What? No LDL Targets?: Review of the 2013 ACC/AHA Blood Cholesterol Guidelines

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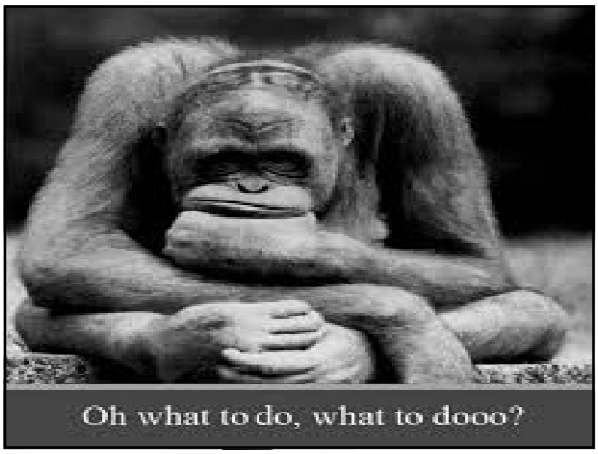
Objectives

- **Identify major changes in treating hyperlipidemia** according to the 2013 ACC/AHA Blood Cholesterol Guidelines
- **Discuss clinical trial data** that impacted the 2013 ACC/AHA Blood Cholesterol Guidelines
- **Apply** the 2013 ACC/AHA Blood Cholesterol Guidelines **to a patient case**

Out with the old, in with the new

- National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines have been used for 12 years
- Can you teach an old dog new tricks? We're about to find out!
- Data has been emerging for several years now…



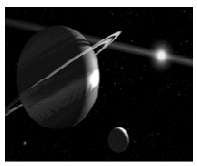
Highlights of Changes: ATP III to 2013 ACC/AHA guidelines

- **No longer targeting therapy to an LDL goal**
  - "The Expert Panel was unable to find RCT to support continued use of specific LDL and or non-HDL treatment targets"
  - **4 statin benefit groups**
- **Non-statin medications**
  - "Non-statin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD"

Stone, et al. J Am Coll Cardiol 2013

Support for lack of LDL goals

- JUPITER (2008)
  - 17800 patients w/ **LDL <130**
  - **Rosuvastatin 20mg** daily or **placebo**
  - Primary endpoint = MI, CVA, arterial revascularization, UA, CV death
  - **Significant ⇩ in major CV events**
  - **Benefit of adding a statin was independent of LDL lowering**



Ridker et al. NEJM 2008.

Support for lack of LDL goals

- **Hayward, et al. 2010**
  - Simulation model from the NHANES data (1988-1994)
  - Treatment per NCEP guidelines vs tailored approach
    - 5-15% risk (simva 40mg), >15% risk (atorva 40)
  - Tailored approach resulted in preventing more CAD and fewer patients on a high-dose statin

Hayward, et al. Ann Intern Med 2010

Why are we using statins?

- "…**high level of evidence** …**statins reduce total mortality** in…**history of prior ASCVD…** with **no prior history of ASCVD**…there is **moderate evidence** that **statins reduce total mortality** in individuals **at increased ASCVD risk.** Two meta-analyses published after the completion of the Expert Panel's… review provide strong evidence that statins reduce total mortality…".

Stone, et al. J Am Coll Cardiol 2013

Why are we using statins?

- **Years of data showing efficacy for CVD**
- **2014 Cochrane Review**
  - **57000 patients in 18 RCTs, primary prevention**
  - Minimum treatment duration of 1 year, 6 months follow-up
  - **All cause mortality & fatal/non-fatal CVD events ⇩**
    - NNT (all cause mortality) = 143
    - NNT (fatal & non-fatal CHD,CVD, stroke) = 72

    *when a "tailored "approach is used, the NNT would be expected to be even lower…

Taylor, et al. Cochrane 2014

Why are we using statins?

- WOSCOPS (1995)
  - 6600 male patients
  - Pravastatin 40mg daily or placebo
  - **Significant ⇩ in MI & CV death**
  - NNT = 17 (high risk group), 66 (low risk group)
- Absolute benefit = greatest in pts w/ highest baseline risk
  - benefit independent of other predictors of outcome (i.e. smoking DM, fam hx, HTN)

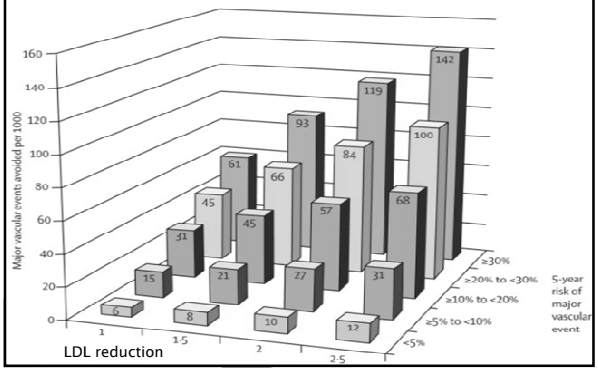
Shepherd et al, NEJM 1995

Why are we using statins?

- **Cholesterol Treatment Trialists' (CTT)**
  - 174000 patients in 27 trials, low risk patients
    - Low risk = <10% 5 yr risk
  - Absolute reduction in major vascular events = 11/1000 over 5 years (graph on next slide)

Mihaylova, et al. Lancet 2012

Why are we using statins?



ASCVD Statin Benefit Groups

- Clinical ASCVD
- LDL >/= 190
- Diabetes type 1 or 2, *age 40-75*
- Estimated 10-year ASCVD risk >/= 7.5%, *age 40-75*

Stone, et al. J Am Coll Cardiol 2013

Statin Guidelines

- High-intensity versus moderate-intensity

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Daily dose lowers LDL by average of ≥50%	Daily dose lowers LDL by average of ~30-50%
Atorvastatin 40-80mg **Rosuvastatin 20**-*40*mg	**Atorvastatin 10**-*20*mg **Rosuvastatin** *5*-**10mg** **Simvastatin 20-40mg** **Pravastatin 40**-*80*mg **Lovastatin 40mg** **Fluvastatin 40mg BID** (*XL 80mg*) *Pitavastatin 2-4mg*

Stone, et al. J Am Coll Cardiol 2013

Support for New Statin Dosage Categories

- **Several trials supporting medium vs. high intensity categories**
  - TNT, PROVE IT, and others
    - TNT: atorva 80mg vs. 10mg = greater risk reduction in pts w/ stable CHD
    - Guideline summary: pts w/ CHD/CVD w/ or w/out DM had a decrease in events w/ a high intensity statin compared to lower intensities

Stone, et al. J Am Coll Cardiol 2013

Which statin category to choose?

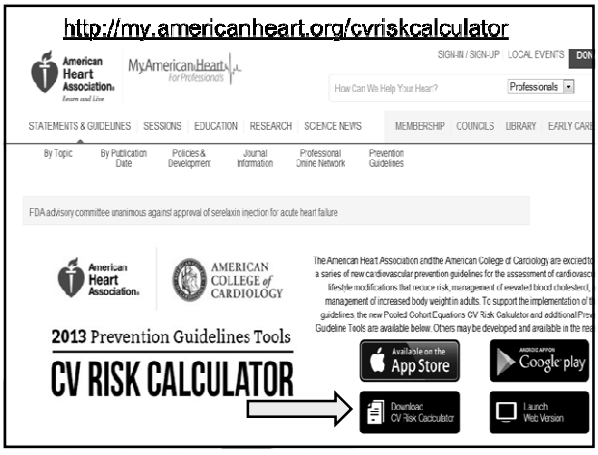
ASCVD	· High-intensity: ≤75 yo · Moderate-intensity: >75 yo or not high-intensity candidate
LDL≥ 190	· High-intensity (moderate-intensity if not high-intensity candidate)
DM,40-75 yo	· Moderate-intensity statin · High-intensity if 10 year risk ≥ 7.5%
10 yr risk ≥7.5%, 40-75 yo	· Moderate-to-high intensity statin

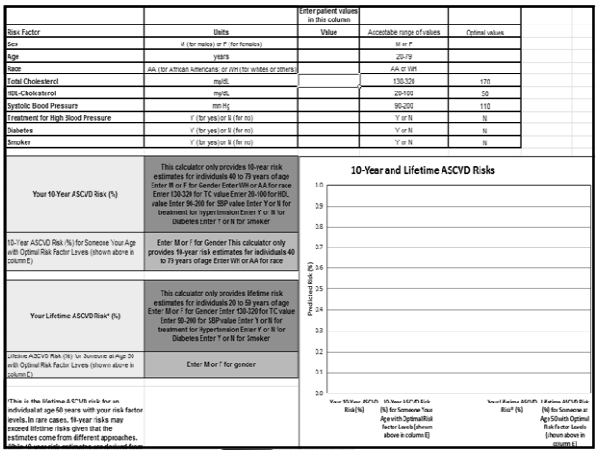
About this new calculator…

- **Pooled Cohort Risk Assessment Equations**
- **Controversial**
- **Editorial by Ridker & Cook – Lancet**
  - May lead to **overprescribing** of statins due to overestimation of primary prevention risk
- **NEJM 3/19/14**
  - May lead to **increased prescribing** due to parameters set for calculated risk/treatment category (i.e. 7.5%)
- In some cases, **risk may be *under*estimated** with the new calculator
- **Must use clinical judgment!**

Ridker, et al. Lancet 2013; Pencina MJ, et al. NEJM 2014

http://my.americanheart.org/cvriskcalculator





Risk Factor	Units	Enter patient values in this column: Value	Acceptable range of values	Optimal values
Sex	M (for males) or F (for females)		M or F	
Age	years		20-79	
Race	AA (for African Americans, or WH (for whites or others)		AA or WH	
Total Cholesterol	mg/dL		130-320	170
HDL-Cholesterol	mg/dL		20-100	50
Systolic Blood Pressure	mm Hg		90-200	110
Treatment for High Blood Pressure	Y (for yes) or N (for no)		Y or N	N
Diabetes	Y (for yes)or N (for no)		Y or N	N
Smoker	Y (for yes)or N (for no)		Y or N	N

Your 10-Year ASCVD Risk (%)	This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age Enter M or F for Gender Enter WH or AA for race Enter 130-320 for TC value Enter 20-100 for HDL value Enter 90-200 for SBP value Enter Y or N for treatment for hypertension Enter Y or N for Diabetes Enter Y or N for smoker
10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)	Enter M or F for Gender This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age Enter WH or AA for race
Your Lifetime ASCVD Risk* (%)	This calculator only provides lifetime risk estimates for individuals 20 to 59 years of age Enter M or F for Gender Enter 130-320 for TC value Enter 50-200 for SBP value Enter Y or N for treatment for hypertension Enter Y or N for Diabetes Enter Y or N for Smoker
Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column C)	Enter M or F for gender
*This is the lifetime ASCVD risk for an individual at age 50 years with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different approaches.	

Example: controversy w/ calculators

- **55 yo male: smoker, HTN (SBP 145), LDL 75, HDL 50**
  - 10 yr risk 9.6% = statin **(ACC/AHA)**
  - 10 yr risk 10% = statin **(Framingham)**
- **60 yo female: non-smoker, no HTN, LDL 180, HDL 50**
  - 10 yr risk 3.8% = no statin **(ACC/AHA)**
  - 10 yr risk 3 % = no statin **(Framingham)**
  - **Moral of the story: Calculators do not fit to all patients – use clinical judgment!**

Ridker, et al. Lancet 2013

Examples: new calculator vs. Framingham

- **56 yo female: smoker, HTN (SBP 132), LDL 119, TC 205, HDL 50, DM. Has CAD & fam hx of early CAD death**
  - 10 yr risk 6.7% = **(ACC/AHA)**
  - 10 yr risk 9% = **(Framingham)**
- **54 yo male: smoker, HTN (SBP 132), LDL 86, TC 132, HDL 29, DM,CAD.**
  - 10 yr risk 15.5% = **(ACC/AHA)**
  - 10 yr risk 10% = **(Framingham)**

Patient Case – statin

Mr. B. Bunny is a 52 year old male patient with a history of diabetes mellitus type 2, MI, HTN, and obesity. His baseline LDL is 176 and has never been on a statin (reason unknown).

Does he have an indication for a statin based on the 2013 ACC/AHA lipid guidelines?

Patient Case – statin answer

- **Yes!**
- **What indication do you base your recommendation on?**
  A. diabetes mellitus type 2
  B. history of MI
  C. baseline LDL
  D. obesity
  E. none of the above

ASCVD Statin Benefit Groups

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- LDL >/= 190
- Diabetes type 1 or 2, *age 40-75*
- Estimated 10-year ASCVD risk >/= 7.5%, *age 40-75*

Stone, et al. J Am Coll Cardiol 2013

Patient Case – indication answer

- **B. history of MI**

Per the guidelines, patient has "clinical ASCVD".

What statin intensity would you like to treat BB with?

A. Moderate intensity

B. High intensity

Which statin category to choose?

ASCVD	· High-intensity: ≤75 yo · Moderate-intensity: >75 yo or not high-intensity candidate
LDL≥ 190	• High-intensity (moderate-intensity if not high-intensity candidate)
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10 yr risk ≥7.5%, 40-75 yo	• Moderate-to-high intensity statin

Patient Case – intensity answer

- **High intensity**

Due to ASCVD and age <75 years with no known history of intolerances or reason why a high-intensity would not be tolerated

Either atorvastatin 40-80mg or rosuvastatin 20mg (to 40mg)

Summary – goals, risk and statins

Guideline Changes for treatment goals and medications used:

- No LDL targets
- 4 "statin" groups
- New risk calculator: use clinical judgment when determining primary prevention risk
- Moderate or high intensity statin at highest tolerable doses

What about those >75 years?

- Evidence supports continuation if already taking/tolerating
- Not included in statin benefit groups for initiation because there is insufficient evidence/lack of data to support use.

Stone, et al. J Am Coll Cardiol 2013

>75 years

- **Few pts** >75 yo studied in RCTs
- **Some data** to support med-intensity for 2ndary prevention, less for primary
- **Life expectancy**
- **Safety concerns**
  - Declining renal function → more prone to myositis
  - More comorbidities

****Must weigh risk versus benefit, ADRs, DDIs, patient preference****

Stone, et al. J Am Coll Cardiol 2013

Other less clear areas

- **Maintenance hemodialysis**
  - No recommendation
- **NYHA class II-IV heart failure**
  - No recommendation
- **LDL <70**

Statins in dialysis patients

- **AURORA (2009)**
  - **2700 patients** on maintenance **hemodialysis**
  - **Rosuvastatin 10mg** daily **or placebo**
  - Primary endpoint = death from CV cause, nonfatal MI or nonfatal stroke
  - Followed for ~4 years
  - Despite LDL lowering, **no benefit** in primary end point

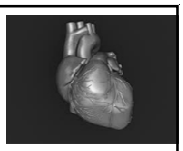
Fellstrom, et al. NEJM 2009

Statins in dialysis patients

- **German Diabetes and Dialysis Study (2005)**
  - **1200 patients** w/ **DM2** and on maintenance **hemodialysis**
  - **Atorvastatin 20mg** daily **or placebo**
  - Primary endpoint = death from cardiac causes, nonfatal MI, and stroke
  - Followed for 4 years
  - **No statistically significant change** in primary endpoint

Wanner, et al. NEJM 2005

Statins in heart failure



- CORONA (2007)
  - **5000 patients** with **NYHA II-IV heart failure**
  - **Rosuvastatin 10mg** daily **or placebo**
  - Primary endpoint = death from CV causes, nonfatal MI, or nonfatal stroke
  - Followed for ~2.5 years
  - Despite LDL and CRP lowering, the **primary outcome** (and death from any cause) was **not reduced**
    - **Life expectancy**

Kjekshus , et al. 2007 NEJM

LDL <70

- **Lack of data to show harm if <70**
- **Cholesterol Treatment Trialists (CTT) (2010)**
- "Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials."
  - Showed no increased risk of cancer or non-vascular death when baseline LDL ~36mg/dL pushed even lower
- **"disproportionate number" of patients included in studies who's cholesterol is reduced by illness**

Stone, et al. 2013 J Am Coll Cardiol 2013; Baigent et al, Lancet 2010.; Taylor, et al. Cochrane 2014

Summary: unclear areas in guidelines

No data to support use of statins in dialysis or NYHA II–IV heart failure

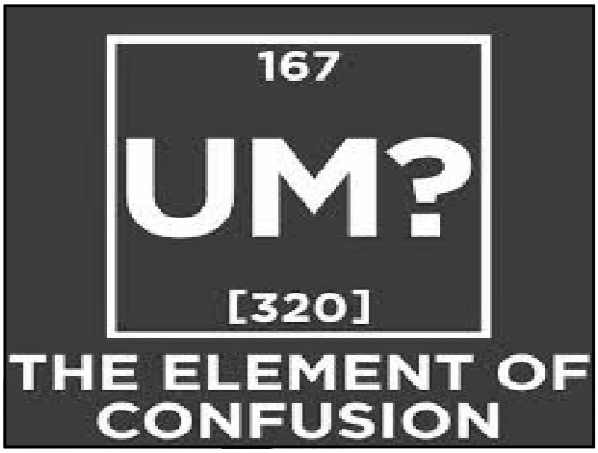
Be **cautious** when using statins in **elderly**

No data to show harm if LDL <70

Where did the non-statin options go?

- "The **panel could find no data supporting the routine use of non-statin drugs** combined with statin therapy to reduce further ASCVD events".
- So, no niacin or fish oil? Lets review why…

Stone, et al. J Am Coll Cardiol 2013



Niacin

- **AIM-HIGH (2011)**
  - **3400 patients** w/ **CVD**
  - **Statin/niacin or statin/placebo**
  - Primary endpoint = death
  - **Trial stopped early due to lack of efficacy**
  - Even though HDL & TG improved, endpoint was not different (i.e. did not decrease cardiac mortality) when niacin was added

Boden, et al. NEJM 2011

Niacin

- **AIM-HIGH (2011)**

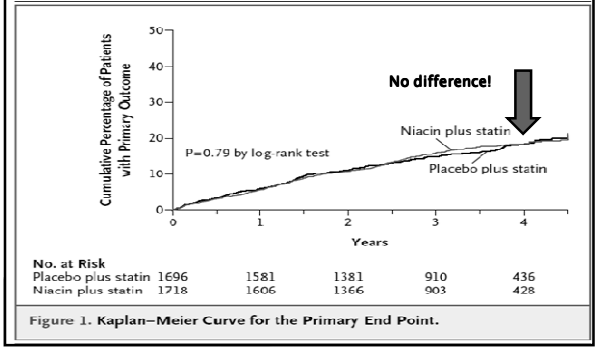


Figure 1. Kaplan–Meier Curve for the Primary End Point.

Omega-3 fatty acids

- **ORIGIN (2012)**
  - **12500 patients** with **DM or impaired glucose**
  - **Fish oil or placebo**
  - Primary endpoint = death from CV causes
  - Followed for 6 years
  - Despite decrease in TG, **no reduction in CV** events, including death
    - No significant impact on vascular events, death

Bosch, et al. NEJM 2012

Fibrates

- **ACCORD – Lipid (2010)**
  - **5500 patients** with **DM**
  - **Simvastatin/fenofibrate or simvastatin/placebo**
  - Primary endpoint = MI, stroke or death from CV cause
  - Followed for >4.5 years
  - **No reduction in MI, stroke, or death**

Ginsberg, et al. NEJM 2010

Ezetimibe

- **ENHANCE (2008)**
  - **720 patients**
  - **Simvastatin 80mg/ezetimibe or simvastatin 80mg/placebo**
  - Primary endpoint = change in carotid artery intima-media thickness
  - Trial duration = 2 years
  - **Although LDL decreased, atherosclerosis did not**

Kastelein, et al. NEJM 2008

Patient case – non-statin

- Mr. B. Bunny is a 52 year old male patient with a history of diabetes mellitus type 2, MI, HTN, and obesity. His baseline LDL is 176 and has never been on a statin (reason unknown).
- **He was trialed on daily doses of all statins and "failed" them.**

Patient Case – non-statin

What are his other options?

- A. niacin
- B. fish oil
- C. ezetimibe
- D. none
- E. weekly statin dosing

Patient Case – non-statin answer

- D? E?
- Lets discuss why.

Patient Case – non-statin answer

- So…the guidelines do not necessarily support adding a non-statin option, but do state that we should use the **"maximum appropriate intensity of a statin that does not cause adverse effects"**
- Could consider doing a trial of once weekly statin dosing (from appropriate category) & titrate to tolerability

Alternate-day statin dosing

- **Several small trials (weekly, QOD, bi-weekly, etc.)**
- **Alternate-day statin therapy for treatment of hyperlipidemia; Annals of Pharmacotherapy 2010.**
  - Meta-analysis of 17 trials.
  - Good tolerability and lowering of LDL
  - Impact (long-term) on CV outcomes unknown
- **Drugs of choice: rosuvastatin or atorvastatin**
- Is this better than doing nothing or using something that we *know* does not improve outcomes?

Reindl, et al. Ann Pharmacother 2010.

Summary – non-statin options

- **Non-statin options are not supported by trial data**, and thus the new guidelines
- Use them only if you have a patient or provider who strongly requests adding a drug, knowing that they will not impact outcomes…
- Can **consider alternate day statin** dosing

Treatment of triglycerides

- **2013 ACC/AHA lipid guidelines** suggests:

TG ≥ 500mg/dL = "severe" and recommend treating if they reach this level.

- **2012 Endocrine Society guidelines** suggests:
  - TG (150-199 mg/dL) = *mild* hypertriglyceridemia
  - TG (200-999 mg/dL) = *moderate* hypertriglyceridemia
    - **Treat w/ medications when TG when approaching "*severe or very severe*", defined as >1000mg/dL or > 2000mg/dL** respectively due to pancreatitis risk

Stone et al. J Am Coll Cardiol 2013; Berglund, et al. J Clin Endocrinol Metab 2012.

Treatment of triglycerides

2012 Endocrine Society guidelines

- Treatment **<1000 mg/dL**=**lifestyle modifications**
- Treatment **>1000mg/dL (or near)**:
  - **Fibrates** = 1st line for risk of pancreatitis
  - **Fibrates, omega 3, niacin** = 1st line alone or w/ statin *** do not use gemfibrozil w/ a statin*
  - **No statin monotherapy for severe or very severe (1000 to >2000) hypertriglyceridemia**

Berglund, et al. J Clin Endocrinol Metab 2012

Treatment of triglycerides

- **Per Endocrine Society**:
- "extent to which elevated triglycerides constitute a direct risk for CVD, or more likely represent a marker for other lipoprotein abnormalities associated with CVD risk, is unknown and under extensive investigation."

Berglund, et al. J Clin Endocrinol Metab 2012

Overall Summary

- **No LDL targets**
- **Statins, statins, statins**
- **4** distinct **treatment groups**
- **Consider Endocrine Society's recommendation** when treating TG
- **Clinical judgment must also be a factor!**

TIME FOR QUESTIONS!

Acknowledgement

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References

- **Baigent** C, Blackwell L, Emberson J, Holland LE, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet.* 2010;376(9753).
- **Berglund** L, Brunzell JD, Goldberg IJ, Sacks F, et al. Evaluation and treatment of hypertriglyceridemia: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*, 2012:97(9):2969-2989.
- **Boden** WE, Probstfield JL, Anderson T, Chaitman BR, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med.* 2011;365(24):2255-2267.
- **Bosch** J, Gerstein HC, Dagenais GR, Diaa R, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med.* 2012;367(4):309-18.
- **Fellstrom** BC, Jardine AG, Schmieder RE, Holdaas H, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med.* 2009;360(14):1395-407.
- **Ginsberg** HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med.* 2010;362(17):1563-74.
- **Hayward** RA, Krumholz HM, Zulman DM, Timbie JW, et al. Optimizing statin treatment for primary prevention of coronary artery disease. *Ann Intern Med.* 2010;152:69-77.
- **Kastelein** JJP, Akdim F, Stroes ESG, Zwinderman AH, et al. Simvastatin with or without ezetimibe n familial hypercholesterolemia. *N Engl J Med.* 2008;358(14):1431-1443.
- **Kjekshus** J, Apetrei E, Barrios V, Bohm M, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med.* 2007;357:2248-61.

References

- **Mihaylova** B, Emberson J, Blackwell L, Keech A, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised tirals. *Lancet*. 2012 ;380(9841):581-90.
- **Reindl**, EK, Wright BM, Wargo KA. Alternate-day statin therapy for treatment of hyperlipidemia. *Ann Pharmacother*. 2010;44:1459-70.
- **Ridker** PM, Danielson E, Fonseca FA, Genest J, et al. Rosuvastatin to prevent vascular events in men and women with elevated c-reactive protein. *N Engl J Med*. 2008;359(21);2195-207.
- **Shepherd** J, Cobbe SM, Ford I, Isles CG, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333;1301-1308.
- **Stone** NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults, *J Am Coll Cardiol*. 2013, doi: 10.1016/j.jacc.2013.11.00.
- **Taylor** F, Huffman MD, Macedo A, Moore THM, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2014, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub5
- **Wanner** C, Krane V, Marz W, Olschewski M, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353(3):238-48.