Lipid Modification Guidelines

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Background

• CVD is leading cause of death
  – 1:3 deaths
  – 124,000 in 2005

• 3 modifiable risk factors are major (80%) contributors to CVD risk
  – Smoking
  – Hypertension
  – Hypercholesterolaemia
Death rates from CHD, stroke and all other diseases of the circulatory system, people aged under 75, 1970-2000, England, with Our Healthier Nation milestone and target.
CHD Mortality Trends

• Between 1981-2000 (England & Wales)
  • Mortality in men decreased by 62%
  • Mortality in women decreased by 45%
  

• 42% of reduction attributed to treatments
  • 11% secondary prevention
    • 13% HF treatments
    • 8% initial MI treatments
    • 3% hypertension
    • CABG 3%, PCI 0.8%, aspirin (primary) 1.6%, statin (primary) 0.2%
CHD Mortality Trends

• 58% of reduction due to population risk factor reductions
  • 48% : smoking reduction (34% reduction over period)
  • 9.5% : hypertension treatment
  • 9.5% : cholesterol treatment
  • - 4.3% : physical activity reduction
  • -3.4% : obesity increase
  • -4.7% : diabetes increase
Statins role: HMG Co-A reductase inhibitors

Meta-analysis of 90 056 patients, 14 randomised trials (Cholesterol Trialist Collaboration)

- 5yr incidence of major coronary events, coronary revascularisation and stroke reduced by
  - 20% per mmol/l reduction in LDL
- 12% reduction in all cause mortality per mmol/l reduction in LDL
- 20% reduction in strokes

Statins’ role

The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials

J J Brugts, doctor,1 T Yetgin, doctor,1 S E Hoeks, epidemiologist,1 A M Gatto, professor, doctor,2 J Shepherd, professor, doctor,2 R G J Westendorp, professor, doctor,2 A J M de Craen, epidemiologist,1 R H Knopp, professor, doctor,2 H Nakamura, professor, doctor,2 P Ridker, professor, doctor,7 R van Domburg, epidemiologist,1 W Deckers, doctor2

Results 10 trials enrolled a total of 70,388 people, of whom 23,681 (34%) were women and 16,078 (23%) had diabetes mellitus. Mean follow-up was 4.1 years. Treatment with statins significantly reduced the risk of all cause mortality (odds ratio 0.88, 95% confidence interval 0.81 to 0.96), major coronary events (0.70, 0.61 to 0.81), and major cerebrovascular events (0.81, 0.71 to 0.93). No evidence of an increased risk of cancer was observed. There was no significant heterogeneity of the treatment effect in clinical subgroups.
Statin Trials: Decrease in Clinical Events Correlates with lower LDL-C

![Graph showing the relationship between LDL-C achieved and event rate in different clinical trials. The graph includes data from AFCAPS, LIPID, CARE, 4S, WOSCOPS, and 20 prevention trials. Different colors represent treatment and placebo groups.](image)
High intensity statins in ACS

**PROVE IT-TIMI 22: A Major Cardiovascular Event Or Death From Any Cause**

Primary End Point

Death Or Major Cardiovascular Event (%)

Standard Care

Intensive Statin Use

$P = .03$

$P = .005$ Overall


Ray and Cannon. *Am J Cardiol.* 2005;96(suppl)54F.

**PROVE IT – TI MI 22 (NEJM 2004;350)**

4162 patients with ACS (within preceding 10 days) with initial chol $< 6.2$mmol/l

40mg pravastatin versus 80mg atorvastatin
Background

• NICE has published guidelines on lipid modification in primary and secondary prevention: 2008

NICE clinical guideline 67
Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease
NICE – Primary Prevention

For the primary prevention of CVD in primary care, a systematic strategy should be used to identify people aged 40–74 who are likely to be at high risk.

The Framingham 1991 10-year risk equations\textsuperscript{5} should be used to assess CVD risk. CVD risk should be calculated as:

\[
\text{CVD risk} = \frac{\text{10-year risk of fatal and non-fatal stroke, including transient ischaemic attack}}{\text{10-year risk of coronary heart disease (CHD)}}
\]
Statin therapy is recommended as part of the management strategy for the primary prevention of CVD for adults who have a 20% or greater 10-year risk of developing CVD. This level of risk should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available or appropriate (for example, older people, people with diabetes or people in high-risk ethnic groups). Treatment for the primary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.
NICE – Secondary Prevention

For secondary prevention, lipid modification therapy should be offered and should not be delayed by management of modifiable risk factors.

- Statin therapy is recommended for adults with clinical evidence of CVD.\(^7\)
- People with acute coronary syndrome should be treated with a higher intensity statin\(^8\). Any decision to offer a higher intensity statin should take into account the patient's informed preference, comorbidities, multiple drug therapy, and the benefits and risks of treatment.
NICE – Secondary Prevention

Treatment for the secondary prevention of CVD should be initiated with simvastatin 40 mg. If there are potential drug interactions, or simvastatin 40 mg is contraindicated, a lower dose or alternative preparation such as pravastatin may be chosen.

In people taking statins for secondary prevention, consider increasing to simvastatin 80 mg or a drug of similar efficacy and acquisition cost if a total cholesterol of less than 4 mmol/litre or an LDL cholesterol of less than 2 mmol/litre is not attained. Any decision to offer a higher intensity statin should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.

NICE recognises that on “standard” therapy only 31% will reach this target “Higher” dose simvastatin will only increase this to 38%
Network CAG Guidelines

• Network CAG & pharmacological advisors were asked to help interpret and aid local implementation of NICE guidelines
  – Also asked to include diabetic patients (NICE guidance 66) into the offered guidance
CAG: Primary Prevention

• Adults aged 40-74 yrs with CVD risk > 20% (Framingham 10 yr risk equation & “adjustments”)

• Before offering statin therapy optimise management of other modifiable risk factors if possible

• Simvastatin 40 mg/day

• No need to recheck cholesterol (no target)
CAG: Secondary Prevention – Established CVD

• Simvastatin 40 mg/day
• If TC >4mmol/l and LDL >2mmol/l
• Consider simvastatin 80mg/day
• Only for very high risk patients consider an alternative higher intensity statin *(higher intensity statins should not be used routinely)*
CAG: Secondary Prevention - ACS

• Initiate higher intensity statin
  – Atorvastatin 80mg /day

• Review at 6 months after last unstable event and place on simvastatin 40mg/day (as per “established CVD”)
### PRIMARY PREVENTION

Identify adults aged between 40 & 74 with a CVD risk >20% based on Framingham 10-year risk equations & clinical judgement.

Before offering lipid modification therapy, optimise the management of other modifiable risk factors if possible. Give information about the patient's absolute risk of CVD & the likely absolute benefits & harms of treatment in ways which they understand. Use the NPCi patient decision aids from [www.npci.org.uk](http://www.npci.org.uk) to illustrate risk/benefits.

**Offer simvastatin 40mg/day**

Higher intensity statins should NOT be used. No need to recheck cholesterol (No target).

Check LFTs prior to treatment and at 3 & 12 months only.

### ESTABLISHED CARDIOVASCULAR DISEASE

**Offer simvastatin 40mg/day**

Trigger Point for further discussion with patient if TC >4mmol/L AND LDL >2mmol/L on simvastatin 40mg/day.

**Consider simvastatin 80mg/day**

Any decision to offer this higher simvastatin dose should take into account the patient's compliance, informed preference, comorbidities, multiple drug therapy & interactions, and the benefits and risks of treatment. Use the NPCi patient decision aid ([see link](http://www.npci.org.uk)) to illustrate small additional benefits & risk of myopathy.

**Remain on simvastatin 80mg/day**

ONLY for patients intolerant (e.g. significant myalgia) to the higher dose of simvastatin 80mg, or for very high risk patients consider an alternative higher intensity statin. Higher intensity statins should not routinely be used.

### ACUTE CORONARY SYNDROME (NSTEMI, STEMI, Unstable Angina)

Initiate a higher intensity statin e.g. atorvastatin 80mg/day.

Review back to simvastatin 40mg/day 6 months after last event (Then treat as per ‘Established CVD’ algorithm).

If there are potential drug interactions or simvastatin 40mg is contraindicated offer a lower dose of simvastatin or pravastatin 40mg. Ezetimibe, fibrates, anion exchange resins (or nicotinic acid only for secondary prevention) may be considered ONLY where statins cannot be used.

### Lipid Modification in NON-DIABETICS

**Identify adults aged between 40 & 74 with a CVD risk >20% based on Framingham 10-year risk equations & clinical judgement.**

**Offer simvastatin 40mg/day**

Higher intensity statins should NOT be used. No need to recheck cholesterol (No target).

Check LFTs prior to treatment and at 3 & 12 months only.
Diabetes

- > 40yrs old
- Simvastatin 40mg/day
- If TC > 4mmol/l or LDL >2mmol/l consider simvastatin 80mg od
Diabetes

• If despite this TC > 4mmol/l or LDL >2mmol/l AND
  – CVD present or
  – Increased albumen excretion
• Higher intensity statin
Diabetes

• Triglycerides
  – $> 4.5 \text{mmol/l}$ offer fibrate first
  – $2.3 - 4.5 \text{mmol/l}$ despite add fibrate
Lipid Modification in People with Diabetes

**Diabetics with or without established cardiovascular disease aged over 40yrs**

Offer simvastatin 40mg/day

Re-check lipid profile after 1 to 3 months

TARGET LEVEL: ONLY in diabetic patients aim for a target of TC<4mmol/L OR LDL<2mmol/L

Consider simvastatin 80mg/day

Any decision to offer this higher simvastatin dose should take into account the patient’s compliance, informed preference, comorbidities, multiple drug therapy & interactions, and the benefits and risks of treatment. Use the NPCi patient decision aid (www.npci.org.uk) to illustrate small additional benefits & risk of myopathy.

If TC >4mmol/L AND LDL-C >2mmol/L AND:

- Increased albumin excretion rate (> 2.5 mg/mmol for men, > 3.5 mg/mmol for women)
- Existing or newly diagnosed CVD

**OFFER A HIGHER INTENSITY STATIN**

**ACUTE CORONARY SYNDROME (NSTEMI, STEMI, Unstable Angina)**

Initiate a higher intensity statin

atorvastatin 80mg/day

Review back to previous statin & dose 6 months after last event

**Triglycerides**
- ➔4.5mmol/L offer fibrate first
- 2.3-4.5mmol/L despite statin add fibrate (monitor carefully)

If there are potential drug interactions or simvastatin 40mg is contraindicated offer an alternative statin depending on local formulary choice. Ezetimibe, fibrates, anion exchange resins or nicotinic acid may be considered where statins cannot be used. Omega-3 fish oils/nicotinic acid also used by specialist

Check LFTs prior to treatment and at 3 & 12 months only.

Ezetimibe is an alternative in non-ACS diabetic patients but does not have any outcome data in diabetic patients to support its use.

**Also consider for <40yrs at very high risk. Consider risk assessing those >40yrs at very low risk.**
Summary: What you having thinking about during the talk

- CONTENT OF TALK 3%
- SEX 60%
- RELATIONSHIPS 20%
- FOOD 17%
4 & 2 targets in Secondary Prevention

- BCS, BHS, Diabetes UK, HEART UK, PCCS, Stroke Association
- Aims: To promote a consistent multidisciplinary approach to management of people with established atherosclerotic CVD and those at high risk of developing symptomatic atherosclerotic disease

JBS 2: Joint British Societies guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005; 91(supplement V)
JBS 2 Guidelines

• Underlying principle of document is that CVD prevention in clinical practice should focus equally on individuals with:
  – Established CVD
  – Diabetes
  – High risk “healthy” individuals
    • CVD risk >20% over 10 years*

• Lifestyle and Risk Factor interventions

• Targets for lifestyle, BP, lipids and glucose given

* Patients with single significantly elevated risk factor eg TC/HDL ratio > 6 also require CVD prevention
JBS 2 Guidelines

• Risk Assessment:
  – Ethnicity
  – Smoking habit
  – FH
  – Weight, Waist circumference
  – BP
  – Non-fasting lipids & glucose

Low risk individuals reassess in 5yrs
JBS 2 Guidelines

- Lipid level targets:
  - T.Chol < 4mmol/l
  - LDL < 2mmol/l

- Principal pharmacological agents to achieve these targets are statins
Effective Lifestyle Measures

Dietary

- Mediterranean
- Increased fish intake
  - 2 portions of oily fish per week
- Low fat, low cholesterol
  - (total fat < 30% of total energy intake, saturated fat < 10%, dietary cholesterol <300mg/day)
- Moderate alcohol intake

Other

- Cessation of smoking
- Exercise (5 times a week moderate exercise for 30-40 mins)
- Weight reduction (if overweight)
Plant sterols/stanols

• Present in:
  – vegetable oils (eg rapeseed, soybean)
  – Nuts
  – grains and seeds
• Block uptake of cholesterol from GI tract
• LDL reduced by ~ 10% by 2g sterols
• Amount needed of “fortified foods” - 8 yoghurts, 750ml of milk etc
Primary prevention

• “Fudge factors”
  – Family history
    • 1.5 x risk
    • 2 x risk (if 2 or more first degree relatives affected)
  – South Asian Men
    • 1.4 x risk
High dose statins – How Low Should We Aim For?

High dose statin therapy trials
• MIRACL – atorvastatin (ACS cases)
• PROVE IT- TIMI 22 - atorvastatin (ACS)
• IDEAL – atorvastatin (post MI)
• TNT – atorvastatin (CHD)
• REVERSAL – atorvastatin (CHD)

The optimal level for LDL cholesterol is still unclear
Cholesterol – How Low Should We Aim For?

MIRACL study

• 3086 Patients with ACS
• Randomised to atorvastatin 80mg od or placebo between 24-96hrs post admission
• FU 16 weeks
• Primary end-point: Death/non-fatal MI, cardiac arrest with resuscitation, recurrent symptomatic myocardial ischaemia requiring rehospitalisation
• Results: 14.8% v 17.4%
• RR 0.84 (0.7-1.0) p = 0.048
• No difference in death, non-fatal MI or cardiac arrest

JAMA 2001;285:1711-8
Cholesterol – How Low?

PROVE IT – TI MI 22  (NEJM 2004;350)

• 4162 patients with ACS (within preceding 10 days) with initial chol < 6.2mmol/l
• 40mg pravastatin versus 80mg atorvastatin
• Primary endpoint: Death, MI, UA requiring hospitalisation, revascularisation and stroke
• Mean FU 24 months
• Non-inferiority trial
Cholesterol – How Low?

PROVE IT – TI MI 22   Results:

• LDL : 1.6mmol/l v 2.46mmol/l
• Primary endpoint: 22.4% v 26.3%
  • 16% reduction in favour of atorvastatin (p=0.005)
  • 69% in each group underwent PCI
  • Event differences evident as early as at 30 days
  • Benefit greatest in those with initial LDL >3.3mol/l
  • No difference in myalgia rates but LFTs elevated in 3.3% v 1.1%
• Data for stable CHD patients less clear cut:
  – TNT
  – IDEAL
High Dose Statins

TNT trial

- 10,001 patients with clinically evident stable CHD and LDL < 3.4mmol/l
- Randomised to Atorvastatin 10 mg v 80mg
- Median FU 4.9 years
- Primary endpoint: occurrence of first major CV event (death form CHD, non-fatal MI, resuscitation after cardiac arrest, or stroke)
  - Mean LDL: 2.6 mmol/l v 2.0 mmol/l
  - Primary event rate: 10.9% v 8.7% HR 0.78, p< 0.001
  - No difference in mortality rate
  - Abnormal LFTs: 0.2% v 1.2%

NEJM 2005;352:1425-35
High Dose Statins

IDEAL trial

- 8888 patients with previous MI
- Randomised to Atorvastatin 80mg od or simvastatin 20mg od
- Median FU 4.8 years
- Primary endpoint: occurrence of first major coronary event (death from CHD, non-fatal MI, resuscitation after cardiac arrest)
  - Mean LDL: 2.5 mmol/l v 2.0 mmol/l
  - Primary event rate: 10.4% v 9.3%  HR 0.89, p= 0.07
  - No difference in mortality rate
  - Non-fatal MI: 7.2% v 6% HR 0.83 p=0.02
  - Abnormal LFTs: 0.1% v 1.0%

JAMA 2005;19:2437-45
Cholesterol – How Low?

• Role of lower LDL versus CRP reduction
• Anti-inflammatory action of statins may be of importance in explaining early efficacy difference
  • CRP level reduction
  • Soluble CD40 ligand level reduction
How long should high dose statin therapy be continued for?

- Plaque modification/stabilisation – ACS cases
- Prevention of plaque progression
High Dose Statins & Plaque Progression

• REVERSAL trial:
  • 654 patients -> 20% CA stenosis
  • LDL 125-210 mg/dl (mean 3.9mmol/l)
  • Atorvastatin 80mg v Pravastatin 40mg
  • Primary endpoint:
    – % coronary plaque volume change - 0.4% v 2.7%

Also:
  – LDL: 2.05 mmol/l v 2.85 mmol/l
  – CRP: 36.4% reduction v 5.2%
• The ASTEROID study

  – Prospective open label trial of 507 patients for 24 months
  – Rosuvastatin 40 mg in patients with >20% luminal narrowing in at least 1 coronary vessel
  – Baseline LDL-C of 3.4 mmol/l
  – Primary efficacy end-point: % change in atheroma volume and in total atheroma volume in the 10 mm sub-segment of the coronary artery with the largest plaque volume at baseline

• Significant 53% reduction in LDL-C (mean post-treatment 1.6 mmol/l, p<0.001)

• Significant regression of atherosclerosis (p<0.001 versus baseline)
  – -0.79 (-1.21 to -0.53) median reduction in percent atheroma volume
  – -5.6 (-6.82 to -3.96) median reduction in most diseased 10 mm sub-segment

Therapy in addition to or alternative to statins

• If statins not tolerated or target LDL not reached potential adjunctive therapy includes:
  – Cholesterol absorption inhibitors eg ezetimibe
  – Bile acid sequestrants – anion exchange resins eg cholestyramine
  – Nicotinic acid
  – Fibrates
Ezetimibe

- Ezetimibe selectively inhibits intestinal cholesterol absorption
  - ↓ intestinal delivery of cholesterol to the liver
  - ↑ expression of hepatic LDL receptors
  - ↓ cholesterol content of atherogenic particles

- Ezetimibe and its active glucuronide metabolite circulate enterohepatically
  - Delivers agent back to the site of action
  - Limits systemic exposure
• **Ezetimibe**
  – Metabolized to its glucuronide in the intestinal wall
  – Transferred to the liver via the portal circulation
  – Excreted back into the duodenum via the bile
  – Once back in the intestine, the ezetimibe glucuronide may be then be deconjugated by intestinal bacterial flora, followed by reabsorption as ezetimibe from the small intestine
  – This repeated enterohepatic recirculation accounts for its long (22-hour) half-life.
  – Its relative limitation to the enterohepatic circulation accounts for its limited systemic exposure and thus potentially lower risk for adverse effects or drug interactions.

• **Ezetimibe is not an inducer or inhibitor of cytochrome P450 enzymes**, reducing the risk for potential drug interactions with many common drugs enzymatically affected by cytochrome P450 enzymes
Dual inhibition\textsuperscript{10,11}

- Liver synthesis: \(~300\) mg/day
- Biliary excretion: \(~1,000\) mg/day
- Dietary intake: \(~300-700\) mg/day
- Small bowel absorption: \(~700\) mg/day
- Faecal loss: 650-850 mg/day

STATINS

X

Circulation

EZETIMIBE
Mean % change in LDL-C from baseline at week 12

Placebo (n=52)
- 0.25 mg (n=47)
  - 4.3
- 1 mg (n=49)
  - 0.29
- 5 mg (n=49)
  - 16.4
- 10 mg (n=46)
  - 18.7

Ezetimibe
- 0.25 mg (n=47)
  - 9.9
- 1 mg (n=49)
  - 12.6
- 5 mg (n=49)
  - 16.4
- 10 mg (n=46)
  - 18.7

Atorvastatin

- 40 mg (n=66)
- 20 mg (n=60)
- 10 mg (n=60)
- 80 mg (n=62)

Ezetimibe + Atorvastatin
- 10 mg (n=65)

Mean % change in LDL-C from untreated baseline

-60% to 0%


P<0.01
Ezetimibe with a statin* in HoFH

-6.7 -7 -20.7 -27.5

Statin (80 mg) (n=17)
Statin (40/10 mg) (n=33)
Statin (80 mg) (n=17)
Statin (80 mg/10 mg) (n=17)

Mean % change from baseline


* Simvastatin or atorvastatin
Ezetimibe as add-on to statin therapy

Ezetimibe added to ongoing statin therapy: The EASE study\textsuperscript{17}

Statin with ezetimibe 10 mg
71.0\% of patients reach targets

Statin with placebo
20.6\% of patients reach targets

**Targets:**
- LDL-C <4.14 mmol/l in patients without CHD and with 0-1 risk factor
- LDL-C <3.37 mmol/l in patients with a ten year risk of CHD of \leq 20\% and with \geq 2 risk factors
- LDL-C <2.59 mmol/l in patients with a ten year risk of CHD of >20\% or with established CHD or CHD risk equivalent

Inegy: Simvastatin+ ezetimibe: Mean % change from baseline in LDL-C at 6 weeks

- Atorva 10 mg: -37.2%
- INEGY 10/10: -46.1%
- INEGY 10/20: -50.3%
Long-term tolerability

% adverse events at end of 48-week trial

- **Simvastatin (10-80 mg), n=78**
- **INEGY (10/10, 10/20, 10/40, 10/80), n=355**

- All adverse events
- Serious adverse events
- Treatment related adverse event
- Discontinuations due to adverse events
Ezetimibe

• No clinical outcome trials yet reported
• Ongoing
  – IMPROVE-IT trial
  – 18000 ACS cases randomised to 40mg simvastatin v 40/10 (S/E)
  – Due to complete 2012
  – Primary end-point: Cv death/MI/stroke/rehospitalisation for ACS/revascularisation
NICE & Ezetimibe: Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia

- Technology assessment published in Nov 2007

- **Recommends as monotherapy**
  - Primary hypercholesterolaemia IF contra-indications to or intolerant of statin

- **Recommends as co-administered therapy with statin**
  - If LDL/T Chol inadequately controlled by statin
Alternatives to statins

• Ezetimibe – 15-20% reduction in LDL
• Cholestyramine – interrupt enterohepatic circulation of bile acids – bind bile acids in intestinal lumen and increase faecal loss, thus increasing conversion of cholesterol to bile acids
  – Dose 4-16g/d
  – LDL reduced by 15-30%
  – HDL increases by 3-5%
  – TRG may increase
  – Side-effects: GI principally
Alternatives to statins

• Nicotinic acid – B vitamin
  – Decreases hepatic synthesis and release of VLDL
  – Thus LDL & IDL reduced
  – HDL catabolism also reduced
  – LDL is reduced by 10-25%
  – TRG by 20-25%
  – HDL increased by 15-35%
  – Principal side-effect is flushing
  – LFTs abnormal in 5%
HDL-Atherosclerosis Treatment Study (HATS)  
Niacin and Statin Outcome Trial

![Bar chart showing reduction in coronary death, MI, stroke, or revascularization.

23.7 in Placebo
2.6* in S + N
21.4 in AV
14.3 in S + N + AV

89% Reduction

*P<.05 vs Placebo

Alternatives to statins

• Fibrates
  – Complex mechanism of action
  – VLDL reduced (increased lipoprotein lipase activity)
  – HDL increases by 10-15%
  – LDL is reduced by 10-15%
  – TRG by 20-50%
  – HDL increased by 15-35%
  – Principal side-effects are GI (~ 5%)
  – Myopathy risk when used in combination with statins
FIELD Study

- 9795 participants – type 2 DM  (Lancet 2005;366:1849-61)
- Not taking statin therapy
- T.chol 3-6.5mmol/l, TC/HDL ratio >4 or TRG 1-5
- Fenofibrate 200mg od v palcebo*
- Primary end-point: Coronary events
- 5 yr follow-up
- 5.2% v 5.9% HR 0.89 p=0.16
- Non-fatal MI reduced by 24% p=0.01
- No difference in mortality

* % on statin at end: 11% v 17%
Combinations

- Statin & ezetimibe
- Statin & fibrate
- Statin & Cholestyramine
- Statin & nicotinic acid
- Statin & omega-3 fatty acids
Combinations

- Statin & ezetimibe: High LDL levels eg Familial hypercholesterolaemia
- Statin & fibrate:
- Statin & Cholestyramine:
- Statin & nicotinic acid
- Statin & omega-3 fatty acids:
Combinations

• Statin & ezetimibe:
• Statin & fibrate: High LDL, low HDL &/or high TRG eg DM dyslipidaemia
• Statin & Cholestyramine:
• Statin & nicotinic acid:
• Statin & omega-3 fatty acids:
Combinations

- Statin & ezetimibe
- Statin & fibrate:
- Statin & Cholestyramine: High LDL levels, eg Familial hypercholesterolaemia
- Statin & nicotinic acid:
- Statin & omega-3 fatty acids:
Combinations

- Statin & ezetimibe:
- Statin & fibrate:
- Statin & Cholestyramine:
- Statin & nicotinic acid: Low HDL eg DM dyslipidaemia
- Statin & omega-3 fatty acids:
Combinations

- Statin & ezetimibe:
- Statin & fibrate:
- Statin & Cholestyramine:
- Statin & nicotinic acid:
- Statin & omega-3 fatty acids: High LDL, high TRG
Future: HDL “Addition”

- HDL – anti-inflammatory, reversal of cholesterol transport, interference with atherogenic lipoproteins, improved endothelial function
- HDL variants have differing actions
- Apo –A1 Milano
- Phase I study of HDL mimic infusion in ACS patients
- IVUS at 5/52: -1% v 0.14% plaque volume change
Future: HDL “Addition”

- CETP Inhibitors
- CETP is a lipid transfer protein secreted by the liver and bound to HDL
- It facilitates transfer of cholesteryl esters from HDL molecules to VLDL, LDL & chlomicrons in exchange for triglycerides.
- Animal studies demonstrate HDL level increase and decrease in atherosclerotic lesions
- Early human work ongoing – torcetrapib - negative trials
# Omega 3 Fatty Acids

<table>
<thead>
<tr>
<th>Fish</th>
<th>Amount of fish (g) for 1g EPA/DHA</th>
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<tr>
<td>Tuna</td>
<td>66-357</td>
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<tr>
<td>Atlantic salmon</td>
<td>42-70</td>
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<tr>
<td>Mackerel</td>
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<td>313</td>
</tr>
<tr>
<td>Scallop</td>
<td>500</td>
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</table>
Optimal Diet

• Low fat diet
• Meta-analysis suggest that in trials lasting longer than 2 years CV events are reduced by up to 24% years of FU
• Reducing calorific % taken as fat, increasing polyunsaturated FA s (omega –6) probably not adequate in itself
Optimal Diet

- Seven Countries Study
- 25 years of FU
- Mortality rates from CHD 25 per 1000 (Greece) to 268 per 1000 (Finland)
- CV mortality
  - Directly correlated with animal food intake
  - Inversely correlated with vegetable, fish* and alcohol intake

* Especially fish rich in omega 3 fatty acids
Optimal Diet

- Population intervention: Finland
- CHD mortality decreased by 55% in men and 68% in women
- ¾ of this was explained by decrease in smoking, BP, serum cholesterol
- Total fat in diet went from 38% to 34%
  - Saturated fat 21% to 16%
  - Polyunsaturated fat 3% to 5%
  - Cholesterol intake decreased by 16%
- Fruit/vegetable intake increased by 2-3 fold
Mediterranean Diet

- Lyon Diet Heart Study Circulation 1999
- 600 patients with recent MI
- Adoption of Mediterranean diet* (advice by cardiologist & nutritionist – 1hr session) resulted in RR of MI or cardiac death of 0.28 (0.15-0.53)
  
  * Increased intake of fish, bread, fruit (every day), root & green vegetables, α linoleic acid (rapeseed oil margarine), reduced meat (poultry instead of red meat)
Optimal Diet

• High in fruit, vegetables & whole grains
• Minimal animal fats
• Fish high in omega 3 fatty acids (or “vegetarian option” – soybean walnut, rapeseed/canola oil)
• ? moderate alcohol intake
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reduction in all-cause mortality (95% C.I.)</th>
<th>Incident rate difference: lives saved /1000 pts treated / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>24% (17-30)</td>
<td>13</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>17% (5-27)</td>
<td>4</td>
</tr>
<tr>
<td>Statins</td>
<td>24% (5-40)</td>
<td>4</td>
</tr>
<tr>
<td>Anti-platelet drugs</td>
<td>16% (2-27)</td>
<td>7</td>
</tr>
<tr>
<td>Cardiac rehabilitation</td>
<td>26% (11-38)</td>
<td>9</td>
</tr>
<tr>
<td>OMACOR</td>
<td>20% (6-33)</td>
<td>5.7</td>
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</tbody>
</table>