PHARMACY VISION 20/20

CSHP SEMINAR 20 • OCTOBER 21-25

Disneyland RESORT

Showdown at the LDL Corral

A Debate of LDL Targets or Fixed-Dose Approaches for CV Event Reduction

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DISCLOSURE

WE HAVE NO POTENTIAL CONFLICTS OF INTEREST TO DISCLOSE.

Learning Objectives

- Summarize the LDL treatment approaches of the last 3 lipid treatment guidelines from the AHA
- Critique the merits of the literature behind treat-to-target and fixed-dose statin treatment strategies
- Recommend best approaches to lipid management considering the current guideline recommendations and available outcomes data

OVERVIEW

- Review of guidelines
- Framing the debate
- Dr. Gupta – In defense of LDL targets
- Dr. Williams – In defense of fixed-dose approaches
- Questions

https://www.pinterest.com/pin/830562356258739972/

GUIDELINE REVIEW

https://www.pinterest.com/pin/425942077248697714/

ADULT TREATMENT PANEL III (ATP III) - 2004

- Update of 2001 recommendations
  - Endorsed by NHLBI/ACC/AHA
- Treatment approach based on LDL level and risk
  - Presence of clinical coronary heart disease (CHD)
  - Major risk factors including:
    - Smoking; HTN; Low HDL; Family Hx of premature CHD; Age
  - Framingham 10-year CHD risk
- Combination of lipid lowering agents encouraged to achieve LDL and non-HDL goals

1. *Circulation*. 2004;110:227-239.
2. *JAMA*. 2001;295:2486-2497.

ADULT TREATMENT PANEL III (ATP III) - 2004

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL ★	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

★ Option to target LDL <70mg/dL

3. https://www.nhlbi.nih.gov/files/docs/guidelines/atglance.pdf

ACC/AHA Cholesterol Guideline - 2013

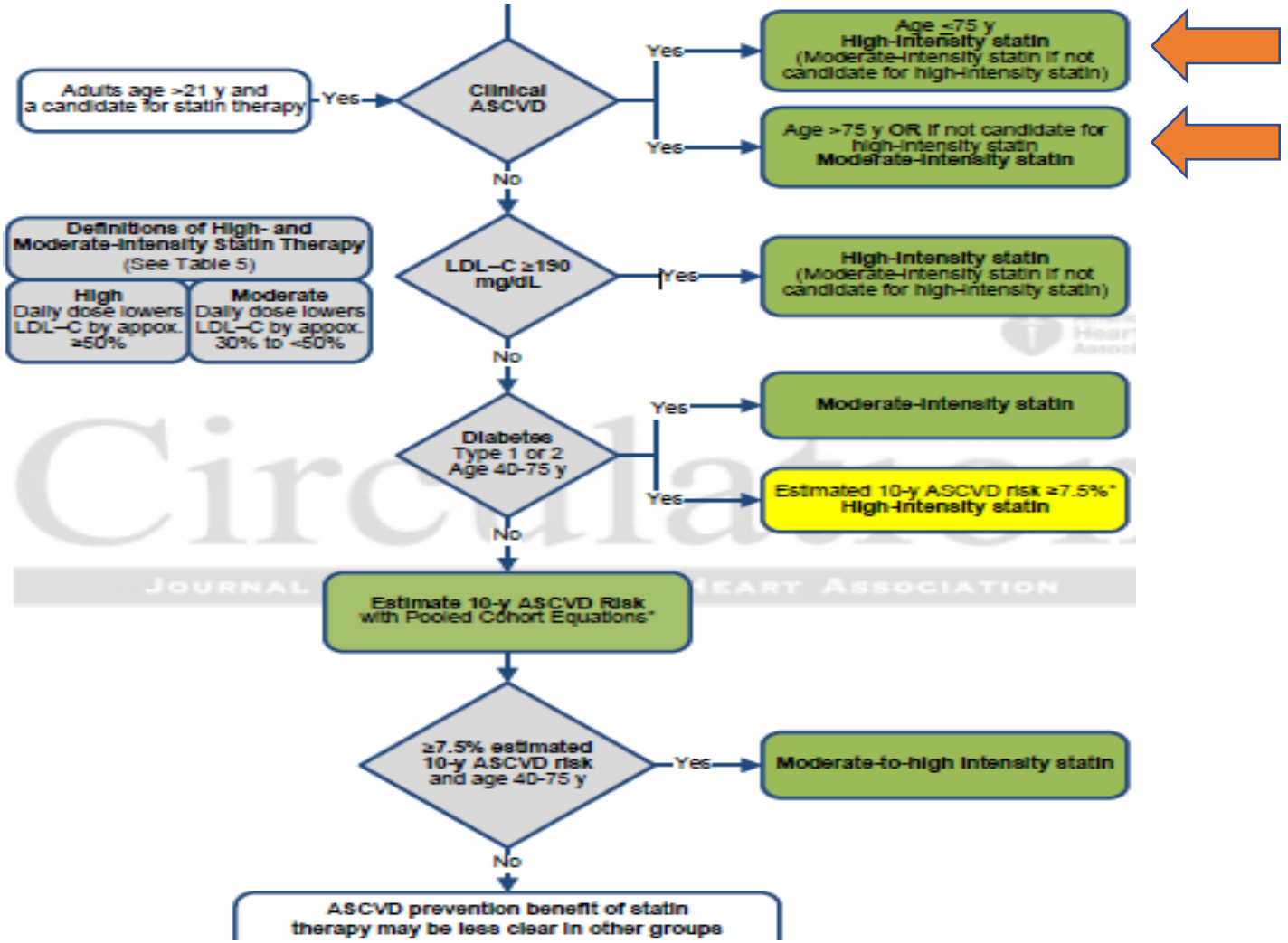
- "The Expert Panel was unable to find RTC evidence to support titrating cholesterol lowering drug therapy to achieve target LDL-C or non-HDL-C levels, as recommended by ATP III."

- Essentially advocates for max-tolerated statin within 4 statin benefit groups:
  - Clinical atherosclerotic cardiovascular disease (ASCVD); LDL > 190mg/dL; Diabetes (DM); Everyone else

- Splits statins into high intensity (>50% LDL reduction) and moderate intensity (30% – 49% LDL reduction)

4. *Circulation*. 2014;129:S1-S45.

ACC/AHA CHOLESTEROL GUIDELINE - 2013



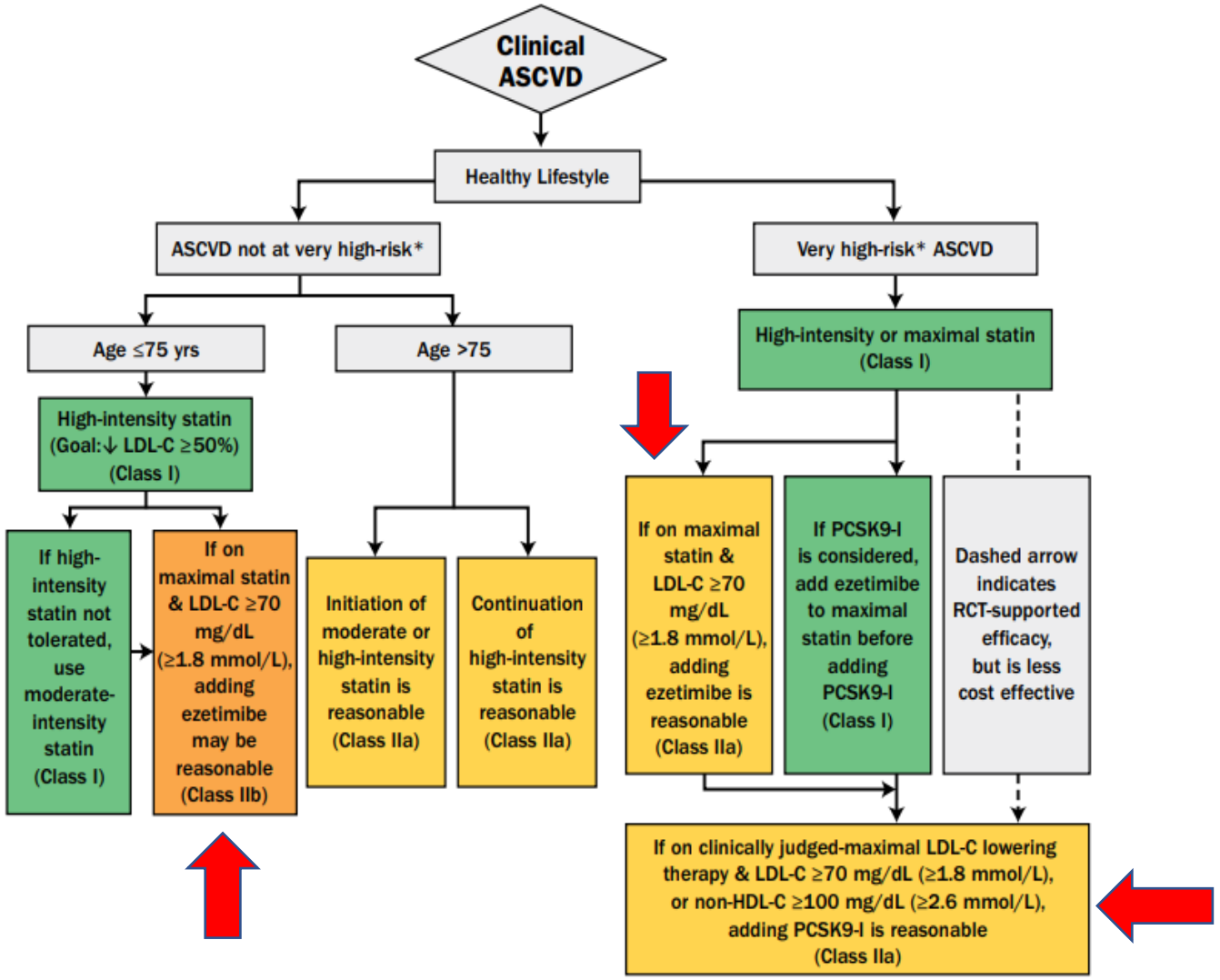
4. *Circulation*. 2014;129:S1-S45.

ACC/AHA Cholesterol Guideline – 2018

- Update of the 2013 guidelines
  - New non-statin data had emerged
  - European societies and AACE updated their recommendations to include LDL targets as low as <55mg/dL for some risk groups in 2016/2017
- Largely preserves the 4 statin benefit groups
  - Recommendations for primary prevention more convoluted
- Recommends LDL <70mg/dL for high-risk ASCVD
  - Combination tx with ezetimibe recommended per IMPROVE-IT

5. *JACC*. 2019;73(24):e285-350.
6. https://www.acc.org/latest-in-cardiology/articles/2017/08/11/08/35/aace-and-eas-lipid-guidelines
7. *N Engl J Med*. 2015;372:2387-2397.

ACC/AHA Cholesterol Guideline - 2018



5. *JACC*. 2019;73(24):e285-350.

Framing the Debate

- Dr. Gupta will argue in favor of the new AHA Guideline recommendations regarding LDL targets for selected populations
- Dr. Williams will argue against the new AHA Guideline recommendations regarding LDL targets for selected populations in favor of fixed-dose statin treatment
- Will not debate primary prevention or familial hyperlipidemia tx recommendations
- Will not debate the use of icosapent ethyl (REDUCE-IT), bempedoic acid (CLEAR Harmony), or other new/promising CV event-reduction treatments not yet mentioned in published guidelines

8. *N Engl J Med*. 2019;380:11-22.
9. *N Engl J Med*. 2019;380:1022-1032.

LDL: Lower is Better

https://www.youtube.com/watch?v=ToWViezZhvM

The New Normal

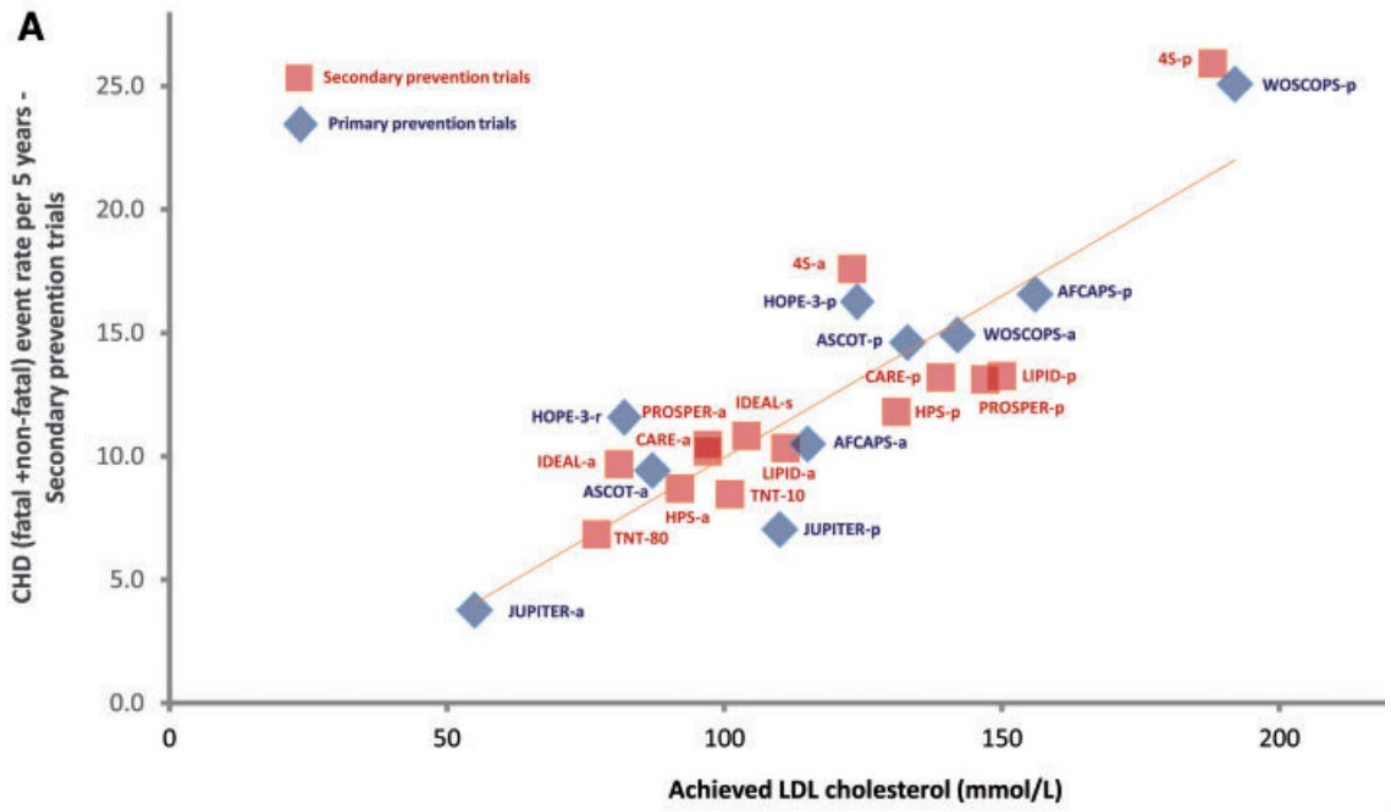
- Evidence from hunter-gatherer populations showed estimated LDL-c levels of 50-70 mg/dl[10, 11]

- Genetic disorders leading to LDL-c as low as 30 mg/dl have been associated with longevity[12]

10. Cordain L, et al. *Eur J Clin Nutr*. 2002.
11. O'Keefe JH, et al. *Mayo Clin Proc*. 2004.
12. Glueck CJ, et al. *Metabolism*. 1997.

BENEFITS OF LDL-C REDUCTION

- Evidence from genetic, epidemiologic, and clinical studies suggest a log-linear relationship between LDL-c levels and CV events



13. Ference BA, et al. *Euro heart J*. 2017.

HEART PROTECTION STUDY (HPS 2002)

- Randomized 20,536 patients
  - Type 1 or 2 DM, prior CHD, non-coronary atherosclerotic disease
- Median follow-up of 5 years
- Primary outcome – All cause mortality, fatal or non-fatal vascular events

	Baseline LDL-c mg/dl	Achieved LDL-c mg/dl	Primary Outcome	HR (95% CI)	P-Value
Simvastatin 40mg	129mg/dl	1mmol/L lower than placebo	12.9%	0.87 (0.81-0.94)	<0.0001
Placebo	129mg/dl		14.7%		

14. Heart protection study collaborative group. *Lancet*. 2002.

PROVE-IT (2004)

- Randomized 4162 patients with TC ≤240mg/dl and a recent ACS
- Mean follow-up of 2 years
- Primary outcome – Composite of MACE

	Baseline LDL-c mg/dl	Achieved LDL-c mg/dl	Primary Outcome	P-Value
Atorvastatin 80mg	106	62	22.4%	0.005
Pravastatin 40mg	106	95	26.3%	

- RRR of 16% (95% CI 5-26%; P=0.005); NNT=26

15. Cannon CP, et al. *N Engl J Med.* 2004.

TNT (2005)

- Randomized 10,001 patients with CAD
- Mean follow-up of 5 years
- Primary outcome – First MACE

	Baseline LDL-c mg/dl	Achieved LDL-c mg/dl	Primary Outcome	HR (95% CI)	P-Value
Atorvastatin 80mg	152	77	8.7%	0.78 (0.69-0.89)	<0.001
Atorvastatin 10mg	152	101	10.9%		

16. LaRosa JC, et al. *New Engl J Med.* 2005.

IMPROVE-IT (2015)

- Randomized 18,144 patients with ACS with LDL-c >50mg/dl
- Median follow-up of 6 years
- Primary outcome – Composite of MACE

	Baseline LDL-c mg/dl	Achieved LDL-c mg/dl	Primary Outcome	HR (95% CI)	P-Value
Simvastatin 40mg + Ezetimibe 10mg	93.8	53.2	32.7%	0.94 (0.89-0.99)	0.016
Simvastatin 40mg	93.8	69.9	34.7%		

7. Cannon CP, et al. *N Engl J Med.* 2015.

FOURIER (2017)

- Randomized 27,564 patients with ASCVD and LDL-c ≥ 70mg/dl
- Median follow-up for 2.2 years
- Primary end point – Composite of MACE

	Baseline LDL-c mg/dl	Achieved LDL-c mg/dl	Primary Outcome	HR (95% CI)	P-Value
Evolocumab	92	30	9.8%	0.85 (0.79-0.92)	<0.001
Placebo	92	80s	11.3%		

17. Sabatine MS, et al. *N Engl J Med.* 2017.

ODYSSEY (2018)

- Randomized 18,924 patients with LDL-c ≥ 70mg/dl and ACS within 12 months
- Median follow-up of 2.8 years
- Primary outcome – Composite of MACE

	Baseline LDL-c mg/dl	Achieved LDL-c mg/dl	Primary Outcome	HR (95% CI)	P-Value
Alirocumab	92	66	9.5%	0.85 (0.78-0.93)	<0.001
Placebo	92	103	11.1%		

18. Schwartz GG, et al. *N Engl J Med*. 2018.

TREAT STROKE TO TARGET (2020)

- Randomized 2860 patients with previous ischemic stroke or TIA
  - Lower-target group: LDL-c <70mg/dl
  - Higher-target group: 90-110mg/dl
- Median follow-up of 3.5 years
- Primary outcome – Composite of MACE

	Baseline LDL-c mg/dl	Achieved LDL-c mg/dl	Primary Outcome	HR (95% CI)	P-Value
Lower-target	135	65	8.5%	0.78 (0.61-0.98)	0.04
Higher-target	135	96	10.9%		

19. Amarenco P, et al. *New Engl J Med.* 2020.

CHOLESTEROL TREATMENT TRIALISTS' COLLABORATION

- 2005 Meta-Analysis
  - Data from 90,056 individuals in 14 randomized trials of statins
  - Results showed reduction in major vascular events of 21% per 1mmol/L decrease in LDL-c regardless of baseline LDL-c levels
- 2010 Meta-Analysis
  - 170,000 participants in 26 randomized trials
  - Results showed
    - Mean CV event reduction of 22% per 1mmol/L decrease in LDL-c regardless of baseline LDL-c levels
    - No LDL-c threshold below which there is no additional CV risk reduction
    - Decreasing LDL-c further was not associated with additional AE

20. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2005.
21. Cholesterol Treatment Trialists' (CTT) Collaboration. *Lancet*. 2010.

SABATINE 2020

- Meta-analysis expanded on the CTT studies
- Investigated the efficacy and safety of further LDL-c lowering in patients with very low levels of LDL-c
- Results showed
  - Decrease in major vascular events by 21% per 1mmol/L reduction in LDL-c regardless of baseline LDL-c levels
    - Even in patients with baseline LDL-c 63mg/dl and achieving a level of 21mg/dl
- No increased risk of serious AEs observed

22. Sabatine MS, et al. *JAMA Cardiol.* 2020.

WANG 2020

- Large meta-analysis of 52 RCTs with a primary composite CV endpoint
- Results showed
  - A direct linear association between LDL-c lowering and RRR in CV events
    - Directly related to the degree of LDL-c lowering achieved, with no differences between drug classes
  - Risk reduction of 19% per 1 mmol/L reduction in LDL-c regardless of baseline LDL-c levels
  - No LDL-c threshold below which there is no additional CV risk reduction using any medication

23. Wang, et al. *Lancet Diabetes Endocrinol.* 2020.

CV Risk Reversal

- LDL-c effect is cumulative starting from young adulthood[24]
- Lower LDL-c levels associated with greater percent atheroma volume (PAV) regression[25, 26, 27]
  - Effect even greater with combination therapy
    - PRECISE-IVUS: Atorvastatin and ezetimibe (LDL-c achieved 63.2mg/dl) versus atorvastatin alone (73.3mg/dl)[28]
    - GLAGOV: Patients with CHD on either high-intensity statin therapy (HIST) and evolocumab (LDL-c achieved 36 mg/dl) or HIST alone (93mg/dl)[29]

24. Zhang Y, et al. *J Am Coll Cardiol*. 2019.
25. Kataoka Y, et al. *Curr Opin Endocrinol Diabetes Obes*. 2017.
26. Elshazly MB, et al. *Curr Opin Endocrinol Diabetes Obes*. 2016.
27. Nicholls SJ, et al. *New Engl J Med.* 2011.
28. Tsujita K, et al. *J Am Coll Cardiol*. 2015.
29. Nicholls SJ, et al. *J Am Med Assoc.* 2016.

OTHER CONSIDERATIONS

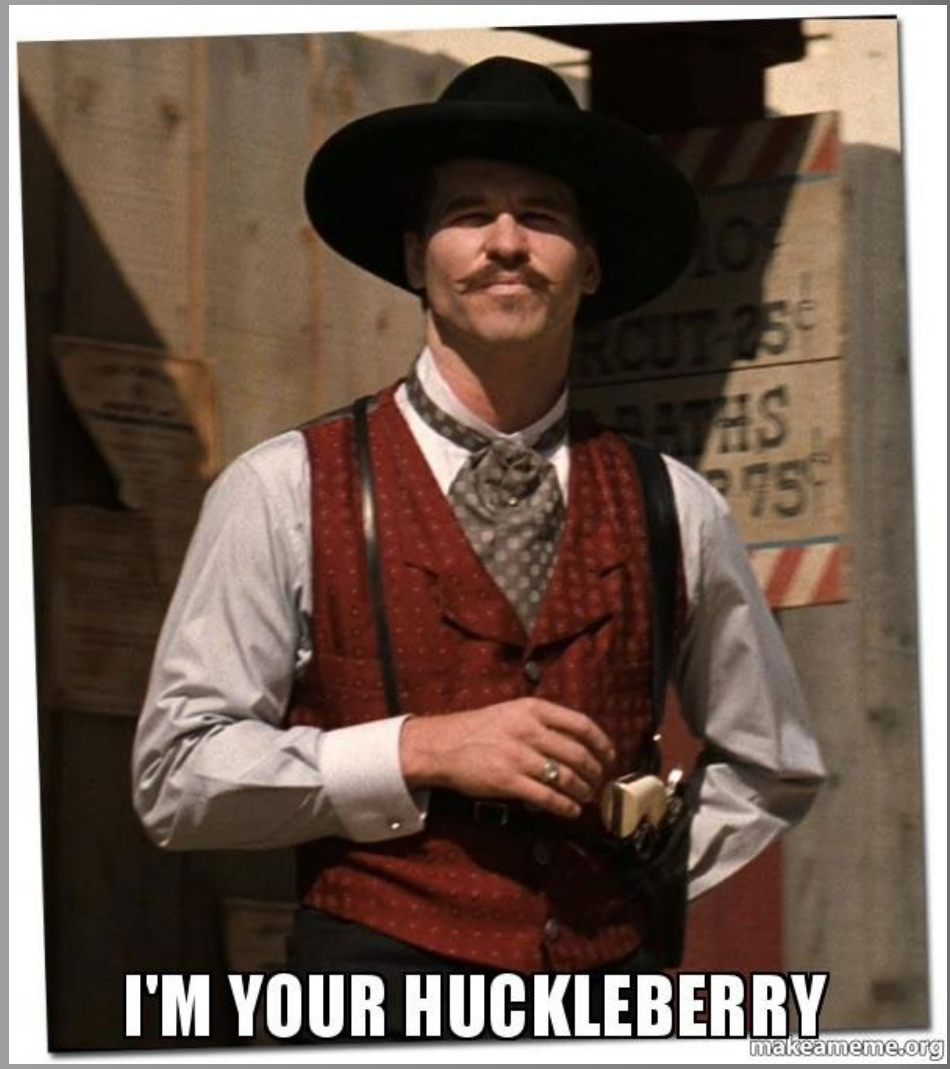
- Adverse Effects based on meta-analyses
  - No difference in the rate of new onset DM, cancer, or hemorrhagic stroke in patients treated to very low LDL-c[30]
  - No increased risk of hemorrhagic stroke
    - Large net benefit with statins and nonstatins even in patients at high risk of hemorrhagic stroke[31, 32]
- Issues with fixed dosing
  - Response to statins varies widely based on adherence and genetic variants[33, 34]
  - Patients may fail to achieve significant LDL-c reduction with target dose

30. Sabatine MS, et al. *JAMA Cardiol.* 2018.
31. Mckinney JS, Kostis WJ. *Stroke*. 2012.
32. Judge C, et al. *J Stroke Cerebrovasc Dis*. 2019.
33. Karlson BW, et al. *Eur Heart J Cardiovasc Pharmacother*. 2016.
34. Akyea RK, et al. *Heart*. 2019.

SUMMARY

- Numerous studies show a continuous relation between LDL-c and CV event risk
- Benefits of LDL-c lowering observed by multiple RCTs and meta-analyses
  - Risk reduction of 19-22% per 1mmol/L decrease in LDL-c regardless of baseline LDL-c levels
  - No LDL-c threshold, below which there is no additional CV risk reduction
- Strength of recommendation is “Moderate”
- Consider efficacy versus safety and cost-effectiveness
- Helpful to have therapeutic goals to prevent underutilization of nonstatin therapies in patients at high risk

FIXED-DOSE APPROACH = EVIDENCE-BASED APPROACH



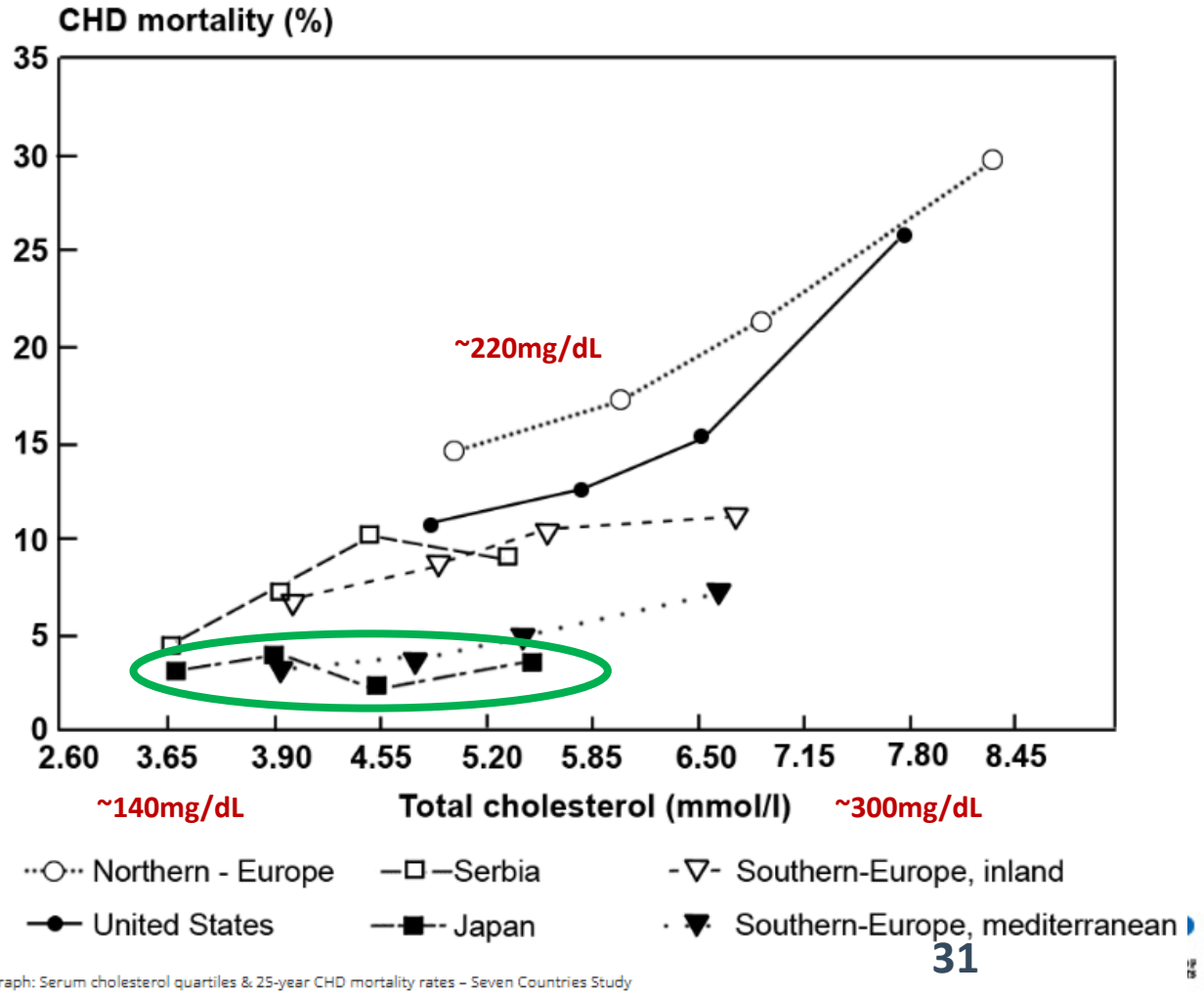
https://twitter.com/mrgiggles20/status/911814490806738945/photo/1

WHY FIXED-DOSE IS THE RIGHT DOSE

- Targets of <100mg/dL in the guideline are an artifact of high-intensity statin, and are rational
- Is the benefit from the achieved LDL or is this an artifact of drug choice?
- Most of the support for LDL targets is corollary extraction
- There are fewer problems with the data supporting fixed-dose approaches

THE BASIS OF THE LIPID HYPOTHESIS

- The Seven Countries Study
  - Association demonstrated between cholesterol and heart disease mortality
  - Northern European countries and th US have high cholesterol and high heart disease mortality
  - Japan and southern Europe have lower cholesterol levels and heart disease mortality



Graph: Serum cholesterol quartiles & 25-year CHD mortality rates – Seven Countries Study

35. Keys et al. Harvard University Pres. ISBN: 0-674-80273-3, 1980:121-135.

The Basis of the Lipid Hypothesis

- The Framingham Heart Study – 30 Year Follow Up
  - Finds correlation between high plasma cholesterol and cardiovascular disease (CVD) mortality
  - Cholesterol levels directly related with CVD mortality for men under 50
  - "After age 50 years there is no increased overall mortality with either high or low serum cholesterol levels."
    - Lower cholesterol levels associated with increased mortality in men over 50

36. *JAMA*. 1987;257:2176-2180.

The Early Trial Data

- Coronary Drug Project (1975)
  - Niacin vs placebo and clofibrate vs placebo
  - Reductions in MI, but no mortality benefit in either arm
- LRC-1 (1984)
  - Cholestyramine reduces cholesterol, MI
  - No mortality benefit
- Helsinki Heart Study (1987)
  - Gemfibrozil reduces cholesterol and MI
  - No mortality benefit
- DART (1989)
  - Eating fatty fish reduced mortality
  - Cholesterol increased

None of these trials targeted a specific cholesterol level

37. *JAMA*. 1975;231(4):360-381. 39. *N Engl J Med*. 1987;317:1237-1245.
38. *JAMA*. 1984;251(3):351-364. 40. *Lancet*. 1989;2(8666):757-761.

ENTER: THE STATINS

- 4S (1994)
  - Simvastatin 20mg (up to 40mg) vs placebo
    - 2/3 of patients only on 20mg (moderate intensity)
    - 5.4-year median follow-up
  - All-cause mortality benefit, NNT = 31
  - Reductions in any coronary event, NNT = 15
  - Ending LDL in simvastatin tx group = 122mg/dL

41. *Lancet*. 1994;344:1383-1389.

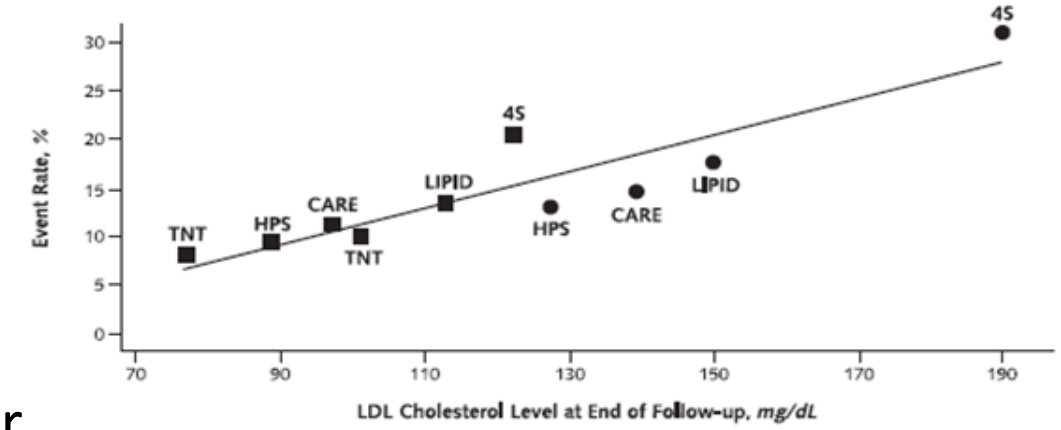
More Statin Data

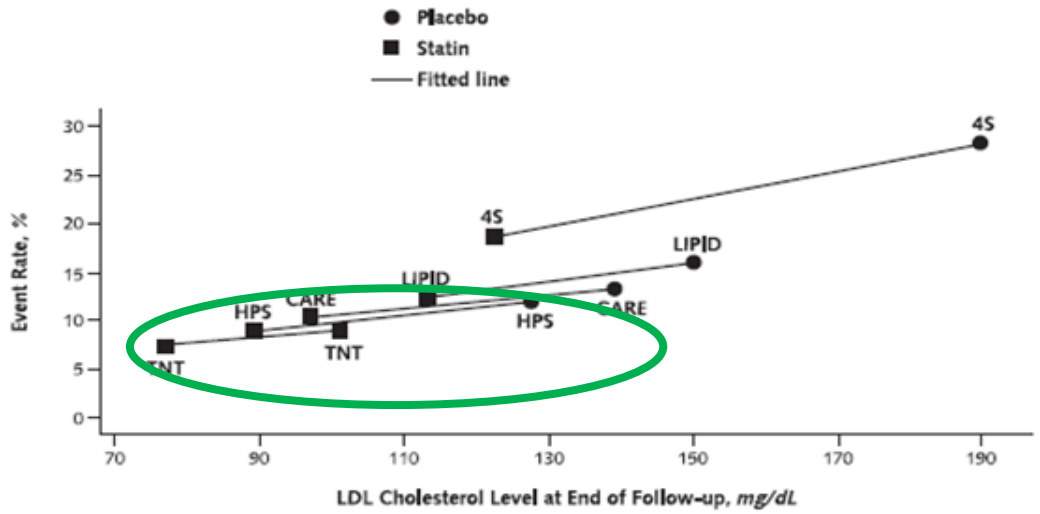
- PROVE IT (2004)
  - Pravastatin 40mg vs atorvastatin 80mg
    - Pravastatin could be increased if LDL>125mg/dL
    - 2-year average follow-up
  - Ending LDL = 95mg/dL vs 62mg/dL
  - MACE = 26.3% vs 22.4% (p = 0.005)
    - All cause mortality (p = 0.07)
    - CV Death (p = 0.06)
- TNT (2005)
  - Atorvastatin 10mg vs atorvastatin 80mg
    - Goal to compare LDL <100mg/dL to LDL <70mg/dL
    - 4.9-year average follow-up
  - Ending LDL = 101mg/dL vs 77mg/dL
  - MACE = 10.9% vs 8.7% (p = 0.001)
    - CV Death (p = 0.09)

15. *N Engl J Med*. 2004;350(15):1495-1504.
16. *N Engl J Med*. 2005;352:1425-1435.

It's Been Weak for a Long Time

- "No … analyses suggesting that the degree to which LDL cholesterol responds to a statin independently predicts the degree of cardiovascular risk reduction."
  - Hayward et al. 2006.





42. *Ann Intern Med*. 2006;145:520-530.

But What About the New Evidence?

- IMPROVE IT (2015)
  - 18,000+ secondary prevention patients (entry LDL <125mg/dL)
    - Simvastatin 40mg + ezetimibe 10mg vs. simvastatin 40mg + placebo
    - 6-year median follow-up
  - Ending LDL = 53mg/dL vs 70mg/dL
  - MACE = 32.7% vs 34.7% (HR 0.94; 95% CI 0.89-0.99) p = 0.016
    - NNT = 100
  - CV Death = 6.9% vs 6.8% (HR 1.00; 95% CI 0.89-1.13) p = 0.34

7. *N Engl J Med* 2015;372:2387-2397.

So Quick to Forget…

- ENHANCE (2008)
  - Simva/ezetimibe 80mg/10mg vs Simva 80mg
    - 720 patients
    - 2-year follow-up
  - Ending LDL = 141mg/dL vs 193mg/dL
  - Change in mean carotid-artery intima-media thickness
    - 0.011 vs 0.0058 (p = 0.29)

- SEAS (2008)
  - Simva/ezetimibe 40mg/10mg vs Simva 40mg
    - 1873 patients
    - 4.5-year follow-up
  - Ending LDL = 67mg/dL vs 135mg/dL
  - Nonfatal MI = 1.8% vs 2.8%
    - HR 0.64; 95% CI 0.35-1.17 (p = 0.15)
  - CV Death = 5% vs 6%
    - HR 0.83; 95% CI 0.56-1.22 (p = 0.34)

43. *N Engl J Med*. 2008;358:1431-1443.
44. *N Engl J Med*. 2008;359:1343-1356.

WHAT ABOUTISM 2.0

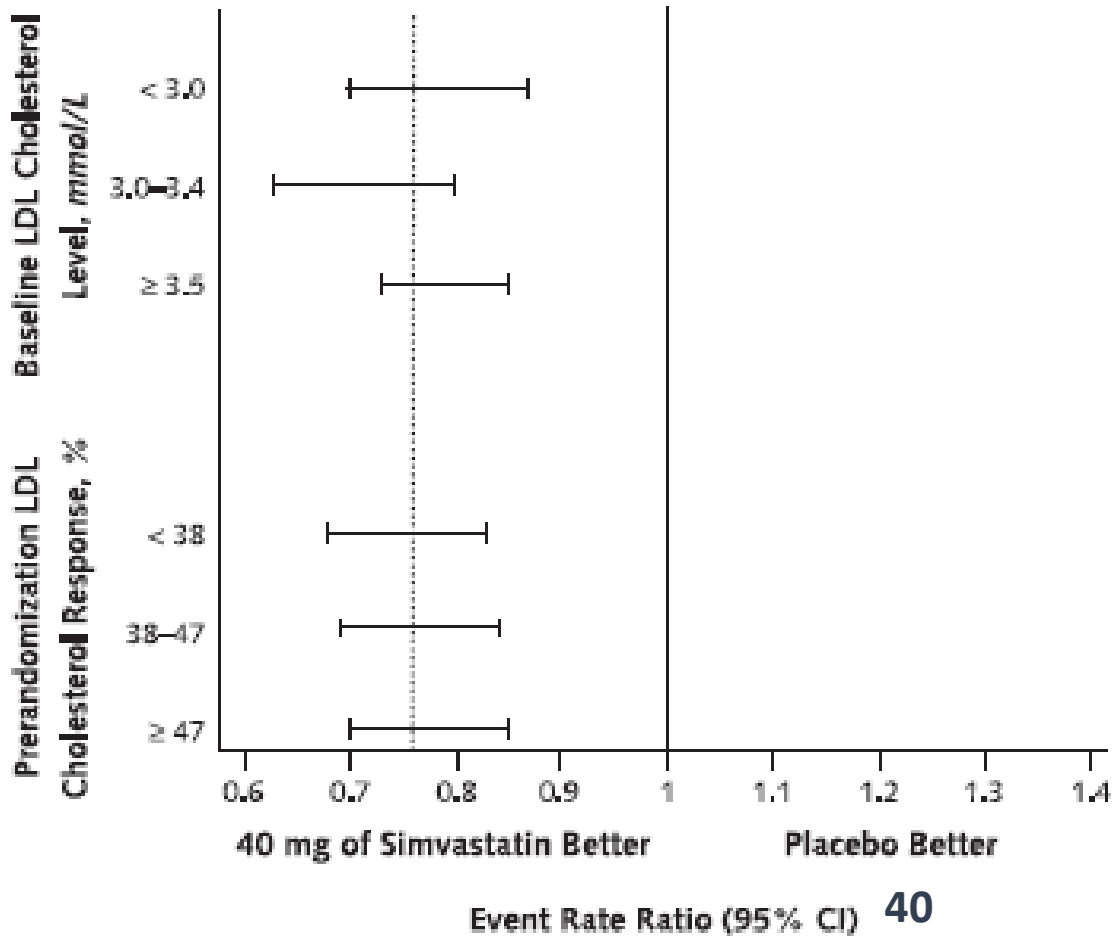
- TST (2020)
  - 2,860 secondary prevention stroke patients (entry LDL ~135mg/dL)
    - Goal to compare LDL target <70mg/dL to LDL target 90-110mg/dL
    - Statin + ezetimibe main drug tx in lower target group (99.7% of patients)
    - 3.5-year median follow-up; stopped early due to lack of funding
  - Ending LDL = 65mg/dL vs 96mg/dL
  - MACE = 8.5% vs 10.9% (HR 0.78; 95% CI 0.61-0.98) p = 0.04
  - Nonfatal MI or urgent revascularization = 1.4% vs 2.2%
    - HR 0.64 (95% CI 0.37-1.13); p = 0.12
  - CV Death = 1.5% vs 2.2% (HR 0.69; 95% CI 0.40-1.18)

19. *N Engl J Med* 2020;382:9-19.

THE CONTRARY EVIDENCE

- Heart Protection Study (2002)
  - 20,000+ UK Patients with CV dx or DM
  - Simvastatin 40mg vs Placebo
  - Huge mortality benefits
  - Mortality benefits in DM
    even if no pre-existing CV dx

Figure 2. **Results for the Heart Protection Study.**



14. *Lancet*. 2002;360(9326):7-22.
42. *Ann Intern Med*. 2006;145:520-530.

More Contrary Evidence

- EMPATHY (2018)
  - 5,042 Japanese patients with DM and high LDL (3-year follow up)
    - Target LDL <70mg/DL vs LDL 100-120 with statins
  - Ending LDL = 77 vs 104
  - Primary Outcome = 5.1% vs 6.1% (HR 0.84; 95% HR 0.67-1.07) p = 0.15
  - Subgroup analysis based on statin intensity shows favorable outcomes with higher intensity statin tx
    - HR 0.48 (95% CI 0.28-082); p = 0.007

45. *Diabetes Care*. 2018;41(6):1275-1284.

FIXED-DOSE EVIDENCE FROM A NON-STATIN TRIAL

- REDUCE IT (2019)
  - 8,179 secondary prevention patients taking statin
    - Entry LDL 40mg/dL-100mg/dL
    - Icosapent ethyl vs placebo
    - 4.9-year follow-up
  - Icosapent ethyl increased LDL 3.1% (~77mg/dL)
  - MACE = 17.2% vs 22.0%; p <0.001
  - CV Death = 4.3% vs 5.2% (HR 0.80; 95% CI 0.66-0.98); p = 0.03
  - Benefit was seen regardless of achieved LDL

8. *N Engl J Med*. 2019;380:11-22.

More Non-Statin Data – PSK-9i Links?

- CANTOS (2017)
  - 10,061 secondary prevention patients with elevated C-reactive protein
    - Canakinumab vs placebo
    - Three doses tested, primary endpoint of MACE
    - 3.7-year follow-up
  - No change in LDL with canakinumab vs. placebo (~83mg/dL)
  - MACE (150mg group) = HR 0.83; 95% CI 0.73 – 0.95; p = 0.005
  - Improvements in MACE across all doses
  - Benefit was seen despite no change in LDL

46. *N Engl J Med*. 2017;377:1119-1131.

THE FIXED-DOSE VERDICT

- Magnitude of benefit from LDL reduction wanes as LDL falls
  - Statin data supports this including 4S (1994), PROVE IT (2004), and TNT (2005)
- IMPROVE IT (2015) and TST (2020):
  - Overpowered and clinically under-significant
  - Potential alpha-error limitations
- PSK-9i Trials:
  - Is achieved LDL the reason for benefit, or is it an artifact of drug choice?
- Better data including HPS (2002), EMPATHY (2018), and REDUCE IT (2019) support fixed-dose approaches as conferring benefit regardless of achieved LDL

FINAL SUMMARY

http://www.bestliberalartscolleges.org/tag/feuds/

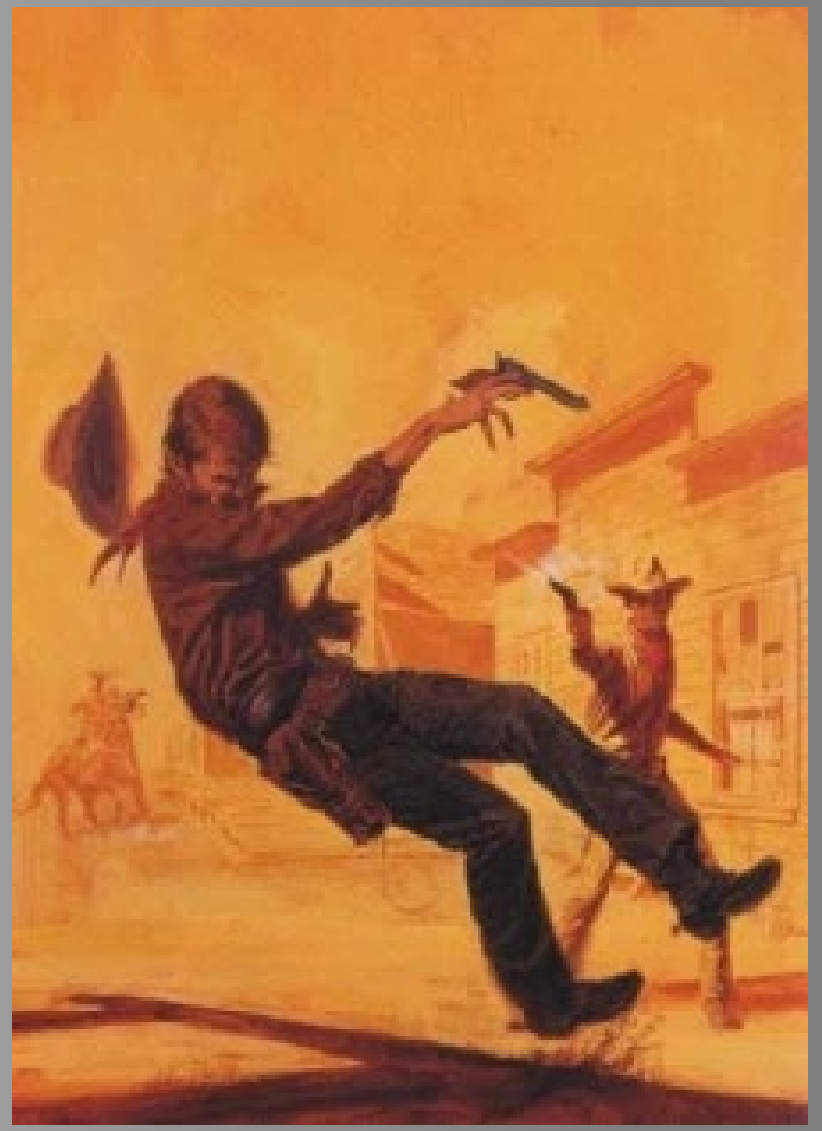
Treat to Target vs. Fixed-Dose Approaches

- Data consistently shows lower CV events correlated with lower LDL levels
- No LDL threshold below which no additional benefit
- Many patients do not achieve adequate LDL lowering from a fixed-dose statin

- Low LDL levels and low mortality are correlated, not necessarily causative
  - Very few cholesterol trials are treat-to-target
- Studies consistently show benefit from large doses of statins
  - Benefit of drugs from other classes are not consistent in trials

El Ultimo Hombre

Questions?



https://mythsoftheamericanwest.wordpress.com/2015/11/26/gunfighting-in-the-west-the-facts-presented/

TEST QUESTIONS

WHICH STATEMENT IS TRUE REGARDING THE ATP III GUIDELINES?

- Treatment with a statin was reserved for secondary CV prevention
- The use of other drugs, such as fibrates and niacin, combined with statins, was acceptable in order to achieve LDL goals
- An LDL goal of <160mg/dL was acceptable for patients with 2 or more risk factors

Test Questions

What did the results of the CTT 2005 and 2010, along with the meta-analysis from Sabatine et al and Wang et al demonstrate?

- No correlation between LDL-c levels and MACE
- A decrease in MACE only occurs if the baseline LDL-c is >200mg/dL
- A decrease in MACE occurs with each 1mmol/L reduction in LDL-c
- A decrease in LDL-c below 100mg/dL increases risk of MACE

Test Questions

Despite an increase in LDL of 3% to an average of 77mg/dL in the treatment group, the REDUCE IT trial demonstrated:

- An increase in MACE for patients in the treatment group
- A decrease in MACE only in patients with an LDL-c <70mg/dL
- A decrease in MACE and CV death regardless of LDL-c levels
- An increase in MACE in patients treated with low/moderate-intensity statins

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