Shifting the Paradigm for Lipid Management: Pathways in Achieving Improved ASCVD Outcomes

What's new?

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- No industry sponsorship

New recommendations will be change on evidence from RCTs

[Evolution of the Lipid Treatment Guideline]

NCEP ATP Ⅰ 1988	NCEP ATP Ⅱ 1993	NCEP ATP Ⅲ 2001	ATP Ⅲ Update 2004	ESC/EAS 2011	ACC/AHA 2013
Exclusive focus on LDL-C	LDL-C goal ≤100 mg/dL for CHD	LDL-C goal <100 mg/dL for CHD equivalent Non-HDL-C as secondary targets	Optional LDL-C goal <70 mg/dL for very high risk Apo-B as secondary targets		

More intensive LDL-C goal recommendation

Change of risk calculator

?

Framingham risk scores

SCORE (Systemic Coronary Risk Estimation)

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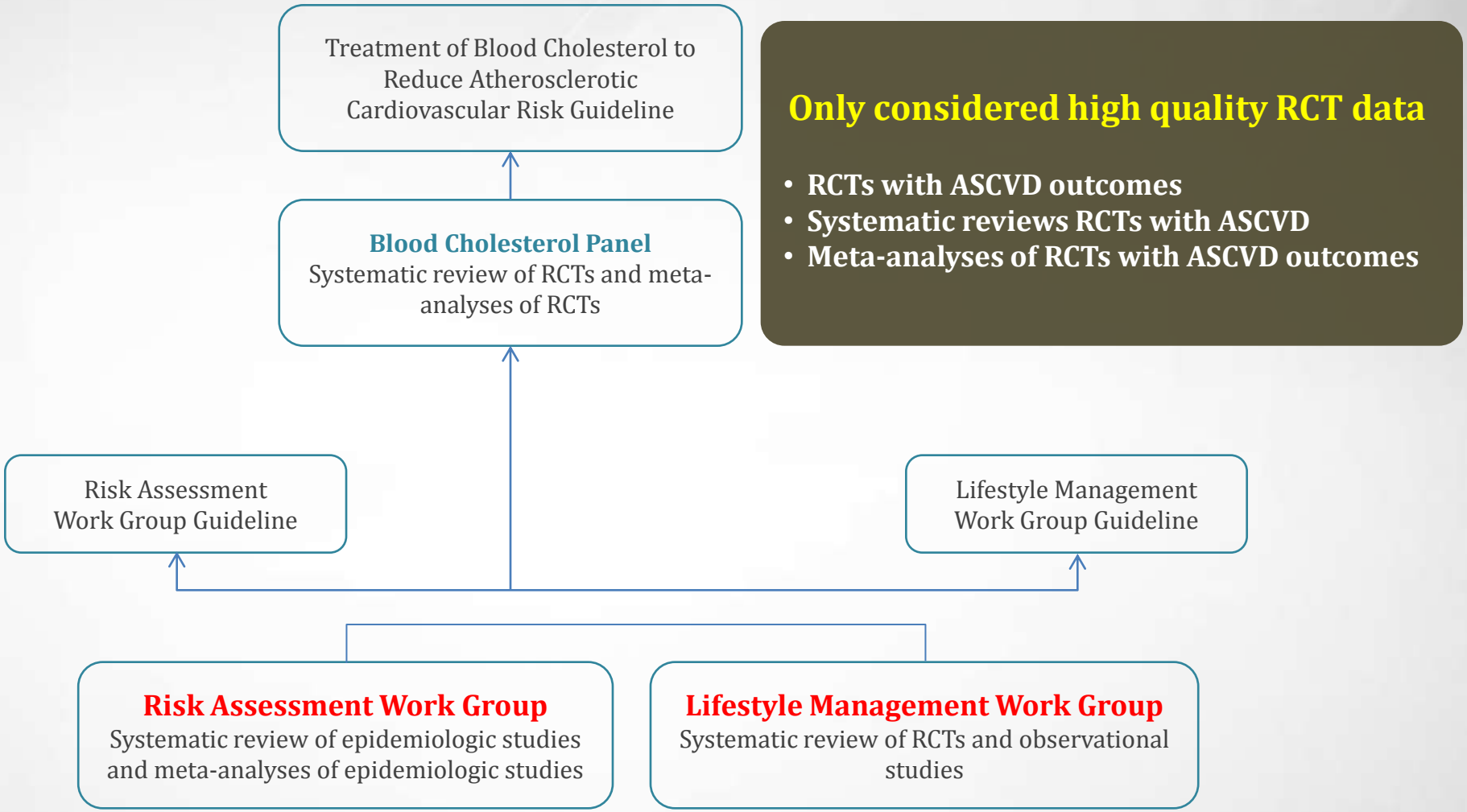
01 What's New in the 2013 ACC/AHA Guideline ?

01 To provide Strong evidence-based foundation



[Overview of the Expert Panel's guideline]

01 Focus on the prevention of ASCVD

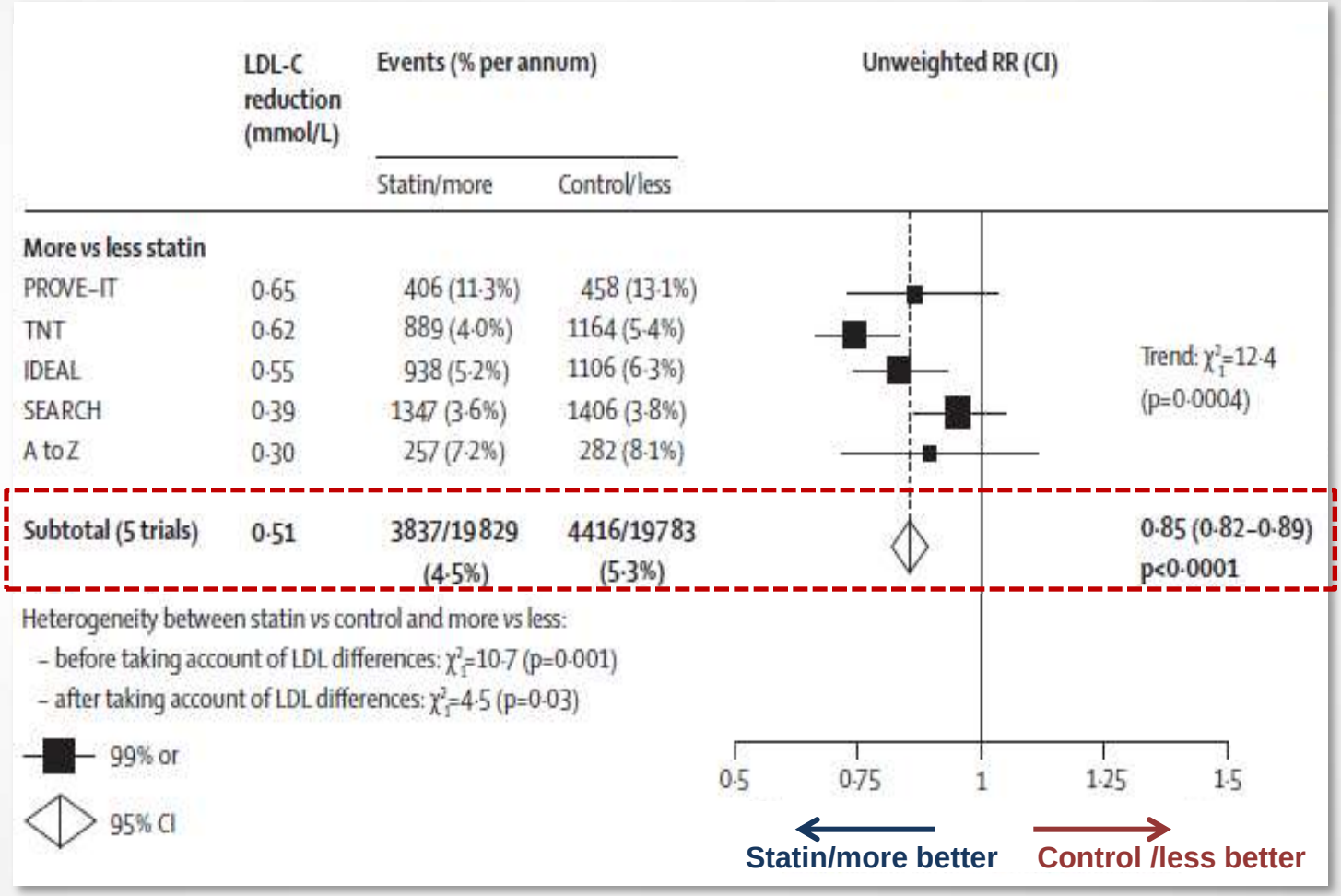
- **This guideline emphasize the treatment of blood cholesterol levels to reduce atherosclerotic cardiovascular disease (ASCVD) risk**

*** Clinical ASCVD - ACS, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD presumed to be of atherosclerotic origin.**

In adults with CHD (including acute coronary syndromes, or a history of MI, stable or unstable angina, coronary revascularization), statin therapy reduced the RR for CVD events by approximately 21% per 1 mmol/L (38.7 mg/dL) LDL–C reduction. This relationship was similar for more intensive compared with less intensive statin therapy and for statin therapy compared with placebo/control.	H	Secondary Prevention	CTT 2010(20)
In adults with CVD other than CHD (including stroke, TIA presumed to be of atherosclerotic origin, or peripheral arterial disease or revascularization), statin therapy reduced the RR for CVD events by approximately 19% per 1 mmol/L (38.7 mg/dL) LDL–C reduction. This relationship was similar for more intensive compared with less intensive statin therapy and for statin therapy compared with placebo/control.	H	Secondary Prevention	CTT 2010(20)- 26 trials

01 More vs. less intensive statin therapy (CTT 2010)

- Meta-analysis of data (5 trials; 39,612 individuals; median follow-up 5·1 years)
- The effects on any major vascular



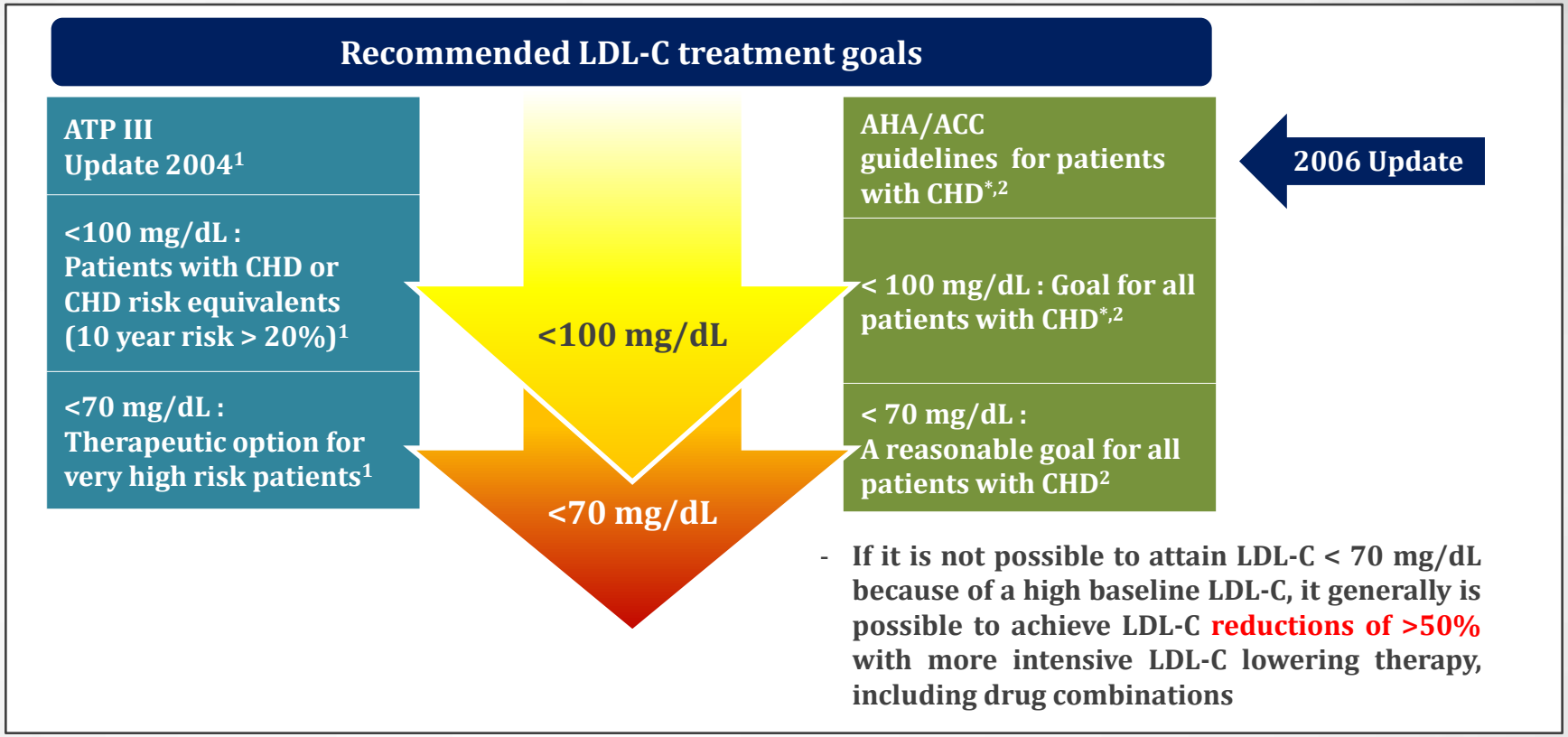
Cholesterol Treatment Trialists' (CTT) Collaboration. Lancet 2010;epub 9 Nov

The RCT evidence clearly shows ..

ASCVD events are reduced
by using the maximum tolerated statin intensity
in those most likely to benefit

01 Treat to goal paradigm

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



† Factors that place a patient at very high risk: established cardiovascular disease plus: multiple major risk actors (especially diabetes); severe and poorly controlled risk factors (e.g., cigarette smoking); metabolic syndrome (triglycerides ≥200 mg/dL + non–HDL-C ≥130 mg/dL with HDL-C <40 mg/dL); and acute coronary syndromes.[1] *And other forms of atherosclerotic disease.[2]

1. Grundy SM et al. Circulation 2004;110:227–239.
2. Smith SC Jr et al. Circulation 2006; 113:2363–2372.

01 But, no evidence for LDL–C and non-HDL–C goals for prevention of ASCVD

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

<NHLBI Evidence Statements>

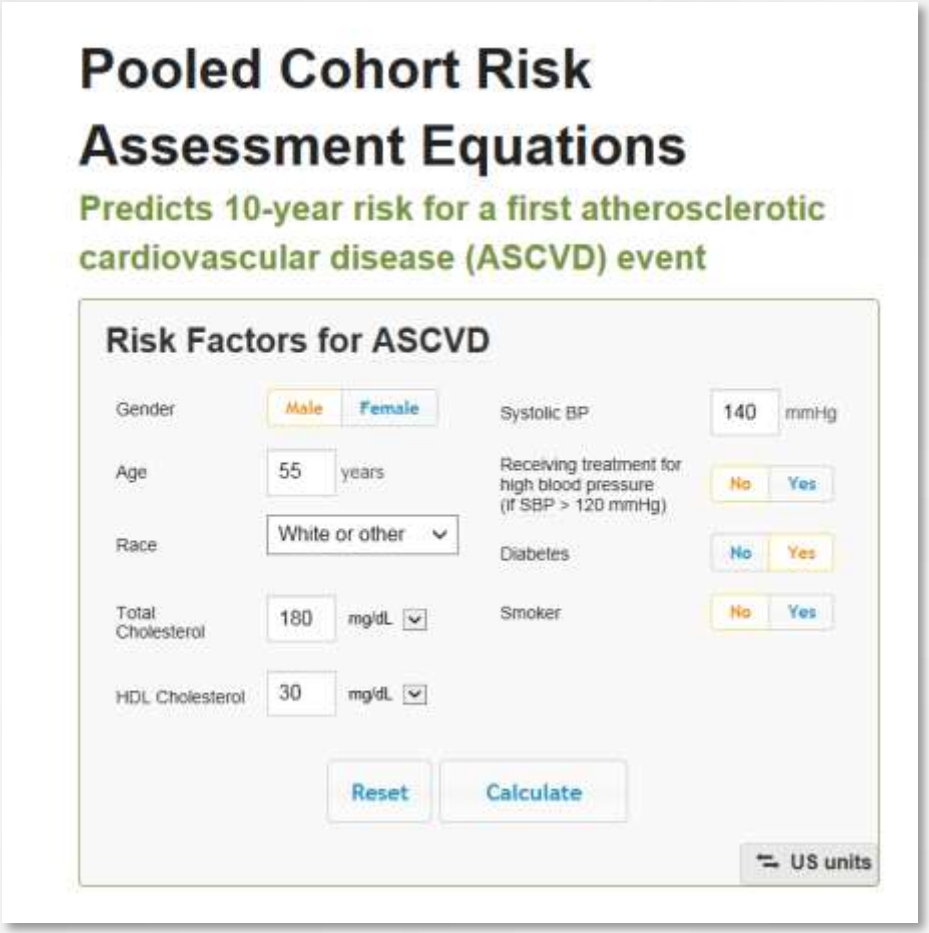
1. No data regarding titration to a specific LDL–C goal *in adults with CHD/CVD.*

2. No trials reporting mean or median on-treatment non-HDL–C levels *in adults with CHD/CVD.*

3. No RCT data regarding dose titration to achieve a specific LDL–C goal in patients *without CHD/CVD.*

4. Insufficient evidence in women *without CHD/CVD* to evaluate the reduction in CVD risk with achieved LDL–C levels <130 mg/dL or <100

01 The new Pooled Cohort Equations to estimate 10-year ASCVD risk



The new Pooled Cohort Equations included

- ARIC study
- Cardiovascular Health Study
- CARDIA study
- Framingham Original
- Framingham Offspring Study

[http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx]

02

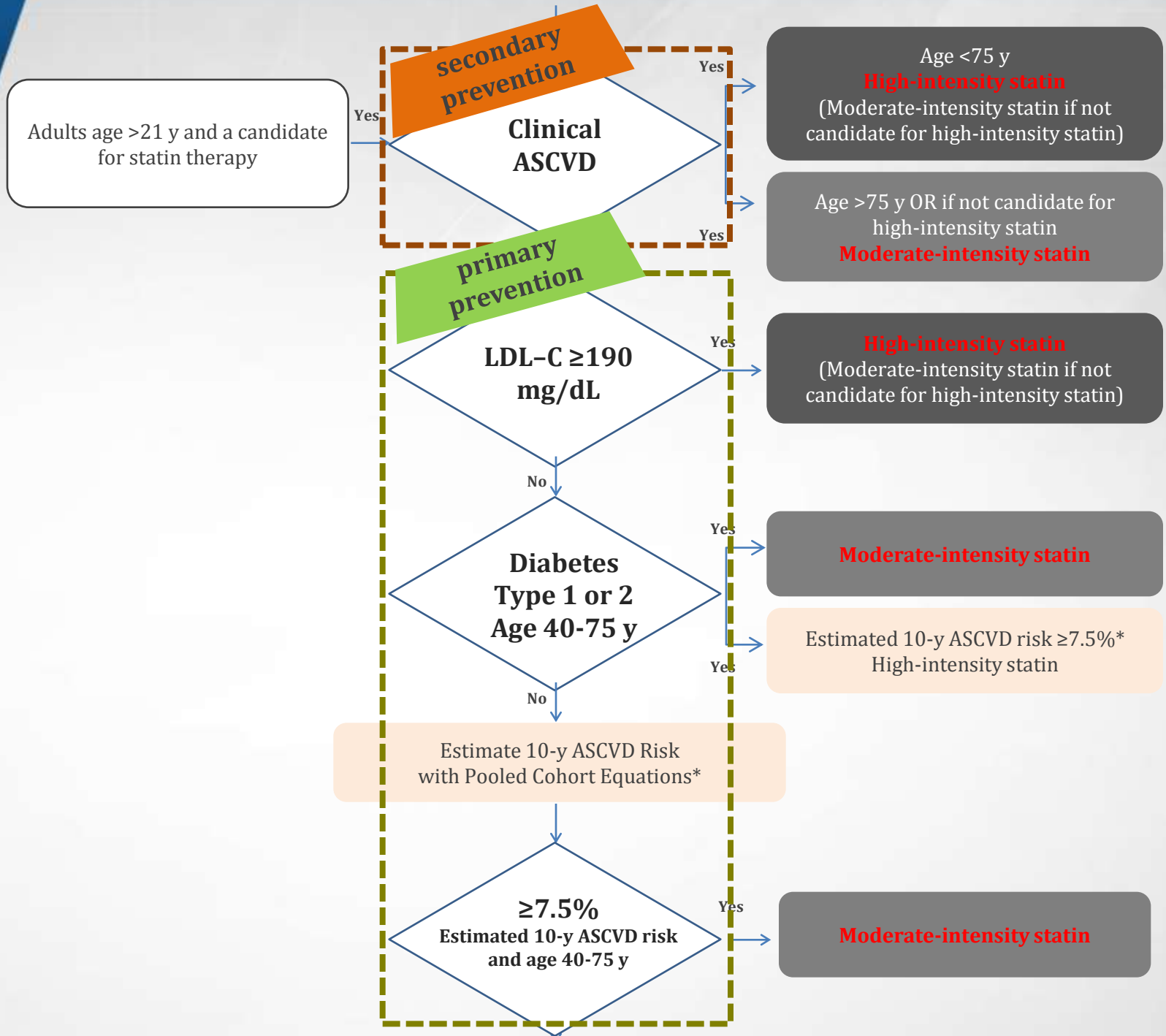
Whom to treat?
(Who are to be benefited by statins?)

4 Major Statin Benefit Groups

- ✓ **With clinical ASCVD***
- ✓ Primary elevations of **LDL–C ≥190 mg/dL**
- ✓ **Diabetes aged 40 to 75 years** with LDL-C 70-189 mg/dL
- ✓ Without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL-C 70- 189 mg/dL and an **estimated 10-year ASCVD risk > 7.5%**

*** Clinical ASCVD - ACS, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD presumed to be of atherosclerotic origin. `**

02


Adults age >21 y and a candidate for statin therapy
Yes
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
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

02 Who are unlikely to be benefited by statin?

Study	populations	Treatment & Follow-up	Primary Endpoint	RR	P value
CORONA[1]	N=5,011 NYHA class II-IV ischemic systolic heart failure	Rosuva 10 mg 2.7 years	CV death, non fatal MI and non fatal stroke	0.92 (0.83-1.02)	p=0.12
4D[2]	N=1,255 Dialysis	Atorva 20 mg 4 years	Cardiac death, non fatal MI and stroke	0.92 (0.77–1.10)	p=0.37
AURORA[3]	N=2,776 Dialysis	Rosuva 10 mg 3.8 years	CV death, non fatal MI and non fatal stroke	0.96 (0.84-1.11)	p=0.59
SHARP[4]	N=3,023 Dialysis	Simva 20-Eze 10 mg 4.9 years	Coronary death, MI, ischemic stroke, or revascularization	0.90 (0.74-0.94)	p=0.21

1. Kjekshus J, et al. *N Engl J Med* 2007;357.
2. Wanner C et al. *N Engl J Med*. 2005;353(3):238–248.
3. Holdaas H et al. *Lancet*. 2003;361(9374):2024–2031.
4 Fellström BC et al. *N Engl J Med*. 2009;360(14):1395-1407.

03 How to assess risk?

03 ATP Ⅲ risk score vs New Pooled Cohort risk equation

< Data source, Population, Outcomes>

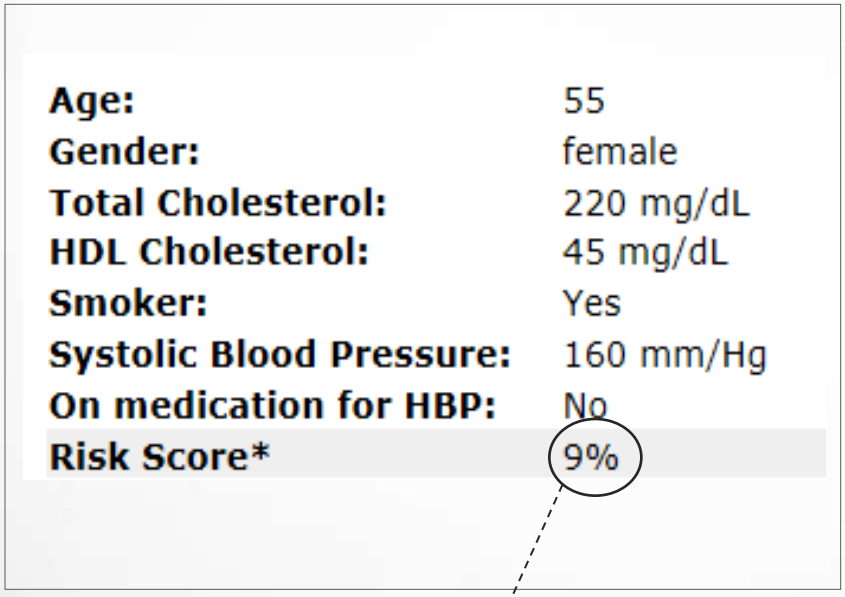
	Population	Study & Region	Data Source	Publication Year	CV outcomes: MI	CHD death	Stroke	Stroke death
					Hard CHD			
ATP Ⅲ risk score	white sample	Framingham MA, USA	EAF, EAM	2001	○	○		
					Hard ASCVD			
New Pooled Cohort risk equation	Whites and African Americans	CARDIA, Framingham , ARIC, CHS, USA	EAF, EAM AAF, AAM	2013	○	○	○	○

03 ATP Ⅲ risk score vs new Pooled Cohort risk equation

<Risk assessment sample >

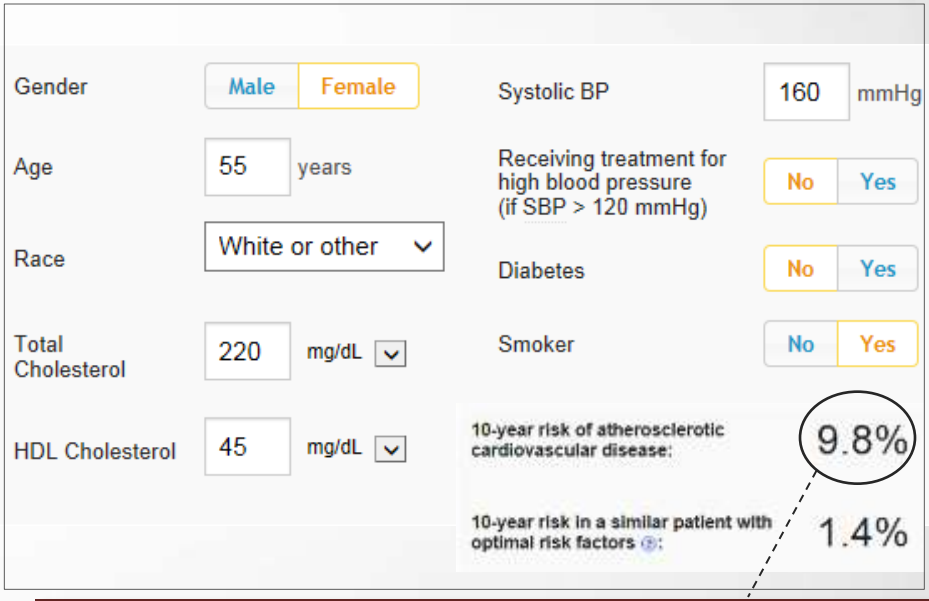
Age	Sex	Race	Total cholesterol	HDL cholesterol	Systolic BP	BP Rx	Diabetes	Smoking
55	female	white	220	45	160	No	No	Yes

CHD risk evaluation



'Low risk' for hard CHD event

ASCVD risk evaluation



'Elevated 10-year risk' for hard ASCVD event

03 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)

04 What treatment, how intensively?

04 Statin Only

The statin RCTs provide the most extensive evidence for the greatest magnitude of ASCVD event reduction, with the best margin of safety.

There was less evidence to support the use of nonstatin cholesterol-lowering drugs for ASCVD prevention.

<The statin RCTs with ASCVD outcomes >

Atorvastatin	Rosuvastatin	Simvastatin	Pravastatin	Lovastatin	Fluvastatin	Pitavastatin
ASCOT-LLA ALLIANCE CARDS GREACE IDEAL MIRACL PROVE-IT SPARCL TNT	JUPITER GISSI-HF AURORA	4S A–Z HATS HPS SEARCH	MEGA PROSPER WOSCOPS CREST LIPID CARE GISSI-P	AFCAPS/ TexCAPS Post-CABG	LIPS ALERT	-

04 Intensity of Statin Therapy

Intensity	High-Intensity	Moderate-Intensity	Low-Intensity
Reduction % In LDL-C	Daily dose lowers LDL-C on average, by approximately ≥ 50%	Daily dose lowers LDL-C on average, by approximately 30 - 50%	Daily dose lowers LDL-C on average, by < 30%
Statin and dose	**Atorvastatin 80** (40) 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***.

04 Intensity of Statin Therapy for Clinical ASCVD (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

- In individuals with clinical ASCVD,
  High-intensity statin therapy should be initiated or continued as first-line therapy .

- If not candidate for high-intensity statin,
  Moderate-intensity statin should be used as the second option.

*** Clinical ASCVD - ACS, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or PAD presumed to be of atherosclerotic origin.**

Atorvastatin 80 mg reduced a mean LDL–C by 42%, the RR for CVD by 16%

PROVE -IT

4,162 Patients aged ≥ 18 years with ACS

- **Pravastatin 40 mg/day**
- **Atorvastatin 80 mg/day**

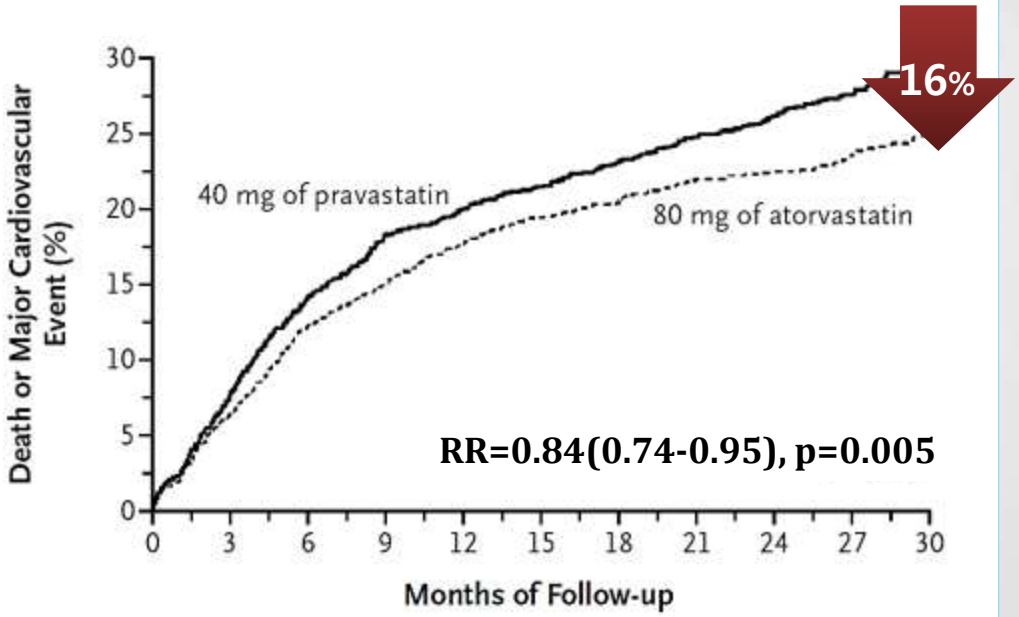
- **Primary endpoint : Death, MI, documented UA requiring rehospitalization, revascularization**
- **Mean follow-up = 24 months**

Change of LDL-cholesterol

	Atorvastatin 80 mg	Pravastatin 40 mg
N	**2,099**	2,063
Baseline median, mg/dl	**106**	106
End of follow-up mean, mg/dl	**62**	95
LDL-C difference (mg/dL)(%)	**-44(-42%)**	-11(-10%)

42%

Primary endpoint



Cannon CP, et al. N Engl J Med 2004;350:1495–504.

Atorvastatin 80 mg reduced a mean LDL–C by 21%, the HR for CVD by 22%

TNT

10,001 Patients aged 35 to 75 years with stable CHD

- **Atorvastatin 10 mg/day**
- **Atorvastatin 80 mg/day**

- **Primary endpoint : CHD death, nonfatal MI, resuscitated cardiac arrest, or stroke**
- **Median follow-up = 4.9 years**

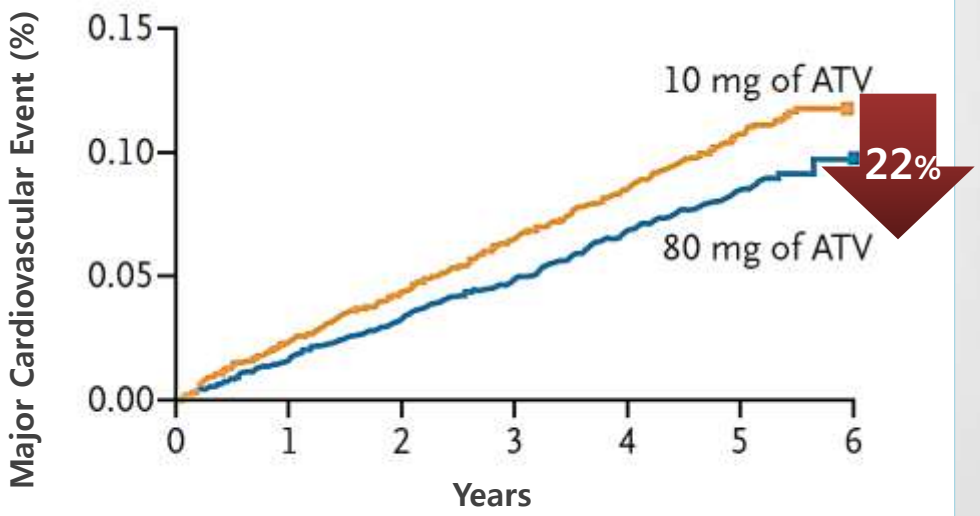
Change of LDL-cholesterol

	Atorvastatin 80 mg	Atorvastatin 10 mg
N	**4,995**	5,006
Baseline median, mg/dl	**97±18**	98±18
End of follow-up mean, mg/dl	**77**	101
LDL-C difference (mg/dL)(%)	**-20(-21%)**	3(3%)

21%

Primary endpoint

HR=0.78 (0.69-0.89), p<0.001



LaRosa JC, et al. N Engl J Med 2005;352:1425–35.

04 Intensity of Statin Therapy for Primary prevention

≥21 Years of Age With LDL–C ≥190 mg/dL

LDL–C ≥190 mg/dL

Yes →

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

- Consider secondary causes of hyperlipidemia
- Use high-intensity statin therapy unless contraindicated or use the maximum tolerated statin
- Consider addition of a nonstatin drug to further lower LDL–C.

Atorvastatin 10-80 mg achieved a mean LDL–C 95 mg/dL reduced the RR for CVD by 17%

ALLIA NCE

2,442 CHD patients aged > 18 years with hyperlipidemia

- Placebo plus usual care
- Atorvastatin 10-80 mg/day

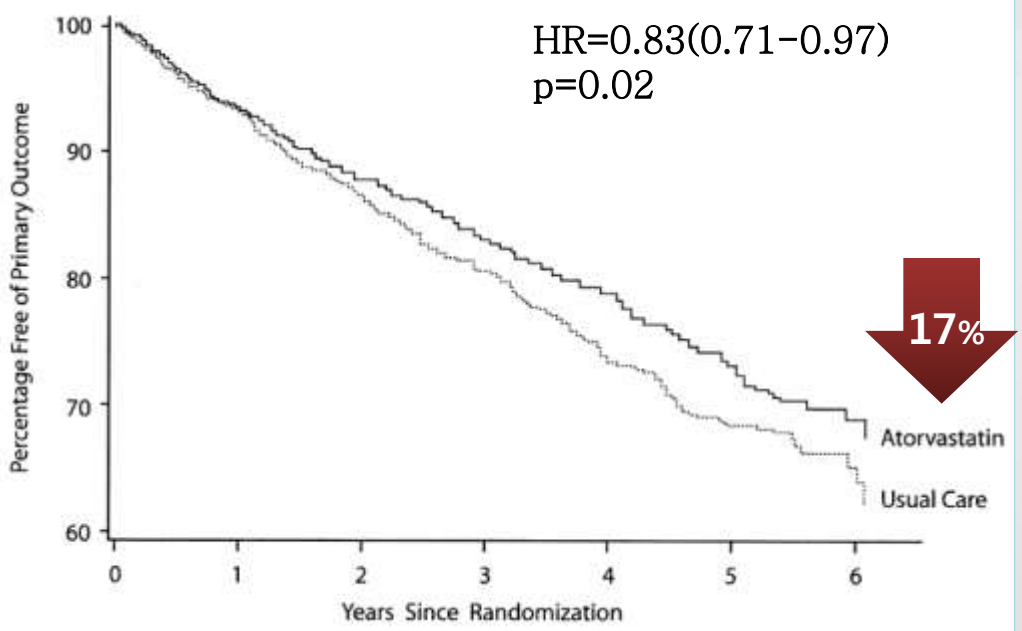
- Primary endpoint : CV death, nonfatal MI, resuscitated cardiac arrest, revascularization, unstable angina
- Mean follow-up = 4.3 years

Change of LDL-cholesterol

	Atorvastatin	Usual Care
n	1,146	725
Baseline mean (SE), mg/dl (mmol/l)	147 (0.8) [3.8 (0.02)]	146 (0.9) [3.8 (0.02)]
Last patient visit mean (SE), mg/dl (mmol/l)	95 (0.8) [2.5 (0.02)]	110 (0.8) [2.8 (0.03)]
LS mean % change (SE)	34.3 (0.7)*	23.3 (0.9)

*p < 0.0001 vs usual care

Primary endpoint



04 Intensity of Statin Therapy for Primary prevention

With Diabetes Mellitus and LDL–C 70-189 mg/dL

Diabetes Type 1 or 2, Age 40-75 y

Yes → Moderate-intensity statin

Yes → Estimated 10-y ASCVD risk ≥7.5%*
High-intensity statin

- In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences

Atorvastatin 10 mg achieved a mean LDL–C 31 mg/dL reduced the RR for CVD by 37%

CARDS

2,838 patients aged 40 to 75 years with diabetes and >1 risk factor

- Placebo
- Atorvastatin 10 mg/day

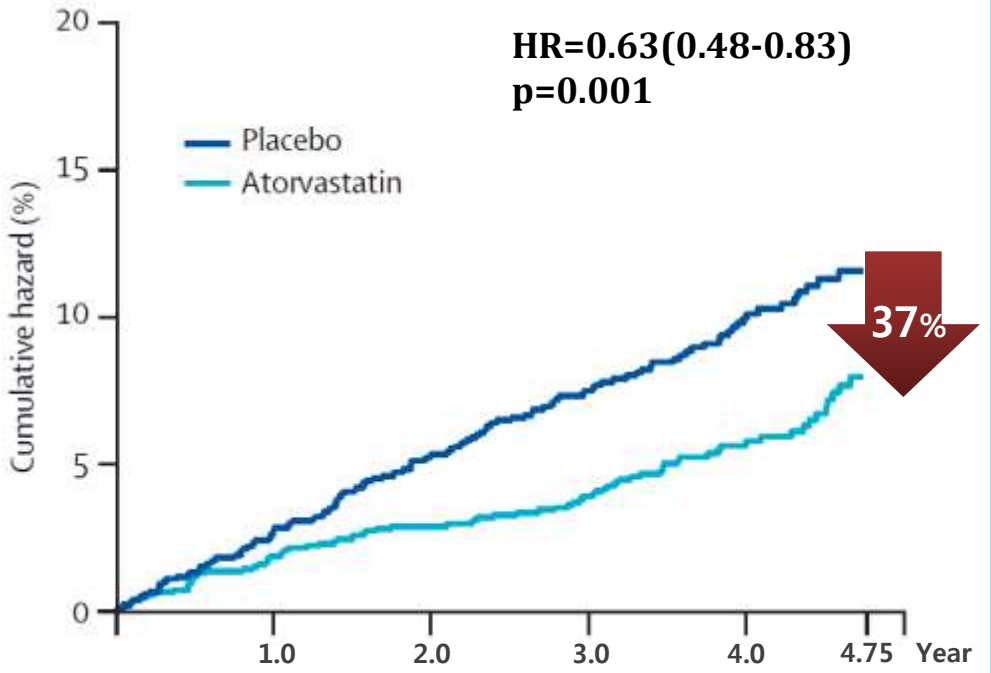
- Primary endpoint
  : Acute CHD event, stroke, coronary revascularization
- Median follow-up = 3.9 years (early closure)

Change of LDL-cholesterol

	Atorvastatin 10 mg	Placebo
N	499	479
Baseline median, mg/dl	118	117
End of follow-up mean, mg/dl	82	116
LDL-C difference (mg/dL)(%)	-36(-31%)	-0.4(-0.3%)

31%

Primary endpoint



Colhoun HM, et al. Lancet 2004;364:685–96.

04 Intensity of Statin Therapy for Primary prevention

Without ASCVD or DM and With LDL–C 70 to 189 mg/dL

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

Yes →

Moderate-High intensity statin

- 5-7.5% estimated 10-y ASCVD risk and age 40-75 y -> Moderate statin
- Considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment.

Future Updates to the Blood Cholesterol Guideline; Medical Unmet Needs

1. The treatment of hypertriglyceridemia
2. Use of non-HDL-C in treatment decision-making
3. Whether on-treatment markers such as Apo B, Lp(a), or LDL particles are useful in guiding decisions
4. Best approaches to use noninvasive imaging for refining risk estimates to guide treatment
5. Optimal age for stating treatment for reducing lifetime risk of ASCVD risk
6. How to do in patients with HF, hemodialysis
7. Long term effects of statin associated new onset diabetes and management
8. Role of pharmacogenetic testing

Conclusion (1)

- **The highest quality evidence derived from well-designed, well-executed RCTs and systematic reviews and meta-analyses of RCTs contribute to develop the guideline.**

- **7 RCTs of atorvastatin trials and 1 RCT of rosuvastatin trial were mainly reflected on high intensity statin strategy in the 2013 ACC/AHA guideline.**

	Atorva 40mg	Atorva 80mg	Rosuva 20mg
# of Clinical Trials	1	7	1
Included Clinical Trials	IDEAL	ALLIANCE GREACE IDEAL, MIRACL SPARCL PROVE-IT, TNT	JUPITER
Patients	CHD, ACS, DM with CHD, Stroke		Healthy LDL ≤130 mg/dl HS-CRP >2.0 mg/l

Conclusion (2)

- **Insufficient evidences to support the treatment or titration to a specific LDL/HDL-C goals were also reflected in the 2013 ACC/AHA guideline.**

- **However, there are still "Evidence Gaps" in the current guideline**

  - primary prevention of ASCVD in adults >75 years of age.
  - titration to specific cholesterol or apolipoprotein goals in high-risk pts.
  - submax. statin doses, combined w/ nonstatin therapies, in statin-intolerant pts
  - incidence, pathophysiology, clinical course, and clinical outcomes of NOD
  - evaluate new lipid-modifying agents to determine the incremental ASCVD event reduction benefits when added to evidence-based statin therapy.

"Continued accumulation of high-quality trial data will inform future cholesterol treatment guidelines."

Limitation

- ✓The new Pooled Cohort Equations for ASCVD 10-year risk prediction was insufficient at the present time to predict patient's progress
- ✓Clinical judgement required individuals who are not included in the 4 statin benefit groups
- ✓Only considered high quality RCT data