Best practice in lipid management

Delivering best practice: 5 Steps / Interactive Case Study

Dr Chris Harris & Dr Youssef Beaini

Chair: Jean Hayhurst

In association with Heart UK
BRADFORD'S HEALTHY HEARTS

Live longer, better

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BRADFORD'S HEALTHY HEARTS
Bold and clear ambition

• By 2020, Bradford Districts CCG will reduce cardiovascular events by 10% which will result in 150 fewer strokes and 340 fewer heart attacks

• We will no longer be the 7th worst CCG in the country! [Bradford Districts CCG has the 7th worst CVD mortality rate under 75 in England]
Important points

• Strategic - Governing Body, Council of Reps, Clinical Board ie ownership
• NHS Right care - the story, workshop, clinical assembly
• Extensive stakeholder involvement/ pt engagement and comms++
• Secondary care supporting a population view
• Workload light for busy clinicians
• Achievable benchmarks of care- QI approach
• Practice champions, incentives, enthusiasm, momentum!!
Our key questions

What’s the target outcome?
How can we be smart about this?
Do we need to amend local clinical guidelines to achieve this?
So what have we done?

- Cholesterol
- Atrial fibrillation
- Hypertension

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Lipids, Statins and the Daily Mail!
STATINS!!

Don’t let Big Pharma ruin your health. Wake up to the cholesterol con!

Muscle aches
Joint pains
Impotence
Extreme lethargy
Tinnitus
Weakness
Weight gain
Cloudy urine
Hopelessness
Memory loss
Rage beyond reason
Personality change
Getting old quickly

STATINS KILL !!!

CHOLESTEROL DOES NOT

What your doctor know

Educate yourself: thincs.org, stopped_our_statins, statins side effects
Pills, Pills, Pills....
Statins have one of the largest evidence bases now
CVD mortality has fallen in the last year however the rate of decrease was lower than in other areas.
Raised blood cholesterol – global view

**Figure 47** World map showing the prevalence of raised blood cholesterol * in males (ages 25+, age standardized) (6), (* ≥ 5 mmol/l or on medication for raised blood cholesterol).
Log linear relations between Cholesterol and CVD event

Epidemiological studies have shown a log-linear relationship between LDL-C levels and relative CHD risk\textsuperscript{7}

Interventional studies have shown a linear relationship between LDL-C levels and major cardiovascular events\textsuperscript{8}
Lipids and Statins

Generally accepted now

- Lipid lowering with statins- similar CV risk reduction across all ranges of baseline dyslipidaemia.
- Clinical benefit is related to the absolute reduction in LDL-C.
- For secondary prevention intensive therapy is safe and arrests atherosclerosis
- In acute coronary syndromes high-dose statins provide a rapid early reduction in clinical events which may be related to non-LDL-C dependent anti-inflammatory effects.
Cholesterol Treatment Trialist’s (CTT) collaborators - meta-analyses of mortality and morbidity from all relevant large-scale randomised trials of statin therapy

- Data on 90,056 individuals from 14 trials were combined. mean follow-up of 5 years [approx 500,000 person years]
- Per 1mmol/l reduction in LDL-C;

- 12% reduction in all-cause mortality
- 19% reduction in coronary mortality,
- 24% reduction in the need for revascularisation
- 17% reduction in stroke and
- 21% reduction in any major vascular event.
- Importantly, a similar proportional benefit was observed in different age groups, across genders, at different levels of baseline lipids [including triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C)] and equally among those with prior CAD and cardiovascular (CV) risk factors as in those without.
The safety data presented in CTT come from randomised control trials some of which (e.g., HPS) have a run-in period and consider only patients who are able to tolerate statin therapy.

- Rhabdomyolysis was 3/100,000 person years,
- Myopathy was 11/100,000 person years,
- Peripheral neuropathy 12/100,000 person years,
- Liver disease even rarer.
Cochrane Collaboration and CTT collaboration 2013

- ‘Evidence now justified the use of statins in people of low cardiac risk’
- Problems with size and length of studies in low risk groups to show outcome benefit

- Cochrane figures for NNT over 5yrs;
  - NNT Low risk [<1% annually]- 167
  - NNT Intermediate risk [1-2% annually]-67
CTT reviews of side effects
BMJ non-cardiovascular effects of statins 2014

- **Myositis**
- CTT 26RCT’s - Rhabdomyolysis 0.5 per 1000 person years, 0.1 per 1000 person years [80mg atorvastatin vs 20mg atorvastatin]
- 35 statin trials - no significant increase in rhabdomyolysis vs placebo

- 60% of cases of rhabdomyolysis related to interactive drugs or high dose simvastatin
- CK rises reported but in statins and placebo

- **Myalgia [muscle pain without CK rise]**
- 21 studies no increased risk but broken down atorvastatin higher risk of myalgia [5% vs 1% approx]
- Finally meta-analysis of primary prevention - no increased risk of myalgia or myositis
- Recent studies show no effect on muscle performance of myalgia
- 2 recent studies found 80% and 90% of patients able to tolerate statins when re-challenged
Current views

• Observational study ‘18% of users had statin-related clinical events that may be interpreted as adverse reactions by patients or clinicians’

• Basis of the anti-statin lobby

• vs the pro-statin lobby;
• ‘in clinical trials just as many people taking placebo had muscle and joint pains as taking statins’

• Go next door for the ongoing debate!!
Risk of Diabetes

- 13 trials reviewed
- 4yr follow up 4.9 vs 4.5% developed DM
- NNH 250 over 4yrs
- Mainly confined to those already at high risk
- Some evidence of higher intensity Statins more likely

But overall benefit greatly outweighed the risk
Liver

- Meta-analysis 75,317 pts
- **Increased transaminases**
- Per 100,000 pt years high vs intermediate vs low dose
  - 271 vs 195 vs 114
- **No cases of liver failure**
- Estimation at one case per million [same as in US population from this report]
- ALT levels tend to normalise ?resolving steatosis
- ?high levels due to liver adaptation and not toxicity
- NB US guidelines – LFT’s initially then no further monitoring
NICE Guidance

- Lipid Modification and CV Risk assessment for the primary and secondary prevention of CVD

NICE guidance June 2014
Recommendations
Key Points

• Qrisk 2 [up to 84yrs!] and highlights a few caveats
• Communication re risk assessment
• Cardio-protective diet [avoid marlin, shark and swordfish]- don’t recommend plant stanols
• Lipids measurement- full lipid profile, risk assess, pick out FH then see specialist if TG’s really high >10 [on rpt fasting level] and TG’s 4.5-9.9 put risk up a bit
Statins

- Atorvastatin 20mg for:
  - Primary prevention [over 10% risk]
  - Type 1 DM [over 40yrs, DM 10yrs, other CVD risk factors]
  - Type 2 DM over 10% CV Risk
  - CKD but increase dose if 40% chol reduction not achieved [specialist input if severe CKD 4/5]

- Atorvastatin 80mg for:
  - Secondary prevention
  - Lower if interaction, very elderly [lower muscle mass], impaired renal function, pt preference

- Cost effective at £20,000 QALY gained
Follow up

• Measure at 3/12 and increase dose if 40% reduction not achieved
• Review, emphasise lifestyle, compliance, consider atorvastatin 80mg
• Discuss with pts on low intensity switch to high intensity
• Annual med review- consider an annual non-fasting blood test to inform discussion
Bradford’s Healthy Hearts programme board issues

• High intensity statin? [UK atorvastatin 20mg vs US atorvastatin 40mg]
• Emphasis on one to one discussions ?practical
• Need for uptitration based on percentage reduction again [all pts started on statin!] ?practical
• FU measurements 3/12 and after 1 year [US no longer recommended]
American College of Cardiology

• High-intensity statin therapy is defined as a daily dose that lowers LDL-C by ≥50% and moderate-intensity by 30% to <50%.

• All patients with ASCVD who are age ≤75 years, as well as patients >75 years, should receive high-intensity statin therapy
### High-Intensity Statin Therapy

- Lowers LDL-C by \( \sim \geq 50\% \)
- Atorvastatin 40*-80 mg
- Rosuvastatin 20 mg (40 mg)

### Moderate-Intensity Statin Therapy

- Lowers LDL-C by \( \sim 30\% \) to \(<50\%\)
- Atorvastatin 10 mg (20 mg)
- Rosuvastatin (5 mg) 10 mg
- Simvastatin 20-40 mg†
- Pravastatin 40 mg (80 mg)
- Lovastatin 40 mg
- Fluvastatin XL 80 mg
- Fluvastatin 40 mg bid
- Pitavastatin 2-4 mg

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*Down titrate if unable to tolerate atorvastatin 80 mg;†Initiation of or titration to simvastatin is not recommended by the FDA due to increased myopathy risk.
Italicics denotes FDA-approved doses that were not tested in trials reviewed for guideline development.
Once-daily doses unless otherwise specified. Avg LDL-C-lowering potential listed expected to vary in clinical practice.

Statins are grouped in this guideline as seen in Table 36. This grouping was agreed by GDG consensus, informed by analyses in the literature. This grouping is discussed further in Section 11.8.

**Table 36: Grouping of statins**

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>% reduction in low-density lipoprotein cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>10%(^1)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>15%(^1)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>23%(^1)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>31%(^1)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>38%(^3)</td>
</tr>
</tbody>
</table>
The base case analysis was based on an assumption of equivalent effectiveness between all high-intensity statins, due to a lack of evidence comparing the effectiveness of the different doses within the high-intensity class in terms of reducing clinical end points, although there is evidence of differing effectiveness of different doses in terms of reducing LDL-cholesterol levels. On this basis the cheapest high-intensity statin – atorvastatin 20 mg – was predicted to be the most cost effective. However, an additional threshold analysis showed that atorvastatin 40 mg would be cost effective compared to atorvastatin 20 mg if it was 1% relatively more effective in decreasing CV events than atorvastatin 20 mg and if there was no loss in utility due to increases in adverse events. It also showed that atorvastatin 80 mg would be cost effective compared to atorvastatin 20 mg if it was 2% relatively more effective than atorvastatin 20 mg in decreasing CV events and if there was no loss in utility due to increases in adverse events.
JBS 3 Recommendations 2014

• Statins are highly effective at reducing CVD events with evidence of benefit to LDL-c levels <2 mmol/L which, justifies intensive lowering.
• Statins are safe
• Drug therapy to raise HDL-c has not been shown to reduce CVD risk and is not currently indicated.
• Statins should be prescribed with a ‘lower is better’ approach to achieve values of at least <2.5 mmol/L for non-HDL-c (equivalent to <1.8 mmol/L for LDL-c).
The Challenge!

CVD patients with Total Cholesterol less than or equal to 4 (in the last 18 months) - District CCG

Target = 87%
BHH Recommendation

• Primary prevention - 40mg Atorvastatin

• Secondary prevention - 80mg Atorvastatin

• Irrespective of Cholesterol level

• FU [cholesterol] and ALT at 3 months - no further monitoring
More ambitious than NICE but in line with ACC and JBS3

CV disease key morbidity in BDCCCG and BCCCG populations

In line with direction of travel

Effective dose first and stop monitoring
• **Fibrates** - FIELD and ADVANCE trials showed no outcome benefit

• **Ezetimibe** - SHARP [benefit in CKD], IMPROVE IT and SEAS trials- issues of statin dose in all 3

• **Niacin** to raise HDL- no outcome benefit

• **PCSK9 inhibitors**!
Lipids/Statins
Examples of simplified approach - statins

• Same multi-faceted approach across the board
• Agreed protocol with secondary care, simplified, aimed at reduced primary care workload and “fire and forget” approach:
  ❖ primary prevention: atorvastatin 40mg
  ❖ secondary prevention: atorvastatin 80mg
• Work at scale with letters sent to patients rather than face-to-face consults. Supported by website, YouTube channel, wide ranging comms package, patient education sessions, patient participation groups.
Lipid management for patients with CVD and risks of CVD

Primary prevention
Atorvastatin 40mg

Patients with:
CKD 3 and above (regardless of cholesterol level or risk of CVD)
aim for cholesterol <4mmol/l with up-titration to 80mg
Atorvastatin if required
Qrisk2>20% 10 year Cardiovascular Risk
Diabetes Type 1
- who are older than 40 or
- nephropathy or
- had DM for more than 10 years or
- other CVD risk factors
Type 2 Diabetes: aim for cholesterol <4mmol/l with up-titration to 80mg Atorvastatin if required

Before starting lipid modification therapy take full lipid profile
Start Atorvastatin 40mg
Repeat lipid profile after 3 months and never after if not indicated

Secondary prevention
Atorvastatin 80mg

Patients with:
established CVD
CHD, Stroke & TIA, PAD

Before starting lipid modification therapy take full lipid profile
Start Atorvastatin 80mg
Repeat lipid profile after 3 months and never after if not indicated

Be aware of
- Familial Hyperlipidaemia in anyone with a cholesterol >7.5mmol/l
- Persistent Triglyceride levels >10
- End stage renal disease
- Consider Diabetes e-consultation or Renal e-consultation in these cases

This guide was developed and agreed with
- Dr Stoves - Consultant in renal medicine
- Dr Lindsay - Consultant cardiologist
- Dr Patterson - Consultant in stroke medicine
- Mr Mercer - Consultant vascular surgeon
- Dr Harris - GP lead Bradford’s Healthy Hearts programme
- Dr Beain - CCG CVD Clinical Lead and GPwSI cardiology
- Mr Fall - Public Health Consultant
- Dr Whitelaw - Consultant in diabetes
Statin switches (1)

• Over **6000 on simvastatin** with total cholesterol above 4 mmol/l or LDL >2 mmol/l were **switched to atorvastatin 40/80mg**: achieved 0.56 mmol/l reduction in LDL (and TC 0.9mmol/l) over 3 months (p<0.001). Some patients had cholesterol improve from 8 to 3!

• Approximately 5,000 for primary prevention and approx 1,000 for secondary prevention
Statin switches (2)

• Innovative work at scale – letters sent out, supported by website, comms, large patient education programme.

• Used complex GP computer searches but simple output – one list of patients, sent letters to these and bulk switch repeat template, takes 1-2 minutes.

• If done in the traditional face-to-face way, statin switches + QRISK work would take approximately an extra 24,000-36,000 appointments across the CCG!
STATIN switch: outcomes achieved

Graph showing outcomes achieved from October 2014 to March 2015 for primary prevention and secondary prevention.
STATIN switch: outcomes

- Patient numbers x treatment uptake x relative mortality reduction x one-year case fatality

0.9mmol/ reduction = 1097 x 78% x 20% x 5.4% = potentially 9 deaths prevented or postponed

0.9mmol/ reduction = 6000 x 78% x 20% x 3% = potentially 28 deaths prevented or postponed

- 37 deaths prevented or postponed in one year
Our website
• New NICE guidance on QRISK2 10-20%
• In Bradford, 4% coded with QRISK2 10-20% (14,000)
• Another 30-40,000 estimated not yet coded/assessed
• Of those with Qrisk2 10-20%, 4,600 (32%) were on statin
• Potential problems with a full implementation due to lack of resources
• Same large scale approach as statin switches – letters sent, supported by comms package, website, etc.

• “Opt in” vs “opt out”

• QRISK2 (10-20 and >20%): overall, 7000 patients offered statin. Preliminary figures show around 70-80% uptake but follow-up figures being compiled currently to assess longer term adherence
Total cholesterol range for QRISK2

**Early results:** (for QRISK 10-20% and >20%)

- n=2163
- Mean total cholesterol reduction was 0.39 mmol/l reduction in that population
- P<0.001 for change
Combined outcomes

To date for Bradford’s Healthy Hearts:

- Switched 6,000 statins
- QRISK >20%: 4000 started on statins
- QRISK 10-20%: 3000 started on statins
- AF: 963 started on OAC
- Hypertension: over 2,500 newly diagnosed, nearly 1% increase in prevalence. Nearly 700 with BP newly to target

Over 15 months more than 17,000 people had an intervention that improved their health.
CVD mortality rate under 75 per 100,000 population pre-BHH versus post-BHH

CVD mortality per 100000


BCCCG
BDCCG
AWCCCG

www.bradfordshealthyhearts.co.uk
### Percentage change in CVD mortality under 75 (absolute numbers)

<table>
<thead>
<tr>
<th>CCG</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airedale, Wharfedale &amp; Craven CCG</td>
<td>Increased 3%</td>
</tr>
<tr>
<td>Bradford City CCG</td>
<td>Reduced 6.5%</td>
</tr>
<tr>
<td>Bradford Districts CCG</td>
<td>Reduced 6.6%</td>
</tr>
</tbody>
</table>
Under 75 non-elective admissions for CVD (MI and stroke)

BHH launched

www.bradfordshealthyhearts.co.uk
Non-elective admissions before BHH intervention vs “control group”, AWC CCG

Airedale, Wharfedale & Craven CCG

• Mean CVD non-elective per month per 100,000 population = 46.4/m/100,000

Bradford Districts CCG

• Mean CVD non-elective per month per 100,000 population = 42.8/m/100,000

P = 0.1 for difference between groups
No statistical difference between groups

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Non-elective admissions after BHH intervention vs “control” group

Airedale, Wharfedale & Craven CCG
- Mean CVD non-elective per month per 100,000 population = 45.7/m/100,000

Bradford Districts CCG
- Mean CVD non-elective per month per 100,000 population = 37.6/m/100,000

P=0.003 for difference between groups
8.1 fewer admissions per month per 100,000
## Non-elective admissions: change over time*

<table>
<thead>
<tr>
<th>CCG</th>
<th>CVD non-elective admissions change over time</th>
<th>Additional CVD events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airedale, Wharfedale &amp; Craven CCG</td>
<td>-1% (-8 fewer CVD events)</td>
<td></td>
</tr>
<tr>
<td>Bradford City CCG</td>
<td>+6% (32 additional CVD events)</td>
<td></td>
</tr>
<tr>
<td>Bradford Districts CCG</td>
<td>-10% (-211 fewer CVD events)</td>
<td>137 fewer MIs and 74 fewer strokes</td>
</tr>
</tbody>
</table>

*As compared to the previous 15 months

[www.bradfordhealthyhearts.co.uk](http://www.bradfordhealthyhearts.co.uk)
Conservative cost savings based on real outcome figures

Cost of stroke = £11,000
74*11000= £814,000

Cost of MI = £5,500
137*5500= £753,500

Gross savings £1,567,500
Net savings approximately £1,200,000 over first 15 months
Winner, BMJ awards 2016:

“Inspirational leadership at scale, taking forward ambitious targets to tackle long standing public health challenges, and the engagement with the public whilst balancing demands on the clinical workforce was impressive.”
Summary

- Population-based mind-set and approach
- Engagement at all levels, across all organisations
- Multiple approaches to the population but not ‘please see your GP/PN to discuss further’
- Flog IT to produce what you want
- Be ambitious and brave!
Thank-you from the clinical leadership team of Bradford Districts CCG
5 Key Messages

1/ Treat based on CV risk
2/ Use an effective dose of Statin first time
3/ Check cholesterol and ALT once
4/ Try 3 Statins before giving up [and explore Statin resistance...]
5/ Don’t feel compelled to use other agents to make the numbers look better!
BRADFORD'S HEALTHY HEARTS

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Case Study

• 49 year old man
• Works on oil rig
• Hypertensive
• Diabetic
• BMI 35
• HbA1c 47
• Qrisk 49%
• TC 7.2  LDL 4.0 HDL 0.8 Triglycerides 3.9  (drinks 10 units alcohol per week and TFT normal)
Case Study – Visit 1

• Attended for BP management
• BP 172/94
• On candesartan 8mg OD, amlodipine 10mg OD
• Opportunistic discussion about CVD risk
• Started atorvastatin 40mg OD
• Candesartan gradually increased to 32mg OD over next few weeks by nurse.
Case Study – Visit 2

• BP 155/88 (Home BP ~150/80)
• Says taking medication regularly
• Allergic indapamide in past (rash). Started on Bendroflumethiazide 2.5mg OD
Case Study – Visit 3

- BP 141/80 (Home BP ~135/80)
- Repeat lipids done:
  - TC 20
  - Triglycerides 72
  - Feels fine
Case Study

• What would you do next?

• Admit
• Start atorvastatin 80mg OD
• Add fibrate
• Add Omacor
• Add nicotinic acid
• Refer to lipid clinic
• Recheck lipids (+-fasting)
Case Study

• Rechecked lipids urgently (was fasted, luckily), similar results later that day
• Results discussed with cardiologist on-call who discussed with lipid chemical pathologist in different city:
  • Stop bendroflumethiazide
  • Add fibrate (and check CK)
  • Add Omacor
  • Keep atorvastatin at 40mg
  • Clear advice about pancreatitis risk
Case Study

2 weeks later, lipids were:
TC 12
Triglycerides 28

4 weeks later:
TC 6
Triglycerides 7

6 weeks later:
TC 4
Triglycerides 2.1
Case Study

Take home messages

Most of our patients with dyslipidaemia will not have a secondary cause. Drugs that can cause dyslipidaemia:

- Thiazides
- Propranolol
- Hormones
- Anabolic steroids
- Glucocorticoids
- Danazol
- Rosiglitazone and pioglitazone
- Amiodarone
- Isotretinoin
- Immunosuppressive drugs (cyclosporin)
- Alcohol
Case Study

Take home messages

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