


THE PHYSICIANS OF  KAISER PERMANENTE.

ALL HEART/PHASE Convening The New Cholesterol Guidelines Should I be on a Statin?


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1

Agenda

- Atherosclerosis / Why Statins?**
- The Paradigm Shift**
- The New Guidelines**
 - **Statins: Benefits and Harms**
 - **Calculating Risk**
- KPNW Implementation Strategy**

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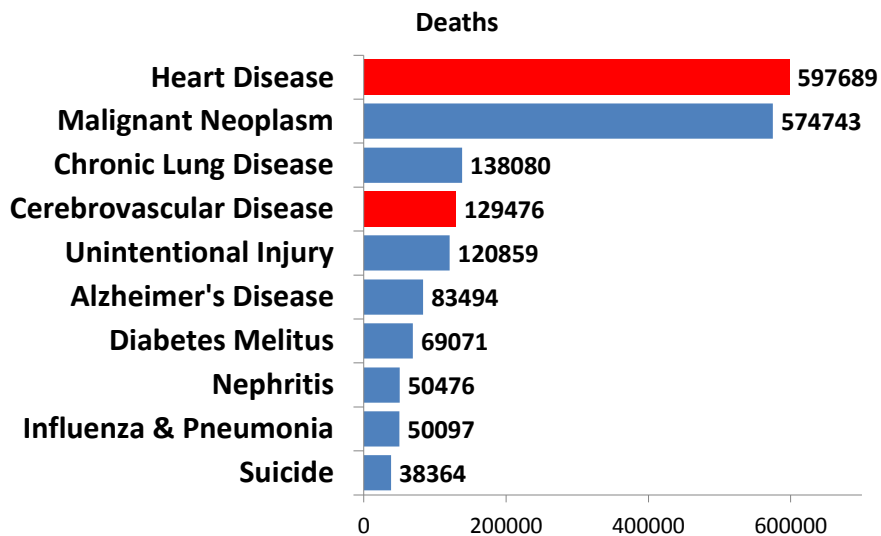
Atherosclerosis and Lipid-Lowering

- Why is Atherosclerotic Cardiovascular Disease (ASCVD) getting all this attention?
- Why do we focus so much on lipids in reducing ASCVD?
- What lipid markers should we focus on?
- Why do we prefer statins to other lipid-lowering drugs?

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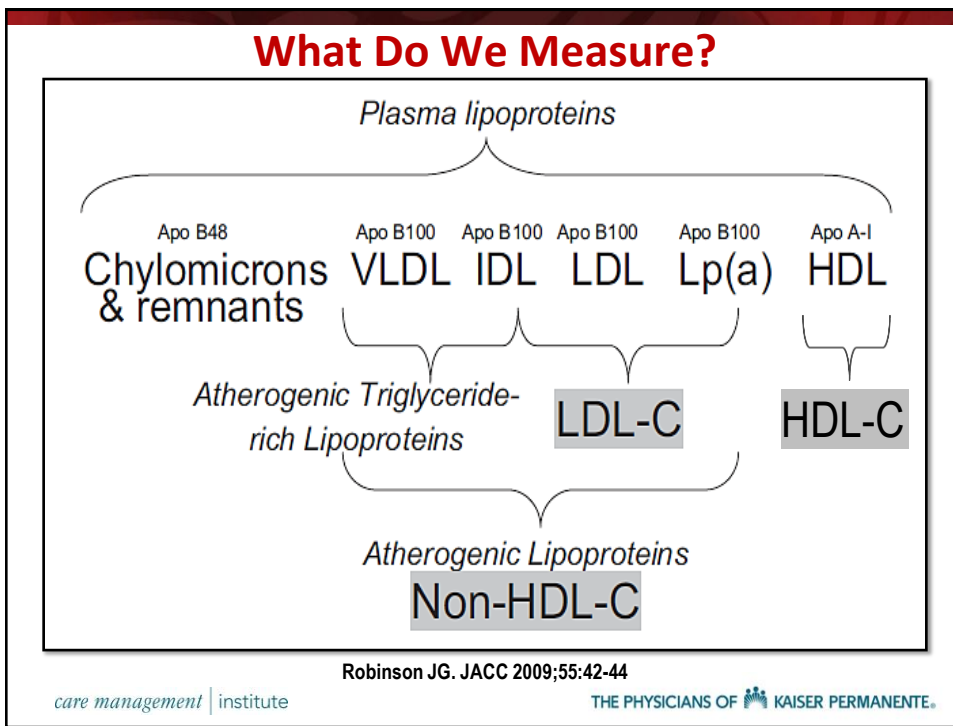
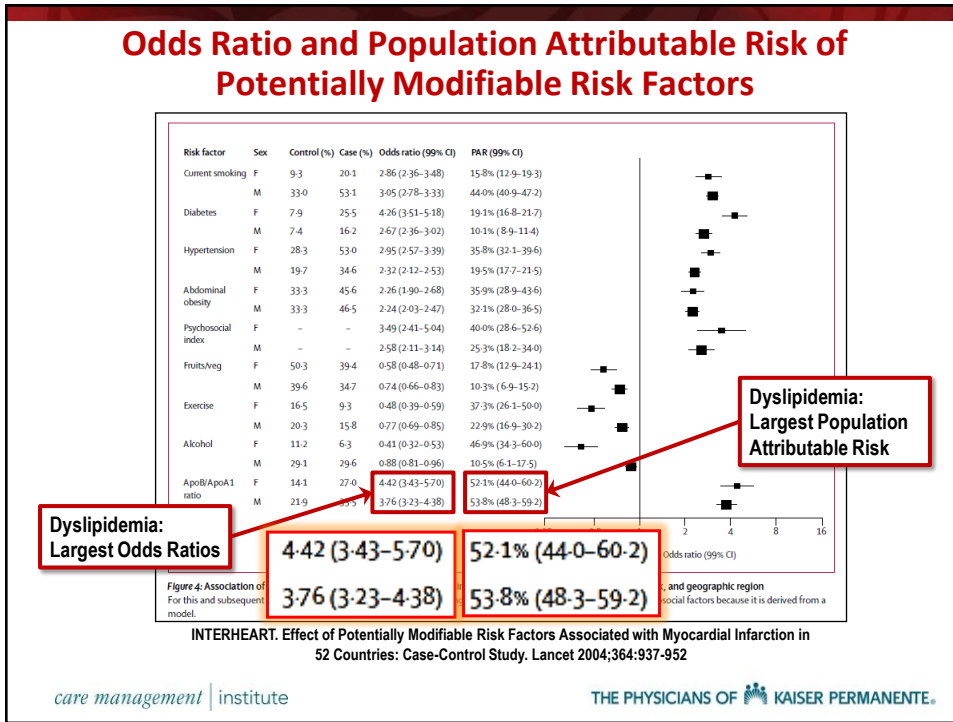
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10 Leading Cause of Deaths (All Ages)



Data Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, CDC using WISQARS™.





Structure of LDL

Surface Monolayer of Phospholipids and Free Cholesterol

Apo B

Hydrophobic Core of Triglyceride and Cholesteryl Esters

Murphy HC, et al. *Biochemistry*. 2000;39:9763-970

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Heterogeneity of HDL

Particle Shape

Discoidal

Spherical

Apolipoprotein Composition

A-I HDL

A-I/A-II HDL

A-II HDL

Particle Size

HDL_{2b}

HDL_{2a}

HDL_{3a}

HDL_{3b}

HDL_{3c}

Lipid Composition

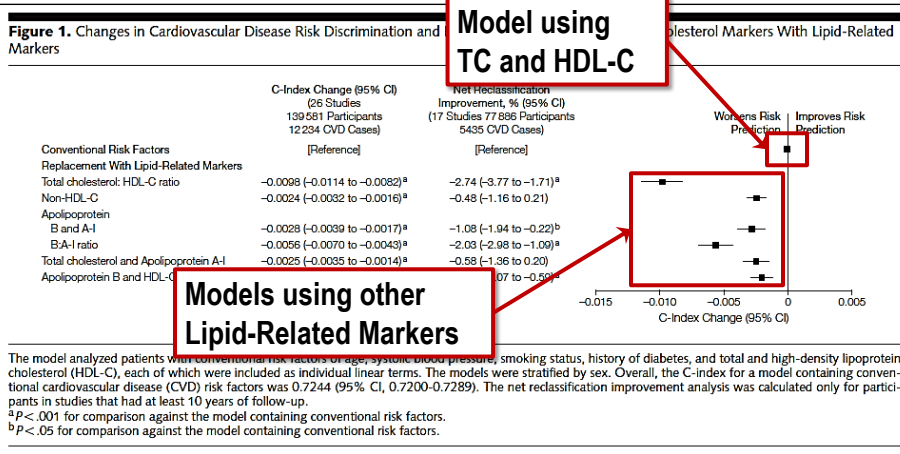
TG, CE, and PL

Rye KA, et al. *Atherosclerosis*. 1999;145:227-238

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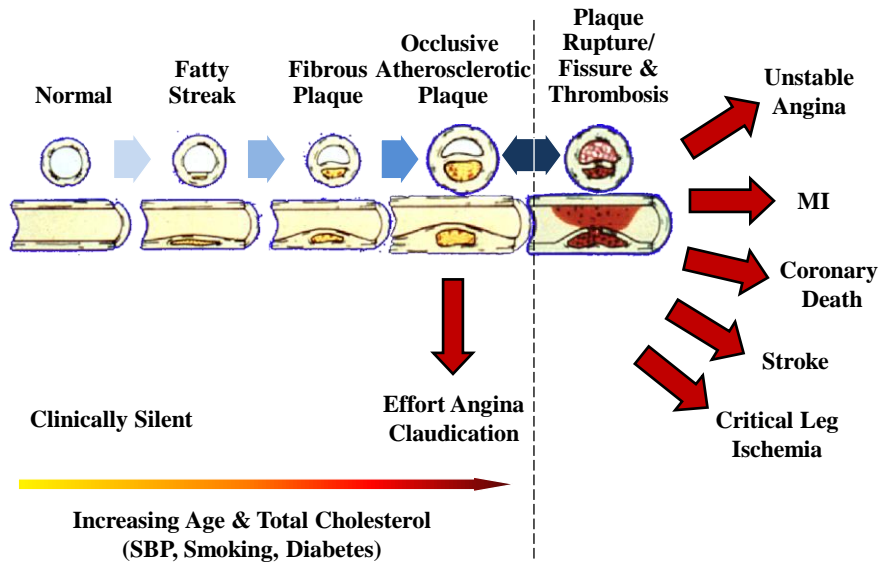
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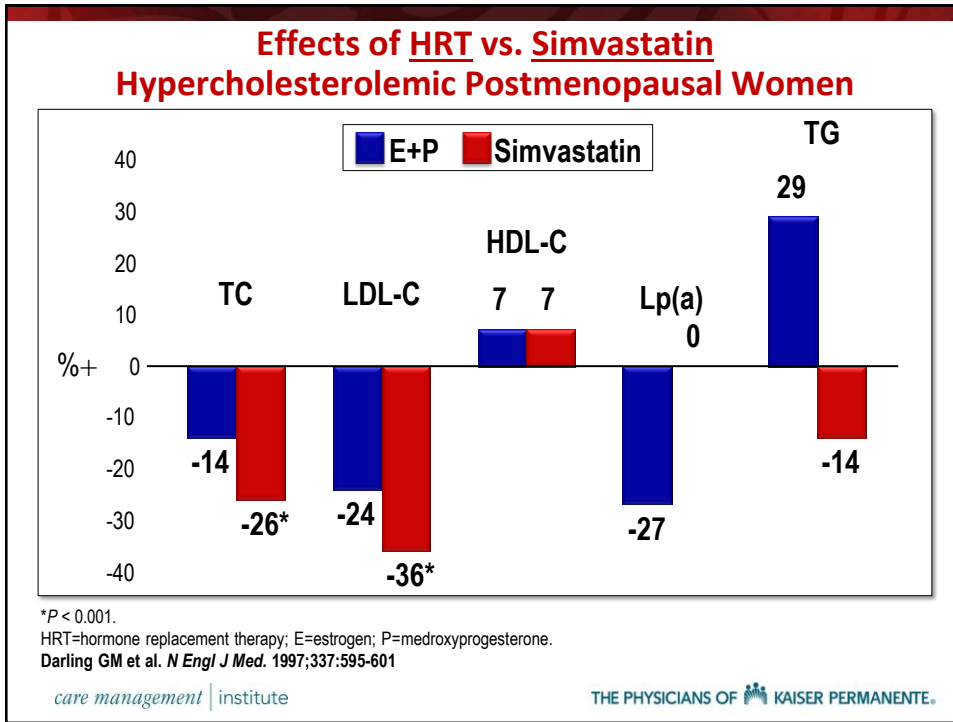
Replacing TC & HDL-C with Lipid-Related Markers Worsens Risk Prediction



Emerging Risk Factors Collaboration. JAMA 2012;307:2499-2506

Atherosclerosis: A Progressive Process

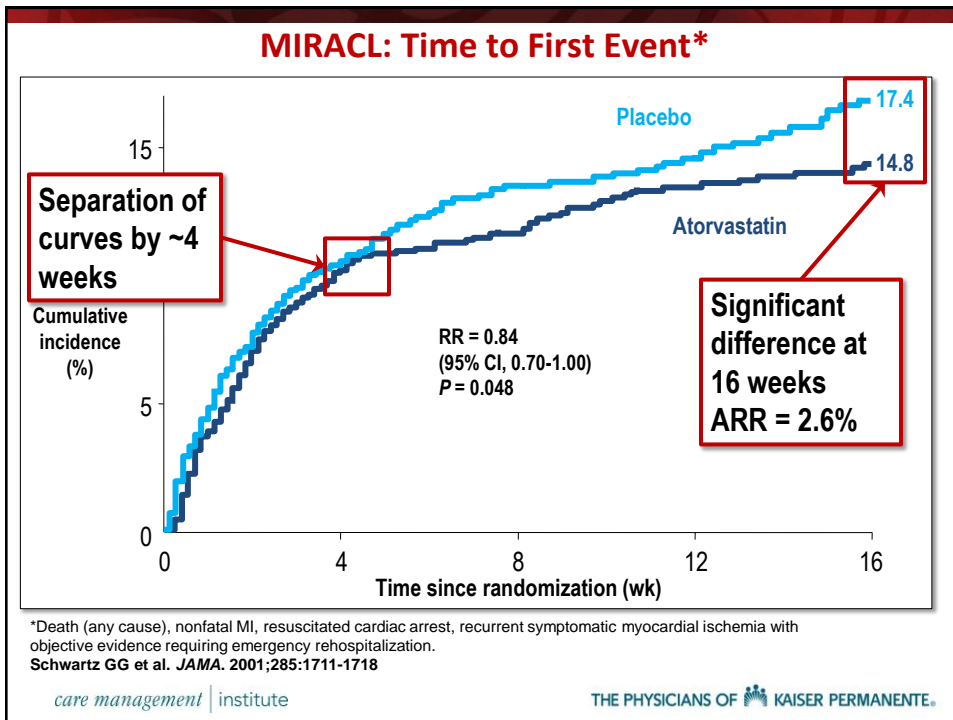
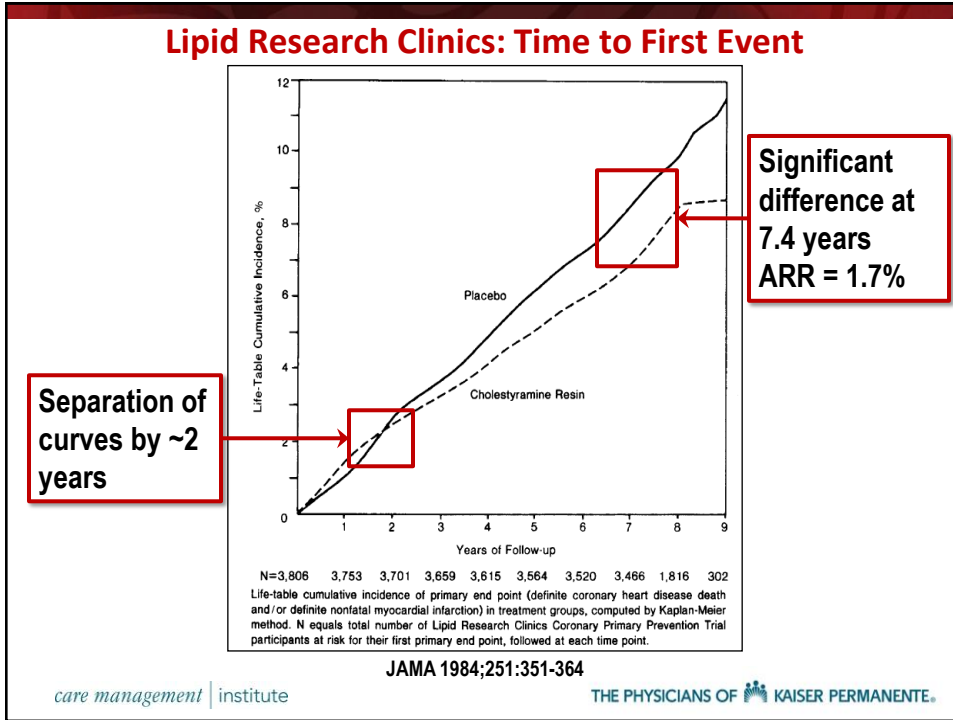


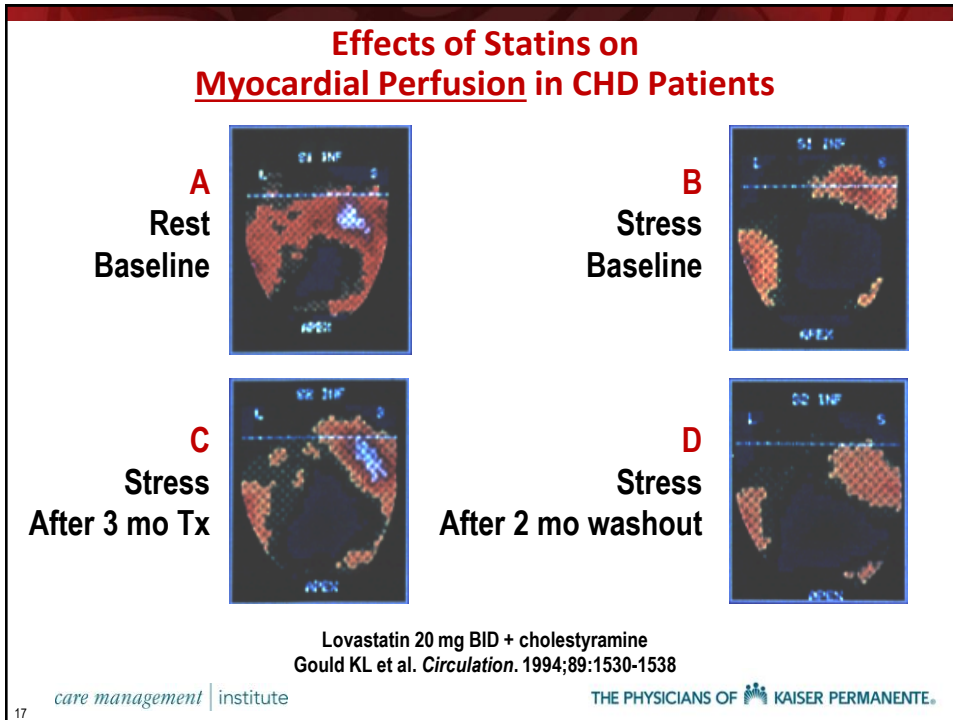


WHI: Estrogen + Progestin Increased CHD, Stroke, VTE, & CVD

Outcomes	Hazard Ratio	Nominal 95% CI
Follow-up time, mean (SD), mo	NA	
Cardiovascular disease†		
CHD	1.29	NA
CHD death	1.18	1.02-1.63
Nonfatal MI	1.32	0.70-1.97
CABG/PTCA	1.04	1.02-1.72
Stroke	1.41	0.84-1.28
Fatal	1.20	1.07-1.85
Nonfatal	1.50	0.58-2.50
Venous thromboembolic disease	2.11	1.58-2.82
Deep vein thrombosis	2.07	1.49-2.87
Pulmonary embolism	2.13	1.39-3.25
Total cardiovascular disease	1.22	1.09-1.36

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- ### Proposed Mechanisms of Event Reduction by Statin Therapy
- **Improved endothelium-dependent vasodilation**
 - **Stabilization of atherosclerotic lesions**
 - Especially nonobstructive, vulnerable plaques
 - **Reduction in inflammatory stimuli**
 - Lipoproteins and modified lipoproteins
 - **Prevention, slowed progression, or regression of atherosclerotic lesions**
- Libby P. *Circulation* 1995;91:2844-2850
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Incremental Benefit of Adding Other Lipid-Lowering Agents to Statins

- **Limited evidence suggests that combinations of lipid-lowering agents do not improve clinical outcomes more than high-dose statin monotherapy.**

Sharma M. Systematic Review: Comparative Effectiveness and Harms of Combination Therapy and Monotherapy for Dyslipidemia. *Ann IM* 2009;151:1622-1630

21

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Atherosclerosis and Lipid-Lowering

- Atherosclerotic Cardiovascular Disease (ASCVD) is the leading cause of death in the US (CDC, 2010)
- Among potentially modifiable risk factors, dyslipidemia has the highest Odds Ratio and Population-Attributable Risk (INTERHEART. *Lancet* 2004)
- Among lipid-lowering agents, statins have:
 - The most extensive evidence, greatest magnitude of ASCVD event reduction, and best safety profile
 - Rapid reduction in ASCVD event rates
 - Effects beyond cholesterol-lowering
 - Improve endothelial function
 - Enhance stability of atherosclerotic plaques
 - Decrease oxidative stress and inflammation
 - Inhibit thrombogenic response
- No evidence of incremental benefit of adding other agents to high-intensity statins (Sharma. *AHRQ* 2009)

22

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Agenda

Atherosclerosis / Why Statins?

The Paradigm Shift

The New Guidelines

- Statins: Benefits and Harms
- Calculating Risk

KPNW Implementation Strategy

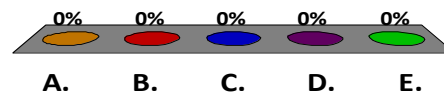
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Audience Response System

How much do moderate-intensity statins reduce the relative risk of ASCVD?

- A. 10%
- B. 25%
- C. 35%
- D. 45%
- E. 60%



24

Why the Major Change?

Old Paradigm

- **LDL-C centric**
 - Epidemiologic and pathophysiologic reasoning
 - Early RCTs designed around LDL-C centric perspective

New Paradigm

- **ASCVD risk & statin-intensity centric**
 - Vast majority of lipid-lowering studies showing efficacy at reducing CVD risk used statins
 - Later RCTs tested statins at ever-lower LDL-C thresholds
 - Latest RCTs imposed LDL-C ceilings
 - Latest RCTs gave fixed-dose statins, based on ASCVD risk
 - Analysis shows that statin CVD Relative Risk Reduction holds across the spectrum of risk, and that statin-intensity explains CVD reduction effect as well as LDL-C-lowering
 - No confidence in determining target LDL-C
 - No evidence that adding non-statins increases benefit

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Relative %Reduction CVD Risk Proportional to %Reduction in LDL-C

Average LDL-C reduction in primary prevention RCTs was 1 mmol/L or 39 mg/dL

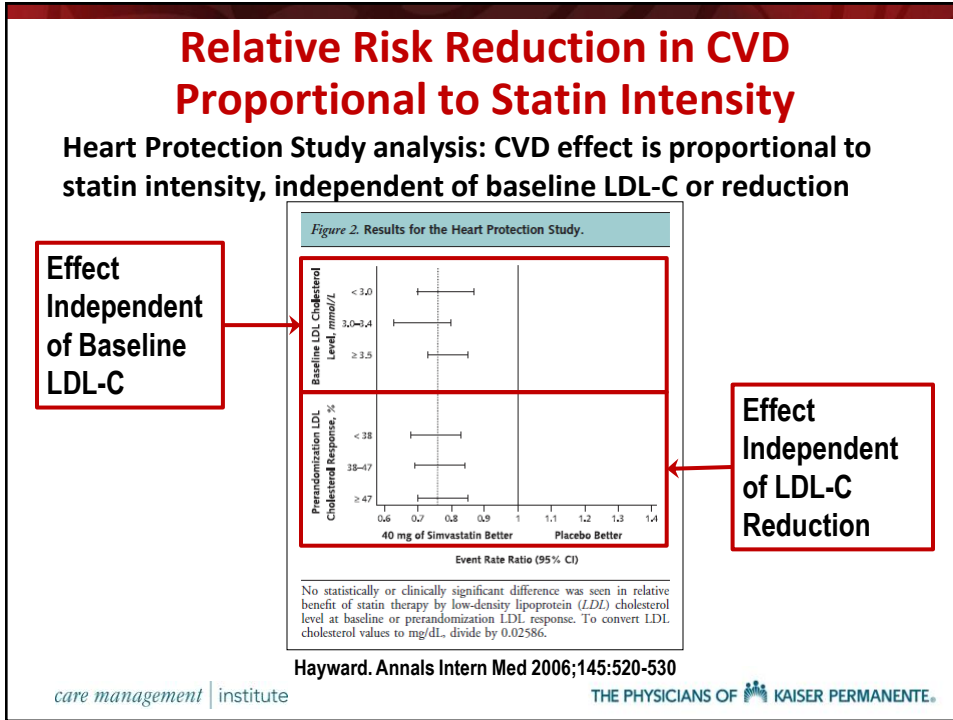
<p>Low-intensity statins</p> <ul style="list-style-type: none"> • Pravastatin 10-20 mg • Lovastatin 10-20 mg 	<p>LDL-C ↓ ≈ <30%</p>	<p>≈ 25% RRR Major CVD</p>
<p>Moderate-intensity statins</p> <ul style="list-style-type: none"> • Pravastatin 40-80 mg • Lovastatin 40-80 mg • Simvastatin 20-40 mg • Atorvastatin 10-20 mg 	<p>LDL-C ↓ ≈ 30%- <50%</p>	<p>≈ 35% RRR Major CVD</p>
<p>High-intensity statins</p> <ul style="list-style-type: none"> • Atorvastatin 40-80 mg • Rosuvastatin 20-40 mg • Simvastatin 80 mg (no new starts) 	<p>LDL-C ↓ ≈ ≥50%</p>	<p>47% RRR Major CVD in JUPITER</p>

CTTC. Lancet 2010;376:1670-1681; Ridker. NEJM 2008;359:2195-2207

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26

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Why the Major Change?


New Paradigm

- **ASCVD risk & statin-intensity centric**
 - RCTs gave fixed dose statins, based on ASCVD risk
 - No confidence in determining optimal LDL-C target
 - Perverse behavior with LDL-C targets
 - No incremental benefit of adding non-statins to high-dose statins
 - This could be upended by new evidence
 - Ezetimibe, CETP inhibitors, PCSK9 inhibitors, ??


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 - **Statins: Benefits and Harms**
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The New Cholesterol Guidelines



- **Dyslipidemia treatment recommendations**
- **Rationale for statin treatment recommendations**
- **10-year ASCVD risk**
 - Differences between risk equations
 - Framingham CAD
 - NHLBI/AHA/ACC ASCVD

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30

Highlights: New Cholesterol Guidelines

2014 NHLBI/AHA/ACC Risk Assessment and Dyslipidemia Guidelines

- **Statin therapy and its intensity based on direct evidence of benefit and ASCVD risk**
 - No longer based on baseline LDL-C (except LDL-C \geq 190 mg/dL)
- **Targets for LDL-C and non-HDL-C removed**
- **New model for 10-year risk of ASCVD**
 - Fatal and non-fatal MI, fatal and non-fatal Stroke
 - Ages 40-79
 - People with DM
 - Race: non-Hispanic Whites & African American

31

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Statin Benefit Groups

1. Adults \leq 75 years of age who have clinical ASCVD

High-intensity statin (Strong recommendation)

Moderate-intensity statin if age \geq 76 years (Weak recommendation)

2. Adults 40 to 75 years of age with diabetes mellitus and LDL-C 70-189 mg/dL

Moderate-to-high-intensity statin (Strong recommendation)

Moderate-intensity statin if age \geq 76 years (Weak recommendation)

3. Adults \geq 21 years of age with primary LDL-C \geq 190 mg/dL

High-intensity statin (Strong recommendation)

4. Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes at elevated ASCVD risk

High-intensity statin if ASCVD risk \geq 15% (KP strong recommendation)

Moderate-intensity statin if ASCVD risk 7.5-14.9% (KP weak recommendation)

32

Estimating Net Benefit

- **Use absolute risk and relative risk reduction to estimate NNT (Number Needed to Treat) to prevent one CVD event**
- **Use absolute risk (and relative risk increase) to estimate NNH (Number Needed to Harm) to cause 1 excess adverse event**
- **Benefits increasingly outweigh harms as NNH increasingly exceeds NNT (ie, $NNH \gg NNT$)**
- **Clinical application:**
 - Identification of candidates for primary prevention with statin therapy
 - Using data from Cholesterol Treatment Trialists' Collaboration 2012 meta-analysis

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Statin Adverse Events

- **Excess risk of myopathy**
 - 0.5 per 1000 statin-treated persons over 5 years
 - Higher with simvastatin 80 mg (lower doses in Asians)
 - 5-year NNH = 2,000
- **Excess risk of hemorrhagic stroke**
 - 0.1 per 1000 statin-treated persons over 5 years
 - Might be higher in populations at ↑ risk hemorrhagic stroke (eg, Asian)
 - 5-year NNH = 10,000

CTTC. Lancet 2012;380:581-590

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Statin Adverse Events

■ Excess risk of new diabetes

- 5 per 1000 statin-treated persons over 5 years
 - Meta-analysis of mostly moderate-intensity statin therapy
 - 5-year NNH = 200
- 15 per 1000 statin-treated persons over 5 years
 - 54 per 8901 statin-treated persons over 2 years with Rosuvastatin 20 mg
 - All cases occurred in those with baseline risk factors (PreDM, BMI \geq 30, metabolic syndrome)
 - 5-year NNH = 66

Sattar. Lancet 2010;375:735-742; Ridker. Lancet 2012;380:565-571

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36

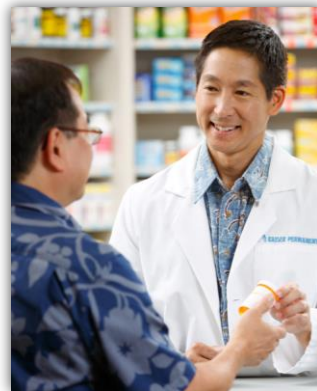
Conservative Approach to Estimating Adverse Effects of Statin Therapy

■ Low to Moderate intensity statin

- 5-5.6 excess cases of adverse effects per 1000 statin-treated persons over 5 years
- NNH = 179-200
- **10-Year NNH = 89-100**

■ High intensity statin

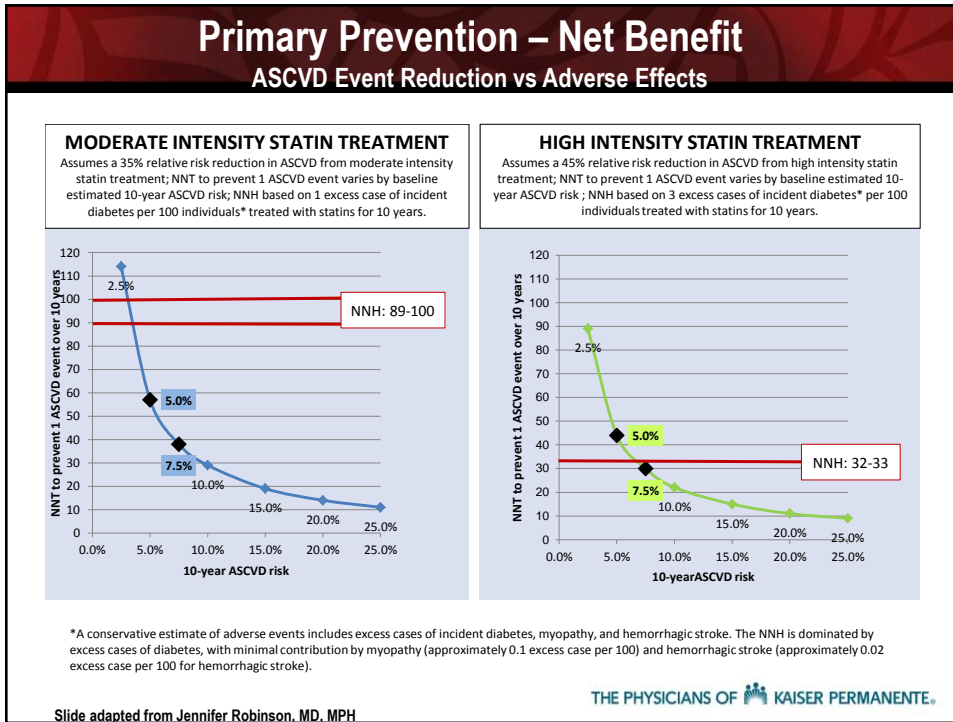
- 15-15.6 excess cases of adverse effects per 1000 statin-treated persons over 5 years
- NNH = 64-66
- **10-Year NNH = 32-33**



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37



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KPNW Implementation Strategy

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Calculating Risk

- **If your patient is in first three categories, you can start treatment simply based on group**
 - Direct, hard-outcomes evidence of benefit
- **For fourth group, calculate ASCVD risk**
- **ASCVD risk based on new NHLBI/AHA/ACC Pooled Cohort Risk Equations**
- **How good are these equations?**

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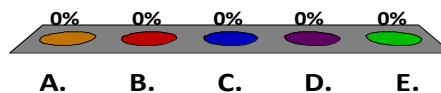
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Audience Response System

What percentage of the population is at or above 5% 10-year risk of ASCVD: Men 50-54 years old?

- A. 5%
- B. 20%
- C. 50%
- D. 80%
- E. 100%



41

Distribution of ASCVD Risk Population Without ASCVD or DM Aged 40-79

% of Gender/Age Group by ASCVD Risk Threshold							
	ASCVD Risk:	<5%	≥5%	≥7.5%	≥10%	≥15%	≥20%
Men:	40-44	89.22%	10.78%	4.19%	2.31%	1.47%	0.72%
	45-49	72.28%	27.72%	13.56%	7.49%	2.67%	0.72%
	50-54	45.53%	54.47%	30.46%	14.36%	5.20%	0.73%
	55-59	12.26%	87.74%	45.33%	28.59%	8.54%	1.42%
	60-64	0.94%	99.06%	81.29%	61.46%	22.43%	6.84%
	65-69	1.33%	98.67%	94.22%	81.10%	52.29%	13.98%
	70-74	0.00%	100.00%	100.00%	99.73%	84.61%	64.53%
	75-79	0.00%	100.00%	100.00%	100.00%	98.86%	96.49%
Women:	40-44	97.21%	2.79%	1.03%	0.38%	0.13%	0.00%
	45-49	94.57%	5.43%	1.57%	0.42%	0.12%	0.00%
	50-54	92.58%	7.42%	1.80%	1.03%	0.00%	0.00%
	55-59	84.97%	15.03%	2.90%	1.71%	0.32%	0.17%
	60-64	57.38%	42.62%	18.47%	7.72%	3.23%	0.12%
	65-69	13.69%	86.31%	49.32%	27.16%	5.52%	1.33%
	70-74	0.00%	100.00%	96.57%	86.72%	51.04%	20.49%
	75-79	0.00%	100.00%	100.00%	99.67%	94.72%	72.57%

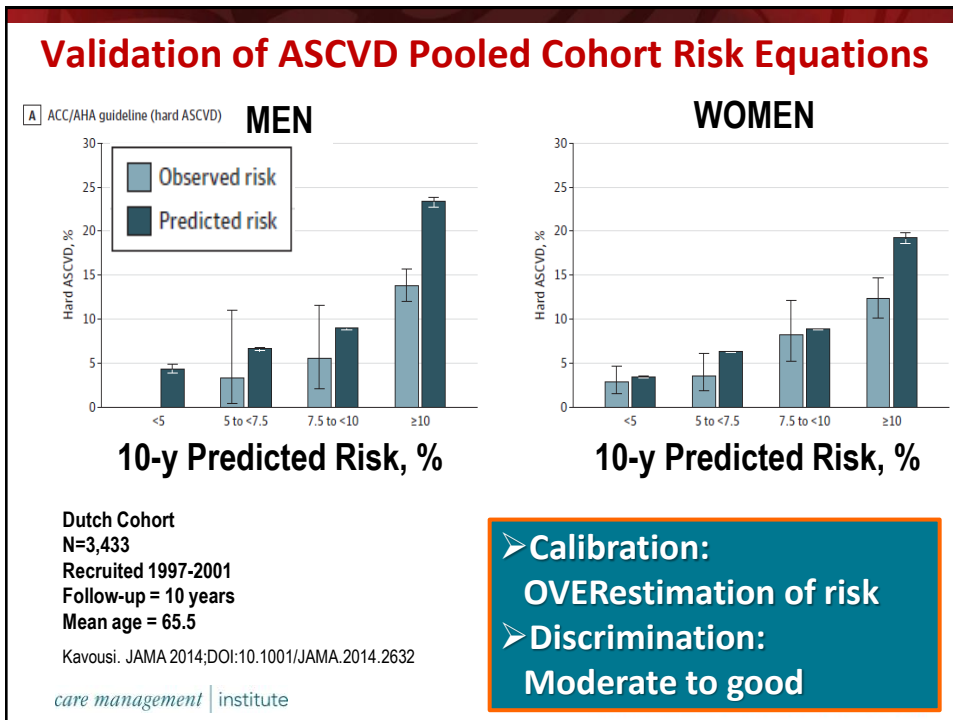
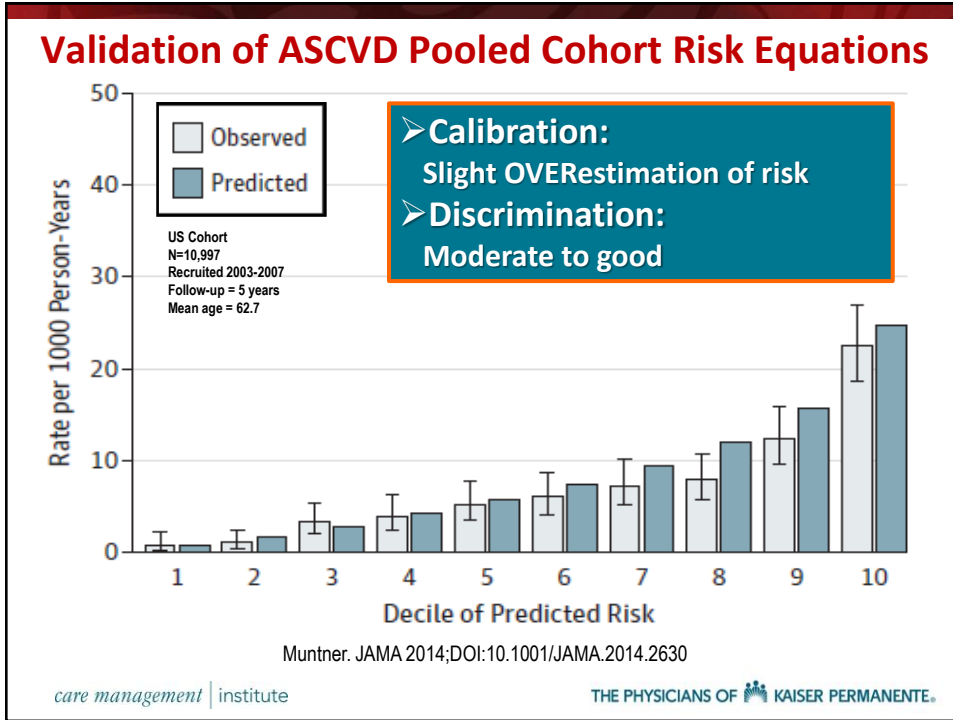
Framingham CAD Risk vs. ASCVD Risk Population Without ASCVD or DM Aged 40-75

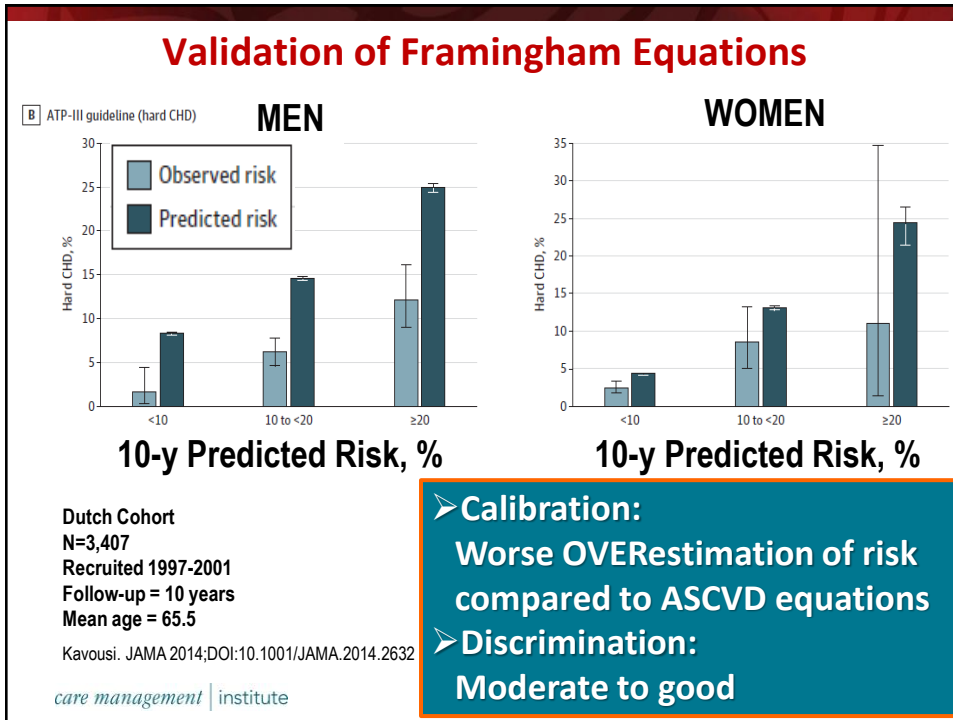
At ≥20% 10-Year Risk				
	CAD	ASCVD	Abs%Δ	Rel%Δ
Men	11.89%	12.30%	+0.4%	+3.5%
Women	5.86%	8.12%	+2.3%	+38.6%
Total	8.76%	10.13%	+1.4%	+15.6%

At ≥10% 10-Year Risk				
	CAD	ASCVD	Abs%Δ	Rel%Δ
Men	25.44%	22.00%	-3.4%	-13.5%
Women	7.30%	12.83%	+5.6%	+75.8%
Total	16.04%	17.25%	+1.2%	+7.5%

Based on Analysis of NHANES 2007-2010 Data
Relative changes ≥10% are highlighted in color

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KPNW Implementation Strategy

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Impact of Guideline Changes in KP

- **Drug Therapy** **Major**
Increased emphasis on statin therapy
 - Removal of LDL-C thresholds and targets for therapy
 - Statins and their intensity based on ASCVD risk
 - Target is adherence to recommended statin intensity
- **Criteria for people with ASCVD Therapy** **None**
- **Criteria for people with DM** **Minimal**
Statin recommended if baseline LDL-C ≥ 70 mg/dL
- **Criteria for people without ASCVD or DM** **Major**
 - Increased emphasis on LDL-C ≥ 190 mg/dL
 - Increased emphasis on ASCVD risk $\geq 15\%$
 - New 10-year ASCVD Risk Equations
 - Expanded population eligible for statin therapy: $\geq 7.5\%$ 10-year risk
 - No “firm” recommendation for statins in people < 40 years old
 - Except if ASCVD or LDL-C ≥ 190 mg/dL

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50

KPNW Implementation Plans

- **High-Priority Quality Metrics (New elements in red)**
 - Statins in people with ASCVD, age 18-80
 - Statins in people with DM and **LDL-C 70-189 mg/dL**, age 40-80
 - **Statins in people without ASCVD or DM, with LDL-C 70-189 mg/dL and 10-year ASCVD risk $\geq 20\%$, age 40-80**
 - **Statins in people with LDL-C ≥ 190 mg/dL, age 21-80**
- **Annual LDL-C Monitoring**
 - PST Care Gaps to remain in place until medication adherence metrics are fully operational
- **HEDIS Metrics**
 - LDL-C screening and control metrics for ASCVD and DM retired, beginning in 2015 measurement period (based on 2014 data)

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KPNW Implementation Plans

PST Statin Care Gaps

Registry	Age	ASCVD Risk	LDL Range	Statin Intensity	Recommendation Strength
NA	21-75	NA	≥190	High	Strong: "Start"
NA	76-80	NA	≥190	Moderate	Weak: "Consider"
ASCVD	≤75	NA	NA	High	Strong: "Start"
ASCVD	76-80	NA	NA	Moderate	Weak: "Consider"
DM / None	40-75	≥15%	70-189	High	Strong: "Start"
DM	40-75	<15%	70-189	Moderate	Strong: "Start"
DM	76-80	NA	70-189	Moderate	Weak: "Consider"
DM	<40	NA (+1 RF*)	70-189	Moderate	Very Weak: "Discuss"
None	40-75	7.5-14.9%	70-189	Moderate	Weak: "Consider"
None	76-80	≥7.5%	70-189	Moderate	Very Weak: "Discuss"
NA	NA	NA	<40	Reduce Intensity	Weak: "Consider"
NA	NA	NA	≥70	Increase Intensity, if <Recommended Intensity	Weak: "Consider"

New Elements Highlighted in Yellow
*RF = Current smoker, HTN, or LDL ≥160

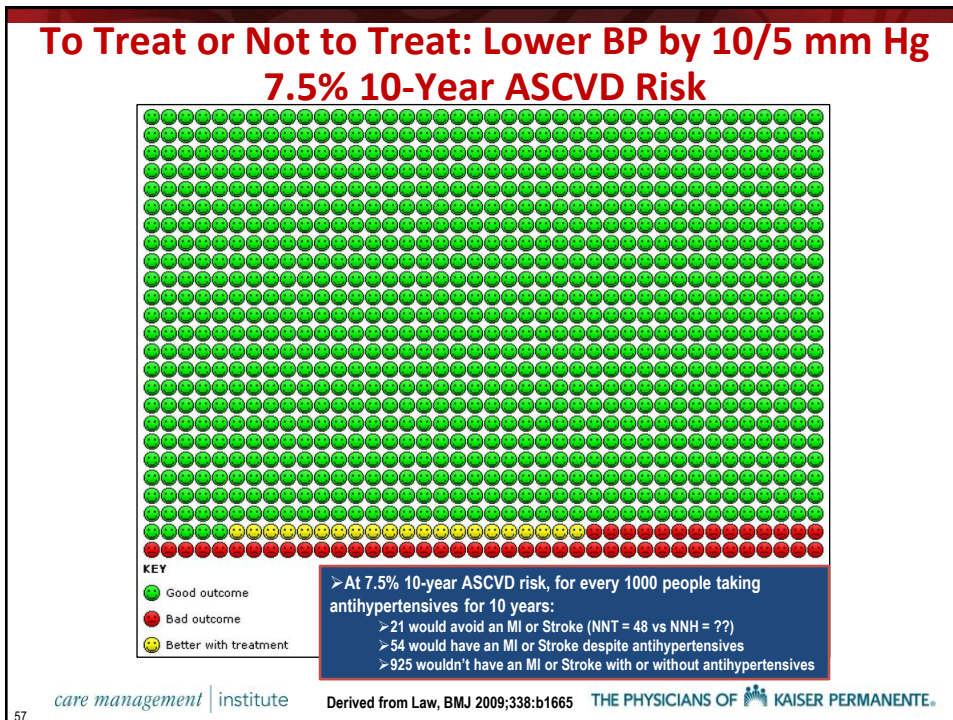
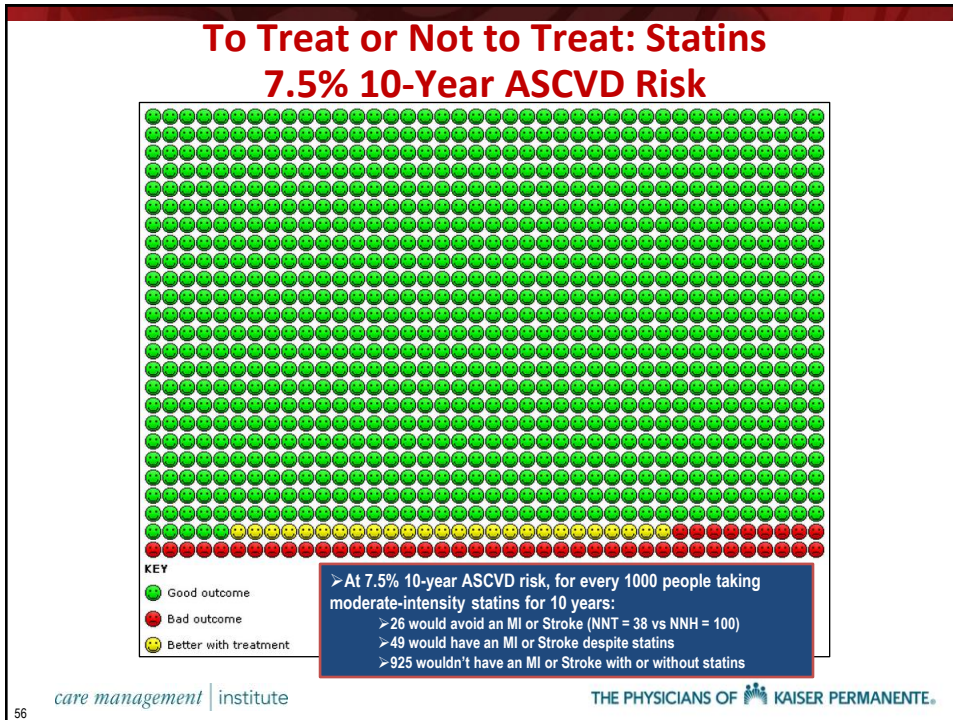
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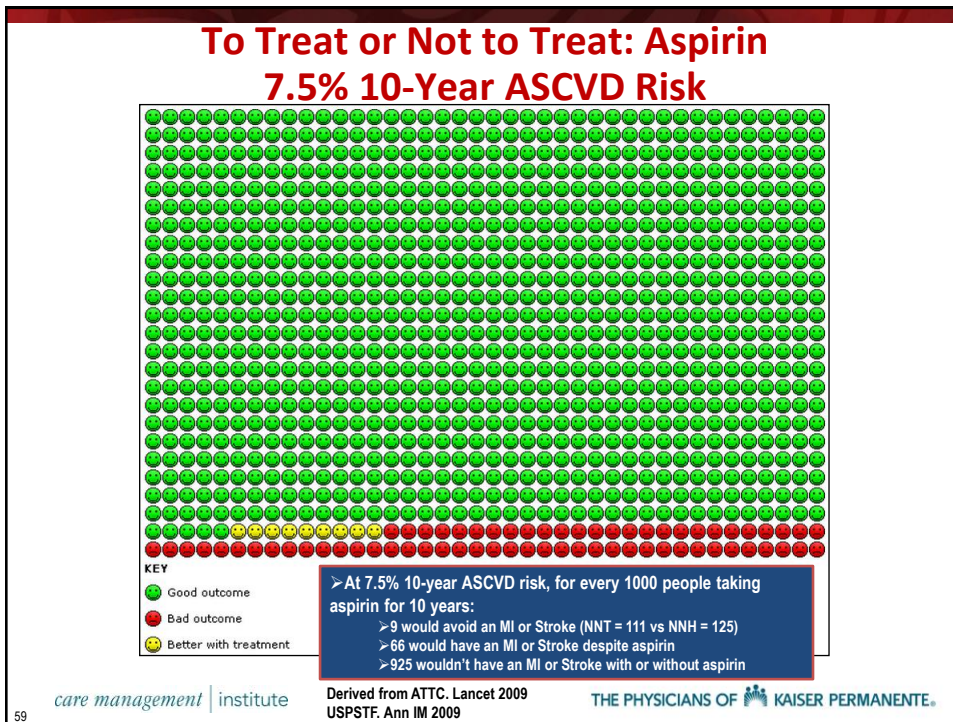
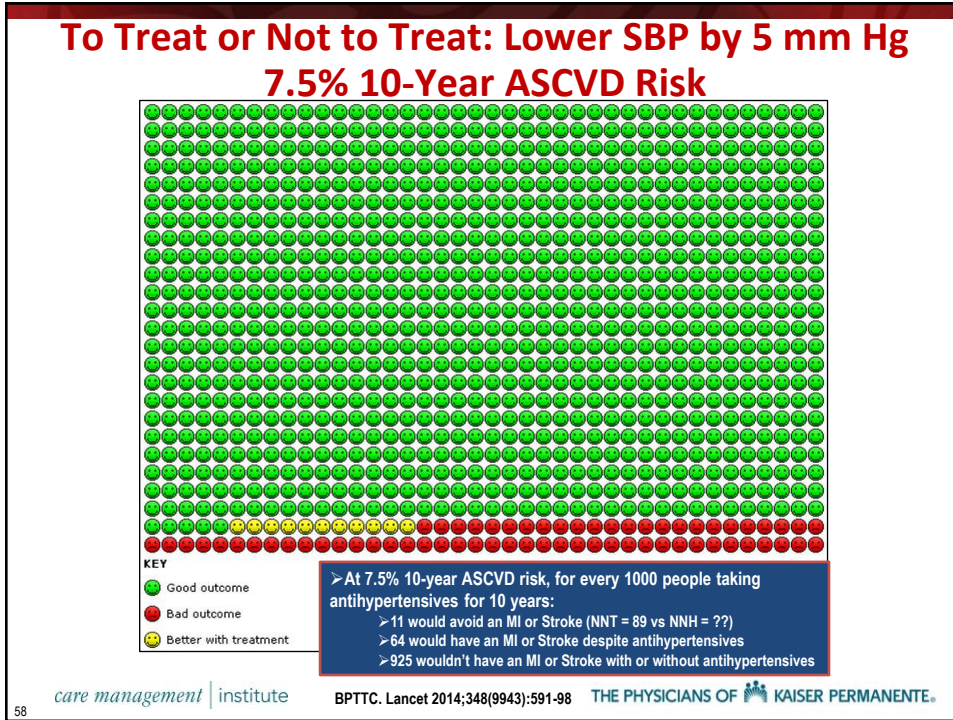
Case Scenario

- 53 year old white man
 - Total cholesterol 200, HDL-C 40, LDL-C 130
 - SBP 150, on no antihypertensives
 - No DM
 - Non-smoker
- What is his 10-year risk for ASCVD?
- To reduce ASCVD risk, you would recommend:
 - No treatment
 - Antihypertensives
 - Aspirin
 - Statin
 - If so, what intensity?

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Case Scenario

- 72 year old white woman
 - Total cholesterol 180, HDL-C 60, LDL-C 100
 - SBP 150, on no antihypertensives
 - No DM
 - Non-smoker
- What is her 10-year risk for ASCVD?
- To reduce ASCVD risk, you would recommend:
 - No treatment
 - Antihypertensives
 - Aspirin
 - Statin
 - If so, what intensity?

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To Treat or Not to Treat: Statins

15% 10-Year ASCVD Risk

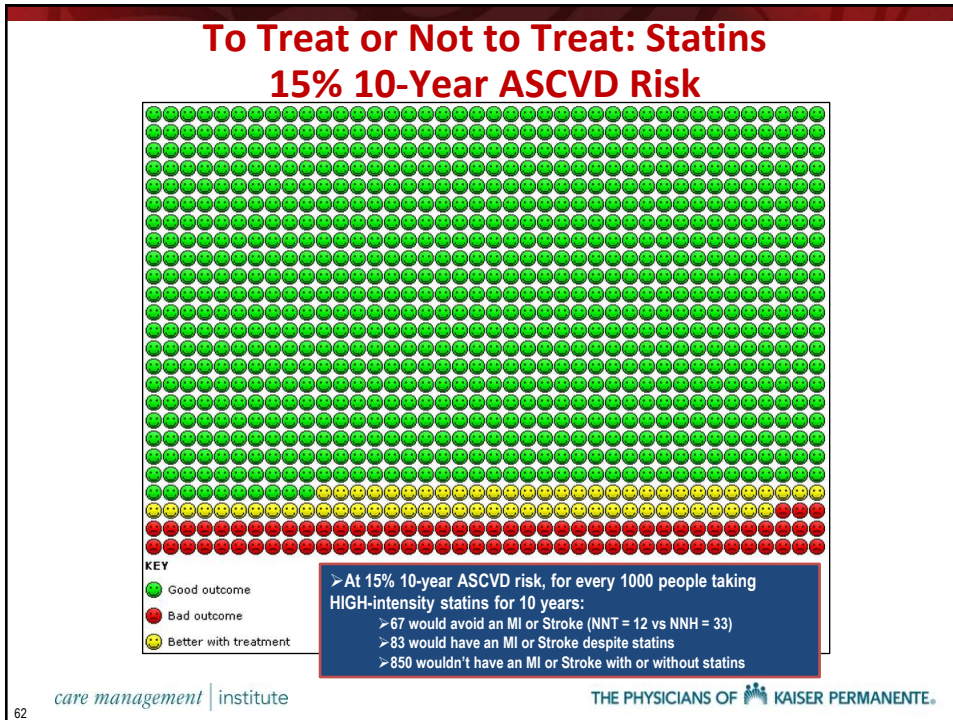
KEY

- Good outcome
- Bad outcome
- Better with treatment

➤ At 15% 10-year ASCVD risk, for every 1000 people taking moderate-intensity statins for 10 years:

- 52 would avoid an MI or Stroke (NNT = 19 vs NNH = 100)
- 98 would have an MI or Stroke despite statins
- 850 wouldn't have an MI or Stroke with or without statins

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Case Scenario

- 56 year old black woman
 - Total cholesterol 200, HDL-C 60, LDL-C 100
 - SBP 140, **on** antihypertensives
 - HbA1c 6.5%
 - Non-smoker
- What is her 10-year risk for ASCVD?
- To reduce ASCVD risk, you would recommend:
 - No treatment
 - Intensify Antihypertensives
 - Aspirin
 - Statin
 - Metformin

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Case Scenario

- 41 year old black man
 - Total cholesterol 170, HDL-C 40, LDL-C 100
 - SBP 120, on no antihypertensives
 - No DM
 - Smoker
- What is his 10-year risk for ASCVD?
- To reduce ASCVD risk, you would recommend:
 - No treatment
 - Antihypertensives
 - Aspirin
 - Statin
 - Smoking Cessation

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To Treat or Not to Treat: Statins

5% 10-Year ASCVD Risk

KEY

- Good outcome
- Bad outcome
- Better with treatment

➢ At 5% 10-year ASCVD risk, for every 1000 people taking moderate-intensity statins for 10 years:

- 17 would avoid an MI or Stroke (NNT = 57 vs NNH = 100)
- 33 would have an MI or Stroke despite statins
- 950 wouldn't have an MI or Stroke with or without statins

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ASCVD Risk and Statin Therapy What Do You Need to Do?

- **Start high-intensity statins in people with clinical ASCVD**
 - Age 18-75 (Consider moderate-intensity at age 76-80)
- **Start high-intensity statins in people with LDL-C ≥ 190**
 - Age 21-75 (Consider moderate-intensity at age 76-80)
- **Start moderate-intensity statins in people with DM**
 - Age 40-75 and LDL-C 70-189 (Consider at age 76-80)

Review ASCVD Risk

- Use PST, web posting or download the app
- **Start high-intensity statins at ASCVD Risk $\geq 15\%$**
 - Including those with DM
 - Age 40-75 and LDL-C 70-189 (Consider moderate-intensity at age 76-80)
- **Consider moderate-intensity statins at ASCVD Risk 7.5-14.9%**
 - Age 40-75 and LDL-C 70-189

Check ALT before initiating statins

68

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Q & A

The New Cholesterol Guidelines

Should I Be on a Statin?

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