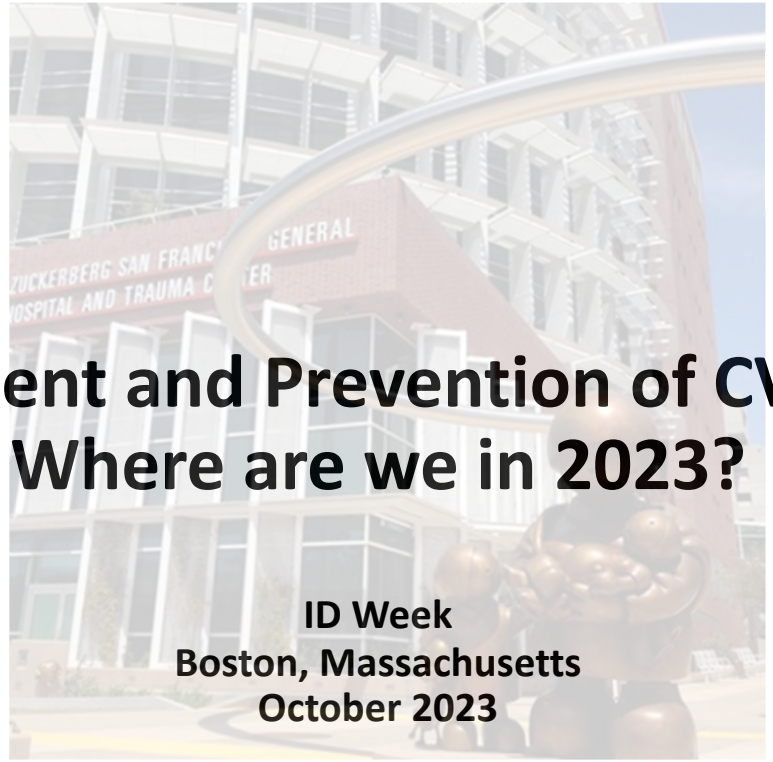


Management and Prevention of CVD in HIV: Where are we in 2023?

ID Week
Boston, Massachusetts
October 2023

Priscilla Hsue, MD FACC FAHA
Professor of Medicine
University of California, San Francisco
Chief of Cardiology, UCSF at Zuckerberg San Francisco General
Maurice Eliaser, Jr., MD, Distinguished Professorship in CVD

Disclosures

- Honoraria from Gilead, Merck
- Study drug from Regeneron, Novartis, Eli Lilly
- Grant support from Novartis, Eli Lilly
- 20 minute talk to cover a large topic – focus on lipids and inflammation
  - Thank you to Dr. Peter Hunt and Dr. Colette Dejong from UCSF
  - Opinions presented are my own

Why is this important?

1990

American Journal of Hematology 35:210–212 (1990)

Acute Myocardial Infarction, Non-Bacterial Thrombotic Endocarditis, and Disseminated Intravascular Coagulation in a Severe Hemophiliac

David Green, Howard Snapper, Graziella Abu-Jawdeh, and Janardan Reddy
Section of Hematology/Oncology, Department of Medicine (D.G., H.S.), and the Department of Pathology (G.A.-J., J.R.), Northwestern University Medical School and Northwestern Memorial Hospital, Chicago, Illinois

First case of CVD in a person with HIV?

2004

Circulation
Volume 109, Issue 13, 6 April 2004; Pages 1603-1608
https://doi.org/10.1161/01.CIR.0000124480.32233.8A

American Heart Association.

CLINICAL INVESTIGATION AND REPORTS

Progression of Atherosclerosis as Assessed by Carotid Intima-Media Thickness in Patients With HIV Infection

Priscilla Y. Hsue, MD, Joan C. Lo, MD, Arlana Franklin, RDMS, Ann F. Bolger, MD, Jeffrey N. Martin, MD, Steven G. Deeks, MD, and David D. Waters, MD

2013

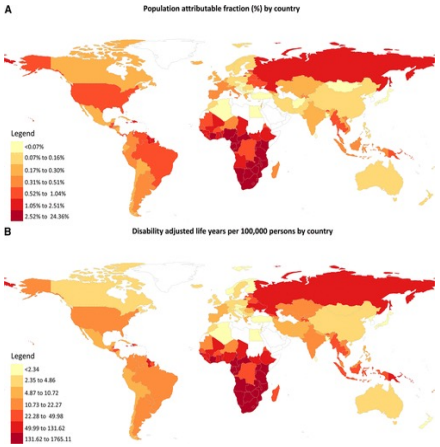
ORIGINAL INVESTIGATION

ONLINE FIRST

HIV Infection and the Risk of Acute Myocardial Infarction

Matthew S. Freiberg, MD, MSc; Chung-Chou H. Chang, PhD; Lewis H. Kuller, MD, DrPH; Melissa Skanderson, MSW; Elliott Lowy, PhD; Kevin L. Kraemer, MD, MSc; Adeel A. Butt, MD, MS; Matthew Bidwell Goetz, MD; David Leaf, MD, MPH; Kris Ann Oursler, MD, ScM; David Rimland, MD; Maria Rodriguez Barradas, MD; Sheldon Brown, MD; Cynthia Gibert, MD; Kathy McGinnis, MS; Kristina Crothers, MD; Jason Sico, MD; Heidi Crane, MD, MPH; Alberta Warner, MD; Stephen Gottlieb, MD; John Gottdiener, MD; Russell P. Tracy, PhD; Matthew Budoff, MD; Courtney Watson, MPH; Kaku A. Armah, BA; Donna Doebler, DrPH, MS; Kendall Bryant, PhD; Amy C. Justice, MD, PhD

2018



PAR (top) and DALY/100000 persons (bottom) for HIV-associated CVD (Shah A Circulation 2018)

People with HIV are twice as likely to develop CVD and the global burden of HIV-associated CVD has tripled in the past 2 decades

2021

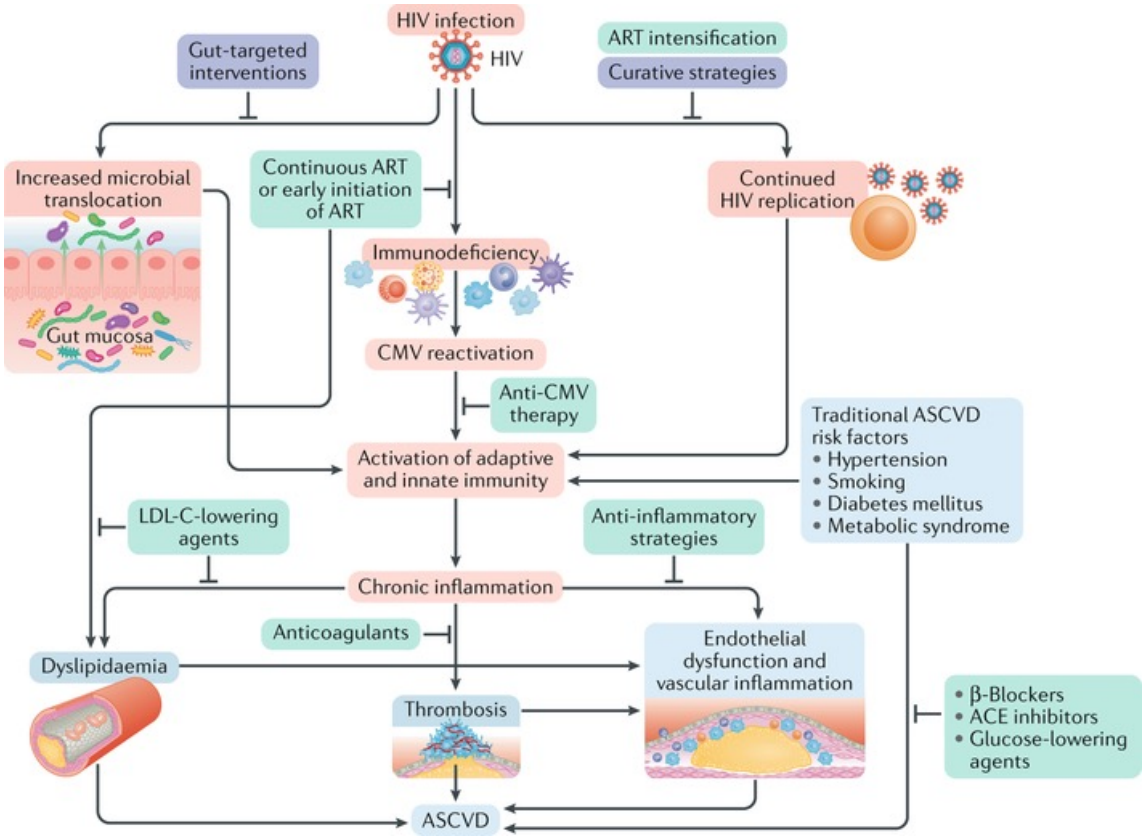
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sudden Cardiac Death and Myocardial Fibrosis, Determined by Autopsy, in Persons with HIV

Zian H. Tseng, M.D., Ellen Moffatt, M.D., Anthony Kim, M.D., Eric Vittinghoff, Ph.D., Phil Ursell, M.D., Andrew Connolly, M.D., Ph.D., Jeffrey E. Olgin, M.D., Joseph K. Wong, M.D., and Priscilla Y. Hsue, M.D.

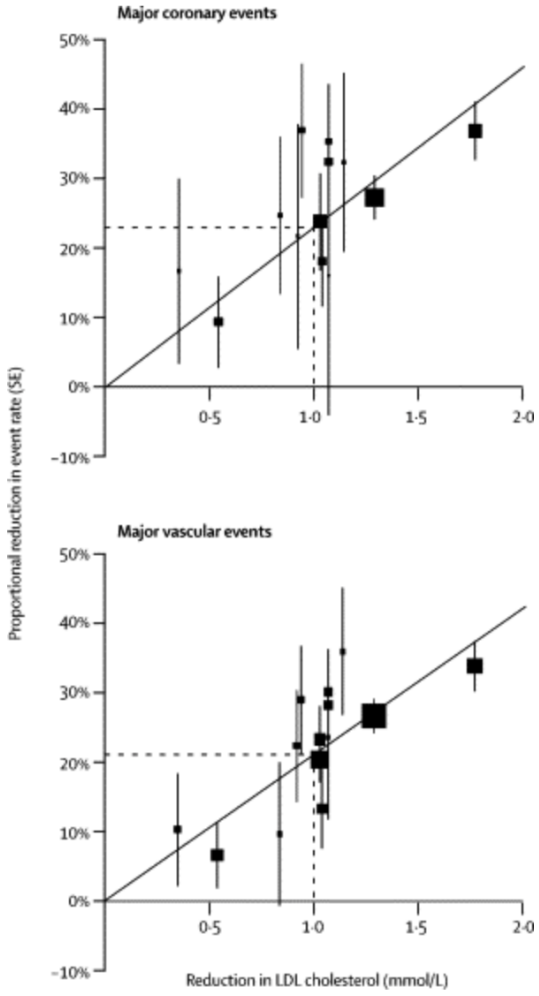
Pathophysiology and management of HIV-associated CVD



Hsue PY Nature Reviews Cardiology 2019

What do we know about statins in general?

Lower LDL-C is Better:



CTT: Data from > 90000 pts on statins in 14 trials

For every 1mmol (38.7mg.dL) reduction in LDL-C, there is a 20% reduction in annual rate of clinical events, irrespective of initial lipids or presenting characteristics

The absolute benefit relates to the individuals absolute risk of events and absolute reduction in LDL-C

Baigent C Lancet 2005

Statins are beneficial in virtually ALL populations

Lancet 2010

Articles

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**

- M/F, young/old, DM/no DM, HTN/no HTN, Smoking/No smoking

Exception: Only population in which statins have not shown benefit is ESRD on HD (Fellstrom BC NEJM 2009, AURORA trial)

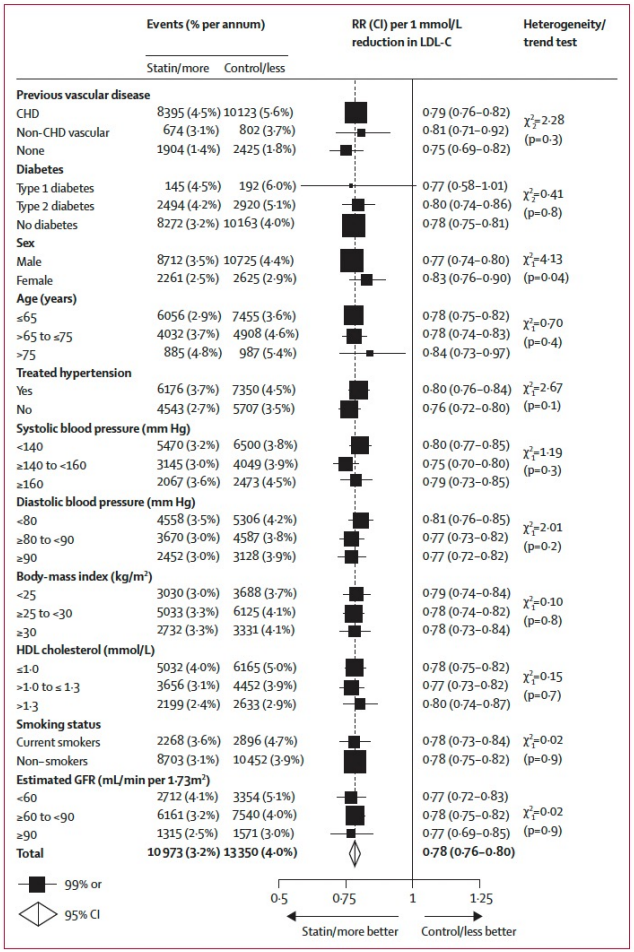


Figure 3: **Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, by baseline prognostic factors**

Rate ratios (RRs) are plotted for each comparison of first event rates between treatment groups, and are weighted per 1·0 mmol/L LDL cholesterol (LDL-C) difference at 1 year. Missing data are not plotted. RRs are shown with horizontal lines denoting 99% CIs or with open diamonds showing 95% CIs. CHD=coronary heart disease. GFR=glomerular filtration rate.

The NEW ENGLAND JOURNAL of MEDICINE

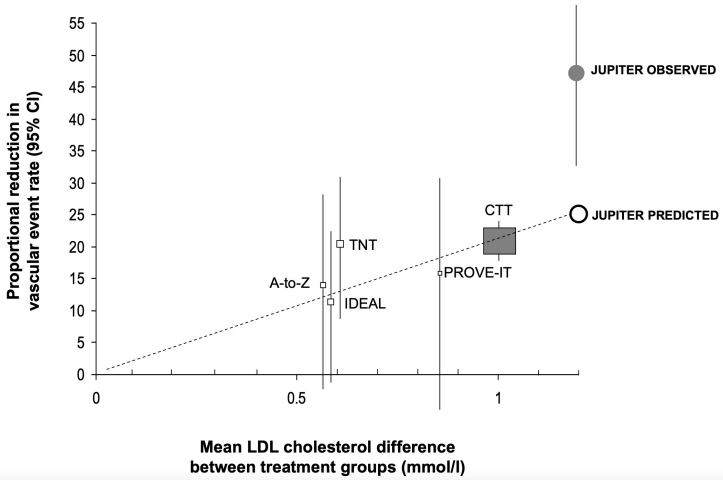
ESTABLISHED IN 1812 NOVEMBER 20, 2008 VOL. 359 NO. 21

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

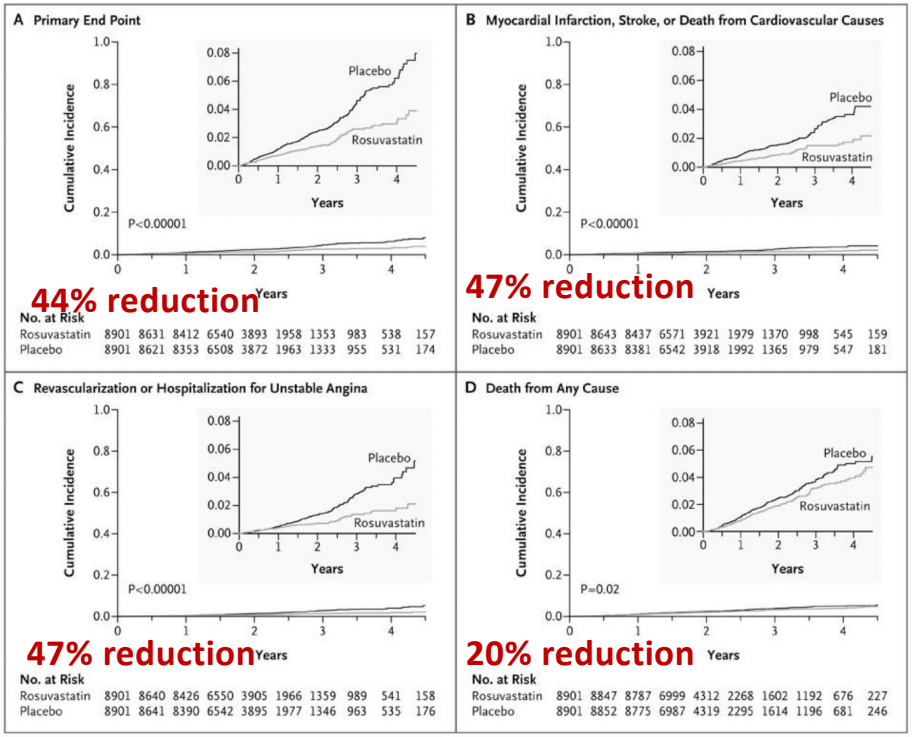
Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

17802 men (>=age 50) and women (>=age 60)
LDL <130mg/dL and hsCRP >=2.0mg/L
LDL-C reduced by 50% and hsCRP by 37%

NNT for 5 years to prevent 1 event is 25

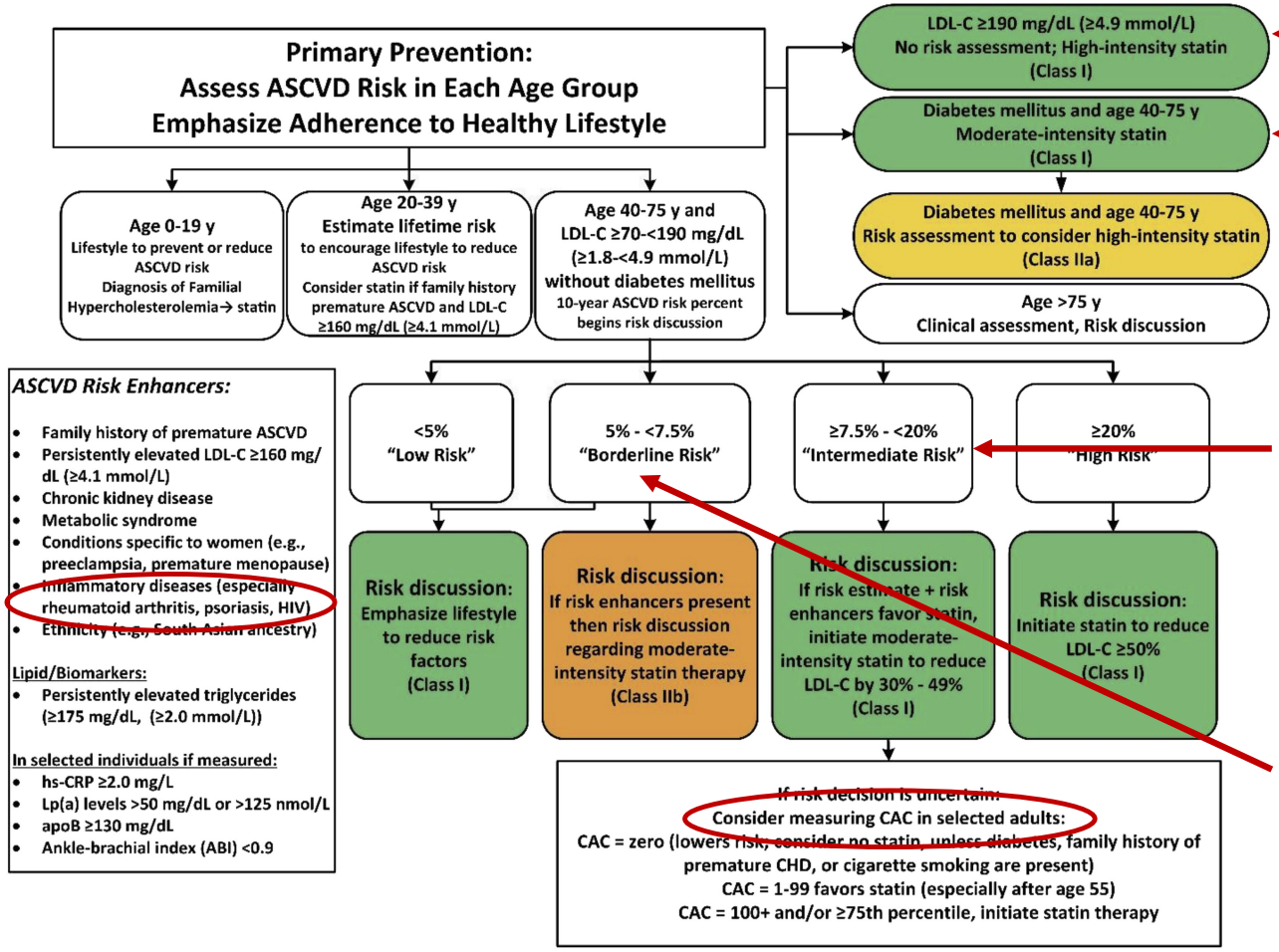


What was the JUPITER study?



Before REPRIEVE, what were the guidelines for statin treatment in PWH?

Grundy SM JACC 2019



CLINICAL PRACTICE GUIDELINE

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

***Moderate intensity statins are recommended for ALL pts (w/wo HIV) with 10 year risk of ASCVD>=7.5**

"Using the PCE, 2013 ACC/AHA guidelines identified >=7.5% risk as RCT supported threshold for benefit of statin tx"

HIV as a "risk enhancer" which would favor starting moderate/high intensity statin among individuals at borderline risk (between 5-<7.5%)

Traditional risk calculators underestimate ASCVD risk in HIV

- Traditional risk factors are associated with increased CVD risk in HIV
- Risk predictors developed in non-HIV populations may not predict risk in HIV due to different etiologies
- HIV-specific calculators have been proposed (biomarkers, ART)
- Multiple different studies have concluded that traditional risk calculators underestimate CV risk in HIV

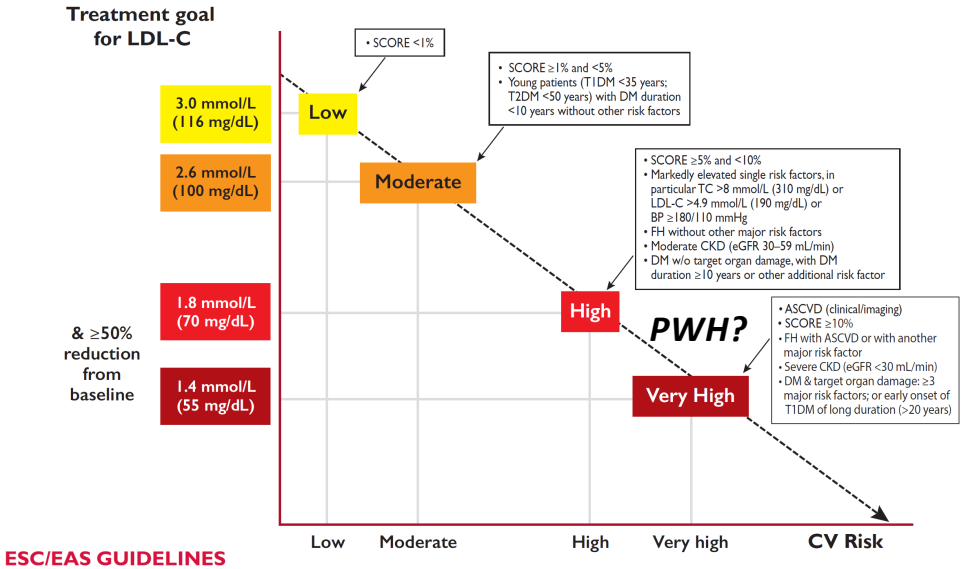
Focusing on only known pathways for CVD risk or limited number of markers may not yield the best risk prediction in HIV

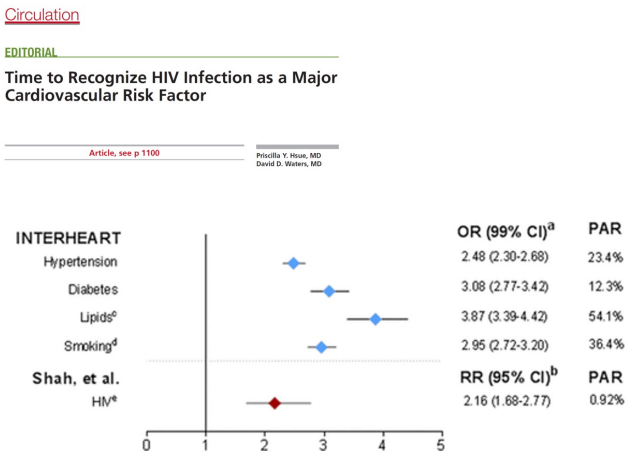
D'Agostino RB JID 2012
Friis-Moller N et al European Jl Preventive Cardiology 2015
Feinstein MJ et al JAMA Cardiol 2017
Thompson-Paul A et al CID 2016
Triant V Circulation 2018

Should HIV be considered a CVD equivalent?

- Association of HIV to atherosclerosis similar to DM (FRAM study)
- Veterans Cohort: HR for HIV infection and acute MI similar DM

2019 ESC/EAS Guidelines for risk assessment and management of dyslipidemia:





Grunfeld C AIDS 2009; 23: 1841-1849.
Freiberg M JAMA IM 2013.
ESC/EAS Guidelines, Eur Heart Journal 2019

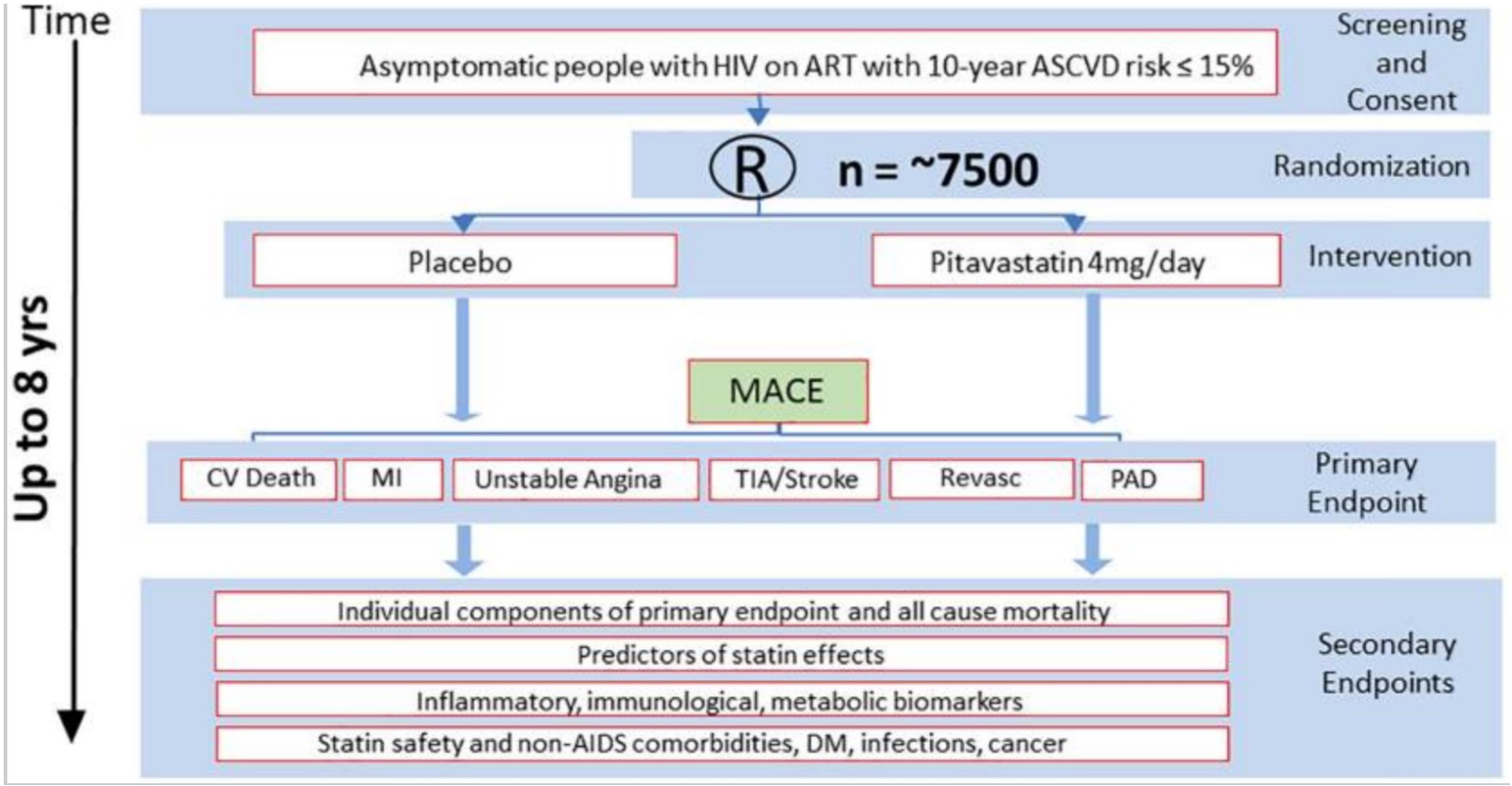
How are we going to get there?

Question:

Does the REPRIEVE trial mean that all PWH should be on pitavastatin?

- Yes!
- No!

REPRIEVE Trial Schema



Grinspoon, Am Heart Journal 2019

Inclusion criteria for REPRIEVE is complicated

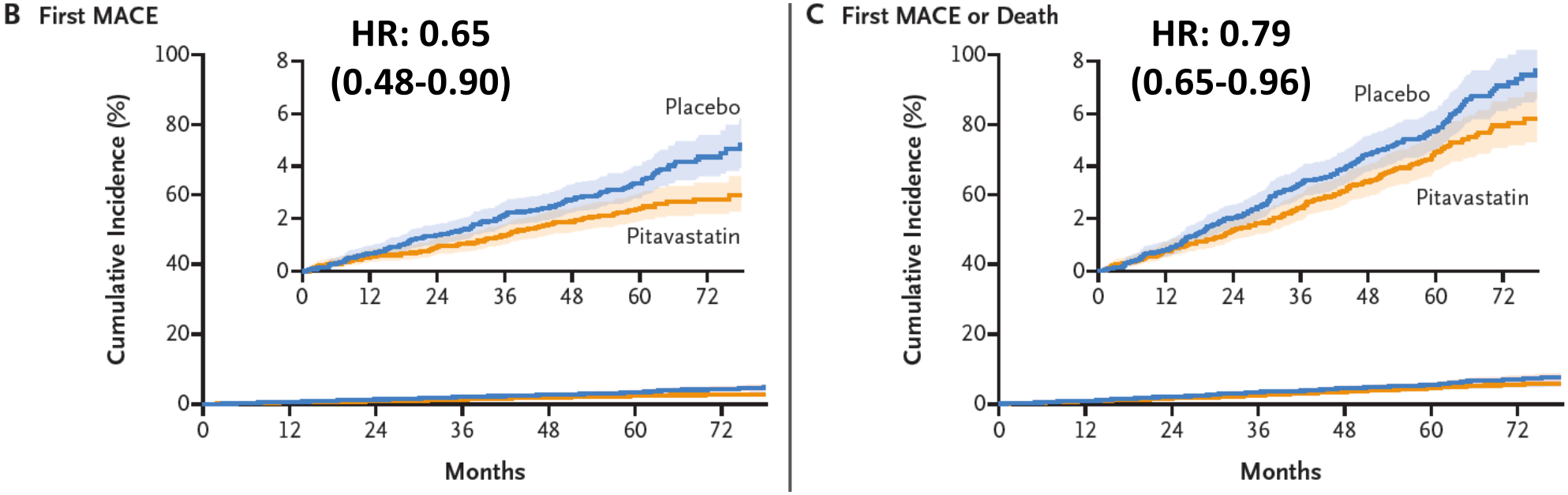
PWH aged 40-75 years, stable ART
Low to moderate risk of ASCVD using 2013 ACC/AHA pooled cohort equation with a risk up to 15%
DM if LDL-C < 70mg/dL
ASCVD risk > 15% if LDL < 70 mg/dL
Median ASCVD risk score of 4.5%, 28% had score of 0 to 2.5
Median LDL at entry of 107mg/dL decreased to 74mg/dL in pitavastatin treated group

Fasting LDL cholesterol as follows:

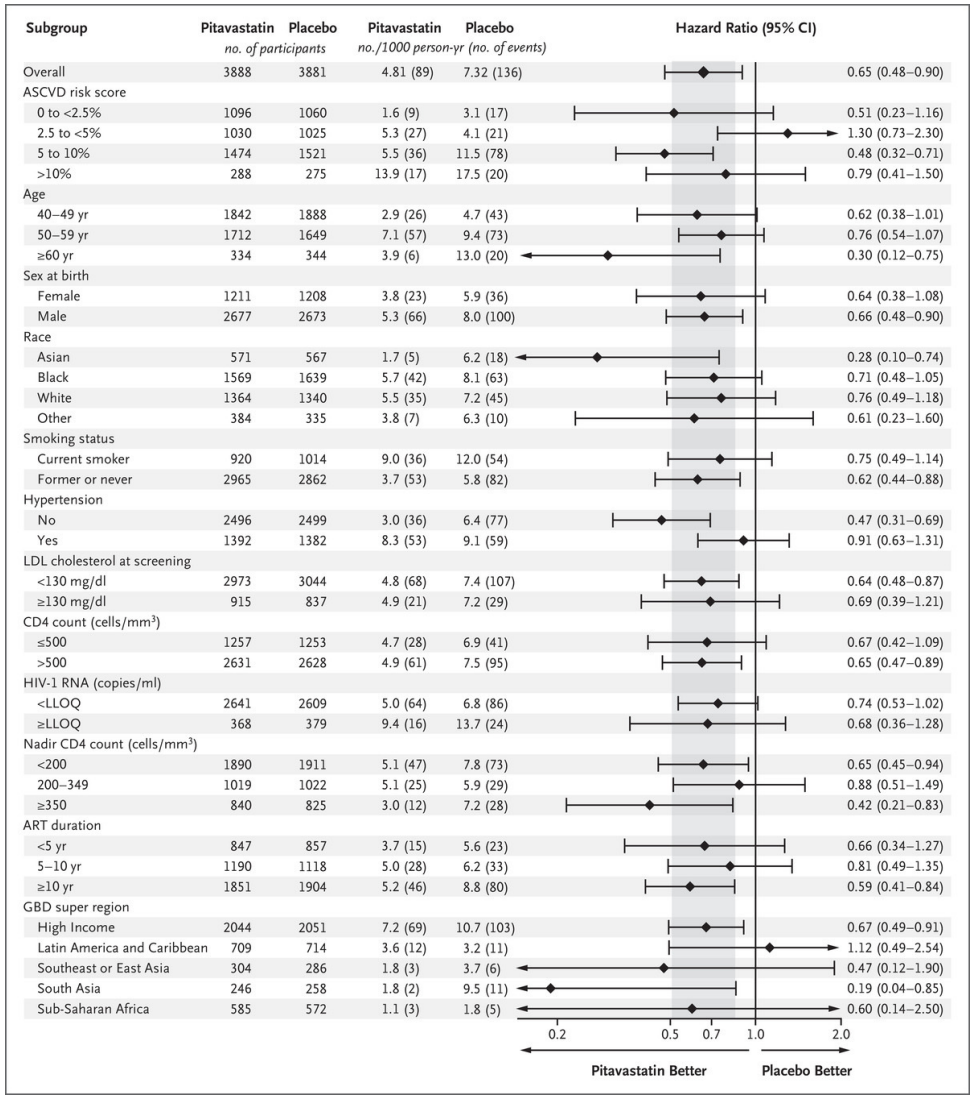
- If ASCVD risk score <7.5%, LDL cholesterol must be <190 mg/dL
- If ASCVD risk score ≥7.5% and ≤10%, LDL must be <160 mg/dL
- If ASCVD risk score >10% and ≤15%, LDL must be <130 mg/dL

NOTE: If LDL <70 mg/dL, participant is eligible regardless of 10-year ASCVD risk score in line with the ACC/AHA 2013 Prevention Guidelines.

REPRIEVE: Main Outcomes



Grinspoon, NEJM, 2023



- Consistent effect among subgroups

Grinspoon S NEJM 2023

Primary Prevention with Statins Guidelines

Based on Predicted ASCVD risk (and NNT)

(https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/)

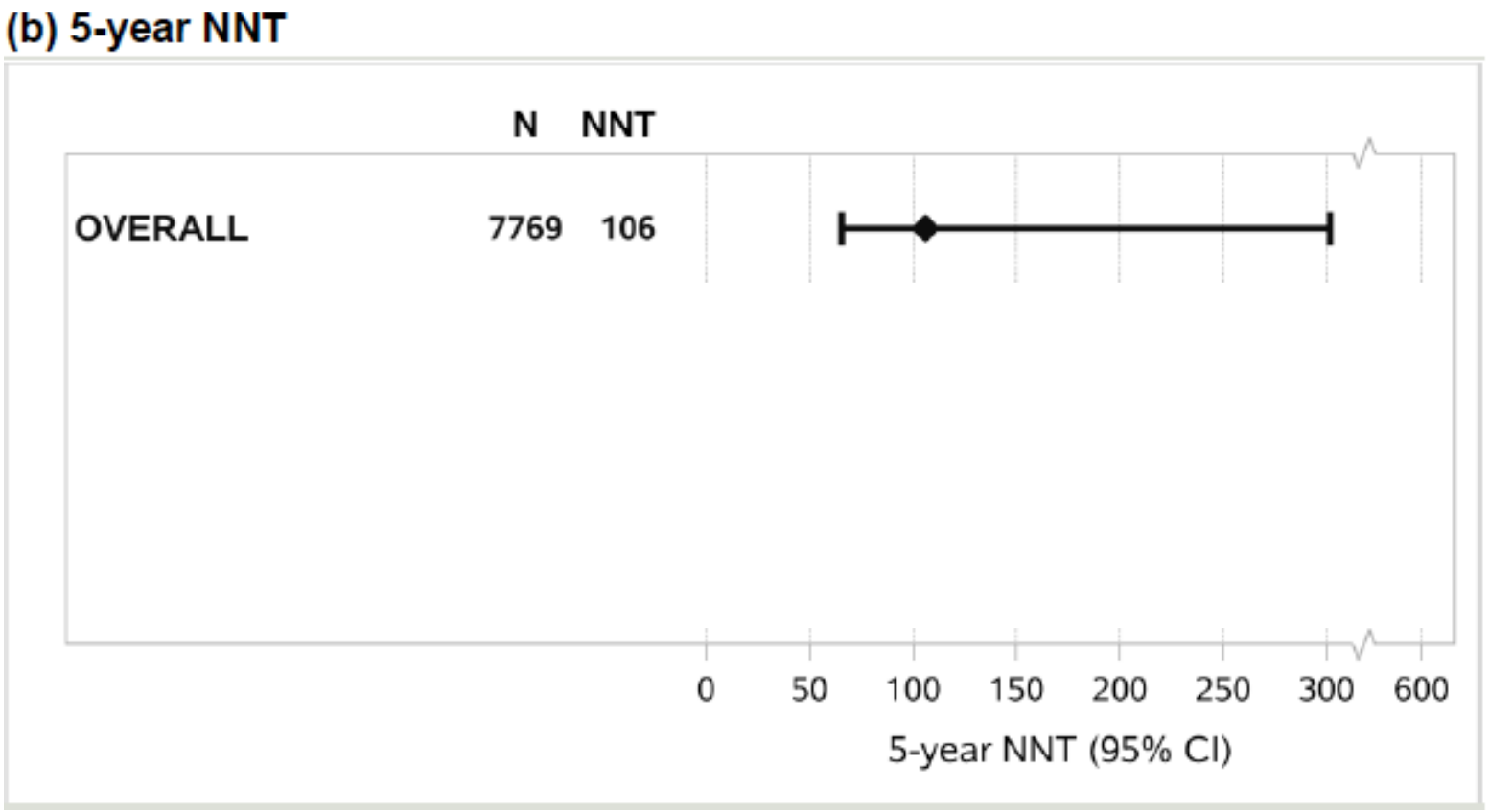
What is the NNT?

ACC/AHA	ASCVD Risk	NNT-5y	USPSTF
Treat	10-20%	40-60	Treat
Consider	7.5-10%	60-80	Consider
	5-7.5%	80-120	Don't Consider
Don't Consider	<5%	>120	

Slide from P. Hunt

AHA/ACC Guidelines, Circulation, 2018; USPSTF, JAMA, 2022

What was the NNT in the REPRIEVE Trial?

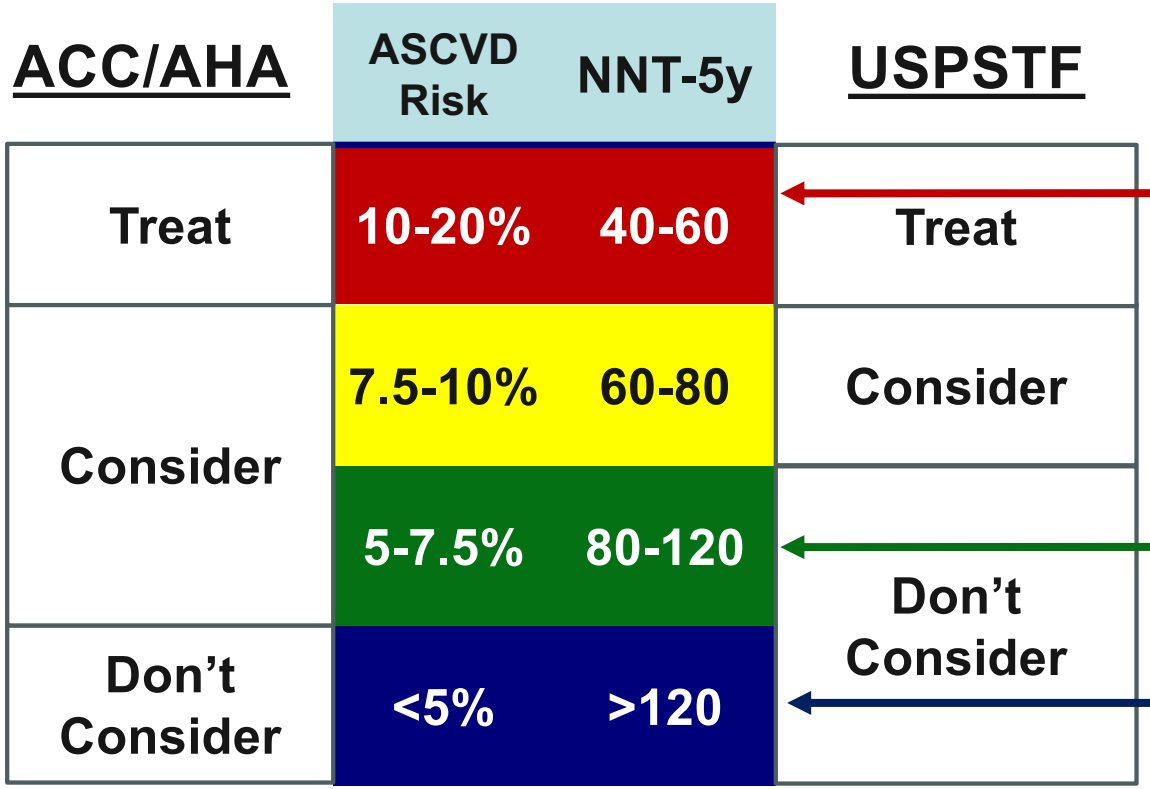


Slide from P. Hunt

How Does REPRIEVE Result Compare to Existing Treatment Thresholds?

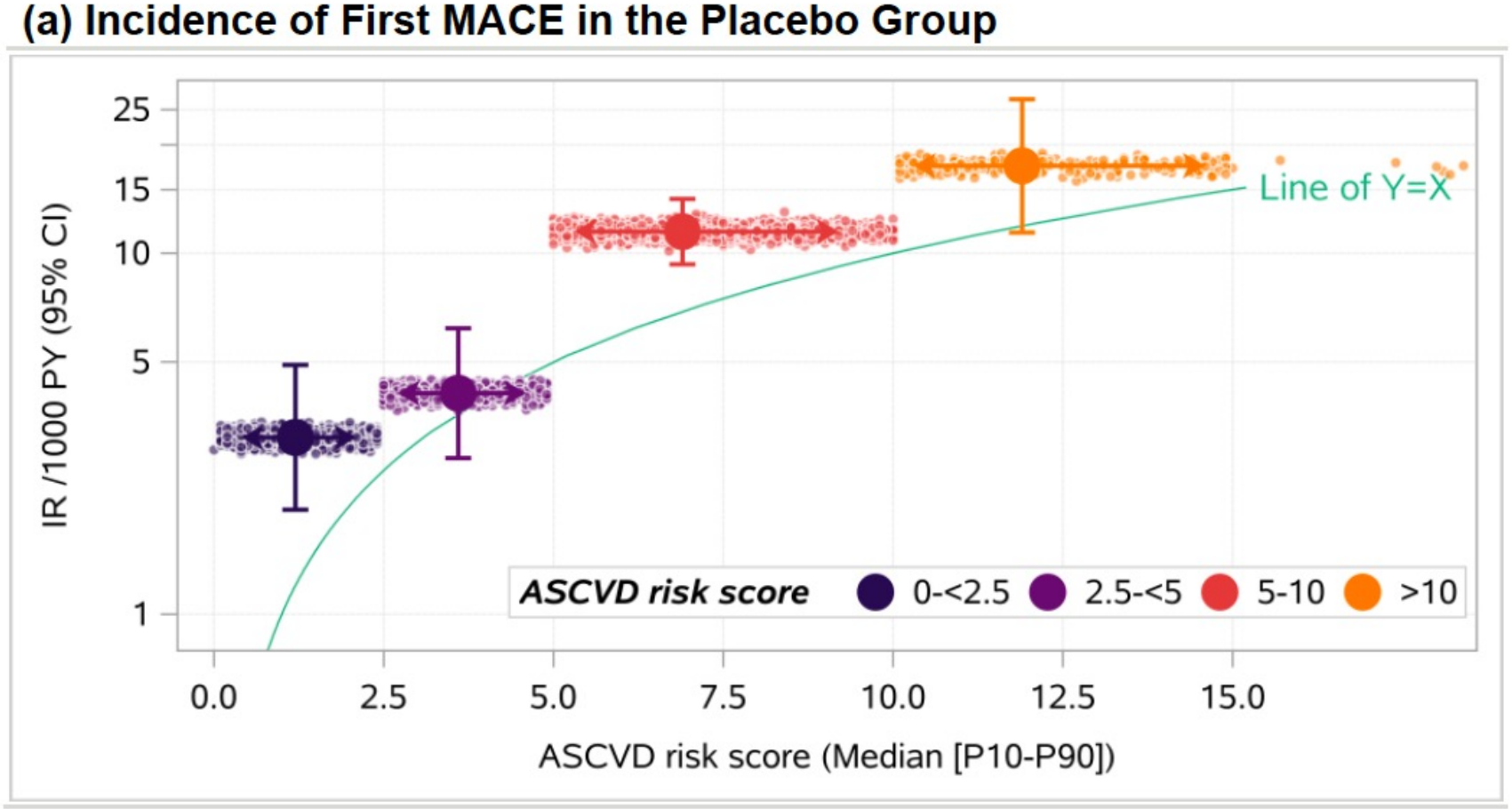
(https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/)

If we follow NNT thresholds used in existing statin guidelines, only PWH with ASCVD scores>5% would be recommended for statins.



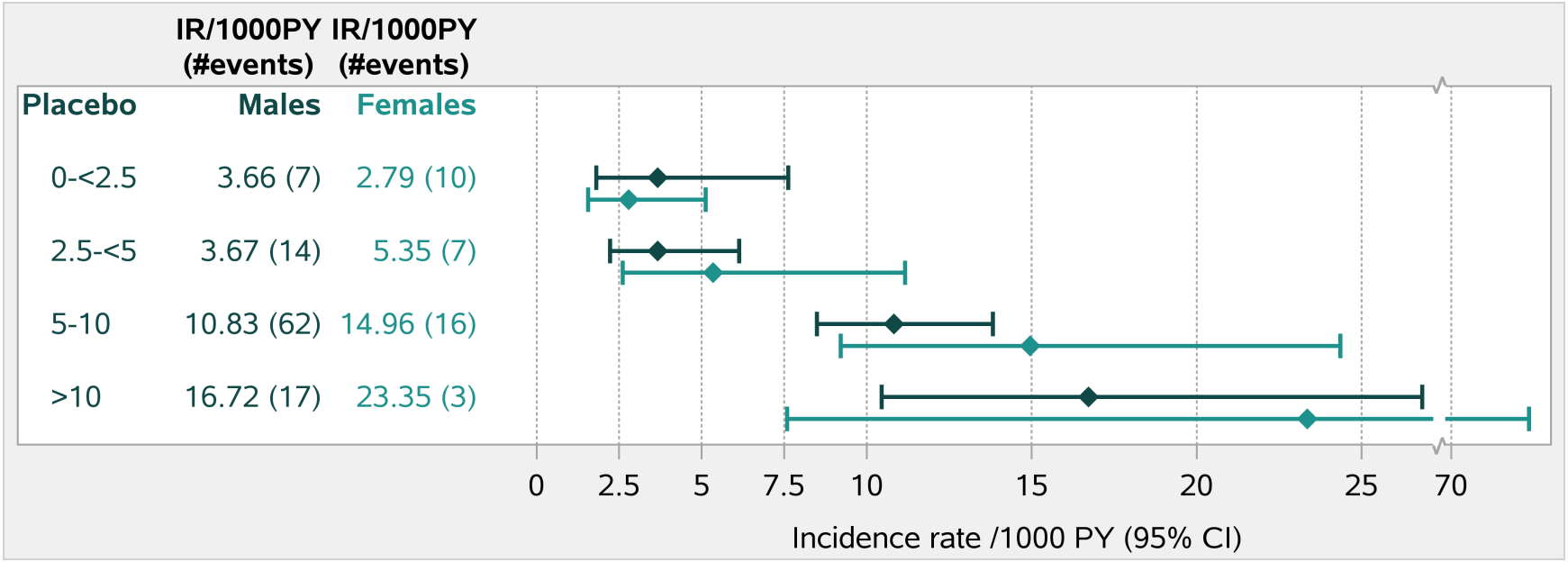
AHA/ACC Guidelines, Circulation, 2018; USPSTF, JAMA, 2022; slide from P. Hunt

HIV Does Increase CVD Risk by ~63%



Slide from P. Hunt

ASCVD Risk Score May Underestimate CVD Risk to a Greater Extent in Women with HIV



- HIV may attenuate the ”female advantage” in CVD risk
- Results raise the question whether more women than men should be newly eligible for statins because of REPRIEVE

Zanni, IAS, 2023

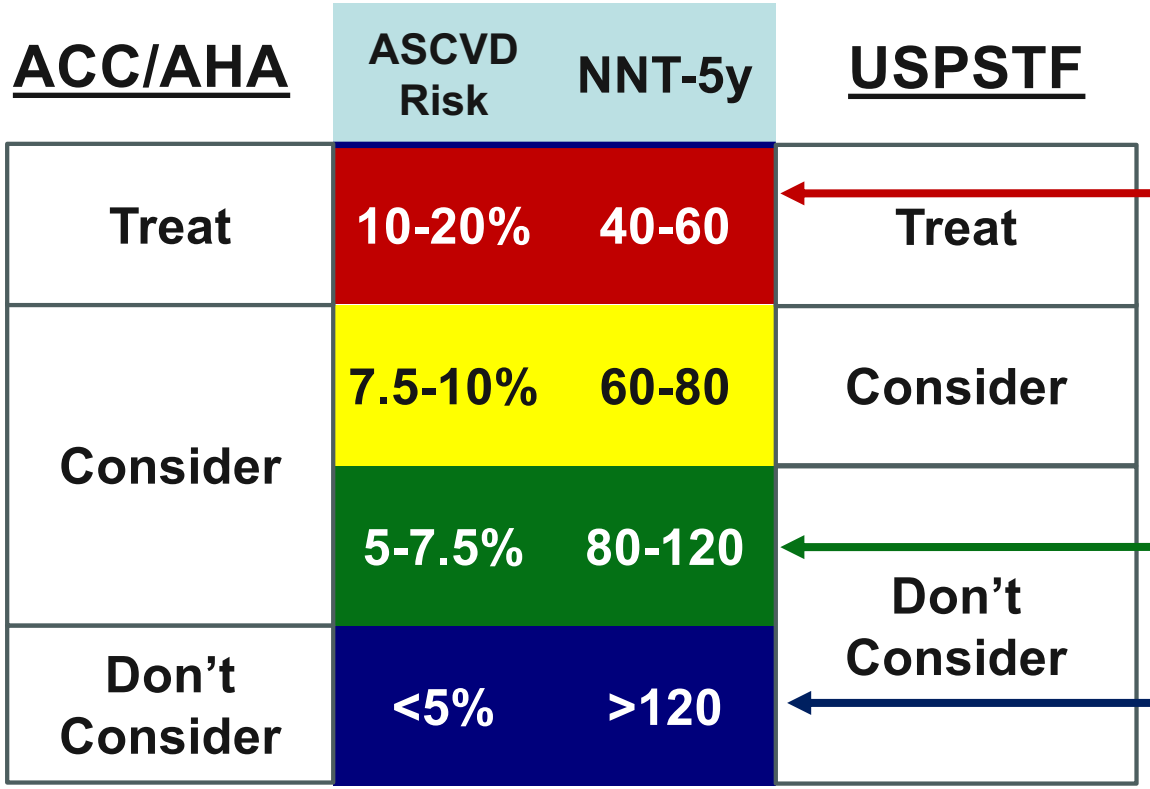
Does low ASCVD risk in PWH = no benefit from statin?

- Using ACC/AHA guidelines, 2/3 of PWH were not recommended to be on statin had evidence of significant carotid plaque (Phan BA, Circ CV Imaging 2017).
- Among PWH with calculated ASCVD risk of < 2.5%, 30% had plaque on CT angiography (Hoffmann U, Jama Network Open 2021).
- 35% of PWH had CAC>0 (Hoffman U, Jama Network Open 2021).
- ***Question: Should we consider imaging in asymptomatic PWH who are at intermediate risk for CVD?***

In PWH with Low ASCVD Risk (2.5-5%), Perhaps more Women than Men Should be Considered for Statins

(https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/)

How would NNT-10y change our thinking?



REPRIEVE with ASCVD score>5% (<1/2 participants)

REPRIEVE women with ASCVD score 2.5-5%

REPRIEVE men with ASCVD score<5%

AHA/ACC Guidelines, Circulation, 2018; USPSTF, JAMA, 2022,slide form P. Hunt

Question:

- Does the REPRIEVE trial mean that all PWH should be on statins?
  - Yes!
  - No!

My answers: not all PWH, but likely increased use among those aged 40-75 –more use among those with ASCVD risk of 5% and higher

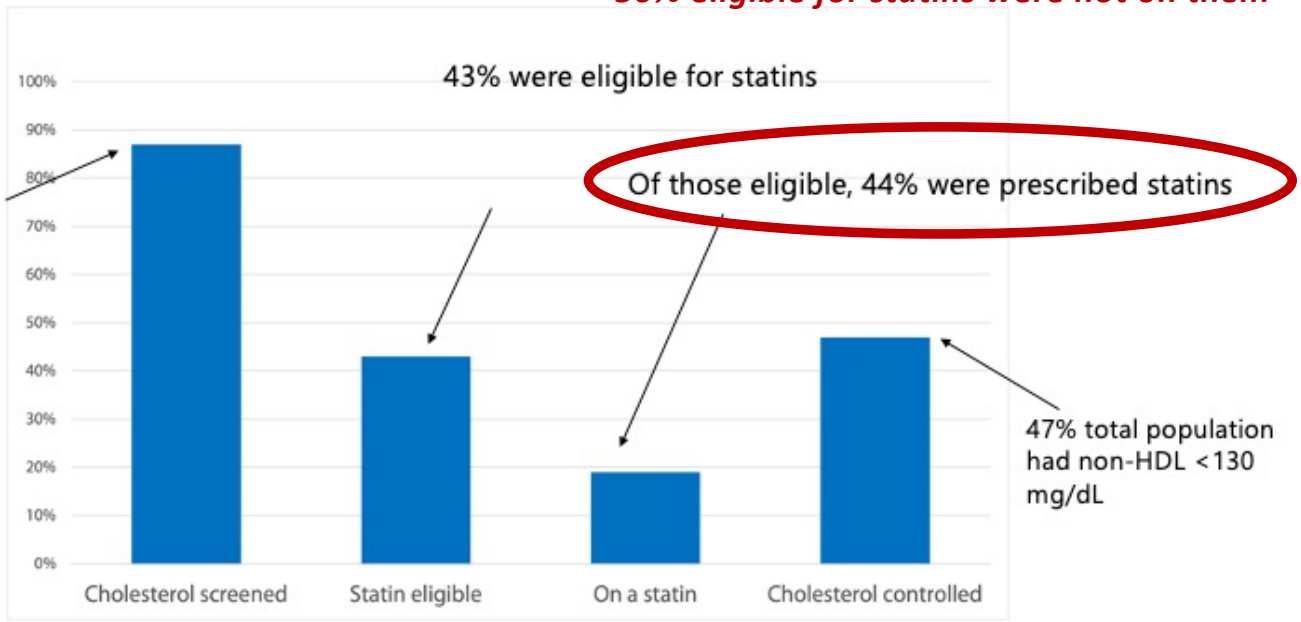
Statin use already indicated in DM (with or without HIV)

Statin use already indicated in persons with risk of 7.5% and above (with or without HIV)

Some PWH with ASCVD risk <=2.5% may benefit from statin

Opportunities for Improvement in Statin use among PWH

> 50% eligible for statins were not on them



REPRIEVE results are an important reminder to all clinicians to think about statins in PWH who meet criteria; even before the study results, PWH were undertreated.

10-year ASCVD risk ≥ 7.5%, LDL-C ≥190 mg/dL, or age 40-75 years with diabetes

Megan Mclaughlin AIDS 2023

Pitavastatin: what do we know?

1. ***T/F:*** *For individuals with ASCVD, Pitavastatin is clinically indicated*
2. ***T/F:*** *Pitavastatin is cost effective for use in PWH*
3. ***Fill in the blank:***

In the past 20 years, Dr. Hsue has prescribed pitavastatin ___ times

Pitavastatin is a moderate intensity statin

- High-intensity statins (≥50% ↓):
  - Atorvastatin 40-80mg
  - Rosuvastatin 20-40mg
- Use high-intensity for:
  - Treatment of ASCVD
  - High-risk primary prevention

Table 1

HMG-CoA Reductase Inhibitors

Intensity (percent-lowering)	Statin	Dosing Range
Low (10%-29%)	Fluvastatin	20-40 mg
	Lovastatin	20 mg
	Pitavastatin	1 mg
	Pravastatin	10-20 mg
	Simvastatin	10 mg
Moderate (30%-49%)	Atorvastatin	10-20 mg
	Fluvastatin	80 mg
	Lovastatin	40 mg
	Pitavastatin	2-4 mg
	Pravastatin	40-80 mg
	Rosuvastatin	5-10 mg
	Simvastatin	20-40 mg
High (≥50%)	Atorvastatin	40-80 mg
	Rosuvastatin	20-40 mg

HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A.
Source: References 2, 4.

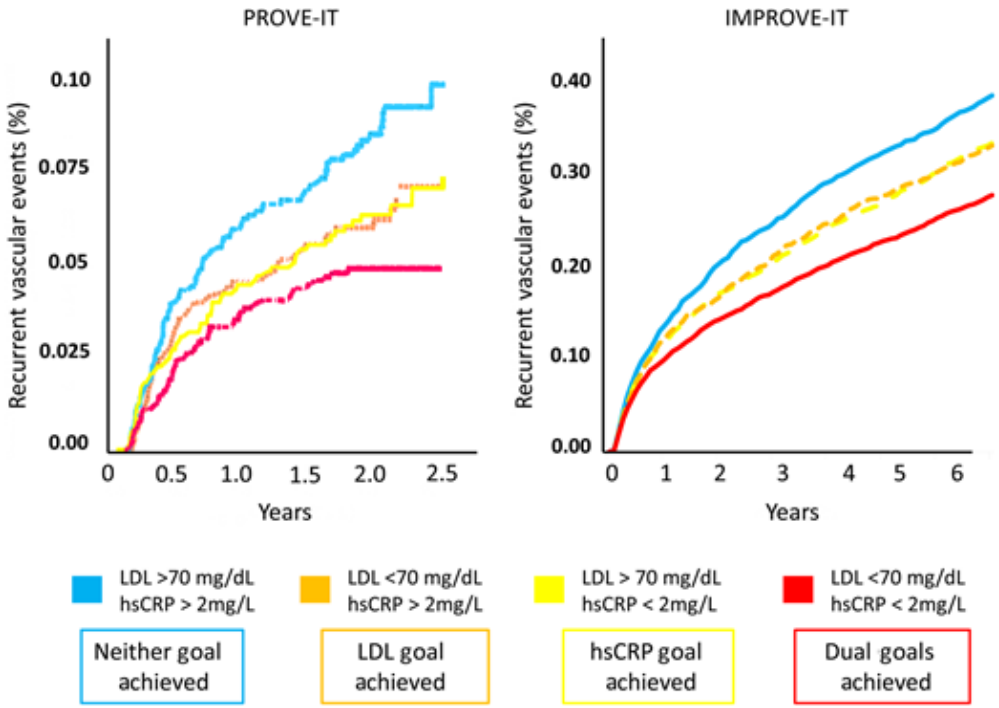
Slide from C. Dejong

Source: US Pharmacist, https://www.uspharmacist.com/article/understanding-cholesterol-therapy-an-update-for-community-pharmacists

Lower is better not only for LDL but also inflammation

Secondary prevention:
simvastatin vs. simva + ezetimibe

Secondary prevention with 80mg atorvastatin vs. 40mg pravastatin



Ridker P European Heart Journal 2016

Anti-inflammatory effects differ among statins

- PROVE IT and MIRACL trials – high-intensity atorva or rosuva reduce MACE after MI
  - Rapid benefit seen within 30 days
  - 34%-38% reduction in hsCRP
- A to Z Trial - high-dose simvastatin after MI did not improve MACE compared to placebo/low-dose, despite achieving similar LDL targets to PROVE IT and MIRACL
  - Only 16.7% reduction in hsCRP
- Benefit cannot be fully predicted from LDL targets – attributed to different pleiotropic effects

Nissen, JAMA, 2004

Slide from C. Dejong

Pitavastatin, rosuvastatin, atorvastatin all have potent pleiotropic effects

Cell type	Pleiotropic effect	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Platelets	Decreased activation	Yes	Yes		Yes [94]		Yes [75]	
	Decreased aggregation		Yes		Yes [95]			
Endothelial cells	Increased eNOS expression/activity			Yes	Yes [100]		Yes [127]	Yes
	Decreased ROS		Yes		Yes [54]			
	Increased endothelial progenitor cell activity/production	Yes						Yes
Vascular smooth muscle cells	Decreased proliferation				Yes [54]		Yes [129]	Yes
	Decreased migration						Yes [129]	Yes
	Increased apoptosis	Yes	Yes	Yes	Yes [128]			Yes
Macrophages/ monocytes	Decreased proliferation						Yes [130]	Yes
	Decreased MMP expression					Yes	Yes [131]	
	Decreased oxidized LDL uptake			Yes	Yes [72]			
Vascular inflammation	Decreased MHC-II expression	Yes [132]		Yes [132]	Yes [58]	Yes [132]		
	Decreased hs-CRP concentrations			Yes	Yes [61]	Yes	Yes [133]	

eNOS, endothelial nitric oxide synthase; hs-CRP, high sensitivity C-reactive protein; LDL, low density lipoprotein; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; ROS, reactive oxygen species.

Davignon, BJCP, 2011

Slide from C. Dejong

Which lowers inflammation more? Rosuvastatin vs. Pitavastatin?

- **Yanagi et al, 2011**: Crossover trial of 90 patients with DM and HLD in Japan
  - 24 weeks: ROS-PIT, PIT-ROS, PIT, or ROS
  - Rosuva 2.5mg led to greater LDL reductions than pitava 2mg (44% vs. 37%)
  - Both lowered inflammatory markers:
    - Rosuva led to greater hsCRP reductions than pitava (20% vs. 12%)
    - Similar reductions in TNF-alpha and plasminogen activator inhibitor-1

- Take-home:
  - Variable pleiotropic effects without sufficient head-to-head comparison among PWH
  - Rosuvastatin, pitavastatin, atorvastatin all affect multiple immune/inflammatory pathways

Slide from C. Dejong

Is pitavastatin cost-effective for primary prevention of ASCVD among PWH?

Boettiger DC et al. *Journal of the International AIDS Society* 2021, **24**:e25690
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25690/full | https://doi.org/10.1002/jia2.25690

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Cost-effectiveness of statins for primary prevention of atherosclerotic cardiovascular disease among people living with HIV in the United States

David C Boettiger[1,2,§], Anthony T Newall[3], Andrew Phillips[4], Eran Bendavid[5], Matthew G Law[2], Lene Ryom[6], Peter Reiss[7,8], Amanda Mocroft[4], Fabrice Bonnet[9], Rainer Weber[10], Wafaa El-Sadr[11], Antonella d'Arminio Monforte[12], Stephane deWit[13], Christian Pradier[14], Camilla I Hatleberg[6], Jens Lundgren[6], Caroline Sabin[4], James G Kahn[1] and Dhruv S Kazi[15,16]

[§]**Corresponding author:** David C Boettiger, Philip R Lee Institute for Health Policy Studies, University of California, San Francisco, 3333 California St, San Francisco, California 94118-1944 USA. Tel: (415) 476 8045. (dboettiger@kirby.unsw.edu.au)

Slide from C. Dejong

Methods

- Population: PWH aged 40-75 on ART, not using lipid-lowering therapy
- Data source: Data collection on Adverse Events of Anti-HIV Drugs (D:A:D) study
- Modelled cost effectiveness of no statin, pravastatin 40mg/day ($236/year), or pitavastatin 4mg ($2,828/year) for primary prevention of ASCVD over 20 years
- Cost-efficacy threshold set at $100,000/QALY
- **Assumptions**:
  - 20.5% LDL reduction for pravastatin and 29.7% reduction for pitavastatin (INTREPID trial)
  - In sensitivity analysis, further 10-20% reduction in ASCVD risk due to anti-inflammatory effects
  - 50% reduction in statin adherence (and costs) after year 1

Slide from C. Dejong

Results

- **Pravastatin compared with no statin:**
  - Pravastatin led to a 9.1%, 8.7% and 5.3% relative reduction in the rate of incident MI, stroke and fatal CVD (less than 1 of each event per 1,000 person years)
  - 0.024 additional QALYs at an incremental cost of $1,338, resulting in an incremental cost effectiveness ratio (ICER) of $56,000/QALY gained

- **Pitavastatin compared with pravastatin:**
  - Pitavastatin had a further 5.0%, 4.8% and 5.6% relative reduction in the rate of MI, stroke and fatal CVD
  - 0.013 additional QALYs at an incremental cost of $18,251, giving an ICER of $1,444,000/QALY gained

- Pitavastatin outperformed pravastatin if the annual cost was reduced to **< $350** (12.4% of the base-case price)

Slide from C. Dejong

Even with 30% additional ASCVD preventative efficacy, the price of pitavastatin needed to drop below 50% of the base-case price to become cost-effective compared with no statin

Boettiger DC et al. *Journal of the International AIDS Society* 2021, **24**:e25690
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25690/full | https://doi.org/10.1002/jia2.25690

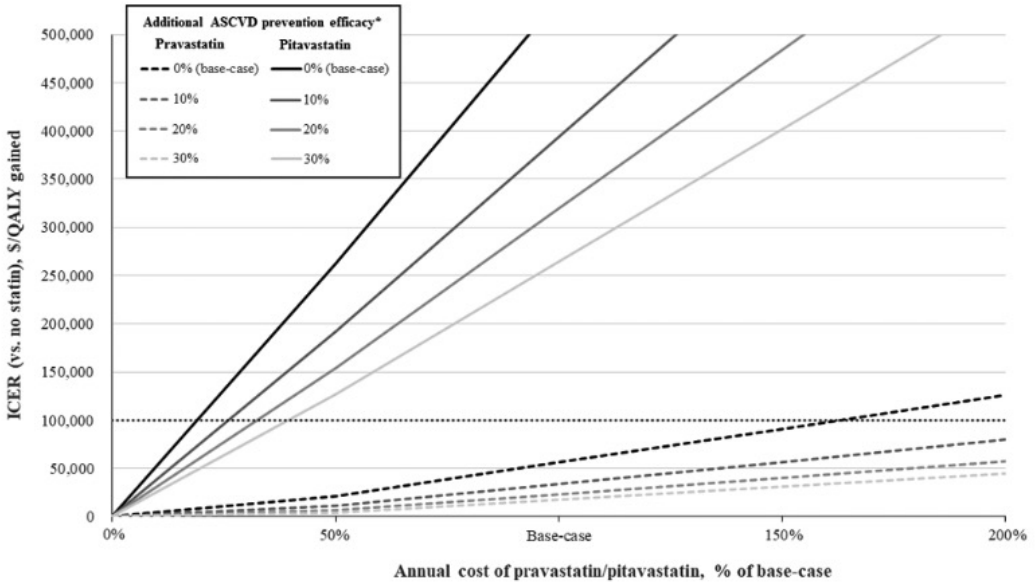


FIGURE 2. ICERs for pravastatin vs. no statin and pitavastatin vs. no statin under various assumptions for statin cost and additional ASCVD prevention efficacy[a]. Horizontal dashed line represents an ICER of $100,000/QALY gained; [a]The base-case probability of ASCVD while using pravastatin was reduced by various percentages to account for the possibility of preventative efficacy associated with the anti-inflammatory properties of statins in PLHIV; ICER, incremental cost-effectiveness ratio; ASCVD, atherosclerotic cardiovascular disease; QALY, quality-adjusted life-year; PLHIV, people living with HIV.

Slide from C. Dejong

Pitavastatin: what do we know?

- *T/F questions:*

  1.T/F: For individuals with ASCVD, Pitavastatin is clinically indicated

  False-it is a moderate intensity statin and for high risk individuals high intensity statins (atorvastatin/rosuvastatin) are indicated

  2. T/F: Pitavastatin is cost effective for use in PWH

  False – Cost of $10 per pill, only cost effective if price reduced to $350 per year; atorvastatin/rosuvastatin, generic which may be alternatives

  3.Fill in the blank: In the past 20 years, Dr. Hsue has prescribed pitavastatin ___ times

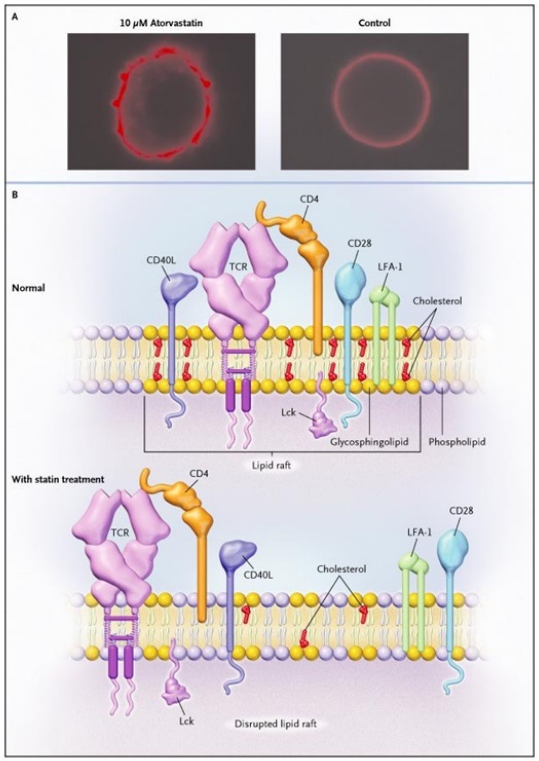
  Answer: 0!

Where do we go from here? Other than statins how are we going to reduce ASCVD risk among PWH?

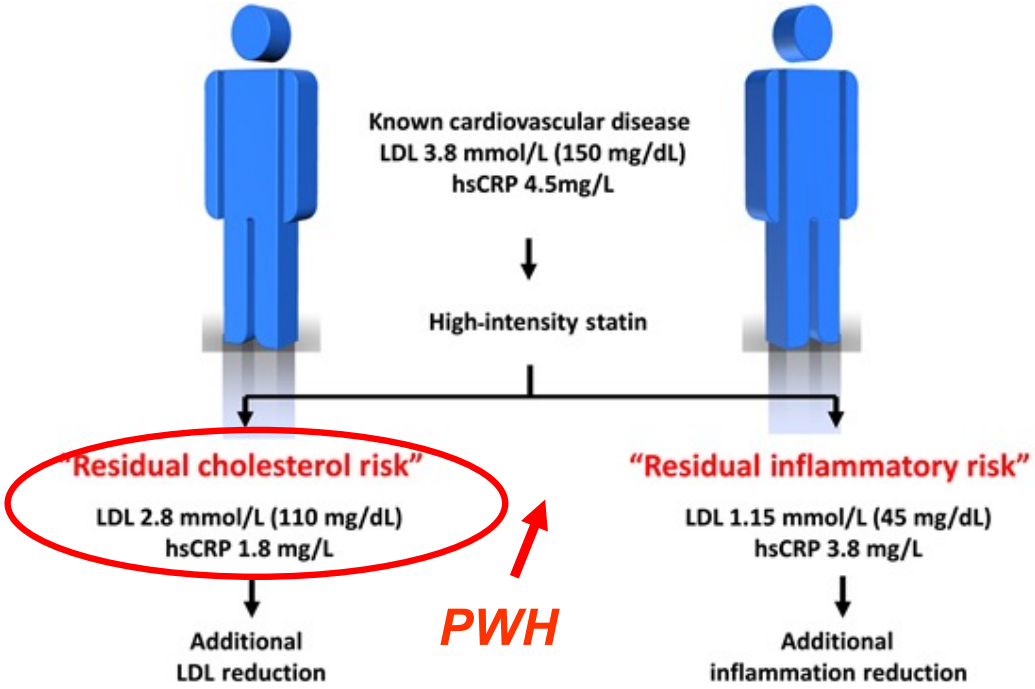
NEJM 2005

Statins for Atherosclerosis — As Good as It Gets?

Michael R. Ehrenstein, Ph.D., F.R.C.P., Elizabeth C. Jury, Ph.D., and Claudia Mauri, Ph.D.

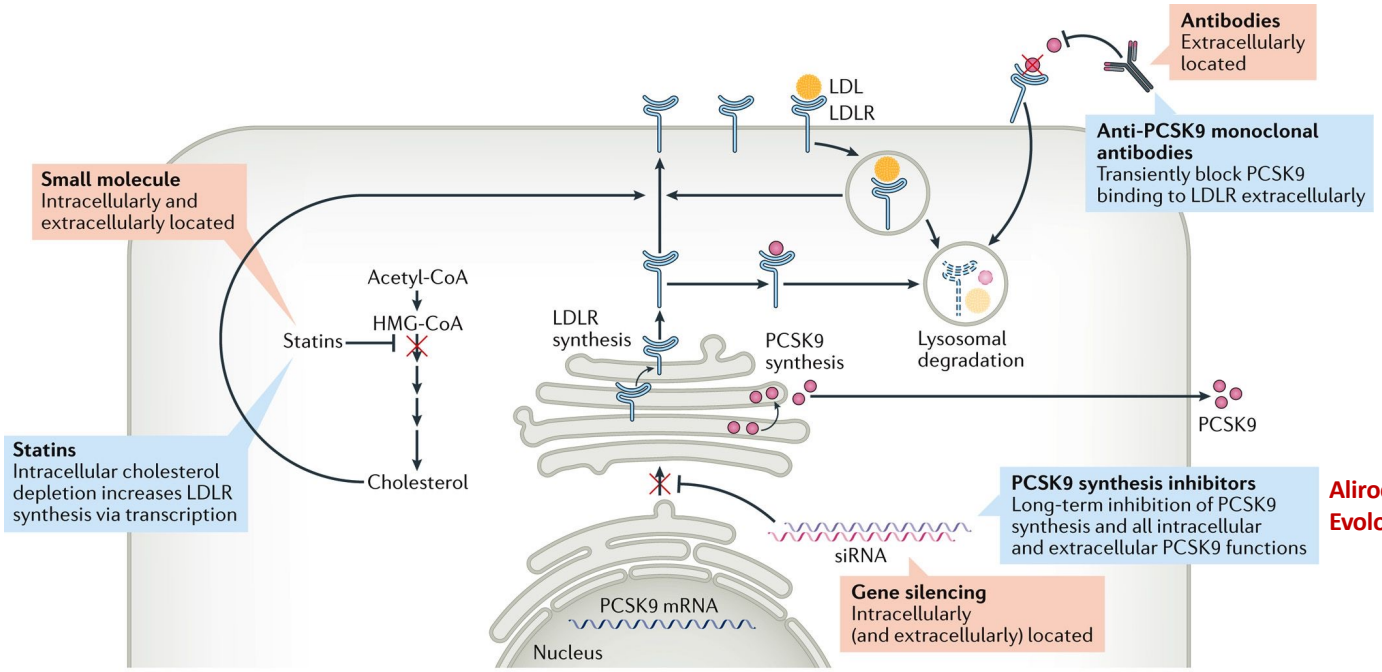


Residual inflammatory risk: what are options after statin treatment?



Ridker PM European Heart Journal 2016

Beyond statins: lipid lowering therapy



Alirocumab – twice weekly injectable
Evolocumab – once month injectable

Inclisiran – small interfering double – stranded RNA
Inhibits production of PCSK9 in hepatocytes
Injection every 6 months

Nordestgaard BG Nat Rev Cardiol 2018

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 29, 2018 VOL. 379 NO. 22

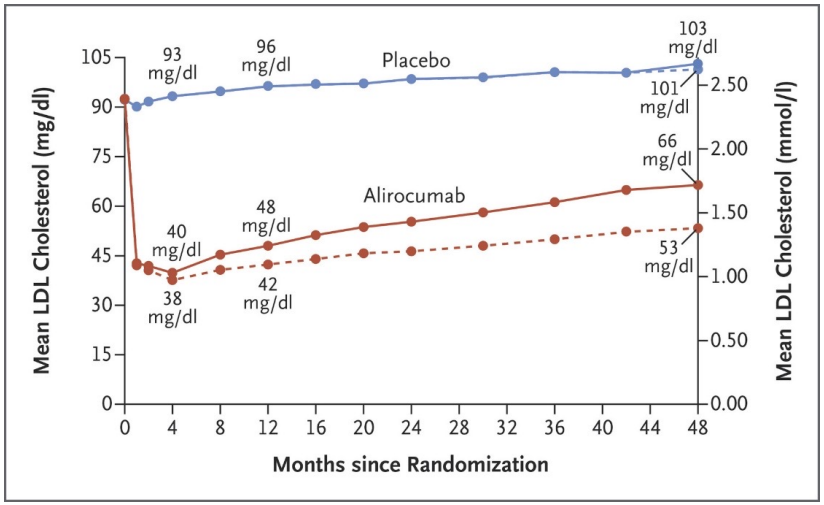
Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

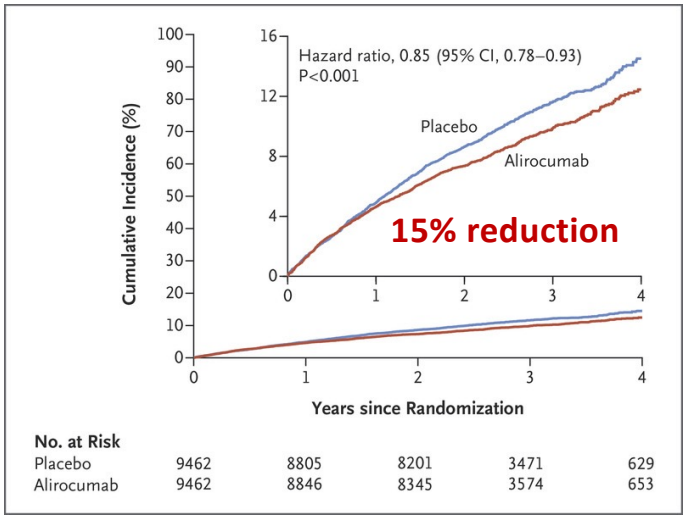
G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

18,924 pts with acute coronary syndrome (ACS) on high intensity statin treated with alirocumab or placebo

Target LDL was 25-50 mg/dL no impact on inflammation

15% reduction in risk of recurrent ischemic CV events





Evolocumab in HIV-Infected Patients With Dyslipidemia

Primary Results of the Randomized, Double-Blind BEIJERINCK Study

JACC 2020

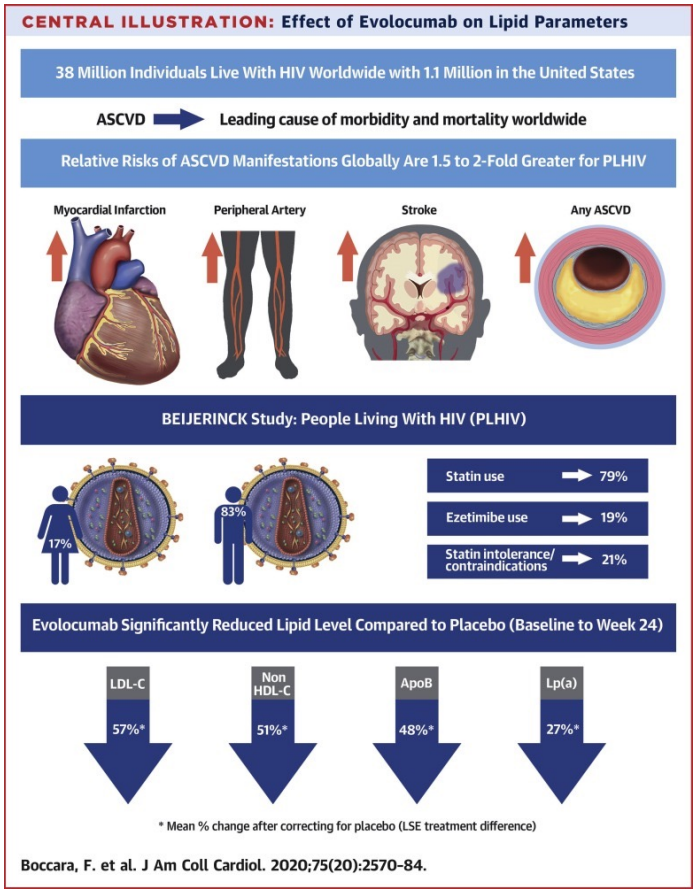
Franck Boccara, MD, PhD,[a] Princy N. Kumar, MD,[b] Bruno Caramelli, MD, PhD,[c] Alexandra Calmy, MD, FMH, PhD,[d] J. Antonio G. López, MD,[e] Sarah Bray, PhD,[e] Marcoli Cyrille, MD,[e] Robert S. Rosenson, MD,[f] for the BEIJERINCK Investigators

464 pts treated with evolocumab for 24 weeks

73% achieved LDL< 70mg/dL

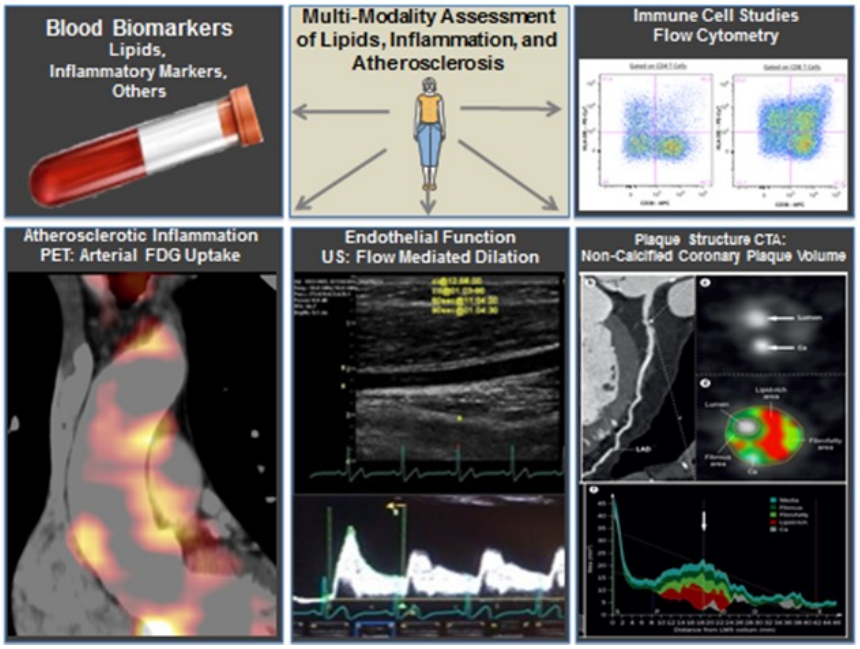
Evolocumab also reduced other atherogenic lipids [non-HDL, apo B, Lp(a)]

Evolocumab overall well tolerated



PCSK9 Inhibition in HIV

- EPIC-HIV Study: A Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of PCSK9 Inhibition in HIV-Infected Subjects at UCSF
- Alirocumab or placebo (n=140) injected subcutaneously every 2 weeks for a duration of 52 weeks



Ahmed Tawakol
MGH Cardiology

Michael Lu
MGH Radiology

R61/R33 HL141047-01, PI: Hsue, Tawakol and Lu

Question:

What LDL-C goal should we target for PWH?

- <100mg/dL
- <70mg/dL
- <50mg/dL
- <25mg/dL

Very low LDL may be beneficial

September 2018

JAMA Cardiology | Original Investigation

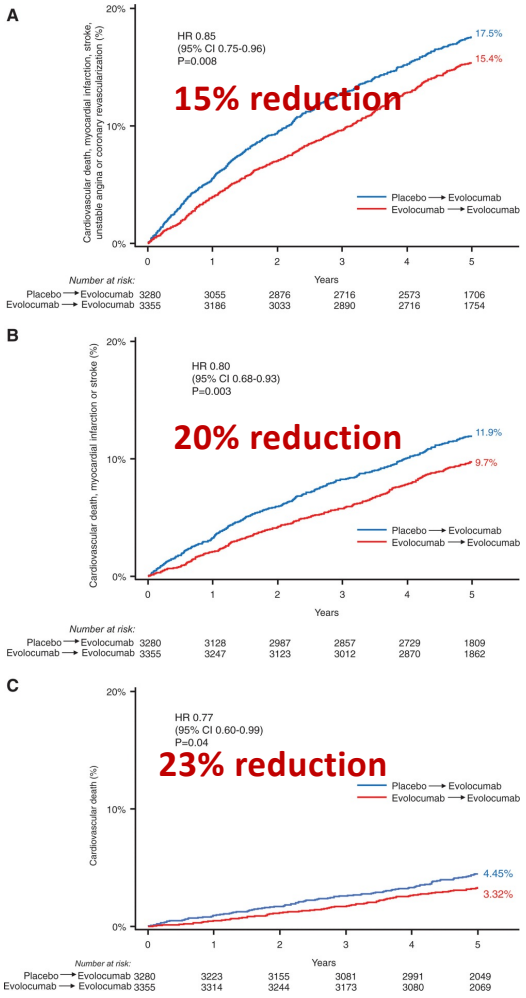
Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels

A Meta-analysis

Marc S. Sabatine, MD, MPH; Stephen D. Wiviott, MD; KyungAh Im, PhD; Sabina A. Murphy, MPH; Robert P. Giugliano, MD, SM

3 trials of nonstatin tx added to background statin (50,627 pts), median LDL of 63-70mg/dL
Nonstatin tx lowered LDL to **11 to 45mg/dL (median of 21mg/dL)**
RR for vascular events was 21% for 38.7mg/dL reduction
LDL lowering NOT associated with SAE, myalgias, LFT elevations, new onset DM, hemorrhagic CVA or cancer

"These data suggest that further lowering of LDL-C beyond lowest current targets would further reduce cardiovascular risk."



Should we lower LDL **earlier** instead of waiting?

Circulation

October 2022

ORIGINAL RESEARCH ARTICLE

Long-Term Evolocumab in Patients With Established Atherosclerotic Cardiovascular Disease

Michelle L. O'Donoghue, MD, MPH; Robert P. Giugliano, MD, SM; Stephen D. Wiviott, MD; Dan Atar, MD; Anthony Keech, MBBS; Julia F. Kuder, MA; KyungAh Im, PhD; Sabina A. Murphy, MPH; Jose H. Flores-Arredondo, MD; J. Antonio G. López, MD; Mary Elliott-Davey, MSc; Bei Wang, PhD; Maria Laura Monsalvo, MD; Siddique Abbasi, MD; Marc S. Sabatine, MD, MPH

Lower rate of MACE In pts getting PCSK9 earlier vs OLE (both getting PCSK9)
PCSK9 safe and well tolerated, majority of pts with LDL< 40mg/dL
23% reduction in CV mortality
CV event rate remained high in both groups

Circulation
Volume 146, Issue 15, 11 October 2022; Pages 1120-1122
https://doi.org/10.1161/CIRCULATIONAHA.122.061727

American Heart Association.

EDITORIAL

Prolonged and Pronounced Low-Density Lipoprotein Cholesterol Lowering: The Gift That Keeps Giving

Article, see p 1109

Michael D. Shapiro, DO, MCR

- *Will a **lower** LDL goal in PWH be beneficial for primary prevention?*
- *Will lowering LDL **earlier** in PWH be beneficial?*

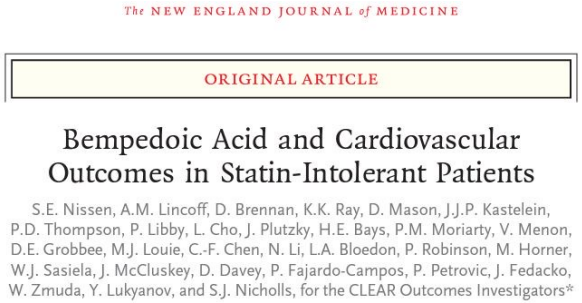
Question:

- What LDL-C goal should we target for PWH?
  - <100mg/dL
  - <70mg/dL
  - <50mg/dL
  - <25mg/dL

Answer is unknown but growing body of evidence suggests that lower is better for LDL-C, and furthermore lowering LDL-C earlier may be beneficial

Other lipid lowering therapies on the horizon…

2023


The NEW ENGLAND JOURNAL of MEDICINE

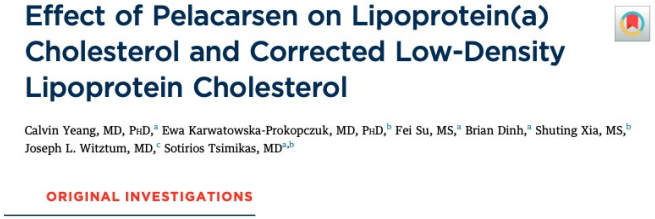
ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

CLEAR Outcomes: Bempedoic acid reduced primary endpoint and MACE by 15%
20% decrease in LDL-C at 6 months, 21.6% reduction in hsCRP

2022


Effect of Pelacarsen on Lipoprotein(a) Cholesterol and Corrected Low-Density Lipoprotein Cholesterol

Calvin Yeang, MD, PhD,[a] Ewa Karwatowska-Prokopczuk, MD, PhD,[b] Fei Su, MS,[a] Brian Dinh,[a] Shuting Xia, MS,[b] Joseph L. Witztum, MD,[c] Sotirios Tsimikas, MD[a,b]

ORIGINAL INVESTIGATIONS

Lp(a): Clinical outcomes trials - OCEAN(a) trial (Amgen),Lp(a) HORIZON (Novartis)

2023


Phase 2b Randomized Trial of the Oral PCSK9 Inhibitor MK-0616

Christie M. Ballantyne, MD,[a] Puja Banka, MD,[b] Gustavo Mendez, MD,[c] Raymundo Garcia, MD,[d] Julio Rosenstock, MD,[e] Anthony Rodgers, MS,[b] Geraldine Mendizabal, MD,[b] Yale Mitchel, MD,[b] Alberico L. Catapano, MDHC, PHD[f,g]

Oral PCSK9 inhibitors

2023


Circulation
Volume 147, Issue 3, 17 January 2023; Pages 242-253
https://doi.org/10.1161/CIRCULATIONAHA.122.062132

American Heart Association.

ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of an Investigational Single-Course CRISPR Base-Editing Therapy Targeting *PCSK9* in Nonhuman Primate and Mouse Models

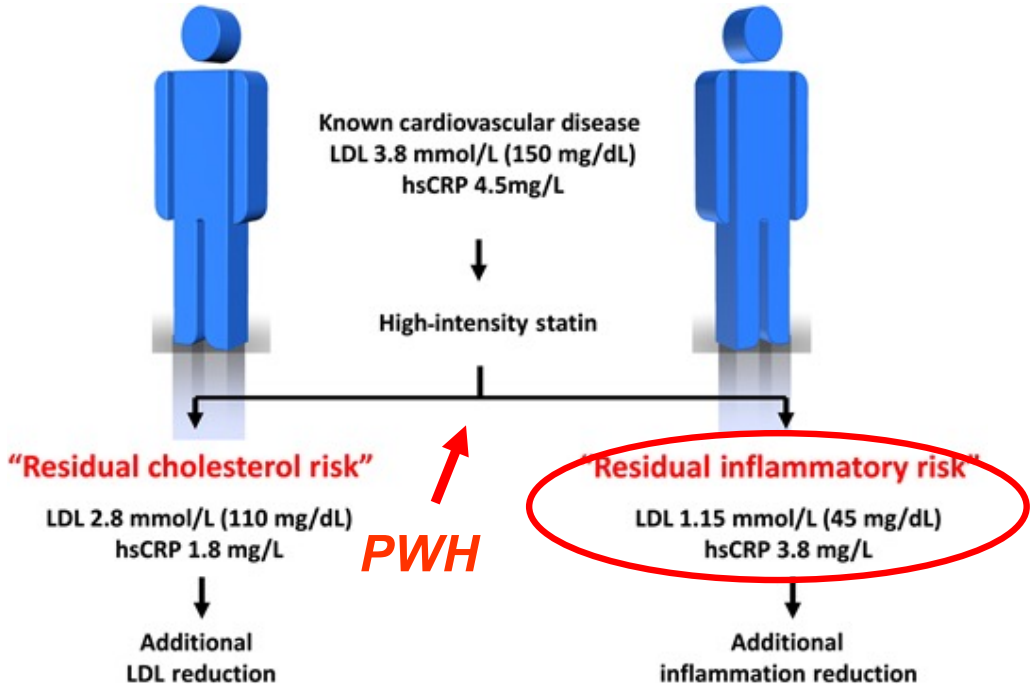
Richard G. Lee, PhD, Anne Marie Mazzola, MS, Maurine C. Braun, MS, Colin Platt, PhD, Scott B. Vafai, MD, Sekar Kathiresan, MD, Ellen Rohde, PhD, Andrew M. Bellinger, MD, PhD, and Amit V. Khera, MD, MSc

Verve trial of gene editing for PCSK9 in humans

- Was benefit of statin tx in REPRIEVE independent of lipid lowering?
  - Yes
  - No
  - I don’t know…

Statins lower both LDL-C and inflammation so challenging to say if the benefit was independent

Residual inflammatory risk: what are options after statin treatment?



Ridker PM European Heart Journal 2016

Role of Inflammation/Immune Activation and CVD in PWH:

- Our group and others defined the key link between immunodeficiency and CVD
- CV risk persists in the setting of treated and suppressed HIV
- Chronic inflammation/immune activation remains elevated in the setting of effectively treated HIV
- In turn, inflammation is independently predictive of CVD
- Focus on inflammation/immune activation as underlying mechanism of HIV-associated CVD and other comorbidities

AIDS. 2012 June 1; 26(9): . doi:10.1097/QAD.0b013e328352ce54.

The Association of CD4+ T-Cell Count on Cardiovascular Risk in Treated HIV Disease

Jennifer E. Ho[a], Rebecca Scherzer[b], Frederick M. Hecht[c], Kristinalisa Maka[d], Van Selby[d], Jeffrey N. Martin[c,e], Peter Ganz[d], Steven G. Deeks[c], and Priscilla Y. Hsue[d]

OPEN ACCESS Freely available online PLOS MEDICINE

Inflammatory and Coagulation Biomarkers and Mortality in Patients with HIV Infection

Lewis H. Kuller[1], Russell Tracy[2], Waldo Belloso[3], Stephane De Wit[4], Fraser Drummond[5], H. Clifford Lane[6], Bruno Ledergerber[7], Jens Lundgren[8], Jacqueline Neuhaus[9], Daniel Nixon[10], Nicholas I. Paton[11], James D. Neaton[9*], for the INSIGHT SMART Study Group

Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis

...nt[b], Amanda Schnell[a], S. Craig Kalapus[a], ...effrey N. Martin[b,c] and Steven G. Deeks[b]

OPEN ACCESS Freely available online PLOS ONE

Inflammation, Coagulation and Cardiovascular Disease in HIV-Infected Individuals

Daniel A. Duprez[1*], Jacqueline Neuhaus[1], Lewis H. Kuller[2], Russell Tracy[3], Waldo Belloso[4], Stephane De Wit[5], Fraser Drummond[6], H. Clifford Lane[7], Bruno Ledergerber[8], Jens Lundgren[9], Daniel Nixon[10], Nicholas I. Paton[11], Ronald J. Prineas[12], James D. Neaton[1] for the INSIGHT SMART Study Group

...le of T-Cell Dysfunction, Inflammation, and Coagulation in Microvascular Disease in HIV

Arjun Sinha, MD, MS; Yifei Ma, MS; Rebecca Scherzer, PhD; Sophia Hur, MPH; Danny Li, BS; Peter Ganz, MD; Steven G. Deeks, MD; Priscilla Y. Hsue, MD

Background—Compared to uninfected adults, HIV-infected adults on antiretroviral therapy are at increased risk of cardiovascular disease. Given the increase in T-cell dysfunction, inflammation, and coagulation in HIV infection, microvascular dysfunction is thought to contribute to this excess cardiovascular risk. However, the relationships between these variables remain undefined.

Methods and Results—This was a cross-sectional study of 358 HIV-infected adults from the SCOPE cohort. Macrovascular endothelial function was assessed using flow-mediated dilation of the brachial artery and microvascular function by reactive hyperemia. T-cell phenotype was determined by flow cytometry. Plasma markers of inflammation (tumor necrosis factor-α, interleukin-6, high-sensitivity C-reactive protein, sCD14) and coagulation (fibrinogen, D-dimer) were also measured. In all HIV+ subjects, markers of inflammation (tumor necrosis factor-α, high-sensitivity C-reactive protein), coagulation (D-dimer) and T-cell activation (CD8+PD1+, CD4+interferon+cytomegalovirus-specific) were associated with worse reactive hyperemia after adjusting for traditional cardiovascular risk factors and co-infections. In treated and suppressed subjects, tumor necrosis factor-α and CD8+PD1+ cells remained associated with worse reactive hyperemia after adjustment. Compared to the untreated subjects, CD8+PD1+ cells were increased in the virally suppressed group. Reactive hyperemia was predictive of flow-mediated dilation.

Conclusions—CD8+PD1+ cells and tumor necrosis factor-α were associated with microvascular dysfunction in all HIV+ subjects and the treated and suppressed group. Additionally, D-dimer, high-sensitivity C-reactive protein, sCD-14, and interleukin-6 were associated with microvascular dysfunction in all HIV+ subjects. Although T-cell dysfunction, inflammation, and microvascular dysfunction are thought to play a role in cardiovascular disease in HIV, this study is the first to look at which T-cell and inflammatory markers are associated with microvascular dysfunction in HIV-infected individuals. (*J Am Heart Assoc*. 2016;5:e004243 doi: 10.1161/JAHA.116.004243)

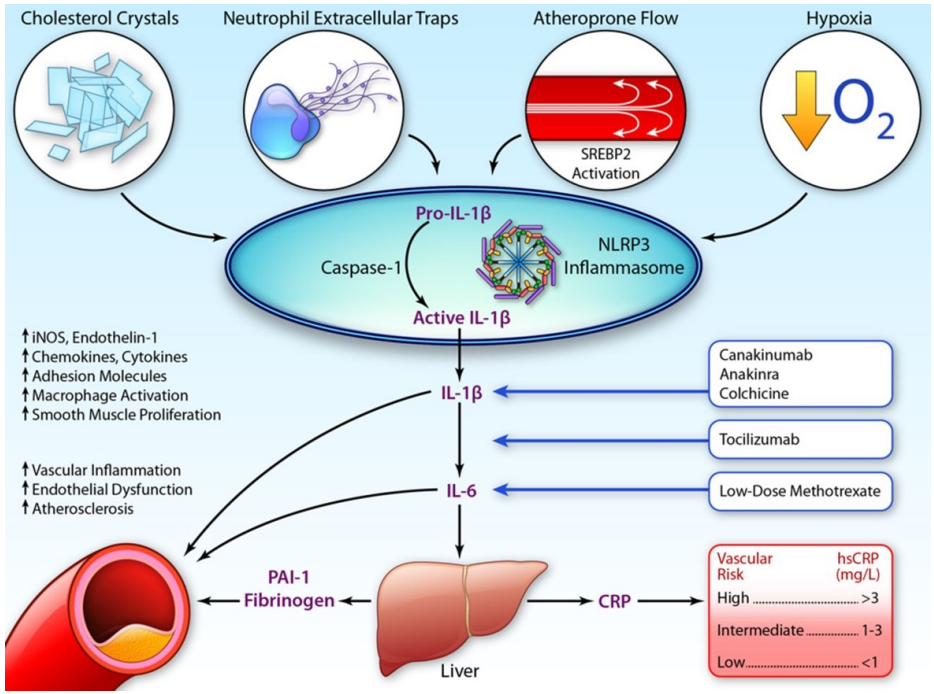
Key Words: coagulation • HIV • immune system • inflammation • microcirculation

ORIGINAL RESEARCH

Carotid Intima-Media Thickness Progression in HIV-Infected Adults Occurs Preferentially at the Carotid Bifurcation and Is Predicted by Inflammation

Priscilla Y. Hsue, MD; Rebecca Scherzer, PhD; Peter W. Hunt, MD; Amanda Schnell, BA; Ann F. Bolger, MD; S.C. Kalapus, RDMS; Kristinalisa Maka, BS; Jeffrey N. Martin, MD, MPH; Peter Ganz, MD; Steven G. Deeks, MD

Targeting IL-1β using canakinumab lower inflammation (not LDL-C) , reduces CV events, and cancer incidence/mortality



Ridker P Circulation Research 2016

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2017 VOL. 377 NO. 12

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

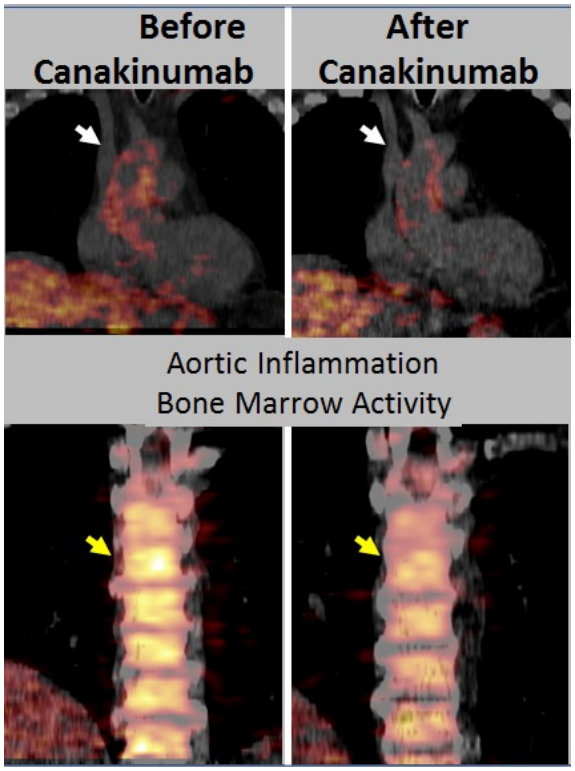
P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

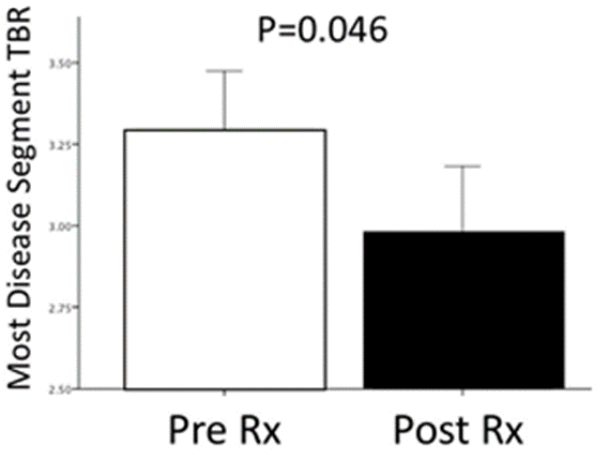
Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

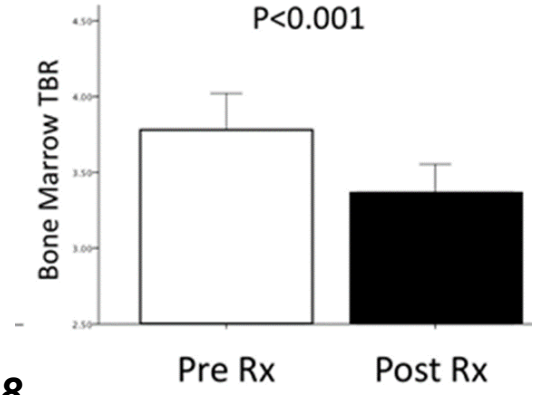
Paul M Ridker, Jean G MacFadyen, Tom Thuren, Brendan M Everett, Peter Libby, Robert J Glynn*, on behalf of the CANTOS Trial Group†*

Ridker P et al Lancet August 27, 2017

IL-1β inhibition with canakinumab reduces both arterial and bone marrow activity

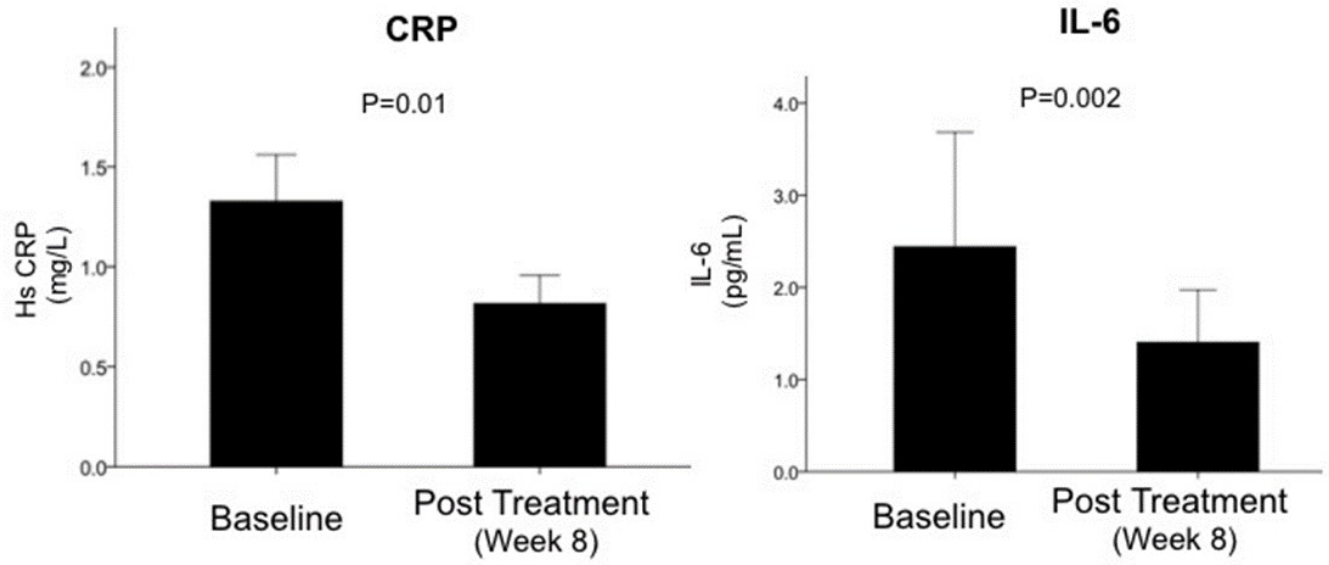






Hsue PY and Tawakol A JACC 2018

Canakinumab significantly reduced inflammatory markers
(N=10 pts, 150mg single dose)



CKB tx: hsCRP reduced by 41% (p=0.039) from BL to week 8
IL-6 reduced by 30% from BL to week 8 (p=0.003)

Hsue PY and Tawakol A JACC 2018

Colchicine as anti-inflammatory agent for ASCVD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 26, 2019 VOL. 381 NO. 26

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D., Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., Petr Ostadal, M.D., Ph.D., Wolfgang Koenig, M.D., Denis Angoulvant, M.D., Jean C. Grégoire, M.D., Marc-André Lavoie, M.D., Marie-Pierre Dubé, Ph.D., David Rhainds, Ph.D., Mylène Provencher, Ph.D., Lucie Blondeau, M.Sc., Andreas Orfanos, M.B., B.Ch., Philippe L. L'Allier, M.D., Marie-Claude Guertin, Ph.D.,

The NEW ENGLAND JOURNAL of MEDICINE

COLCOT: 30 days after MI, colchicine reduced risk of ischemic CV events 23% vs. placebo

ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease

S.M. Nidorf, A.T.L. Fiolet, A. Mosterd, J.W. Eikelboom, A. Schut, T.S.J. Opstal, S.H.K. The, X.-F. Xu, M.A. Ireland, T. Lenderink, D. Latchem, P. Hoogslag, A. Jerzewski, P. Nierop, A. Whelan, R. Hendriks, H. Swart, J. Schaap, A.F.M. Kuijper, M.W.J. van Hessen, P. Saklani, I. Tan, A.G. Thompson, A. Morton, C. Judkins, W.A. Bax, M. Dirksen, M. Alings, G.J. Hankey, C.A. Budgeon, J.G.P. Tijssen, J.H. Cornel, and P.L. Thompson, for the LoDoCo2 Trial Investigators*

LoDoCo2: 31% reduction in MACE when colchicine added to std prevention tx

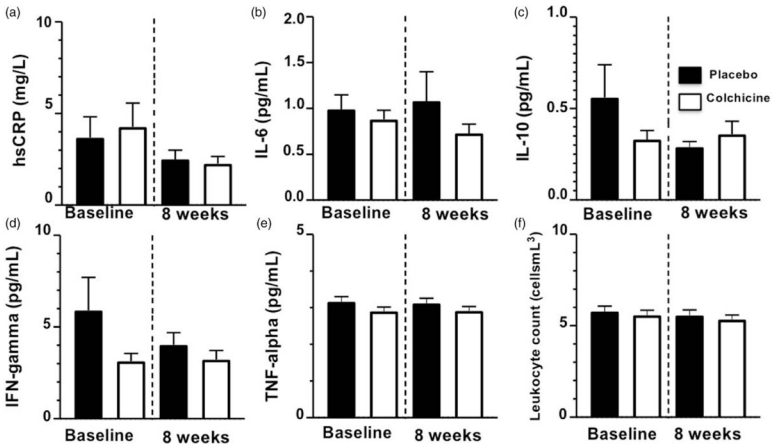
June 20, 2023: FDA approves colchicine as first anti-inflammatory drug to reduce risk for MI, CVA, revascularization and CV death in pts with established ASCVD or risk factors for CVD

Colchicine in HIV?

RCT of 81 PLWH to test whether colchicine at 0.6mg daily impacts coronary endothelial function

No impact on inflammatory markers or coronary or systemic endothelial function

Hays AG, et al AIDS 2021



Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials

Paul M Ridker, Deepak L Bhatt, Aruna D Pradhan, Robert J Glynn, Jean G MacFadyen, Steven E Nissen, on behalf of the PROMINENT, REDUCE-IT, and STRENGTH Investigators

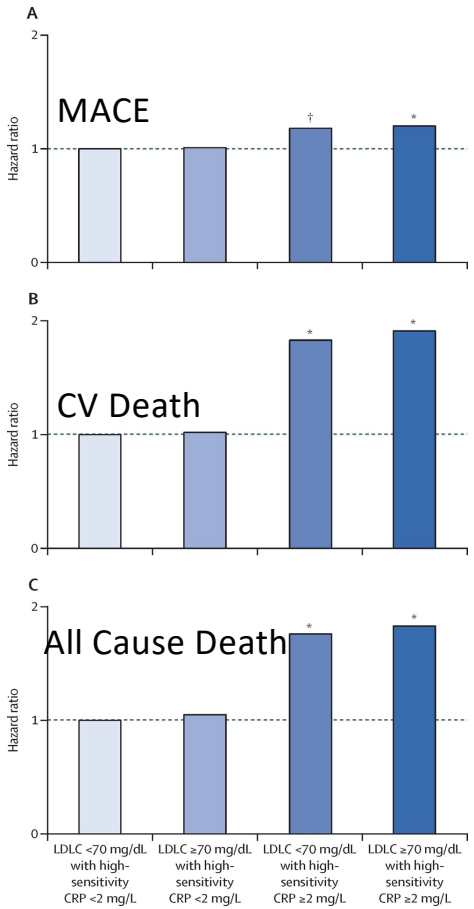
Lancet 2023

Pts with or at high risk of ASCVD receiving contemporary statins N=31245

Residual inflammation (hsCRP) was significantly associated with:
incident MACE, CV death, all cause death

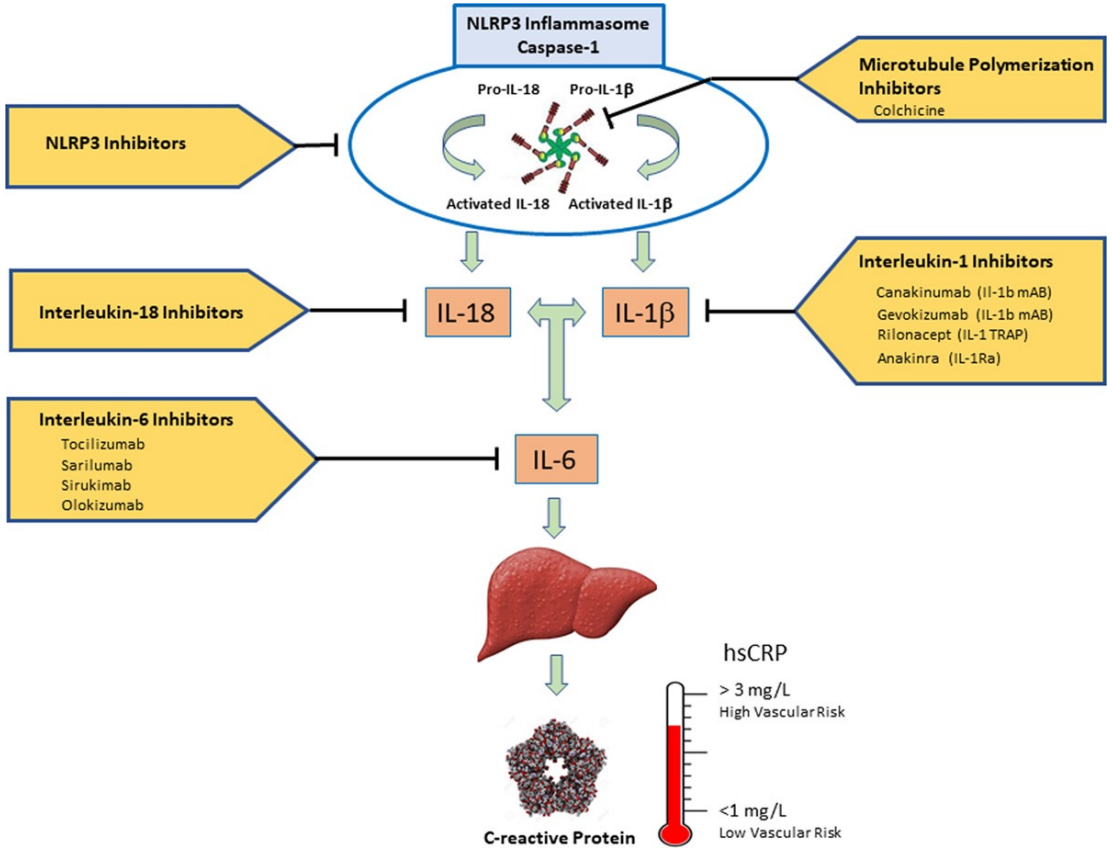
Residual cholesterol was neutral for MACE, low magnitude for cv death and all cause death

"We believe that combined use of aggressive lipid-lowering and anti-inflammatory therapies might become standard of care for atherosclerotic disease in the future."



LDL<=70 CRP<2 **LDL>=70 CRP<2** **LDL<70 CRP>=2** **LDL>=70 CRP>=2**

From CANTOS to CIRT to COLCOT to Clinic…



Ridker PM Circulation 2020

Articles

IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised placebo-controlled, phase 2 trial

Paul M Ridker, Matt Devalaraja, Florian M M Baeres, Mads D M Engelmann, G Kees Hovingh, Milana Ivkovic, Larry Lo, Douglas Kling, Pablo Pergola, Dominic Raj, Peter Libby, Michael Davidson, on behalf of the RESCUE Investigators*

Lancet May 2021

77-92% reduction in hsCRP among individuals with CKD and >2mgL hsCRP

Summary:

- Statins have been shown to be beneficial in virtually all populations, including PWH
- Regardless of HIV status, all persons with DM or with calculated ascvd risk of 7.5% or higher should be on moderate intensity statin
- For PWH: Reprieve suggests benefit for statins
  - Likely with ASCVD risk of 5% and above
  - However, some PWH with low calculated ASCVD risk may benefit from statin, role of imaging?
- Pitavastatin is a moderate intensity statin; other statins such as atorvastatin/rosuvastatin could be considered, particularly given cost differential

Looking forward, how do we reduce ascvd risk among PWH?

- Should statin be started earlier instead of later?
- Will there be a benefit of achieving a lower LDL-C in PWH using different lipid lowering agents?
- What anti-inflammatory therapies could be used on top of statin to reduce risk?
- Can we use imaging to ascertain statin decision in PWH at low calculated ASCVD risk?

Circulation

July 2019

AHA SCIENTIFIC STATEMENT

Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV

A Scientific Statement From the American Heart Association

ABSTRACT: As early and effective antiretroviral therapy has become more widespread, HIV has transitioned from a progressive, fatal disease to a chronic, manageable disease marked by elevated risk of chronic comorbid diseases, including cardiovascular diseases (CVDs). Rates of myocardial

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