%)	202 (12%)	1677 (100%)	142 (8%)	0
HPS	20536	S40 vs placebo	5·4	3·38	−1·29	5082 (25%)	5963 (29%)	13386 (65%)	8865 (43%)	3161 (15%)
PROSPER	5804	P40 vs placebo	3·3	3·79	−1·04	3000 (52%)	623 (11%)	1881 (32%)	1026 (18%)	3254 (56%)
ALLHAT-LLT	10355	P40 vs usual care	4·9	3·76	−0·54	5051 (49%)	3638 (35%)	1188 (11%)	1788 (17%)	8037 (78%)
ASCOT-LLA	10305	A10 vs placebo	3·3	3·44	−1·07	1942 (19%)	2527 (25%)	15 (<1%)	1435 (14%)	8860 (86%)
ALERT	2102	F40 vs placebo	5·5	4·14	−0·84	715 (34%)	396 (19%)	400 (19%)	241 (11%)	1702 (81%)
CARDS	2838	A10 vs placebo	4·1	3·03	−1·14	909 (32%)	2838 (100%)	9 (<1%)	97 (3%)	2738 (96%)
ALLIANCE**	2442	A10–80 vs usual care	4·7	3·80	−1·16	434 (18%)	540 (22%)	2442 (100%)	162 (7%)	0
4D**	1255	A20 vs placebo	4·0	3·25	−0·89	578 (46%)	1255 (100%)	630 (50%)	666 (53%)	344 (27%)
ASPEN**	2410	A10 vs placebo	4·0	2·93	−0·99	811 (34%)	2410 (100%)	578 (24%)	302 (13%)	1663 (69%)
MEGA***††	8214	P10–20 vs usual care	5·0	4·05	−0·67	5547 (68%)	1686 (21%)	42 (<1%)	53 (<1%)	8119 (99%)
JUPITER**	17802	R20 vs placebo	2·0	2·70	−1·09	6801 (38%)	76 (<1%)	0	0	17802 (100%)
GISSI-HF**	4574	R10 vs placebo	4·2	3·06	−0·92	1032 (23%)	1196 (26%)	1797 (39%)	4574 (100%)	0
AURORA**	2773	R10 vs placebo	4·6	2·58	−0·99	1050 (38%)	731 (26%)	659 (24%)	743 (27%)	1663 (60%)
Subtotal (21 trials)	129526	NA	4·8‖	3·70‖	−1·07‖	37828 (29%)	26580 (21%)	48291 (37%)	21543 (17%)	70025 (54%)
Total (26 trials)	169138	NA	4·9‖	NA	NA	45495 (27%)	32210 (19%)	87903 (52%)	25920 (15%)	70025 (41%)

More vs less statin 5 trials, 39,612 patients

Statin vs control 21 trials, 129,526 patients

CTT Collaboration, et al. Lancet 2010;376:1670–1681.



CTT 2010

Nonstatin Tx

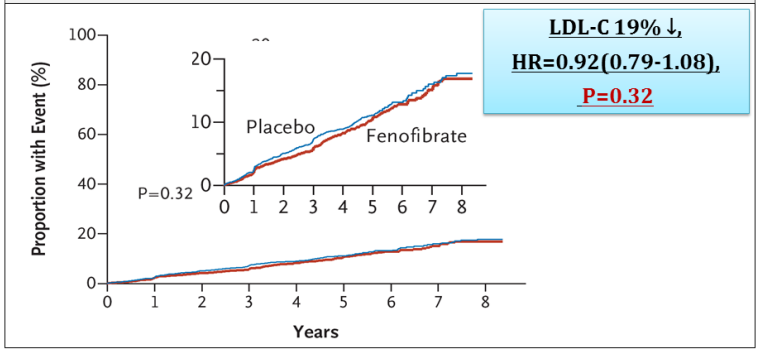
Nonstatin therapy
: Effects of Fenofibrate-Simvastatin in Patients Type 2 DM

[ACCORD]

5,518 Patients HbA1c ≥ 7.5% with type 2 DM

- Fenofibrate 160 mg/day + Simvastatin
- Placebo + Simvastatin

- Primary endpoint : nonfatal MI, nonfatal stroke, or CV death.
- Mean follow-up = 4.7 years



LDL-C 19% ↓, HR=0.92(0.79-1.08), P=0.32

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

Nonstatin therapy
: Effects of Niacin-Simvastatin in Patients with ASCVD

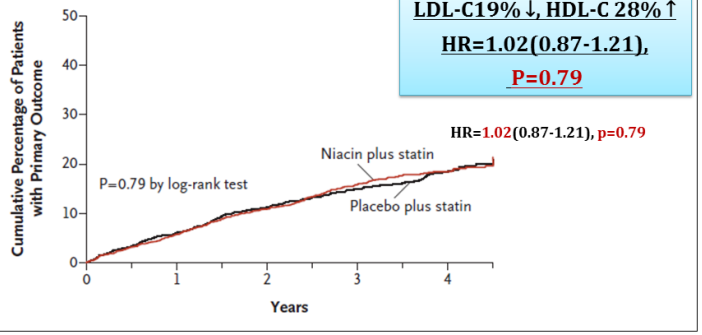
[AIM-HIGH]

3,414 Patients aged ≥ 45 years with CVD, low HDL-C, high TG

- Niacin + Simvastatin
- Placebo + Simvastatin

- Primary endpoint : CHD death, nonfatal MI, ischemic stroke, hospitalization for an ACS, revascularization.
- Mean follow-up = 3 years

(Stopped prematurely because of futility)



LDL-C19% ↓, HDL-C 28% ↑ HR=1.02(0.87-1.21), P=0.79

HR=1.02(0.87-1.21), p=0.79

Ref. The AIM-HIGH Investigators, et la. N Engl J Med 2011;365:2255-67.

The RCT evidence clearly shows ..

2013 ACC/AHA guideline

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ASCVD events are reduced
by using the maximum tolerated statin intensity
in those groups shown to benefit

Current RCT data do not support that
the routine use of nonstatin drugs combined with statin
therapy to reduce further ASCVD events.

No recommendation for non-statin therapy

2014 NICE guideline

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- **Do not routinely offer** fibrates for the prevention of CVD
- **Do not offer** nicotinic acid, bile acid sequestrants, omega-3 fatty acid compounds for the prevention of CVD
- **Do not offer the combination** of a bile acid sequestrant, fibrate, nicotinic acid or omega-3 fatty acid compound **with a statin** for the prevention of CVD
- **Ezetimibe** should be considered to treat for people with **primary hypercholesterolaemia**

Intensity of Statin Therapy

2013 ACC/AHA guideline

Intensity	High-Intensity	Moderate-Intensity	Low-Intensity
Reduction % in LDL-C	> 50% reduction of LDL with daily statin	30-50% reduction of LDL with daily statin	<30-50% reduction of LDL with daily statin
Statin and dose	**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 demonstrated a reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA ***but were not tested in the RCTs reviewed are listed in italics***.

Intensity of Statin Therapy

2014 NICE guideline

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%	**High intensity if the reduction is above 40%.**
%	**Medium intensity if the reduction is 31% to 40%**
%	**Low intensity if the reduction is 20% to 30%**
-	**Not available in the UK.**

[Grouping of statins]

Dose (mg/day)	5	10	20	40	80
Fluvstatin	10%	15%	**21%**	**27%**	**33%**
Pravastatin	15%	**20%**	**24%**	**29%**	33%
Simvastatin	23%	**27%**	**32%**	**37%**	**42%**
Atorvastatin	31%	**37%**	**43%**	**49%**	**55%**
Rosuvastatin	**38%**	**43%**	**48%**	**53%**	58%

Cholesterol-Lowering Therapy by Risk Levels

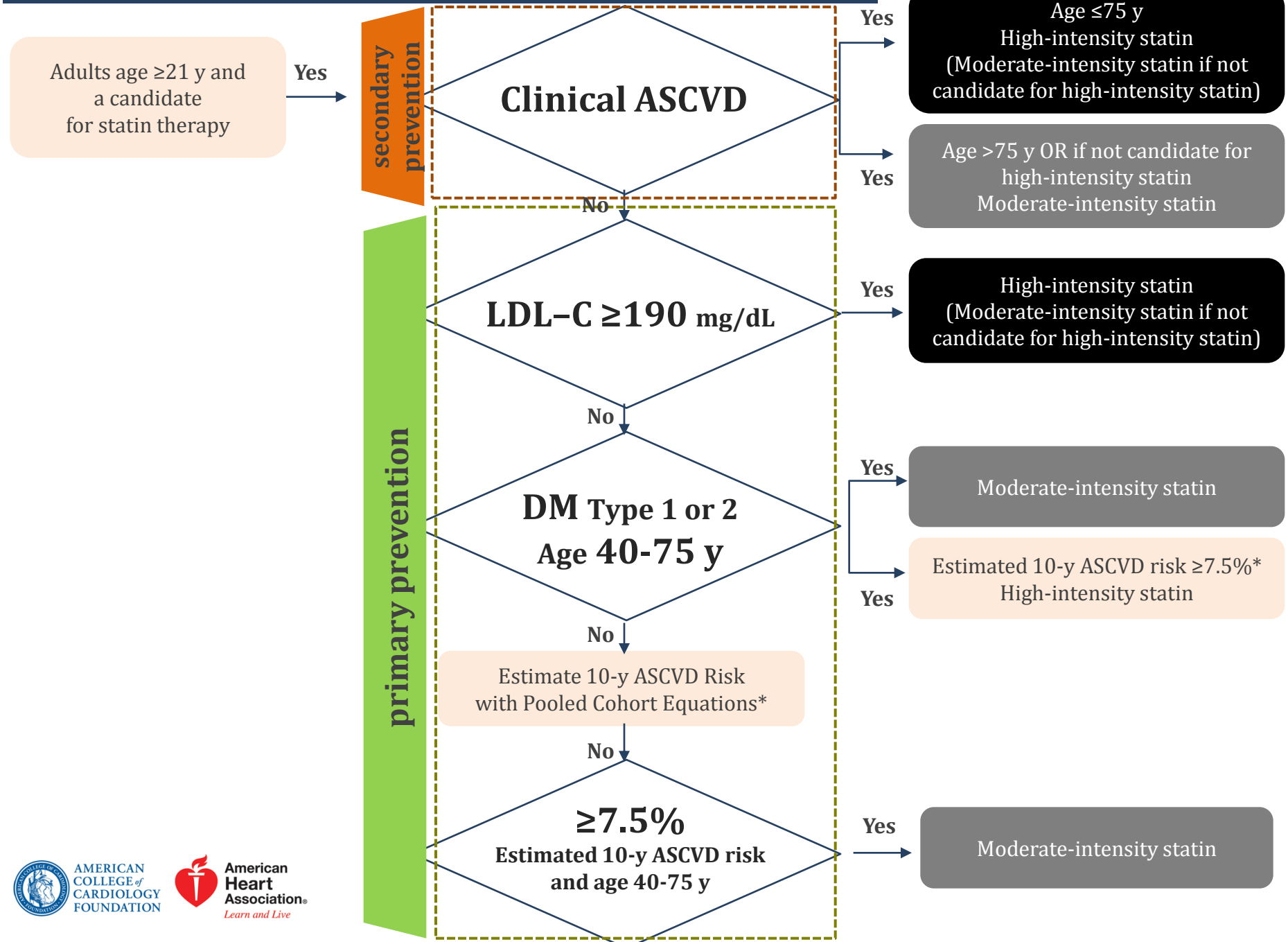
2013 IAS guideline

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Risk Level to Age 80 Yrs	Low (< 15%)	Moderate (15-24%)	Moderately High (25-40%)	High (> 40%)
Therapeutic Intensity	-	Moderate	Moderately High	High
Specific Therapy	Public health recommendation[a]	MLT[b] + CLD[c] optional[d]	MLT[b] + CLD[c] consideration	MLT[b] + CLD[c] indicated[f]

a Persons at low risk for ASCVD should be treated according to national recommendation for the general public. These recommendations should accord with IAS recommendations for lifestyle therapies.
b MLT, maximal lifestyle therapies.
c CLD, cholesterol-lowering drug, usually a statin.
d Cholesterol-lowering drug therapy usually reserved for patients with high levels of atherogenic cholesterol.
e Statin therapy is widely recommended for this risk category, although it is not accepted in many countries because of cost considerations. If drugs are employed, the dose should be adequate to achieve optimal atherogenic-cholesterol levels.
f Cholesterol-lowering drug therapy is usually indicated in this category. The dose should be adequate to achieve optimal atherogenic-cholesterol levels.

2013 ACC/AHA guideline : 4 statin benefit group



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American Heart Association. Learn and Live

Statins are first line therapy

2013 IAS guideline

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	Optimal lipid levels	Treatment
Secondary prevention	• **LDL-C < 70 mg/dL or non-HDL-C < 100 mg/dL**	• **Maximal statin therapy if tolerated.** • If statin intolerant, - combination moderate dose of statin with nonstatin.
Primary prevention	• **High-risk populations** LDL-C < 100 mg/dL or non-HDL-C < 130 mg/dL • **Low-risk populations** LDL-C 100 - 129 mg/dL or non-HDL-C 130 -159 mg/dL	• **Statins are first line therapy.** • If statin intolerant, - use of nonstatin alone or combination.

Atorvastatin is cost effective for CVD prevention

2014 NICE guideline

NICE National Institute for Health and Care Excellence

	Target lipid levels	Treatment
Secondary prevention	No target	• **Atorvastatin 80 mg is cost effective.** • With CVD ⇨ Treat with atorvastatin 80 mg • With CVD and CKD ⇨ Start with atorvastatin 20 mg Increase the dose If eGFR ≥ 30 ml/min/1.73 m2 and non HDL≤ 40%
Primary prevention		• **Atorvastatin 20 mg is cost effective** • 10-y CVD risk ≥ 10 % • Individuals aged ≥ 85 yrs • Type 1 DM* • Type 2 DM with 10-y CVD risk ≥10 % ⇨ Treat with atorvastatin 20 mg • With CKD ⇨ Start with atorvastatin 20 mg Increase the dose If eGFR ≥ 30 ml/min/1.73 m2 and non HDL≤ 40%

* Type 1 DM who are older than 40 years **or** have had diabetes for more than 10 years **or** have established nephropathy **or** have other CVD risk factors.

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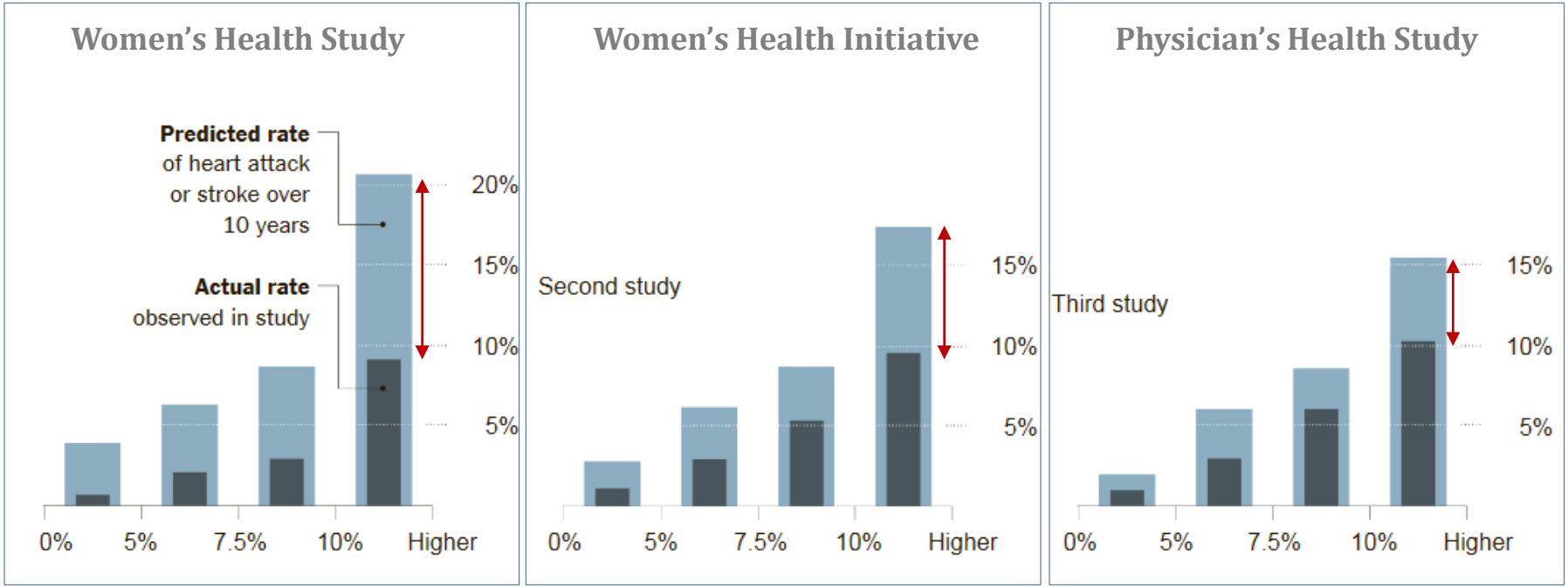
ISSUE of New Assessment Tool

#1. Pooled Cohort Equations have a need for validation.



New calculator overestimates CV risk with 75 to 150%

It has been estimated that the new guidance could result in 33 million adults in the USA being eligible for statins for primary prevention and would apply to approximately 920 million people worldwide were this approach to be adopted internationally.

Drs Paul Ridker and Nancy Cook (Brigham and Women's Hospital, Boston, MA) calculated

The New York Times

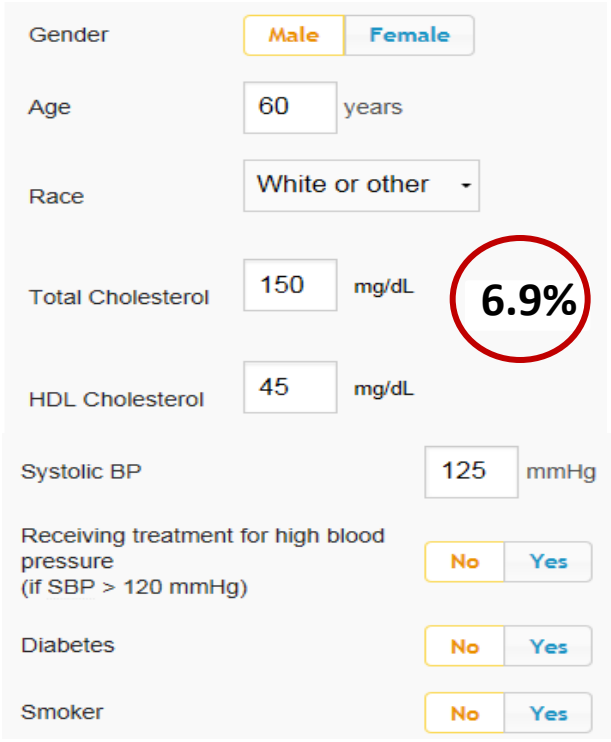
ISSUE of New Assessment Tool

#2. Age and race seem to drive it a lot

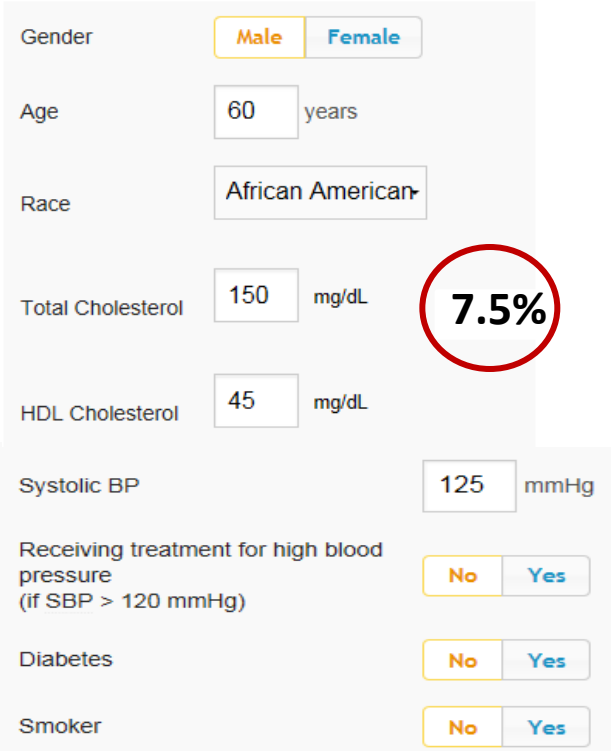
<hypothetical case>

	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
Case 3	**65**	male	Black	150	45	125	No	No	No

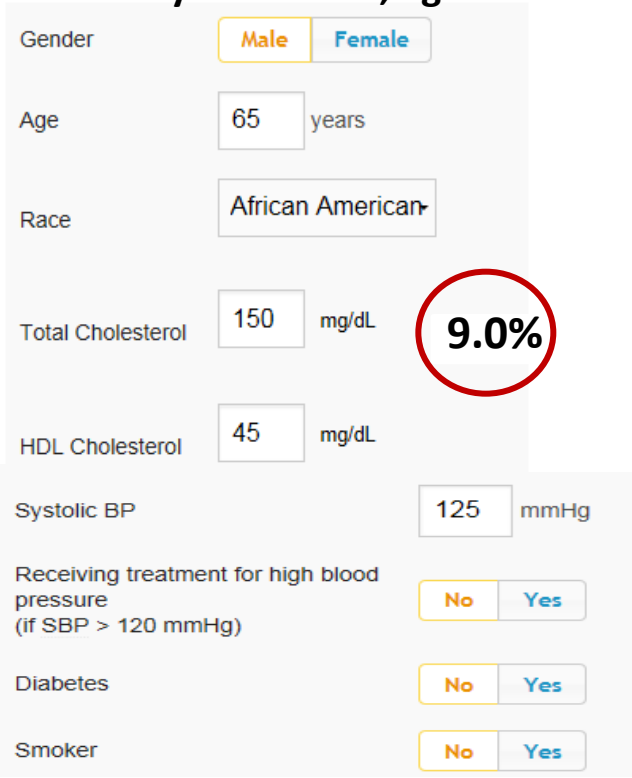
1. healthy white man, age 60



2. healthy black man, age 60



3. healthy black man, age 65



ISSUE of Non-Statin therapy

#3. Ezetimbe may have benefits for prevention of CVD

Non-statin therapy

Improving
CV Outcomes

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

Study Design

National Lead Investigators and Steering Committee (1158 sites, 39 Countries)

IMPROVE-IT

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

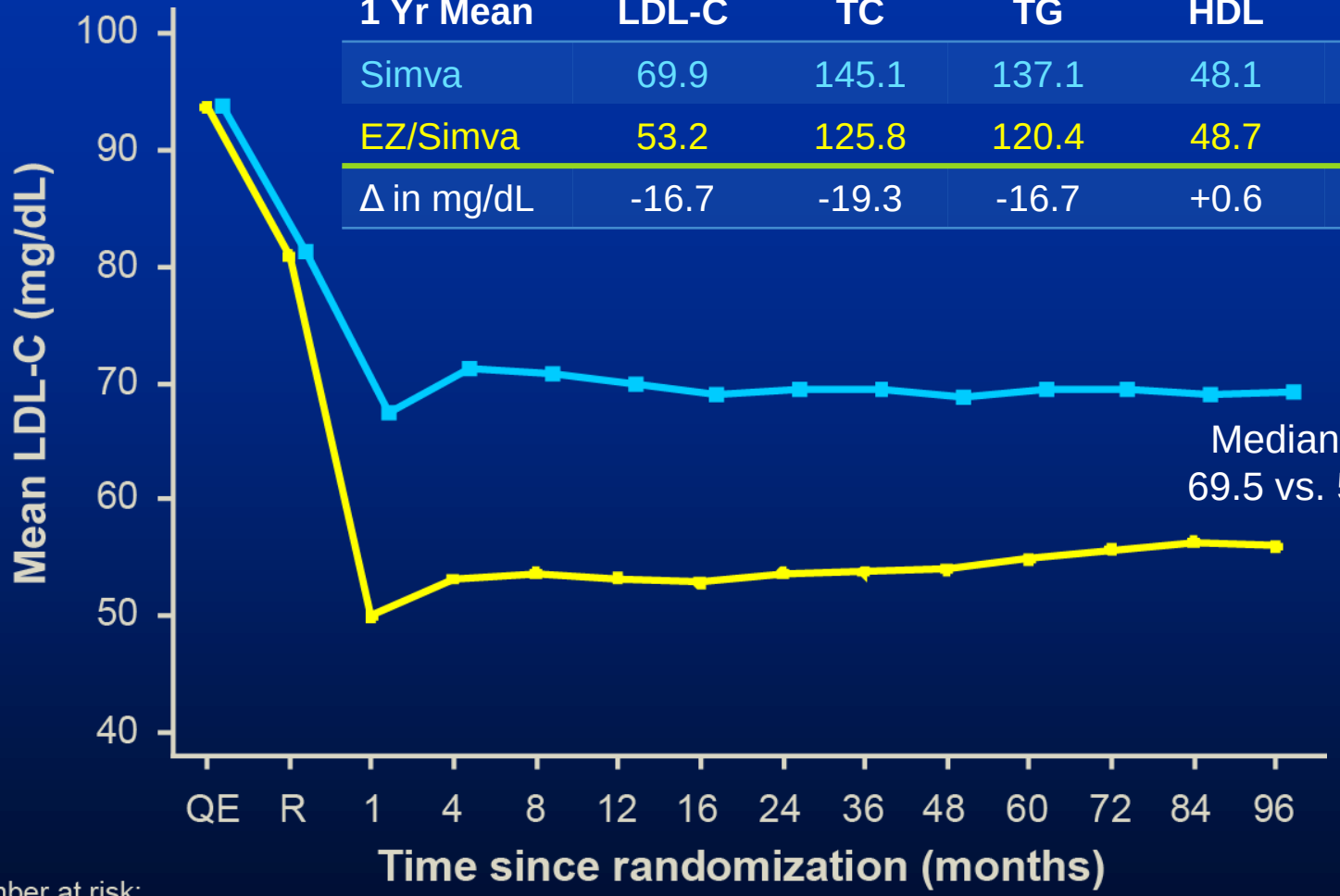
Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

LDL-C and Lipid Changes

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



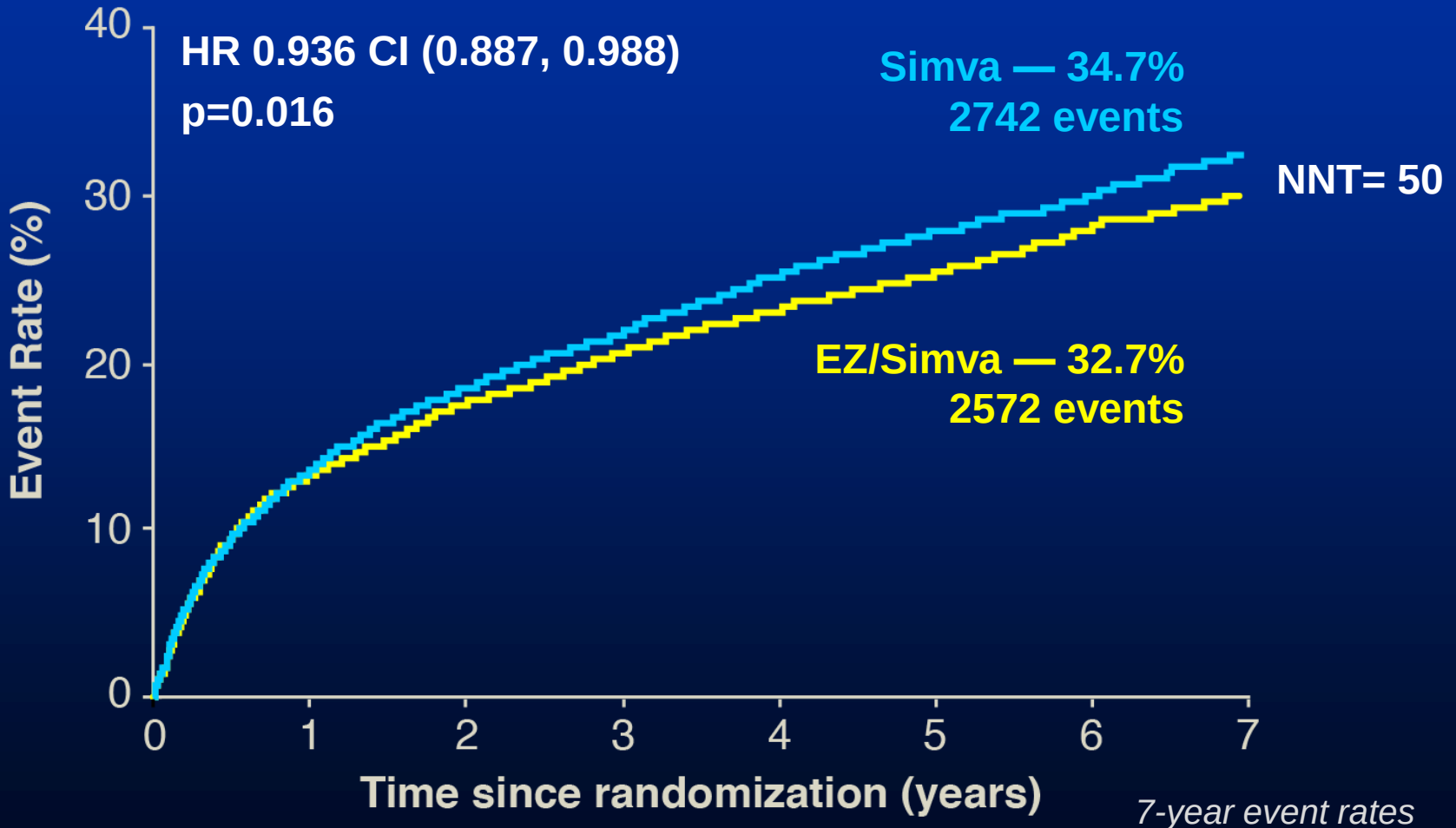
Median Time avg
69.5 vs. 53.7 mg/dL

Number at risk:

EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

Conclusion (I)

- Recommendations of new guidelines were based on the **highest quality evidence** from RCT data.

- **New risk assessment tools** were conducted to estimate the 10- year or lifetime risk of ASCVD for primary prevention.

- New guidelines recommend the **appropriate intensity** of **statin** therapy to reduce CVD risk (2013 ACC/AHA and 2014 NICE guideline recommend moderate to high-intensity statin therapy) and **minimized** use of **nonstatin** therapies.

Conclusion (II)

- Recommend starting with **high-intensity** statin therapy for most **secondary**-prevention patients, with **moderate**-intensity statin therapy for most **primary**-prevention patients.
- Adequate validation will be need for assessment of long-term CV outcomes in the new risk assessment tools.
- Reconsideration may be needed regarding no recommendation of nonstatin therapy, especially for ezetimibe.

Thank you for attention

Target Patient Group

Who are unlikely to be benefited by statin?

(2013 ACC/AHA guideline)

Heart Failure Hemodialysis

Yes →

No recommendations regarding the initiation or discontinuation of statins

Recommendation	NHLBI Grade	NHLBI Evidence statement	ACC/AHA COR	ACC/AHA LOE
The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis.	N (No recommendation)	71,72	-	-

No recommendation for non-statin therapy

2013 ACC/AHA guideline

AMERICAN COLLEGE of CARDIOLOGY FOUNDATION

American Heart Association. Learn and Live

Current RCT data do not support that the routine use of nonstatin drugs combined with statin therapy to reduce further ASCVD events.

2014 NICE guideline

NICE National Institute for Health and Care Excellence

- Do not routinely offer fibrates for the prevention of CVD
- Do not offer nicotinic acid, bile acid sequestrants, omega-3 fatty acid compounds for the prevention of CVD
- Do not offer the combination of a bile acid sequestrant, fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the prevention of CVD
- Ezetimibe should be considered to treat for people with primary hypercholesterolaemia