An Update on Diagnosis and Treatment of Lipid Disorders

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LDL Cholesterol reduction

- By the early 1970's the association between LDL levels and CV mortality and MI was proven
- Unclear if reducing LDL cholesterol decreased mortality
- Resins, nicotinic acid and fibrates developed - (unpleasant, ineffective)
- Drugs rarely used except in cases of familial hyperlipidaemia

LRC Trial
1984

- Started in 1973 and sponsored by the NIH
- 3806 middle aged men with type 2 hyperlipidaemia randomized to cholestyramine 24g/Day or placebo.
- Followed for and average of 7.5 years
- Treatment poorly tolerated and less than half prescribed dose actually taken
- Cholesterol decreased 20% v 8% palcebo

LRC trial

- 24% decrease in CVD death and 19% decrease in non fatal MI
- Combined endpoint occurred in 8.6% in control versus 7.0% in treated
- Absolute benefit small
- Differences only just statistically significant
- Only middle aged men included
- Drug poorly tolerated

LRC Trial

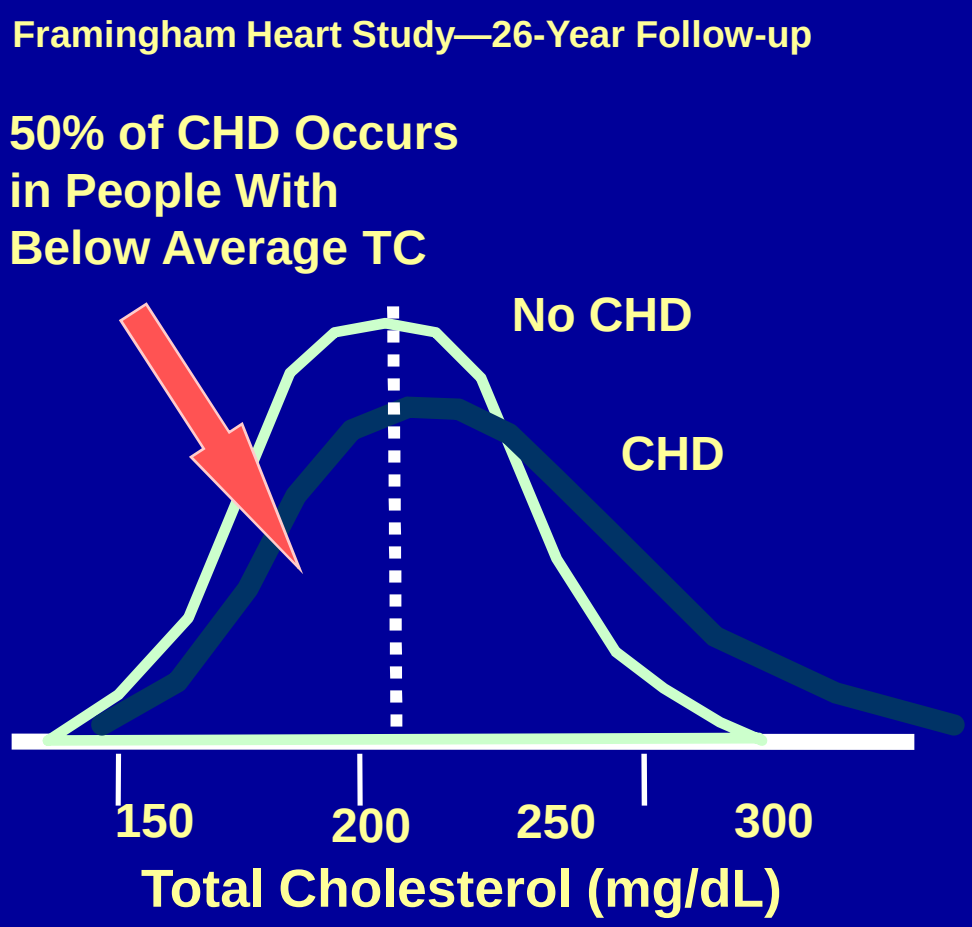
- First trial to show a benefit

- Many physicians still not convinced
- Some patients with high cholesterol never develop IHD
- Many patients with events have normal LDL levels

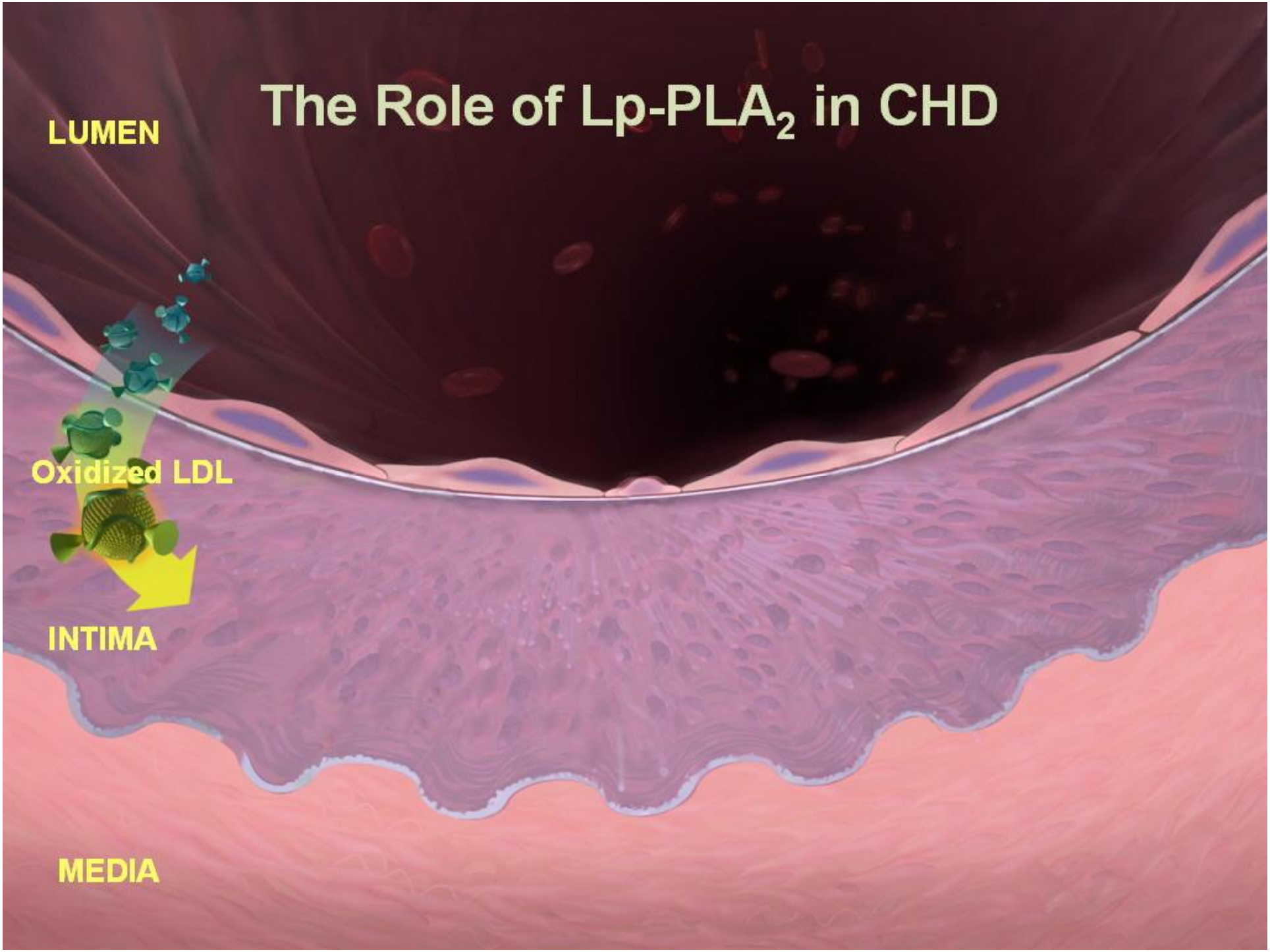
Unmet Need

In spite of major advances made in the screening, detection, and management of heart disease, a major need exists for more ways to predict CV risk

- Approximately 50% of individuals diagnosed with coronary artery disease do not have high blood cholesterol levels

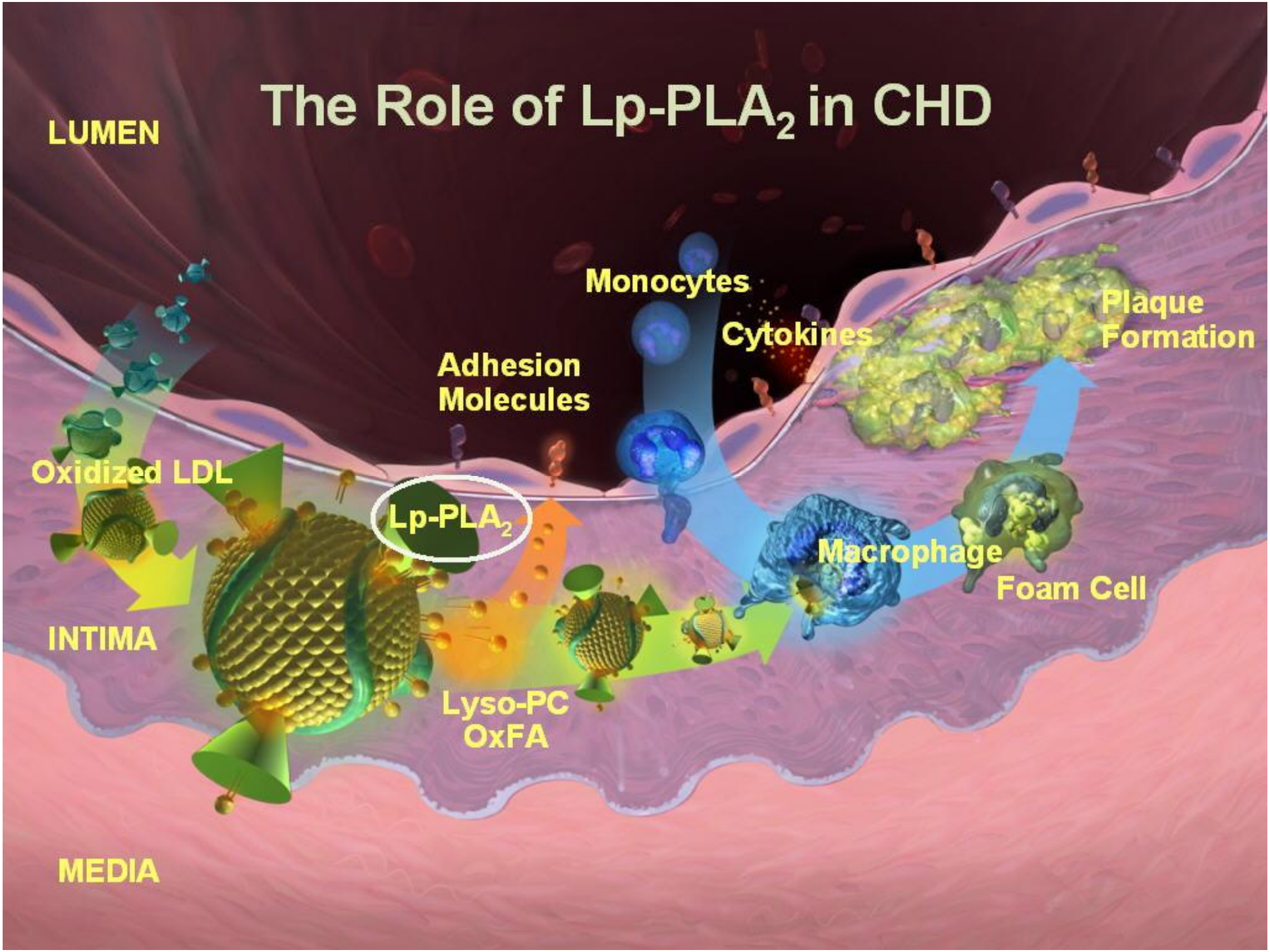


Adapted from Castelli W. *Atherosclerosis* 1996;124(suppl):S1-S9.


The Role of Lp-PLA2 in CHD
LUMEN
Oxidized LDL
INTIMA
MEDIA

Factors affecting oxidation

- PARTICLE SIZE - Small densely packed cholesterol particles are more atherogenic as they may be oxidized more easily
- Two patients may have the same cholesterol concentration, but one patient may have twice as many particles
- All lipids packaged with proteins to create water soluble particles – each LDL has 1 Apo B, so Apo B is a measure of particle size
- Elevated Apo B seen in patients with metabolic syndrome and diabetes who usually have depressed HDL
- HDL may act as an antioxidant
- FRENCH PARADOX – eat slowly, eat biggest meal at lunch, eat fresher food,
- ? Exposure to increased dietary anti-oxidants in foods over a lifetime may be very important
- ? Flavoids, cocoa, red wine, dietary antoxidants


The Role of Lp-PLA2 in CHD
LUMEN
Monocytes
Cytokines
Plaque Formation
Adhesion Molecules
Oxidized LDL
Lp-PLA2
Macrophage
Foam Cell
INTIMA
Lyso-PC
OxFA
MEDIA

Lipid Abnormalities Associated with Atherosclerosis

- Elevated LDL cholesterol
- Elevated TG
- Low HDL
- Elevated LP a

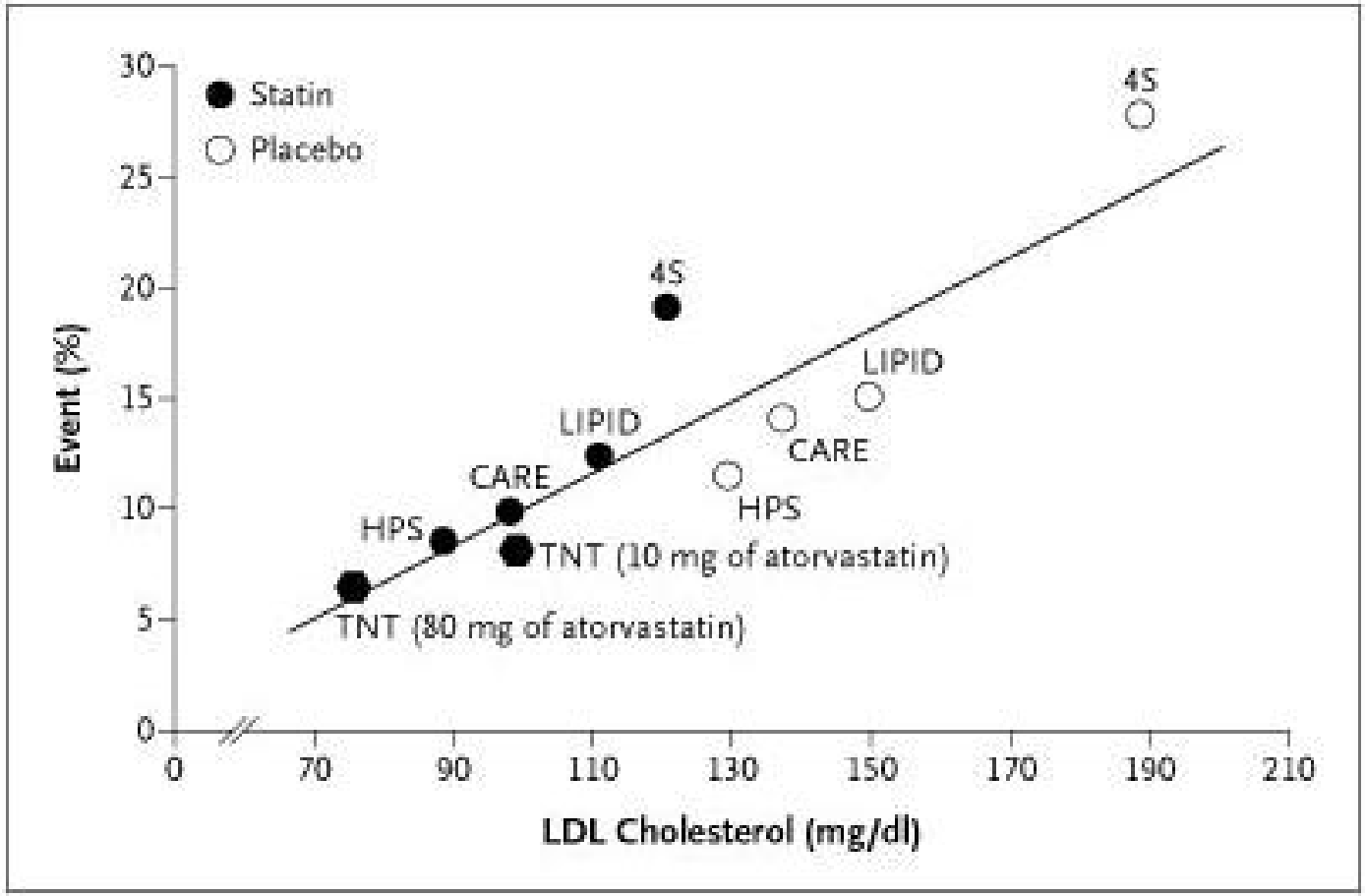
LDL cholesterol

- Strongest data linking lipid disorders to CHD relates to LDL cholesterol
- A 10% increase in LDL results in a 20% increase in risk of developing IHD
- Reducing LDL cholesterol in patients with high lipid levels reduces the incidence of coronary events
- Reducing LDL cholesterol in patients with relatively normal levels also reduces risk

Control of LDL

- pivotal role of LDL receptor, located in the liver, receptors dispose of LDL
- In familial hyperlipidaemia receptor number is decreased
- Receptors may be down regulated by high intracellular levels of LDL in hepatocytes
- Receptors are upregulated by any drug that decreases intracellular LDL (almost all lipid lowering agents except fibrates)

Event Rates Plotted against LDL Cholesterol Levels during Statin Therapy in Secondary-Prevention Studies



LaRosa, J. et al. N Engl J Med 2005;352:1425-1435

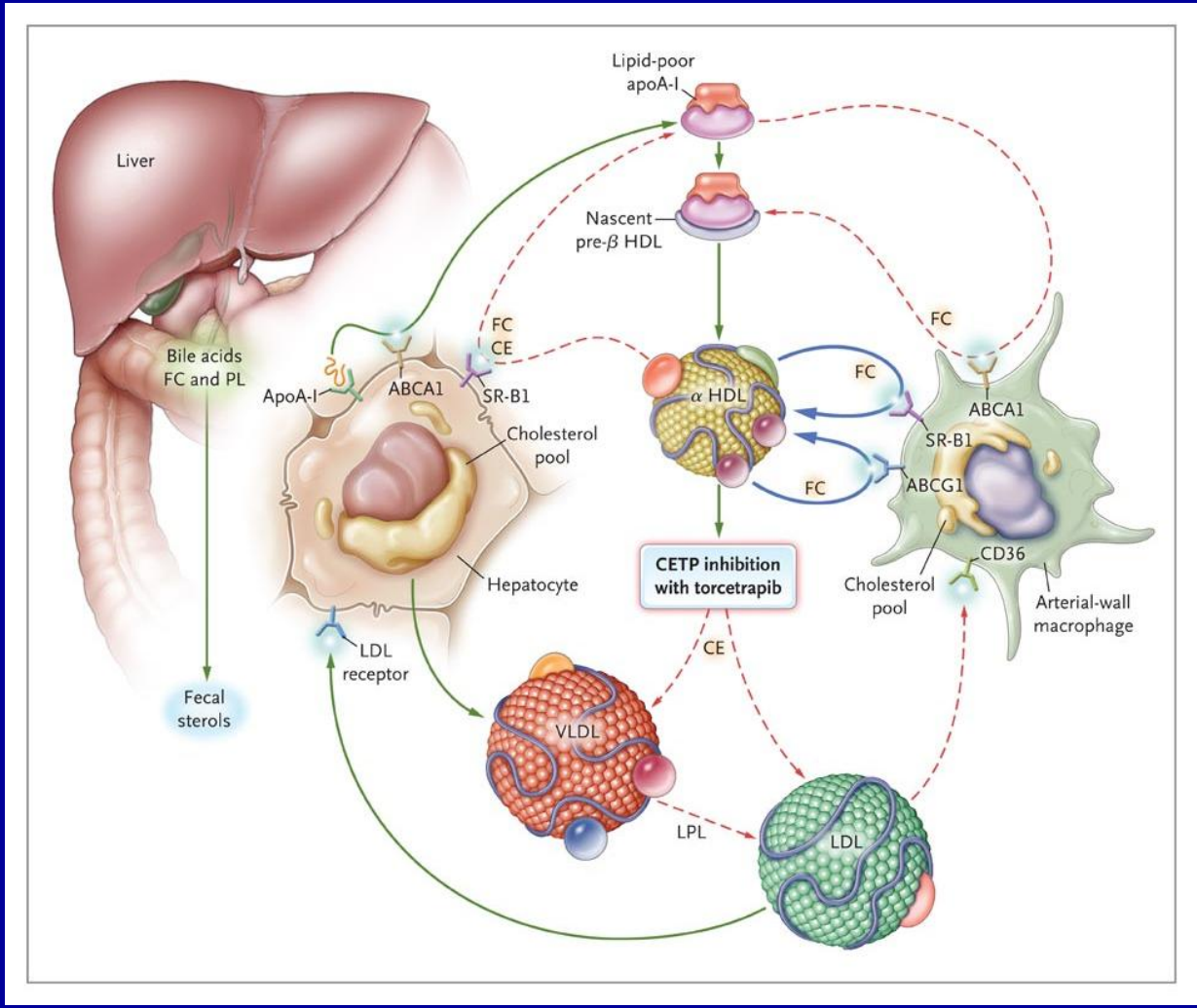
Triglyceride

- Much argument about its importance in reducing future risk
- Most recent data suggests it is an independent risk factor especially in women and diabetic patients
- Usual management is by lifestyle change
- Targeted drug therapy not common

HDL

- Low HDL an independent risk factor
- Few studies showing increasing HDL reduces risk
- Exercise and diet may increase HDL levels
- Currently available drugs have a minimal effect on HDL – CETP inhibitors in Phase 3 trials

Schematic Representation of the Metabolism of HDL Cholesterol



Nissen SE et al. N Engl J Med 2007;356:1304-1316

Torcetrapib Study

- Torcetrapib combined with atorvastatin compared to a atorvastatin alone
- Study was stopped early because of excess mortality in the torcetrapib/statin group
- The drug was associated with an elevation in blood pressure
- May not apply to all CETP inhibitors

Lipoprotein a

- Molecule of Apo a binds to the Apo B on LDL
- Apo a molecular weight is highly variable
- LP a may bind to small or large LDL particles and have low or high molecular weight
- May explain why it appears a risk factor in some patient group but not others (men ++) versus women
- Current drugs are ineffective in altering levels
- It is unknown if reducing levels will decrease risk

Who requires Drug therapy

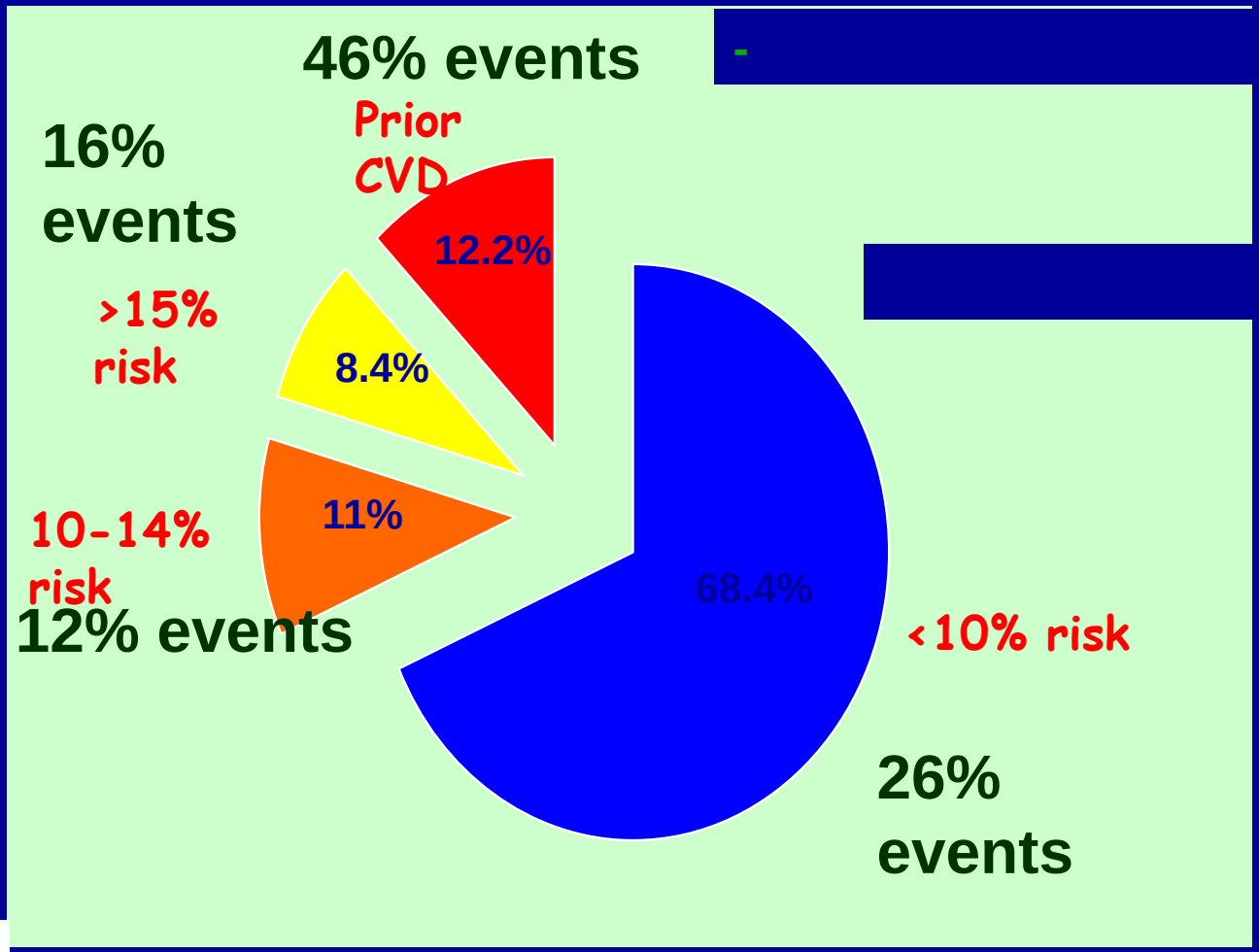
- All patients with symptomatic vascular disease – cerebral, cardiac, peripheral vascular regardless of their lipid levels
- Asymptomatic atherosclerosis diagnosed by investigative tests – degree probably important
- Higher risk asymptomatic patients

Screening in Asymptomatic patients

- Primary driver of NZGG was to identify higher risk patients who are more likely to have events in the near future and make sure they are treated – "biggest problem is under-treatment"

- Considered not cost effective for the country to treat lower risk patients with drugs because of cost of the medication, cost of repeat medical visits and lab measurements
- Should not be taken as proof that treating lower risk patients not worthwhile – 5 year risk is a population strategy targeting those where most benefit will occur.

NZGG CVD Risk Assessment

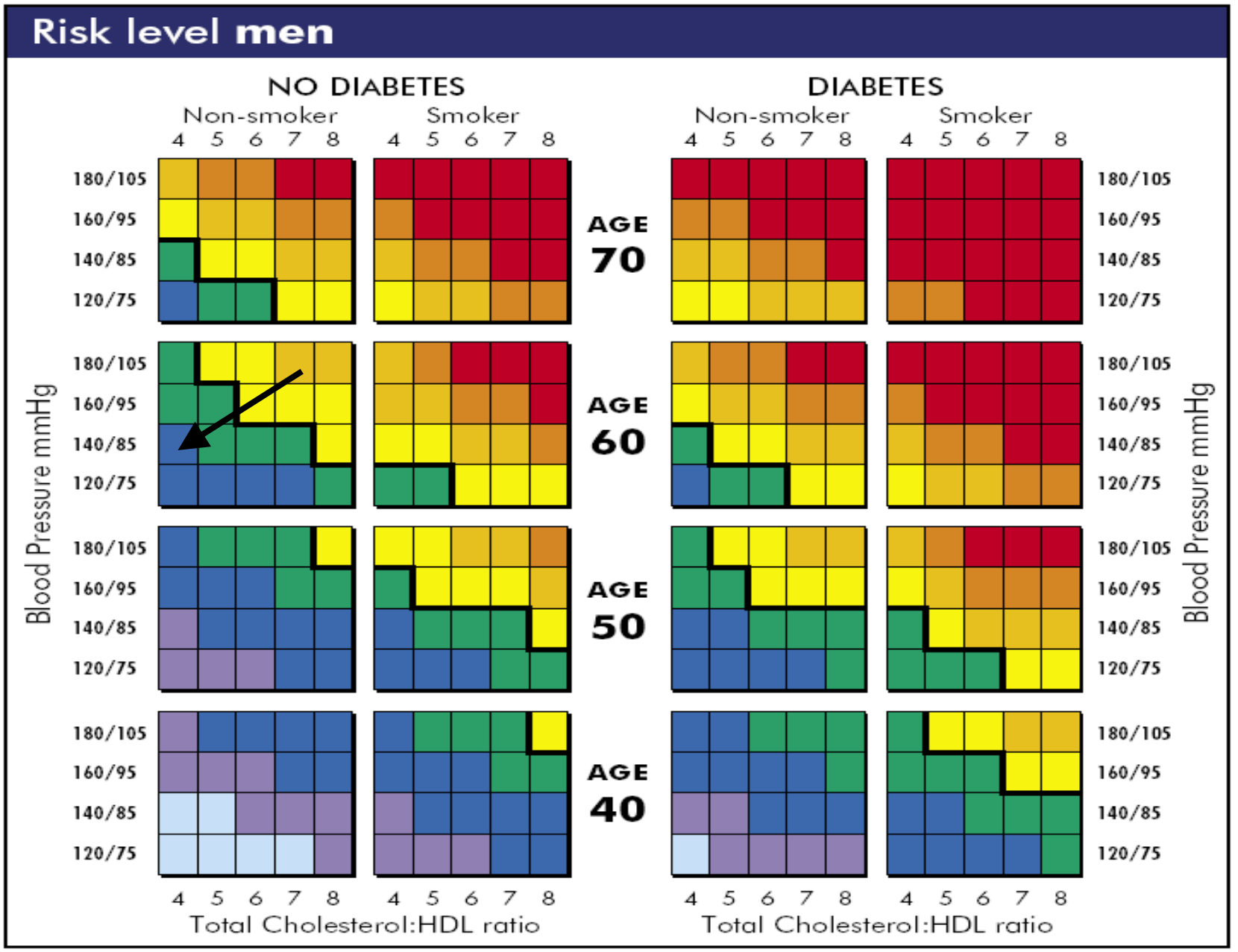


HRC PREDICT data 2008

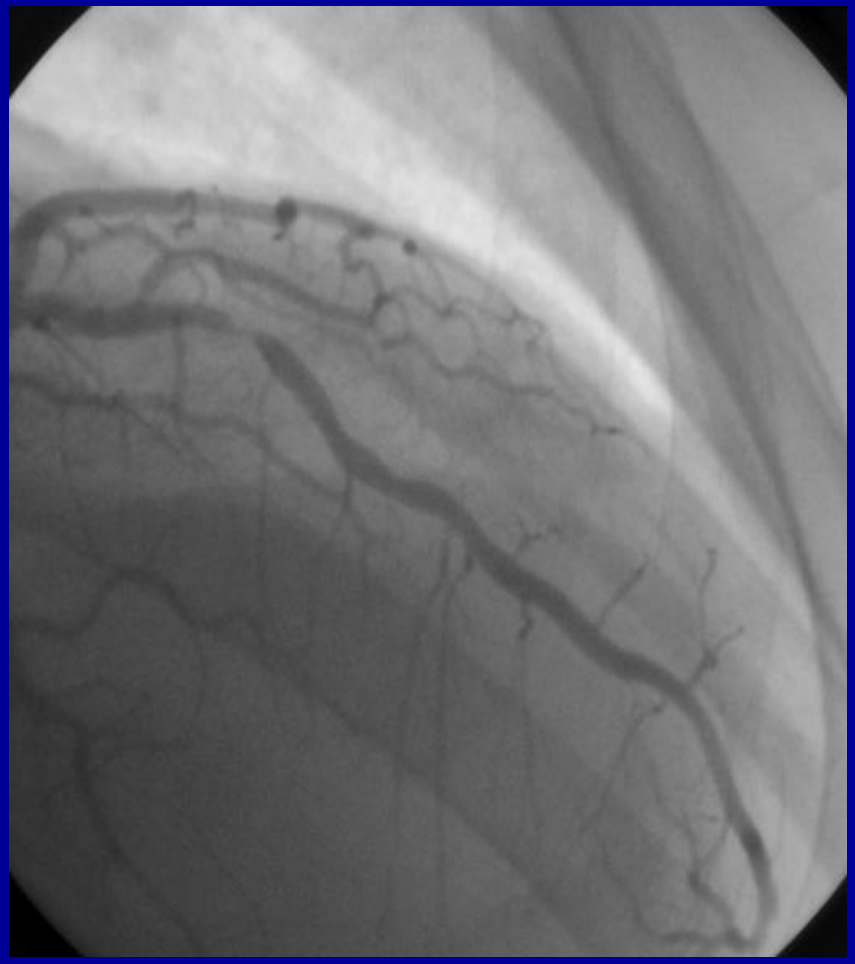
THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

Would you treat this patient ?

- 61 Year old man
- Asymptomatic severe MR
- TC 4.8, HDL 1.1, LDL 2.9
  Ratio 4.4
- BP 140/85
- South Asian descent
- Non Smoker
- -ve Family History
- Central obesity BMI 36
- Waist 107cm


Risk level men
NO DIABETES
DIABETES
Non-smoker
Smoker
4 5 6 7 8
180/105
160/95
140/85
120/75
AGE 70
AGE 60
AGE 50
AGE 40
Blood Pressure mmHg
Total Cholesterol:HDL ratio

Would you treat this patient ?



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Problems with Guideline approach

- Age alone is the most powerful risk, is preventing an event in an 80 year old on multiple therapies more important than preventing a young person having a premature event?
- Lifetime risk in a younger patient may be very important
- Many events occur in lower risk patients
- Cost of treating lower risk patients is over stated.
- Over reliance on the ratio (doesn’t work so well at the extremes)
- Classification as low risk, if interpreted incorrectly, may dissuade lifestyle changes that benefit everyone

Thresholds for treatment

Risk	Total	LDL	Target total	Target LDL
0/1	>7.0	>5.0	In the 4's	In the 2's
2 or more	>6.0	>4.0	In the 4's	In the 2's
Established disease	All	All	<4.0	<2.0

Modify for low HDL < 1.3 in women and < 1.2 in men

Include race, family history as risk factors

Assume diabetics have established disease

Drug Therapy - Statins

- Inhibit the rate limiting step of cholesterol production
- Reduce LDL by decreasing production and up regulating LDL receptor
- Proven mortality and morbidity benefit for coronary and cerebrovascular disease
- Statins have effects over and above just lowering cholesterol

Other Benefits of Statins

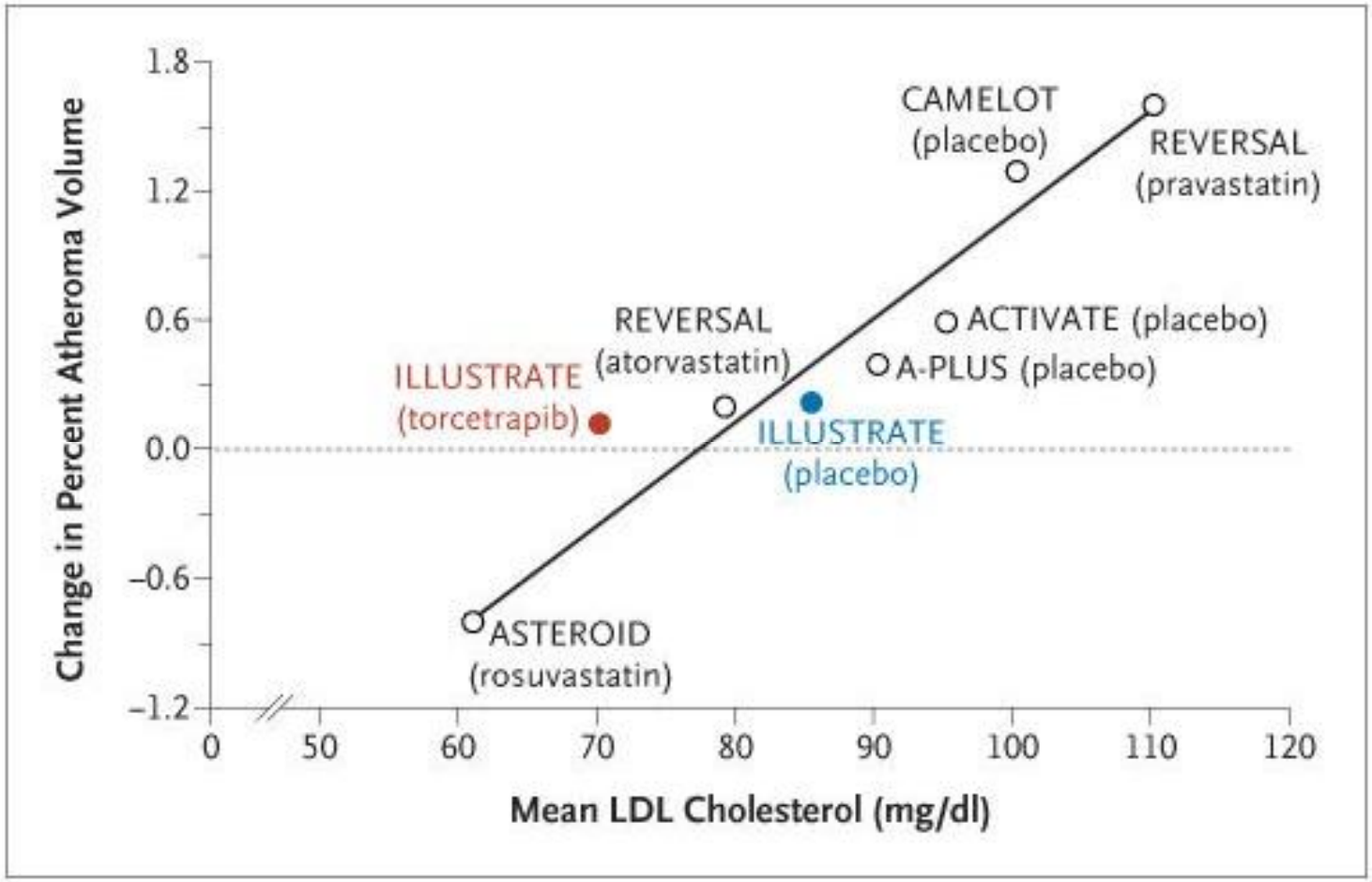
- Decreased fibrinogen
- Activation of endothelial NO
- Suppression of release of tissue factor
- Decrease viscosity

- May be the reason why they help all patients with IHD regardless of their lipid levels

Adverse Effects - Statins

- GI upset, may be pronounced, usually doesn't help to switch statin, sometimes lower dose tolerated
- Muscle aches – CK, Q10
- Sleep disturbance, concentration problems (may be due to lipid reduction rather than the drug)
- LFTs – dose related
- Serious effects very rare
- How to handle anti-statin sentiment

Relationship between the Change in Percent Atheroma Volume and LDL Cholesterol in Regression-Progression Trials Using Intravascular Ultrasonography



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Fibrates

- Have a modest effect on LDL, but a greater effect on TG and HDL
- Use has decreased with increasing efficacy of statins
- Useful alternative in mild cases where a statin is not tolerated, can be combined with ezetemibe
- Rash, GI symptoms and myositis may occur, LFTs also.
- Serious question about mortality reduction – await results of completed “FIELD” trial

Nicotinic acid

- Useful to increase HDL and has a modest LDL lowering effect
- May be used in combination therapy
- Has to be taken multiple times each day
- Side effects a big problem (flushing, GI, LFT’s)
- Slow release Niacin plus prostaglandin inhibitor in clinical trials (laropiprant)

Ezetemibe

- Inhibits the absorption of cholesterol from the brush border of the intestine (most cholesterol is from bile, so works when dietary intake low)
- Upegulates the LDL receptor
- Used alone it reduces LDL by 20%, increases HDL by <5% and decreases TG by about 10%, synergistic with statins
- No outcome data – 36 million Americans take it
- There is no theoretical reason why this drug should not reduce mortality

Approach to Patient requiring drug therapy

- Use Simvastatin to achieve target LDL
- If target not achieved with maximum tolerated dose change to atorvastatin
- If target still not achieved add Ezetemibe
- Ezetemibe with low dose statin in patients with dose related statin side effects
- Ezetemibe alone or with nicotinic acid or bezalip in patients who are statin intolerant

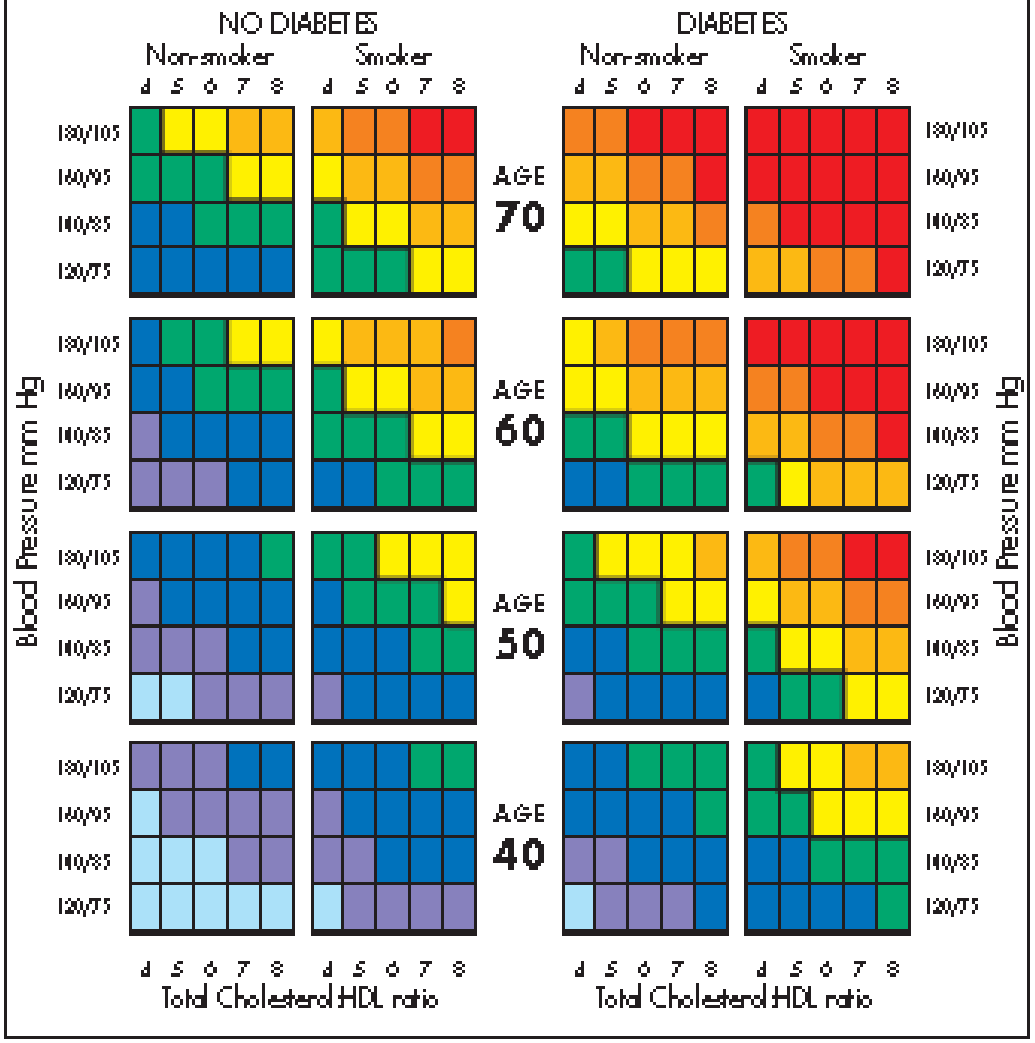
Familial Hyperlipidaemia

- Familial Hyperlipidaemia, LDL > 5.0 use high dose atorvastatin plus Ezetemibe plus nicotinic acid if necessary

Summary

- Aggressive reduction of LDL indicated in patients with disease and those at increased risk
- Lifetime risk in younger patients should be considered before withholding drugs
- Drugs to raise HDL on the horizon
- Targeted vessel wall treatment will be important in the future

Risk level **women**



Risk Level
5 year CVD risk (non-fatal and fatal)

- Very High: >30%, 25–30%, 20–25%
- High: 15–20%
- Moderate: 10–15%
- Mild: 5–10%, 2.5–5%, <2.5%

How to use
+ Identify the
+ Within the
When the
+ For examp
years and
People wh