



# Broadcast Summary

## The Evidence Base

With Dr Malcolm Kendrick

*First broadcast on 20<sup>th</sup> May 2015*

### Malcolm Kendrick

- A practising GP, also working in Intermediate Care
- Original Member of The Centre For Evidence-Based Medicine
- Original Member of The International Network of Cholesterol Sceptics (THINCS – a small, select group of subject-matter experts)
- Set up the online education system for the European Society of Cardiology

### The Cholesterol Hypothesis

- The hypothesis changes and mutates (possibly in order to try to accommodate inconvenient evidence which contradicts the hypothesis!)
- The hypothesis:
  - You eat cholesterol
  - The level of cholesterol in your blood rises
  - The arteries become narrowed by plaques of cholesterol
  - This ultimately leads to heart attacks and strokes
- The hypothesis was “justified” by research conducted by Nikolay Anichkov, who showed in 1913 that rabbits (vegetarians, remember) developed arterial plaques if injected with cholesterol (found only in food from animal sources). The same research, on other animals, showed no such effect, however. Not to mention the fact that it wasn’t actually cholesterol that Anichkov injected – it was oxidized cholesterol, a very different substance!
- Hypothesis really took off in post war USA, when heart disease increased massively.

- Ancel Keys decided that cholesterol was the cause, but could not prove the theory in humans
- Regarded as most dangerous was the LDL (low-density lipoprotein)<sup>1</sup>
- Keys then decided the answer was saturated fat, and by a highly selective process (ie excluding countries that didn't fit the model), showed a linear relationship between saturated fat intake and heart disease
- In fact, statistics show that heart disease rates have been falling steadily in all first world countries over the last 40 – 50 years
- In Eastern Europe the rates increased dramatically as the Berlin Wall came down:
  - Average male life expectancy fell by 7 years
  - Possibly due to migrational stress
- Data since the late 70s pretty consistent due to the MONICA (MONItoring trends and determinants in CARDiovascular disease) study – 32 centres in 21 different countries
- Problems:
  - Cholesterol is water insoluble, so cannot float in the bloodstream, therefore, it is transported in lipoproteins.
  - The liver produces cholesterol naturally (about the equivalent amount to that in 40 eggs – every day). It's essential for cells – the brain is 25% cholesterol, almost all of synapses are cholesterol.
  - Natural feedback mechanisms are designed to maintain cholesterol at the required level.
  - It goes to the liver for repackaging. It was proposed that the liver converted saturated fat to cholesterol, but there is no logic to this, and it requires the conversion of a very simple molecule to a very complex one
  - There is no evidence at all linking raised cholesterol to strokes
- A modification of the theory:
  - Consumption of saturated fats reduces LDL receptors, hence the level of blood LDL increases
  - But there's no realistic way for this to happen!
- Arterial plaques are NOT made up of cholesterol
  - This idea first proposed by Virchow, in the 1850s
  - In fact what Virchow observed was cholesterol crystals, which only exist as part of red blood cell membranes
  - They contain SOME cholesterol, but to assume that this caused the plaque is illogical (Uffe Ravnskov – see the (long!) list of papers in the Annex)
  - Cholesterol is a repair substance and will therefore be found wherever there is damage

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<sup>1</sup> Note that subsequent trials of drugs to *increase* HDL levels ("good" cholesterol) were stopped when they were found to increase mortality...

- It is one of very many substances found in plaques
- The cholesterol hypothesis has a remarkable capacity to withstand unwelcome, contradictory evidence :
  - In 1970s, Scotland reputed to have highest rate of heart disease in the world (probably not quite the case)
  - Scots never ate as much saturated fat as the French
  - Heart disease much lower in France (at that time the rate was 1/5<sup>th</sup>)
- Very many, similar contradictions worldwide, eg: in the 1950s, the Japanese had very low cholesterol levels AND very low rate of heart disease (1/25<sup>th</sup> that of USA), said to be due to their diet of rice, fish and little meat. However, over the last 50 years, the Japanese fat intake has increased 200%, cholesterol levels have gone up 30%, and heart disease rate has *fallen* by 60%.
- Note that cholesterol tests are very inaccurate.
- Some people's total cholesterol, esp LDL may appear to rise on a high fat, low carb diet, but the effect of diet varies (even within individuals). May be due to effect on way liver handles lipoproteins, but very uncertain.

## Statins

- Statistics “prove” the life-saving value of statins (but see Malcolm Kendrick's book “Doctoring Data” for examples of how statistics are manipulated)
- Worthy of note that, before statins, there were other drugs that lowered cholesterol, but they *increased* heart disease in some cases, or had no effect on it.
- Evidence shows that you live longer if cholesterol higher (an indisputable fact).
- With the advent of statins, both cholesterol levels and rate of heart disease went down, giving new credence to the cholesterol hypothesis. But note:
  - This *association* does not necessarily mean that lowered cholesterol was the reason for the fall in CVD.
  - The effect on incidence of stroke (which is of course an element of CVD) was minimal
  - Statins do however, increase synthesis of nitric oxide, aka endothelial dilating factor, which
    - Causes arterial dilation and
    - Is the most powerful anticoagulant known (most heart attack and strokes are caused by clots)
- Also worth remembering that reduction in death from heart disease does not necessarily mean decrease in overall mortality: “taking statins may change what's written on your death certificate, but it won't change the date”<sup>2</sup>.

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<sup>2</sup> Dr Kendrick's illustration is his patented treatment for cancer, which guarantees a 100% decrease in death from that cause: pushing people off cliffs. The incidence of death from cancer falls to zero, but the effect on overall mortality...

- Current NICE guidelines: if risk of a cardiac event in the next 10 years is 10%, you should take statins (which therefore includes just about everyone over 50)
- Drug-related adverse effects of statins:
  - Aches and pains (very common)
  - Tiredness
  - Stomach aches
  - Rashes/eczema
  - Transient global amnesia
  - Amyotrophic lateral sclerosis (rare, but irreversible). A WHO warning on this was not acted on.
  - Interstitial pulmonary fibrosis
- Statins are also reported to lower Coenzyme Q10. Reduced CoQ10 leads to reduced ATP, with reduced cellular energy. The most energy hungry muscle is cardiac. May be the reason for muscle pains and weakness associated with statins, but this is not clear.
- Why are the adverse effects ignored/underreported? It's difficult to be certain.
  - Statins are the most profitable meds in history – this may well have had an effect on data manipulation. Research organisations are often (almost always) funded by pharma.
  - Studies are generally conducted over 5 years, but statins are a lifelong drug.
  - People want to feel that they are being protected.
  - Placebo effect (just the taking of the tablet) is very important.
  - Poor questioning is another possibility. GPs (who generally have a very short time with patients) may ask “How are you getting on with the statins?”, and be told “Fine” by a patient who either wishes to please or does not connect the effects with the drug.
- It's important not to assume that, because research is funded by pharma, finance is the driving force. But the human instinct is to please, so having been given a gift/dinner/money, it's hard to criticise the donor.
- Increasing numbers of GPs are questioning the statin guidelines (in 2014 the BMA voted unanimously to reject the latest guidelines on statins, as did the GPC – but this had no effect on guidelines).
- When are statins indicated? For high risk patients – those who have already had a “cardiac event”. Here the evidence shows that statins can be of value.
- Statins can take a very long time to clear the system
  - Neurological damage may be irreversible.
  - Muscle pains probably reverse quite quickly.

## Cardiovascular Disease

- There is a move towards arterial scanning to check for thickening/scanning, but evidence for and against is confusing. Calcification is not a straightforward indicator. Even the relationship between atherosclerosis and dying from CVD is unclear.

- Probably better to assess CVD risk by testing clotting factors (eg Hughes syndrome (Antiphospholipid Syndrome)<sup>3</sup>, which can lead to heart attacks and strokes at young age (1:100)).
  - One problem, however, is that there's nothing you can do about many clotting factors.
  - Also, there are about 600 factors to measure.
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- "Pre-hypertension", like pre-diabetes, is an invented disease, designed to sell more drugs.
- Healthcare advice:
  - Take exercise
  - Get out in the sun (sunshine causes nitric oxide synthesis in skin – reduces risk of clotting).
  - Don't smoke.
  - Do what you can to reduce stress (have a look at *The Blue Zones Solution* – Dan Buettner).
  - Strong social bonds are vital.
  - Insufficient evidence that Vit K is beneficial, but it's increasing.
  - L-Arginine is the only substance which can naturally increase NO synthesis, therefore beneficial in lowering BP and clots.

## Stress

- Some stress is changeable (job, for example), some is not (financial, domestic stress).
- Psychosocial stress seems particularly connected to CVD. It's known that reducing stress makes blood less coagulable.
- Several relevant studies:
  - Robert Sapolsky<sup>4</sup> (Stress in Baboons)
  - Michael Marmot<sup>5</sup> (The Whitehall Study)
  - Finland had the highest rate of CVD in world in the late 50's/early 60's. This followed the largest forced migration of people proportionally in history (over 500,000 Finns forced to repatriate from Russia). The rate is now reducing.
- Japanese who move to USA end up with American rates of CVD (unless they maintained Japanese cultural lifestyle (regardless of diet).
- Rosetta community (from S Italy) set up in USA – maintained Italian lifestyle – no recorded CVD at all until very recently.
- In a study comparing Swedish and Lithuanian CVD, Swedish rates of CVD were one quarter of that in Lithuania. The only differences noted were the levels of social support and stress.

## Hypertension

- Anti-hypertensive drugs are over-prescribed.
- The drugs are very complicated. Average number of tablets for patients in Malcolms intermediate care unit is 10.3 (possibly 3 times a day). The interactions can cause great harm. Many geriatricians believe that their job is to get patients off tablets.
- In the elderly, drug induced postural hypotension possibly more dangerous than the hypertension.

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<sup>3</sup> An autoimmune, hypercoagulable state caused by antiphospholipid antibodies.

<sup>4</sup> Sapolsky, Robert M. (1990). "Stress in the Wild". *Scientific American*, **262**. 106–113

<sup>5</sup> *J Epidemiol Community Health* 2000;**54**:178-184 doi:10.1136/jech.54.3.178

- What is an ideal systolic BP? Risk curve is not linear – it rises dramatically at about 160. Before that, it is unclear that risk is significant, therefore controlling BP with drugs is questionable below 160mmHg.

### Advising Patients

- What can we say to patients on a cocktail of drugs?
  - Look quizzical.
  - Instruct pt to be more assertive. Often pts won't tell GP about the problems, but some GPs very willing to listen.
  - Make sure they do discuss the problems with the GP.
  - Get them to write a list of symptoms before attending their appointment (wives/partners/spouses may be better at spotting these side-effects).
- GP can suggest stopping the drug(s) for a period if symptoms appear connected, then restarting to see if side-effects disappear/reappear (challenge-rechallenge). Then let pt make decision:
  - Do they feel the benefits outweigh the side effects (which will last for rest of life).
  - But assessment of risk/benefit is very difficult – often the benefit will only be a (possible) very short extension of life.
  - Movements now arising within medical profession which are concerned about over prescribing.

Annex:

### Uffe Ravnskov (Related Papers)

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