Lipid Management – What's New

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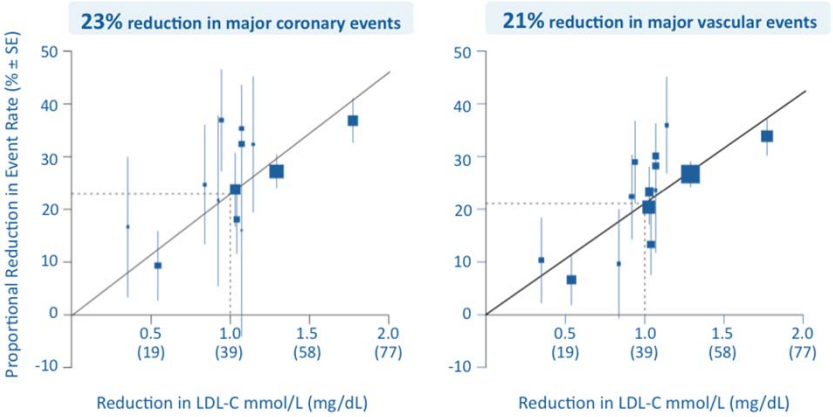
Outline

1. LDL-C as primary target – statin therapies and management of statin intolerance
2. Treating the residual risk – the role of fibrates
3. Emerging HDL targeted therapies

LDL cholesterol as prime target for CV risk reduction

A prospective meta-analysis of data from 90,056 individuals from 14 statin trials: *A 1-mmol/L (39 mg/dL) reduction in LDL-C was associated with a…*



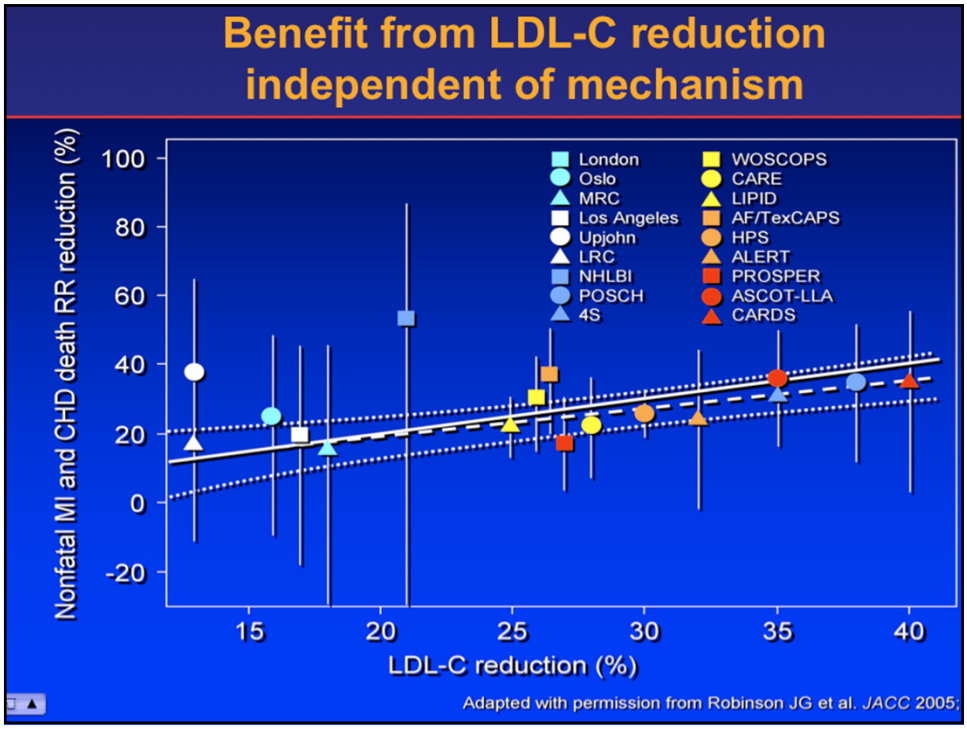
Adapted from Baigent C et al, for the Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet* 2005;366:1267–78.

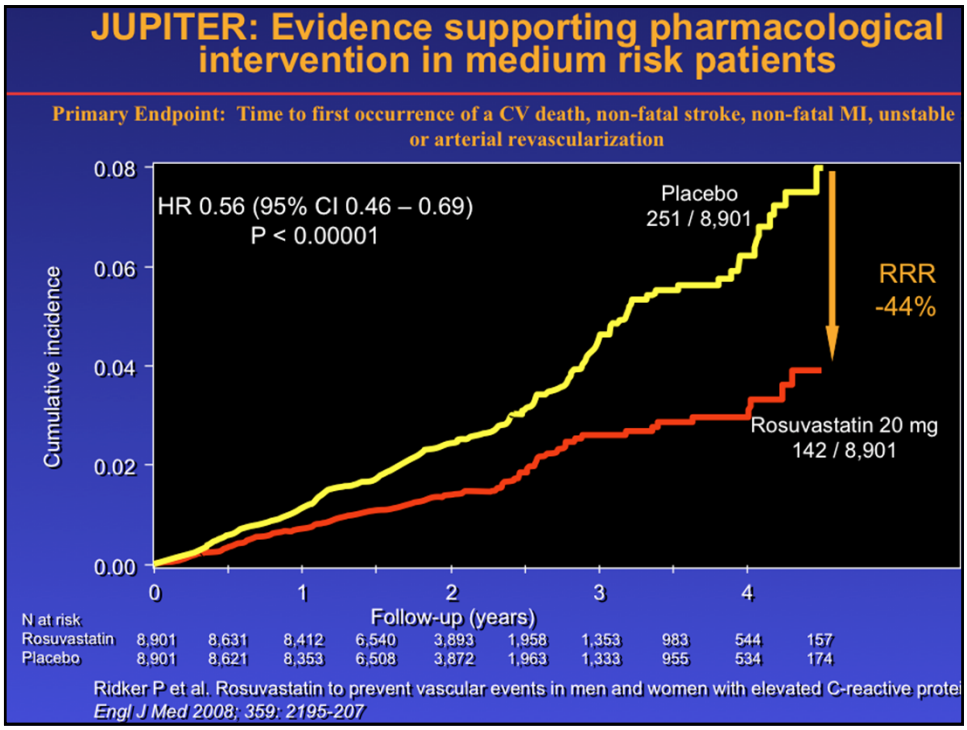
2009 Guideline Lipid Targets

Risk Assessment	Initiate/Consider Treatment If Any of the Following	Primary Target: LDL-C	Class, Level
HIGH *CAD* *PAD* *Atherosclerosis* *Most diabetic pts* *FRS ≥ 20%* *RRS ≥ 20%*	*Consider treatment in all patients*	LDL-C < 2 mmol/L *or* ≥ 50% ↓LDL-C	Class I, Level A
MODERATE *FRS 10%–19%*	• LDL-C > 3.5 mmol/L • TC/HDL-C > 5.0 • hsCRP > 2 mg/L* - in men > 50, women > 60 • Family history and/or hsCRP modulates risk (RRS) *Strive towards →*	*Primary Alternate Target:* Apo B < 0.80 g/L	Class IIa, Level A
LOW *FRS < 10%*	• LDL-C > 5.0 mmol/L	≥ 50% ↓ LDL-C	Class IIa, Level A

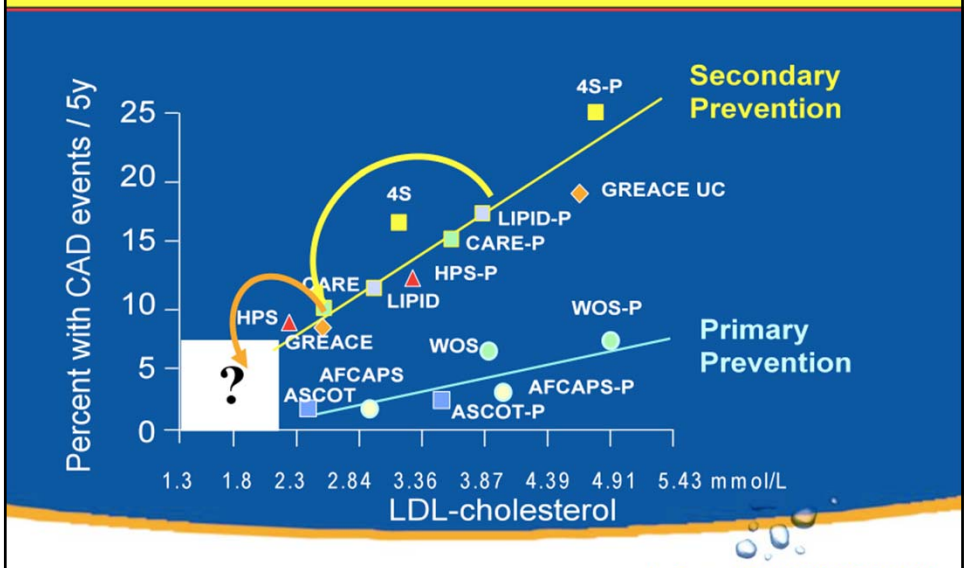
* Only screen for hsCRP in men > 50 years and women > 60 years if they are at moderate risk for CVD AND have LDL-C < 3.5 mmol/L

Genest J et al. *Can J Cardiol* 2009;25(10):567–79.


Benefit from LDL-C reduction independent of mechanism
Nonfatal MI and CHD death RR reduction (%)
100
80
60
40
20
0
-20
15
20
25
30
35
40
LDL-C reduction (%)
London
Oslo
MRC
Los Angeles
Upjohn
LRC
NHLBI
POSCH
4S
WOSCOPS
CARE
LIPID
AF/TexCAPS
HPS
ALERT
PROSPER
ASCOT-LLA
CARDS
Adapted with permission from Robinson JG et al. JACC 2005.

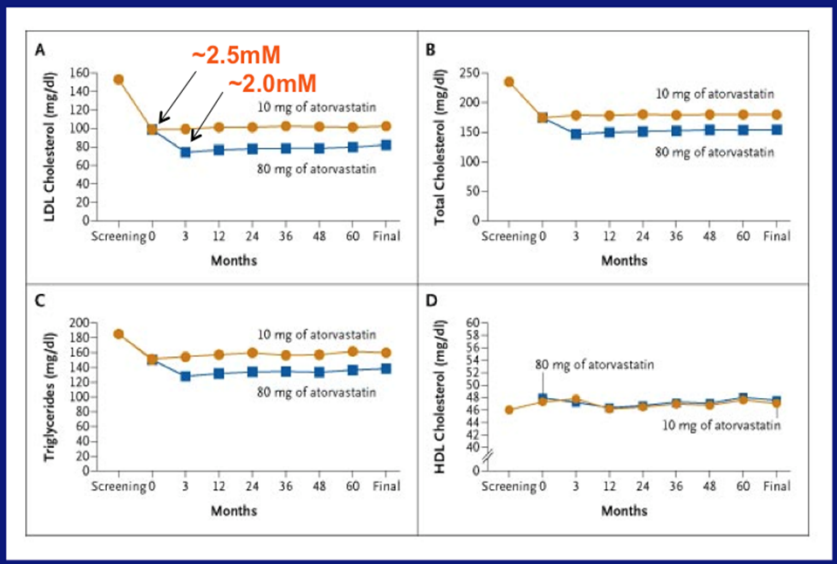

JUPITER: Evidence supporting pharmacological intervention in medium risk patients
Primary Endpoint: Time to first occurrence of a CV death, non-fatal stroke, non-fatal MI, unstable or arterial revascularization
HR 0.56 (95% CI 0.46 – 0.69)
P < 0.00001
Placebo
251 / 8,901
RRR
-44%
Rosuvastatin 20 mg
142 / 8,901
Cumulative incidence
0.08
0.06
0.04
0.02
0.00
0
1
2
3
4
Follow-up (years)
N at risk
Rosuvastatin 8,901 8,631 8,412 6,540 3,893 1,958 1,353 983 544 157
Placebo 8,901 8,621 8,353 6,508 3,872 1,963 1,333 955 534 174
Ridker P et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protei
Engl J Med 2008; 359: 2195-207

The Treating to New Targets (TNT) Study: Rationale

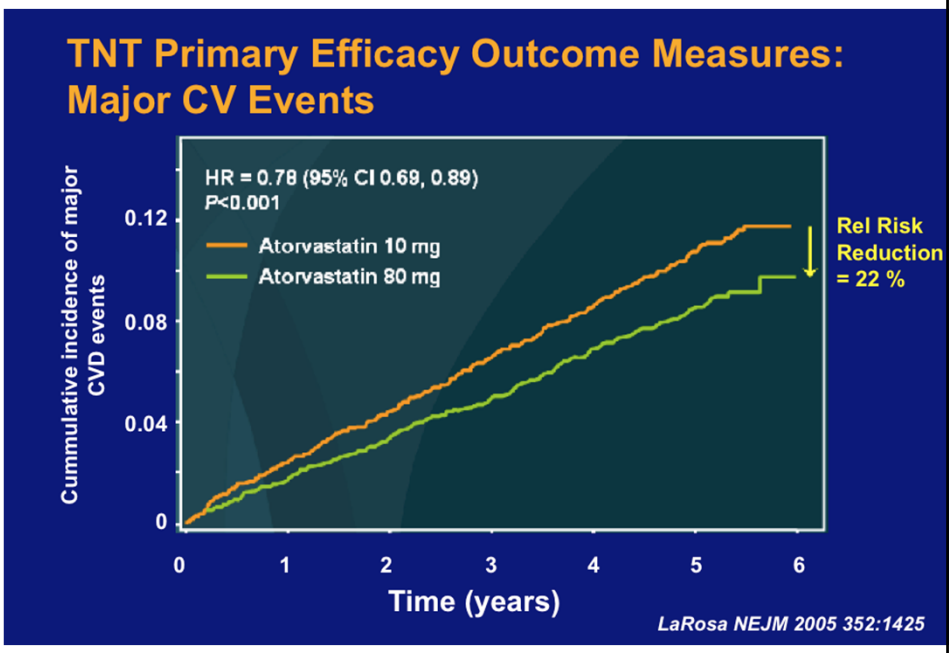


LaRosa NEJM 2005 352:1425

TNT Lipid changes



LaRosa NEJM 2005 352:1425



	All Patients		
	HR*	95% CI	p Value
Lipid biomarker			
LDL-C	2.09	1.48–2.95	<0.0001
HDL-C	0.35	0.26–0.47	<0.0001
Triglycerides	1.27	1.10–1.46	0.0012

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Biomarkers

Prediction of Cardiovascular Events in Statin-Treated Stable Coronary Patients by Lipid and Nonlipid Biomarkers

Table 4 Relationships of MCVEs to Biomarker Levels Measured at Time of Randomization

	All Patients			Atorvastatin 10 mg			Atorvastatin 80 mg		
	HR*	95% CI	p Value	HR*	95% CI	p Value	HR*	95% CI	p Value
Lipid biomarker									
LDL-C	2.09	1.48–2.95	<0.0001	2.27	1.42–3.64	0.0006	1.90	1.14–3.15	0.0134
HDL-C	0.35	0.26–0.47	<0.0001	0.36	0.23–0.55	<0.0001	0.33	0.23–0.51	<0.0001
Triglycerides	1.27	1.10–1.46	0.0012	1.31	1.08–1.59	0.0068	1.21	0.99–1.50	0.0691

Table 4 Relationships of MCVEs to Biomarker Levels Measured at Time of Randomization

	All Patients			Atorvastatin 10 mg			Atorvastatin 80 mg		
	HR*	95% CI	p Value	HR*	95% CI	p Value	HR*	95% CI	p Value
Nonlipid biomarker									
Adiponectin	0.96	0.87–1.05	0.3280	1.04	0.89–1.22	0.5940	0.91	0.82–1.01	0.0690
HMW adiponectin	0.98	0.91–1.07	0.6960	1.02	0.91–1.14	0.7450	0.94	0.84–1.06	0.3400
HMW/total adiponectin	1.01	0.91–1.13	0.8250	1.00	0.86–1.17	0.9950	1.03	0.88–1.19	0.7400
CRP	1.04	0.99–1.09	0.1090	1.07	1.01–1.14	0.0243	0.99	0.92–1.07	0.8170
Cystatin C	1.03	0.92–1.16	0.6200	1.06	0.91–1.24	0.4610	0.99	0.83–1.17	0.8700
Insulin	1.06	0.95–1.17	0.3200	1.12	0.97–1.29	0.1110	0.96	0.82–1.14	0.6540
Lp-PLA2	0.99	0.80–1.23	0.9450†	1.21	0.91–1.61	0.2000	0.77	0.56–1.06	0.1070
Lp(a)	0.99	0.94–1.05	0.8070	0.97	0.90–1.04	0.3830	1.02	0.95–1.11	0.5700
MCP-1	1.02	0.91–1.14	0.7950†	0.90	0.77–1.06	0.2110	1.15	0.98–1.35	0.0900
MMP-9	0.99	0.91–1.08	0.8110	0.97	0.85–1.12	0.6790	1.00	0.89–1.14	0.9540
MPO	1.01	0.96–1.06	0.7930	0.99	0.93–1.06	0.8540	1.02	0.95–1.09	0.5920
Neopterin	1.00	0.85–1.17	0.9590	1.10	0.89–1.36	0.3890	0.89	0.71–1.12	0.3200
NT-proBNP	1.10	0.95–1.28	0.1850	1.07	0.87–1.31	0.5360	1.15	0.93–1.42	0.2060
Osteopontin	0.90	0.84–0.97	0.0030	0.88	0.80–0.97	0.0101	0.92	0.83–1.03	0.1420
RAGE	1.06	0.92–1.22	0.4270†	1.22	1.01–1.46	0.0362	0.88	0.72–1.09	0.2450
sCD40L	0.98	0.93–1.02	0.3150	1.00	0.93–1.06	0.9040	0.95	0.89–1.02	0.1760
sICAM-1	0.99	0.87–1.12	0.8360	1.03	0.86–1.23	0.7640	0.95	0.79–1.13	0.5460
sVCAM-1	1.03	0.86–1.22	0.7570†	1.31	0.99–1.72	0.0590	0.88	0.73–1.07	0.1930

How important is it to monitor on-treatment

(A) Lipids ?

YES → Predicts residual risk due to dyslipidemia

(B) Non lipid markers ? eg hsCRP

NO, according to the most recent post-hoc analysis on the TNT trial

Contradicts the findings from the post-hoc analysis on the PROVE-IT trial

Optional Secondary Targets for High-Risk Patients Only After LDL-C at Target

Test	Target	Intervention
TC/HDL-C	<4.0	Niacin Fibrate
Non HDL-C	<3.5 mmol/L	Niacin Fibrate
Apo B/A1	<0.8	Niacin Ezetimibe
Triglycerides	<1.7 mmol/L	Fibrate Niacin
hsCRP	<2.0 mg/L	Statin Ezetimibe

Clinical advantages of secondary targets, with respect to patient outcomes, remain to be proven

Genest et al. *Can J Cardiol* 2009;25:567-79

Many Canadian high risk patients are not achieving LDL-C goals on statin monotherapy

Study	n	LDL-C goal (mmol/l)	% Achieved
VP and GOALL registries[1]	8056	< 2.6	51
Farahani[2]	1103	< 2.5	62
Calipso 2[3]	1795	< 2.0	30
GUIDE[4]	2256	< 2.0	41

(1) Yan A, *et al*; Vascular Protection (VP) and Guidelines Oriented Approach to Lioid Lowering (GOALL) Registries Investigators. *Am J Med* 2006; 119: 676-683.

(2) Farahani P, et al: Goal attainment for multiple cardiovascular risk factors in community-based clinical practice (a Canadian experience). *J Eval Clin Pract 2009; 15(1):212-6.*

(3) Sénécal M, Fodor G, Gagné C et al. Limitations of statin monotherapy for the treatment of dyslipidemia: a projection based on the Canadian lipid study- Observational. *Curr Med Res Opin 2009;25 (1): 47-55*

(4) Teoh H et al; Usefulness of statin-ezetimibe combination to reduce the care gap in dyslipidemia management in patients with a high risk of atherosclerotic disease. *Am J Cardiol. 2009 Sep 15;104(6):798-804*

Statin treatment in other populations

- End-Stage Heart Failure (LVEF < 30%)
  - GISSI-HF
  - CORONA
- End-Stage Renal Disease- (Hemodialysis patients)
  - 4-D
  - AURORA

Statin therapy did not reduce mortality or morbidity

Clinical judgment must be applied. Patients on dialysis awaiting renal transplantation may still benefit from statin therapy.

(1) Kjekshus J et al; Rosuvastatin in older patients with systolic heart failure. *N Engl J Med 2007; 357: 2248-61.*

(2) Tavazzi L et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI_HF trial): A randomized, double-blind, placebo-controlles trial. *Lancet 2008; 372: 1231-9.*

(3) Wanner C et al. German Diabetes and Dialysis Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med 2005; 353: 238-48.*

(4) Felström BC et al. AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med 2009; 360: 1395-407.*

Case: Presentation

- Katherine, 59-year-old female
- Presents for a routine physical
- Past medical history (risk factors)
  - Sedentary lifestyle
  - Obese
  - Smoker, occasional drinker (<5 alcoholic drinks/wk)
  - No regular medications
- Family history
  - Type 2 diabetes (mother)
  - CHD (father, MI at age 62 y)

Case: Assessment

- Physical exam
  - BMI 30, waist circumference 98 cm
  - BP 128/84 mm Hg
- Lab tests:
  - TC 6.30, LDL-C 4.19, HDL-C 0.85, TG 2.8 mmol/L, TC/HDL-C 7.4
  - FPG: 6.2 mmol/L
  - Urinalysis: normal
  - ECG: normal

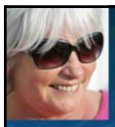
Question #2

What is Katherine's cardiovascular risk?

Framingham Assessment of Katherine's CHD Risk

Points	Age	HDL-C (mmol/L)	TC	SBP not treated	SBP treated	Smoker	Diabetic	
-3				<120				
-2		>1.6						
-1		1.3-1.6			<120			
0	30-34	1.2-1.3	<4.1	120-129		No	No	
1		0.9-1.2	4.1-5.2	130-139				
2	35-39	<0.9		140-149	120-129			
3			5.2-6.2		130-139	Yes		
4	40-44		6.2-7.2	150-159			Yes	
5	45-49		>7.2	>160	140-149			
6					150-159			
7	50-54				160+			
8	55-59							
9	60-64							
10	65-69							
11	70-74							Total points
12	75+							
Points allotted	8	2	4	0	--	3	0	**17**

Genest et al. *Can J Cardiol* 2009;25:567-79



Framingham Assessment of Katherine's CHD Risk

Points	Risk, %	Points	Risk, %	Points	Risk, %
-2 or less	<1	6	3.3	14	11.7
-1	1.0	7	3.9	15	13.7
0	1.2	8	4.5	16	15.9
1	1.5	9	5.3	17	18.51
2	1.7	10	6.3	18	21.5
3	2.0	11	7.3	19	24.8
4	2.4	12	8.6	20	27.5
5	2.8	13	10.0	21+	>30

Katherine's 10-year CHD risk = 18.5%

Genest et al. *Can J Cardiol* 2009;25:567-79

2009 CCS Guidelines

Katherine is classified at "moderate risk"

Risk assessment	Initiate treatment if:	Primary targets	
		LDL-C	Alternate
High CAD, PVD Atherosclerosis Most patients with diabetes FRS ≥20% RRS ≥20%	▪ Consider treatment in all patients	<2 mmol/L or ≥50% decrease in LDL-C	apoB <0.80 g/L
Moderate **FRS 10-19%**	▪ **LDL-C >3.5 mmol/L** ▪ **TC/HDL-C >5.0** ▪ **hs-CRP >2 mg/L*** ▪ **Family history and hs-CRP modulates risk (RRS)**	**<2 mmol/L or ≥50% decrease in LDL-C**	**apoB <0.80 g/L**
Low FRS <10%	▪ LDL-C ≥5.0 mmol/L	≥50% decrease in LDL-C	

*Only screen for hsCRP in men >50 y and women >60 y if they are at moderate CVD risk and have LDL-C <3.5 mmol/L

Genest et al. *Can J Cardiol* 2009;25:567-79

Modifiers of Risk

- Framingham score can be adjusted for:
  - Family history (<60 years old)
  - Metabolic syndrome

Genest et al. *Can J Cardiol* 2009;25:567-79

Question #3

Does Katherine have metabolic syndrome?

Katherine and Metabolic Syndrome

Factor	IDF criteria*	Katherine
Central obesity	Males ≥94 cm Females ≥80 cm	**98 cm**
TG level	>1.7 mmol/L	**2.8 mmol/L**
HDL-C	Males: <1.03 mmol/L Females: <1.3 mmol/L	**0.85 mmol/L**
BP	>130/85 mm Hg (or treatment for hypertension)	**128/84 mm Hg**
FPG	>5.6 mmol/L	**6.2 mmol/L**

*IDF defines metabolic syndrome as the presence of central obesity PLUS any two additional factors listed above

Genest et al. *Can J Cardiol* 2009;25:567-79; Alberti et al. *Lancet* 2005;366:1059-62

2009 CCS Guidelines

Katherine is now classified as "high risk"

Risk assessment	Initiate treatment if:	Primary targets	
		LDL-C	Alternate
High **CAD, PVD** **Atherosclerosis** **Most patients with diabetes** **FRS ≥20%; RRS ≥20%**	▪ **Consider treatment in all patients**	**<2 mmol/L or ≥50% decrease in LDL-C**	**apoB <0.80 g/L**
Moderate FRS 10-19%	▪ LDL-C >3.5 mmol/L ▪ TC/HDL-C >5.0 ▪ hs-CRP >2 mg/L* ▪ Family history and hs-CRP modulates risk (RRS)	<2 mmol/L or ≥50% decrease in LDL-C	apoB <0.80 g/L
Low FRS <10%	▪ LDL-C ≥5.0 mmol/L	≥50% decrease in LDL-C	

*Only screen for hsCRP in men >50 years and women >60 years if they are at moderate risk for CVD and have LDL-C <3.5 mmol/L

Genest et al. *Can J Cardiol* 2009;25:567-79

Question #4

What should Katherine be treated with?

Katherine Gets a Statin

- Baseline
  - TC 6.30
  - LDL-C 4.19
  - HDL-C 0.85
  - TG 2.8 mmol/L
  - TC/HDL-C 7.4

Statin therapy

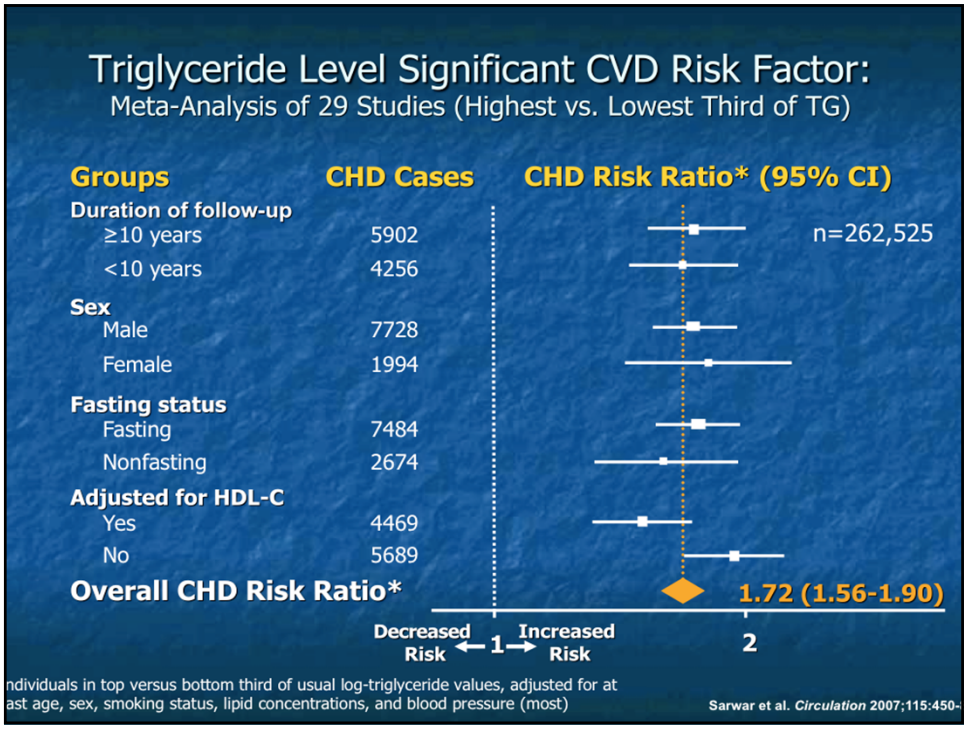
- Scenario 1
  - TC 4.0
  - LDL-C 2.0
  - HDL-C 1.3
  - TG 1.7 mmol/L
  - TC/HDL-C 3.0
- Scenario 2
  - TC 4.0
  - LDL-C 2.0
  - HDL-C 0.9
  - TG 2.4 mmol/L
  - TC/HDL-C 4.4

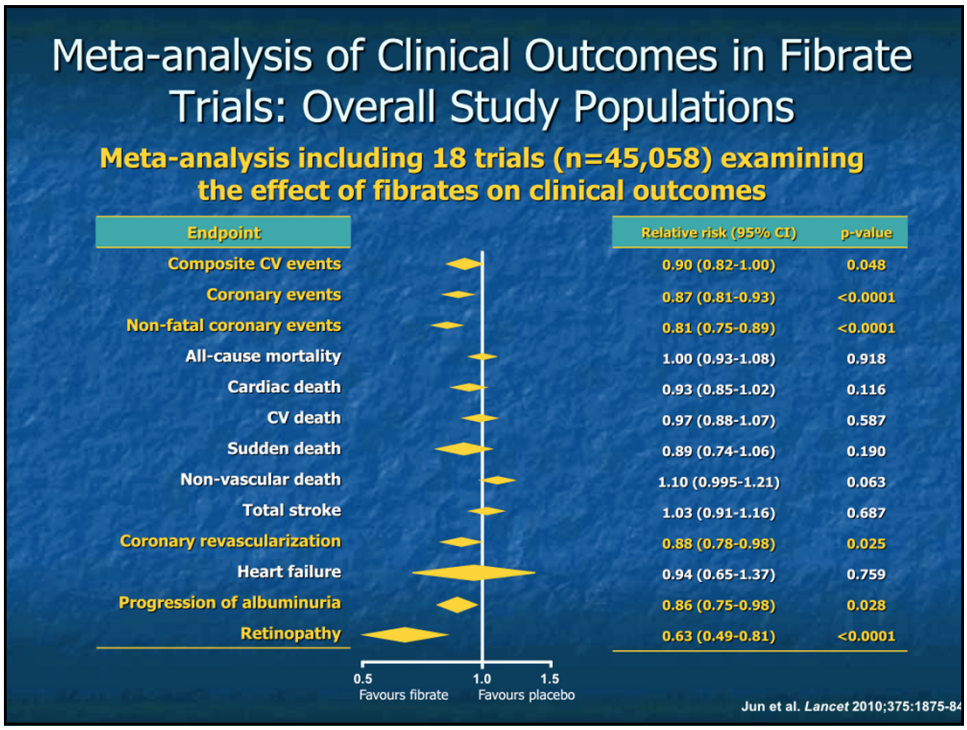
Optional Secondary Targets for High-Risk Patients Only After LDL-C at Target

Test	Target	Intervention
TC/HDL-C	<4.0	Niacin Fibrate
Non HDL-C	<3.5 mmol/L	Niacin Fibrate
Apo B/A1	<0.8	Niacin Ezetimibe
Triglycerides	<1.7 mmol/L	Fibrate Niacin
hsCRP	<2.0 mg/L	Statin Ezetimibe

Clinical advantages of secondary targets, with respect to patient outcomes, remain to be proven

Genest et al. *Can J Cardiol* 2009;25:567-79


Triglyceride Level Significant CVD Risk Factor:
Meta-Analysis of 29 Studies (Highest vs. Lowest Third of TG)
Groups
CHD Cases
CHD Risk Ratio* (95% CI)
Duration of follow-up
≥10 years 5902
<10 years 4256
Sex
Male 7728
Female 1994
Fasting status
Fasting 7484
Nonfasting 2674
Adjusted for HDL-C
Yes 4469
No 5689
Overall CHD Risk Ratio*
n=262,525
1.72 (1.56-1.90)
Decreased Risk
1
Increased Risk
2
ndividuals in top versus bottom third of usual log-triglyceride values, adjusted for at
ast age, sex, smoking status, lipid concentrations, and blood pressure (most)
Sarwar et al. Circulation 2007;115:450-


Meta-analysis of Clinical Outcomes in Fibrate Trials: Overall Study Populations
Meta-analysis including 18 trials (n=45,058) examining the effect of fibrates on clinical outcomes
Endpoint
Relative risk (95% CI)
p-value
Composite CV events 0.90 (0.82-1.00) 0.048
Coronary events 0.87 (0.81-0.93) <0.0001
Non-fatal coronary events 0.81 (0.75-0.89) <0.0001
All-cause mortality 1.00 (0.93-1.08) 0.918
Cardiac death 0.93 (0.85-1.02) 0.116
CV death 0.97 (0.88-1.07) 0.587
Sudden death 0.89 (0.74-1.06) 0.190
Non-vascular death 1.10 (0.995-1.21) 0.063
Total stroke 1.03 (0.91-1.16) 0.687
Coronary revascularization 0.88 (0.78-0.98) 0.025
Heart failure 0.94 (0.65-1.37) 0.759
Progression of albuminuria 0.86 (0.75-0.98) 0.028
Retinopathy 0.63 (0.49-0.81) <0.0001
0.5
1.0
1.5
Favours fibrate
Favours placebo
Jun et al. Lancet 2010;375:1875-84

Clinical Outcomes in Fibrate Trials:
High Risk, Diabetes, or Metabolic Syndrome Subgroups

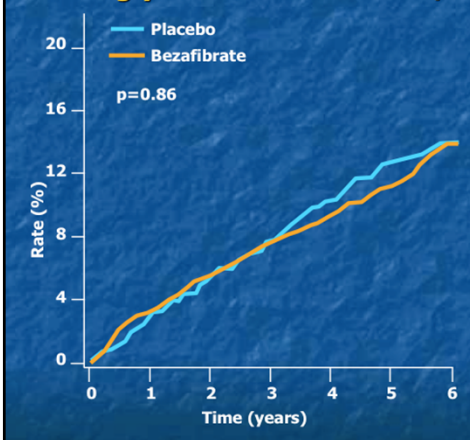
Trial	Patient profile (lipid values in mmol/L)	n	Major CVD Event Rate (%)		ARR (%)	*P*
			Fibrate	Placebo		
Primary Prevention						
HHS[1]	High-risk, TG >2.3 + LDL-C:HDL-C >5	292	3.9	13.0	9.4	<.005
FIELD[2]	Diabetes, subgroups without CVD, HDL-C 1.09 + TG 1.7	7664	8.9	10.8	1.9	.004
Secondary Prevention						
BIP[3]	Met.Syn, HDL-C 0.86 + TG 1.9	1470	14.1	18.4	4.3	.03
VA-HIT[4]	Diabetes, HDL-C 0.83 + TG 1.8	627	28.5	36.5	8.0	.05

ARR=absolute risk reduction

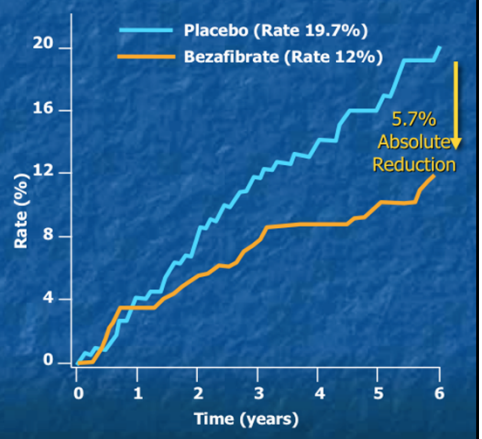
1. Manninen et al. *Circulation* 1992;85:37-45; 2. Keech et al. *Lancet* 2005;366:1849-61;
3. Tenenbaum et al. *Arch Intern Med* 2005;165:1154-60; 4. Rubins et al. *N Engl J Med* 1999;341:410-8

BIP: Greatest Benefit Seen in Patients with High TG + Low HDL-C

Triglycerides <2.26 mmol/L



Triglycerides ≥2.26 mmol/L



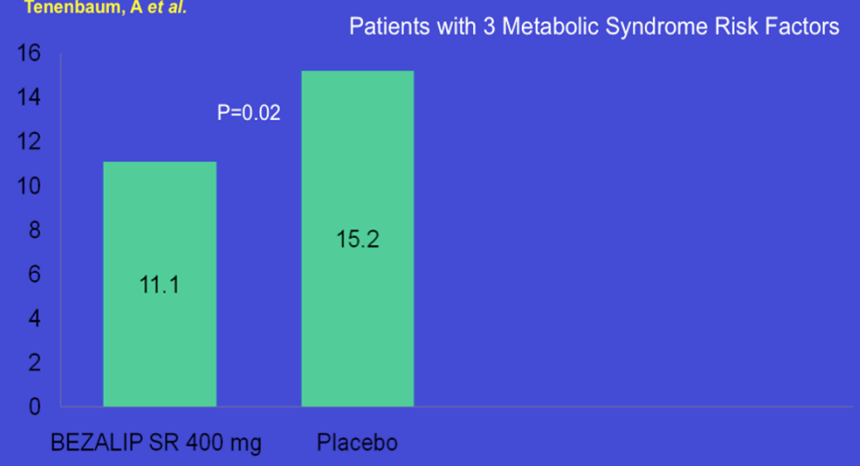
Benefit was greater when HDL-C <0.9 (41.8%) vs. HDL-C ≥0.9 (35.9%)

aseline LDL-C: ~3.8 mmol/L

BIP Study Group. *Circulation* 2000;102:21-7

Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome

Tenenbaum, A *et al.*



New MI Recorded

Arch Intern Med. 2005;165:1154-1160

Long term benefit of high-density lipoprotein cholesterol-raising therapy with bezafibrate. 16 Year Mortality Follow Up of the BIP Trial.

Ilan Goldengerg, MD; Valentina Boyko, MA; Alexander Tenenbaum, MD, PhD; David Tanne, MD; Solomon Behar, MD; Victor Guetta, MD.

Adjusted Risk for Long-term Mortality by Triglyceride Response

Response Group	HR (95% CI)	P value
Triglyceride Response		
Upper tertile, >0.486 mmol/L increase vs placebo	0.82 (0.68-0.99)	0.03
Lower tertile, ≤ 0.486 mmol/L increase vs placebo	0.93 (0.81-1.06)	0.28

Arch Intern Med. 2009;169(5):508-514

Long term benefit of high-density lipoprotein cholesterol-raising therapy with bezafibrate. 16 Year Mortality Follow Up of the BIP Trial.

Ilan Goldengerg, MD; Valentina Boyko, MA; Alexander Tenenbaum, MD, PhD; David Tanne, MD; Solomon Behar, MD; Victor Guetta, MD.

Adjusted Risk for Long-term Mortality by HDL-C Response

Response Group	HR (95% CI)	P value
HDL-C Response		
Upper tertile, >0.207 mmol/L increase vs placebo	0.78 (0.65-0.94)	0.008
Lower tertile, ≤ 0.207 mmol/L increase vs placebo	0.95 (0.83-1.08)	0.43

Arch Intern Med. 2009;169(

Statin Intolerance

Adverse Muscle Effects – myalgia, myositis, rhabdomyolysis

Hepatic Effects – “transaminitis”, hepatocellular toxicity

Neurologic Effects – hemorrhagic stroke, cognitive decline, peripheral neuropathy,

Neuropsychiatric Effects and Insomnia – insomnia, somnolence, agitation, confusion, halluciation

Renal – proteinuria

Diabetes – slight increased incidence of new onset diabetes (not class effect)

Alopecia

Erectile Dysfunction

Interstitial Lund Disease

Diagnosis of Statin Intolerance

- Withdrawal and re-challenge – best diagnostic tool to ascertain a statin-induced side effect

- Myopathy:

  1) Myalgia : symptoms – flu-like muscle pain mostly in proximal muscles - often no associated CK level elevation

  2) Myositis: CK > ULN but below 10X ULN

  3) Rhabdomyolysis – CK > 10X ULN w/wo associated renal dysfunction, myoglobinuria, DIC (rare)
- R/O other co-existing myopathic conditions
- Myalgia is common cause of discontinuation of statin
- If CK > 5 x ULN, should D/C and consider alternate statin or alternate Rx

- Liver effect:

  1) transaminitis

  2) decompensated liver dysfunction (jaundice, elevated bilirubin)

  Statins have been shown to be relatively safe in patients with stable NAFLD, chronic hepatitis B/C if no sign of liver decompensation

General approach: if LFT < 3x ULN, continue

If LFT > 3x ULN, may continue with caution or D/C and reassess

Alternate statin or alternate Rx may be considered

Alternate Rx in statin intolerance

1) Diet
2) Alternate 1 – statin based:
   Alternate statin, fluvastatin XL 80 mg/day
3) Alternate 2 – non-statin based
   - Ezetimibe monotherapy
   - Ezetimibe with fluvastatin XL, other low dose statins, alternate day statins
   - Niacin w/wo low dose statin (mixed dyslipidemia)
   - Fibrates w/wo low dose statin (mixed dyslipidemia)
   - Bile acid sequestrants