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 an average of 7.5 years
- Treatment poorly tolerated and less than half prescribed dose actually taken
- Cholesterol decreased 20% vs 8% placebo
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
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-PLA$_2$ 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 antioxidants
The Role of Lp-PLA₂ in CHD

- Lumen
- Monocytes
- Cytokines
- Adhesion Molecules
- Oxidized LDL
- Lp-PLA₂
- Lyso-PC OxFA
- Intima
- Macrophage
- Foam Cell
- Plaque Formation
- 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

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

Torcetrapib Study

- Torcetrapib combined with atorvastatin compared to 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.
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
Non-smoker
Smoker

DIABETES
Non-smoker
Smoker

Blood Pressure mmHg

Total Cholesterol: HDL ratio

AGE 70

AGE 60

AGE 50

AGE 40
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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

<table>
<thead>
<tr>
<th>Risk</th>
<th>Total</th>
<th>LDL</th>
<th>Target total</th>
<th>Target LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/1</td>
<td>&gt;7.0</td>
<td>&gt;5.0</td>
<td>In the 4’s</td>
<td>In the 2’s</td>
</tr>
<tr>
<td>2 or more</td>
<td>&gt;6.0</td>
<td>&gt;4.0</td>
<td>In the 4’s</td>
<td>In the 2’s</td>
</tr>
<tr>
<td>Established disease</td>
<td>All</td>
<td>All</td>
<td>&lt;4.0</td>
<td>&lt;2.0</td>
</tr>
</tbody>
</table>

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

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)
- Upregulates 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