Familial Hypercholesterolaemia: Finding FH and Primary Prevention

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(Relatively) Simple Genetics!

Familial Hypercholesterolaemia

- FH one of the most common genetic disorders known in humans.
- Monogenic condition, prevalence 1:500.
- Raised LDL-cholesterol.
- Premature CHD - if untreated!
Pathophysiology / treating FH
Mortality with Familial Hypercholesterolaemia

• **Simon Broome Register – FH patients**
  - Cohort 605 men and 580 women definite FH – 21 lipid clinics
  - Age 20-79 years
  - Prospective follow up 1980 – 1995

• **Untreated : cumulative risk for premature CHD**
  - men (>50% by 50 years )
  - women (>30% by 60 years)

"Diagnosing and treating people with FH and ‘cascade’ screening their families provides an opportunity for preventing the damage caused by coronary heart disease"
Latent disease: birth – 30s
Symptomatic CHD: 30s onwards

FH patients have high LDL-C from Birth → high LDL-C BURDEN

By 45yrs FH patient has accumulated LDL-C exposure of non-FH 70yr old, explaining high CHD risk and need for aggressive lipid-lowering
Management of FH patients

– NICE CG 71:
  – Consider prescribing a **high-intensity statin** to
  – achieve a reduction in LDL-C concentration
  – of greater than 50% from baseline.

• First line – higher intensity statin therapy
  (maximum tolerated dose)
• 2nd line – ezetimibe / fibrates / bile acid
  sequestrants
Dose-related reduction in LDL-C concentrations with increasing statin doses

Mean reduction in LDL-C in a meta-analysis of 37 studies, which included over 32,000 patients

<table>
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<th>Statin</th>
<th>Dose (mg)</th>
<th>Reduction in LDL-C</th>
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<td>Simvastatin</td>
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<td>27.4%</td>
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<td>40</td>
<td>38.9%</td>
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<td>Rosuvastatin</td>
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<td>20</td>
<td>41.4%</td>
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<td>46.2%</td>
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<tr>
<td></td>
<td>80</td>
<td>50.2%</td>
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In a separate trial (STELLAR), pravastatin 40 mg reduced LDL-C by 29.7%.

CRESTOR 5 mg is the recommended start dose for patients of Asian origin and those with pre-disposing risk factors for myopathy.

FH in Wales and the UK

- 1 in 500
- Autosomal Dominant
- 110,000 in UK
- ~6000 in Wales
- <20% diagnosed and treated
Provision of adult and paediatric clinic slots have increased across Wales – Including new clinics throughout BCUHB (since 2011).
Finding Index Cases - Clinical Signs
Why genetic testing?

Lipid profiles can give equivocal results for family testing

DNA versus cholesterol-based diagnosis ~ 15-20% of family members would have been incorrectly classified based on cholesterol testing alone
Umans-Eckehausen et al. Review of the first 5 years of screening for familial hypercholesterolaemia in the Netherlands Lancet 357: 165-168
Case history – one family’s experience of FH...

41 yo fit and active civil servant.
Admitted on Boxing Day 2010 with central chest pain
Anterior NSTEMI, Tchol 9.7 mmol/L
Transferred to Liverpool Heart & Chest Hosp:
proximal LAD 99% stenosis ( PCI to LAD )
Good recovery post PCI.

Currently 19 individuals have been tested
8 people tested +ve, 12 tested –ve.
Once Successfully Treated - Most Pt’s with History of Significantly Elevated LDL Levels are Not Considered for Genetic Testing / FH
Offering FH genetic screening direct to primary care

• THE PROBLEM

• Historically FH largely missed / not diagnosed or treated, often because it fell between professional groups.

• Many FH patients have been treated and well managed in primary care. Current lipid levels are within acceptable limits.

• Unless the original baseline (untreated) results are reviewed, these patients would not have a diagnosis of FH clearly defined.
Lab Based Cholesterol Testing Review (BCUHB)

• PROPOSED SOLUTION

• Cholesterol tests ~ 6000 per hospital / month or 216,000 per year total across BCUHB!

• Historical results available going back to the last 10 years or more.

  • Search Criteria :
    • LDL 6.5 or Higher (triglycerides < 2.5) - Data from 3 DGH’s
    • across BCU done in the last 10 years
High LDL levels in N. Wales - pop: 703,950

<table>
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<th>Nov-14</th>
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<th>Total</th>
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<td>36</td>
<td>131</td>
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<tr>
<td>Ysbyty Glan Clwyd</td>
<td>88</td>
<td>51</td>
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<tr>
<td>Wrexham Maelor</td>
<td>100</td>
<td>39</td>
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</table>
Aims of Primary care FH genotyping programme

1. Proactively identify lists of patients who have historical LDL > 7.5mmol/L who would qualify for genotyping programme.

2. Work together with primary care to have these patients consented for genotyping by the BCUHB genetics department (with FH nurse).

3. Patients who are tested positive for FH mutation will then go for directly for family cascade screening.

4. Shared care together with primary care in these patients and their families FH management.

5. Potentially simple project can be used for audit / Quality improvement as part of Appraisal process.
BCUHB: LDL >7.5mmol

Results (Trigs <2.5mmol)
Process for Proactive Engagement with GP’s – sharing of LDL search data

- Approval granted by:
  - North Wales Cardiac Network Board
  - BCUHB Clinical Effectiveness / Audit team and
  - BCUHB Information Governance departments (Caldicott Guardian)
  - North Wales Local Medical Committee
  - Local patient / service user group
“I am so glad that there is, and will be, clinics for these families; anything that can prevent needless loss of life is worth doing, so please tell the powers that be that we need more of these clinics.

Diagnosis is paramount, I don't think I am speaking out of turn to say that we all agreed it was a good thing”
+ve FH Mutations with LDL $\geq 7.5$ mmol
Cardiac Cath Lab LDL Audit

• Over 100 individuals LDL ≥6.5 known to have attended Ysbyty Glan Clwyd Cath Lab.

• Prospective work ongoing identifying patients & offering genetic testing

Initial retrospective review – carried out by local cardiologist & FH Nurse. ~1 in 120 eligible for genotyping.

Prospective audit ongoing: ~1 in 80 pts eligible for genotyping.
74yo lady (LDL>8.5mmol) +ve FH
Summary

• FH is relatively common cause of premature CVD.
• Improving rates of finding index patients needs close work between primary and secondary care!
• Identifying pre-symptomatic family members through cascade testing can provide an effective form of preventative cardiology.
Thank You!

• www.FHwales.co.uk
Patients 40 years and over

Pre-existing CVD

SECONDARY PREVENTION

Chronic kidney disease (CKD)

NO

YES

Other high-risk groups
- CKD (eGFR <60ml/min/1.73m² and/or albuminuria)
- Type I diabetes (especially if >10-year history, established nephropathy or other CVD risk factors)
- Age ≥85 years
  Note: Familial lipid disorders - see NICE Clinical Guideline CG71

Perform clinical assessment, offer lifestyle advice and manage modifiable risk factors (see box 1)

Estimate 10-year CVD risk using QRISK2 equation and clinical judgment

≥10% risk

<10% risk

Risk modifiers
- Ethnicity
- Family history of premature CVD
- Other considerations
  - socioeconomic status
  - BMI >40kg/m²
  - type II diabetes
  - serious mental health problems
  - treated with antihypertensives, lipid-modifying drugs, antipsychotics, corticosteroids or immunosuppressants
  - recently stopped smoking
  - treated for HIV
  - systemic inflammatory disorders

Perform clinical assessment, offer lifestyle advice and manage modifiable risk factors (see box 1)

Atorvastatin 80mg
- Use lower dose if potential drug interactions, high risk of adverse effects or patient prefers
- Perform clinical assessment and offer lifestyle advice (see box 1)
- Management of modifiable risk factors should be performed but must not delay statin treatment

Follow-up of patients taking statins

Efficacy monitoring
- Measure TC, HDL-C and non-HDL-C at 3 months – If <40% reduction in non-HDL-C, check adherence, timing of dose, diet and lifestyle measures and consider increasing dose if <80mg and patient at high risk (seek specialist advice if eGFR <30ml/min/1.73m²)
- Review patients annually thereafter and consider measuring non-HDL-C to inform discussion
- Consider switching patients taking a low- or medium-intensity statin to a high-intensity statin (see box 2)

Safety monitoring
- Measure transaminases within 3 months and at 12 months (not again unless clinically indicated)
- Advise patients to report muscle pain, tenderness or weakness; measure creatine kinase if occurs
- Advise women to stop taking statin if pregnancy is a possibility or 3 months before attempting to conceive

Atorvastatin 20mg

High-intensity statin not tolerated (see box 2)

≥10% risk

<10% risk

- Reduce to maximum tolerated dose
- If adverse effects on high-intensity statin:
  - Interrupt treatment and restart to check symptoms related to statin
  - Reduce dose
  - Change to lower-intensity statin (see box 2)
- Seek specialist advice if patient in high-risk group and intolerant to 3 different statins

KEY: Non-HDL-C = TC – HDL-C
Most FH due to LDLR mutations, 5% by APOB, 2% PCSK9

Removal of LDL from the blood dependent on 3 proteins

gain of function mutations increasing the degradation of the LDL receptor
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<th>LDL</th>
<th>Mutation</th>
<th>No Index</th>
<th>Case</th>
<th>Notes</th>
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<td>9</td>
<td>LDL Flange - 6.69-9.8mmol (3-10mmol)</td>
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<td>11.1</td>
<td>Deletion of LDLR promoter to exon 1</td>
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<tr>
<td>10.5</td>
<td>Deletion of exon 7 LDLR</td>
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**common deletion of exons 2-6 of the LDLR gene**

This deletion is the most common mutation in the LDLR gene detected to date in the North-West Region of the UK.
BCUHB. Patients whose LDL > 6.5mmol/L & Trigs < 2.5mmol/L

By Age Range

- Aged less than 25 years = 25
- Aged between 25 – 34 years = 48
- Aged between 35 – 44 years = 132
- Aged between 45 – 54 years = 325
- Aged between 55 – 64 years = 621
- Aged between 65 – 74 years = 676
- Aged 75 years or older = 519
GPs N. Powys

- Llanfyllin Medical Centre, High Street, Llanfyllin, Powys, SY22 5DG (Evans HC)01691 648054
- Welshpool Health Centre, Salop Road, Welshpool, Powys, SY21 7ER (Lewis MR)01938 553118
- The Surgery, Church Road, Guilsfield, Powys, SY21 9NJ (Branch Surgery)01938 553858
- Health Centre, Llanfair Caereinion, Welshpool, Powys, SY21 0RT (Evans AV)01938 810279
- Glantwymyn Health Centre, Cemmaes Road, Machynlleth, Powys, SY20 8LB (Morpeth S)01650 511227
- Machynlleth Health Centre, Forge Road, Machynlleth, Powys, SY20 8EQ (Upadhyay M)01654 702224
- Newtown Medical Centre, Park Street, Newtown, Powys, SY16 1EF01686 611611
- Montgomery Health Centre, Well Street, Montgomery, Powys, SY15 6PF (Reid A)01686 668217
- Arwystli Medical Practice, Mount Lane, Llanidloes, Powys, SY18 6EZ (Leslie SM)
- Caersws Health Centre, Llys Meddyg, Manthrig Lane, Caersws, Powys, SY17 5EX (Branch Surgery)01686 688225

Family Hypercholesterolaemia

Wales
Care Integration Awards 2013
The FH Wales Service has made it on to the shortlist for the Care Integration Awards 2013.

Familial Hypercholesterolaemia (FH) is a common inherited condition affecting around 1 in 500 of the UK population. It is caused by an abnormal gene which results in very high cholesterol levels in the blood.

People with FH, if untreated, are at an increased risk of early coronary heart disease. The FH Wales Service identifies and treats individuals and families in Wales.

FH Resources
News from the FH Service
News articles from the service

FH Articles and News Reports
Links to Hypercholesterolaemia articles

FH Information Links
Links to on-line resources and health organisations

The FH Service for Wales aims to diagnose individuals and families affected by FH so that treatment can prevent early onset heart disease.