A historical timeline for atherothrombotic cardiovascular disease
The past – present – future continuum for risk factors, diagnostic tools and treatments
My mummy had severe atheroma

Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations

CT of 137 Egyptian, Aleutian, Puebloan and Peruvian mummies
34% had “atheroma”: 20% had aortic, 18% had proximal PVD, 18% had distal PVD, 12% had carotid, but only 6% had coronary “atheroma”.

Lancet Mar 10th 2013
Gene / environment interactions; The latter have changed more than the former

- Environmental factors (diet & exercise) determine **HOW MANY**
- Genetic factors select those susceptible **WHO**

<table>
<thead>
<tr>
<th>NUTRIENT</th>
<th>THEN</th>
<th>NOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>34%</td>
<td>12%</td>
</tr>
<tr>
<td>Fat</td>
<td>21%</td>
<td>36%</td>
</tr>
<tr>
<td>P:S</td>
<td>1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Fibre</td>
<td>46g</td>
<td>20g</td>
</tr>
<tr>
<td>Salt</td>
<td>690mg</td>
<td>2-7g</td>
</tr>
<tr>
<td>Calcium</td>
<td>1580 “</td>
<td>740mg</td>
</tr>
<tr>
<td>Vit C</td>
<td>390mg</td>
<td>88mg</td>
</tr>
</tbody>
</table>
Heart Disease – Ancient History


- 1913: Anitschlow, St Petersburgh. Induced atherosclerotic coronary disease in cholesterol-fed rabbit model.
Heart Disease – Things get worse


- 1938, C Mueller & S Thannhauser, Oslo & Boston Identify Familial Hypercholesterolaemia and its acceleration of CHD.
Heart Disease – Things get even worse

- 1951, Barr, Russ & Eder, Bethesda, Identified associations between CHD and increased beta (LDL), decreased alpha (HDL) lipoproteins

- 1955, Havel, Eder & Bragdon, Bethesda, Separated lipoproteins by preparative ultracentrifugation.
1963, Ancel Keys, Seven Countries Study implicates saturated fat and plasma cholesterol levels.

1964, Konrad Bloch, Cambridge, Nobel Prize for elucidation of Cholesterol synthesis via HMGCoA Reductase.

1967, Fredricksen, Levy & Lees, Bethesda, Clinical Classification System based on lipid EPG findings (Types I – V)
Heart Disease – Turning the corner

1969, Meyer Burstein, Paris
Precipitation of lipoproteins, fore-runner of automated HDL-C.

1973, Robert Friedewald, Bethesda,
Calculation of LDL cholesterol from automated cholesterol, triglyceride and HDL-C results.

1975, Various authors, Framingham,
Major risk factors for CHD identified and targeted.
Heart Disease – The remarkable decline 1975 - 2015

Risk factors and biomarkers for risk assessment

Therapy

Public health guidelines

Note: Age-standardised to the 2001 Australian population.

Figure 3.12: Cardiovascular disease death rates, by sex, 1907-2007
Risk factors and biomarkers

Lipoprotein (a) etc  
Kare Berg discovers Lp(a) 1965

Inflammation etc  
Paul Ridker treats hs-CRP 2008

Metabolic Syndrome etc  
Salim Yusuf reports Interheart

Genetics etc  
Ruth MacPherson uses GWAS to implicate Ch 9 SNP 2006
1985: NIH identifies LDL cholesterol as CHD risk factor and target for therapy.

1988: Adult Treatment Panel 1 Guidelines, revised 1991

2003: ATP 3 includes risk calculator

2013: ATP 4 emphasises absolute risk (>7.5% / 10y) but abandons LDL targets and non-statin therapy.
1955: R Altschul, Toronto, reports that Niacin reduces cholesterol.

1975: P Canner, Bethesda, reports that Niacin reduces CHD in Coronary Drug Project. Later reports mortality benefit.


1987: Heike Frick reports that Gemfibrozil prevents CHD in Helsinki Heart Study.

2006: Tony Keech and others report that fibrates prevent CHD in patients with dyslipidaemia (High TG, low HDL)

1997: Harry David, New Jersey, reports that blockade of NCP1L1 transporter with ezetimibe reduces LDL-C

2014: Anticipated report of IMPROVE-IT trial of ezetimibe.

2006: Philip Barter, Sydney, reports premature cessation of 1st CETPI trial (with Torcetrapib) due to excess CVD.
1975, Akira Endo, Tokyo, extracts compactin from fungus Penecillium Citrium.

1987, Al Alberts and Roy Vagelos, Rahway, develop lovastatin and gain marketing approval.

1994, Terje Pedersen, Oslo, reports mortality benefit in 4S trial of Simvastatin.

2012, Taylor et al compile Cochrane systematic review which concludes that statin treatment is safe, and associated with reduced mortality, even in primary prevention.
Where to from here?
Risk factors and biomarkers

Diagnostic trends: Friedewald LDL-C may not last:

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>CHD RR, 95% CI</th>
<th>P-Trend</th>
</tr>
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<tbody>
<tr>
<td>LDL-C</td>
<td>2.07 (1.24 – 3.45)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>2.75 (1.62 – 4.67)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Apo B</td>
<td>2.98 (1.76 – 5.06)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Effects of Anti-PCSK9 or CETP Inhibitors therapy
Where to from here?
Risk factors and biomarkers such as Lp(a)

Atherogenic actions

Significant association with CHD
By Mendelian Randomisation
Where to from here?
Diagnostic tools: Non-invasive imaging

Discriminates intermediate risk?
New entity of “sub-clinical cardiovascular disease between Primary and secondary prevention

? Suitable for serial studies

[Graph showing event rate distribution and cumulative MI-free survival over years of follow-up]
Where to from here?
Diagnostic tools:
Next generation sequencing eg in FH

FH accelerates CHD by 20 – 40 years.
“Low hanging fruit” for prevention
Requires Index Case detection and
Family cascade Screening

Figure 1 | Changes in instrument capacity over the past decade, and the timing of major sequencing projects. Top, increasing scale of data output per run plotted on a logarithmic scale. Middle, timeline representing major milestones in massively parallel sequencing platform introduction and instrument revisions. Bottom, the timing of several projects and milestones described in the text.
Unexplained FH due to gain-of-function Proprotein Convertase Subtilisin Kexin-9 (PCSK9). CHD protection in loss-of-function
New therapies: Anti PCSK9 antibodies.
Where to from here?
Therapy: Antisense oligonucleotides and gene therapy

Rapid antisense development: Anti Apo B (mipomersin)
Anticipate anti-PCSK, anti Apo C3 etc antisense.

EMA approval for gene replacement therapy for Lipoprotein Lipase deficiency
Summary:

Atherothrombotic heart disease has caused immeasurable morbidity and mortality.

Research into its underlying aetiology and treatment has a long history of incremental progress and eventual success.

Significant levels of CHD persist, but sophisticated new techniques offer hope of eventual prevention.