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Q1 You've described cardiology as a logical specialty with huge potential to improve patient outcomes. Looking back, what specific clinical problems or unanswered questions first drew you in, and do you still see those problems today in the same form, or have they evolved?

Cardiology attracted me because it was a logical specialty. At that time, it was relatively limited, and we often thought in terms of causes leading to mechanisms, and then, through a series of cascades, to disease. Tackling disease meant intervening at different points along that pathway. It has since become much more complex, not illogical, but far more intricate, as our understanding has grown.

Today, cardiovascular diseases account for about one-third of deaths and disability worldwide. What is remarkable is that we have substantially reduced this burden in high-income countries, particularly for heart attacks and strokes. In contrast, in lower-income countries, the burden remains higher, with varying patterns: rising in some countries, stable in others, and declining in some upper-middle-income settings.

There are also clear regional differences. For example, strokes are more common than heart attacks in China and sub-Saharan Africa, whereas the opposite is seen in Western countries.

Some conditions, such as rheumatic heart disease, are

declining in many parts of the world due to improved living standards and better treatment of streptococcal infections. In contrast, conditions like aortic stenosis are increasing as populations age.

Hypertension is probably the single most important known risk factor for both heart attacks and strokes. Tobacco use is another major factor, although it is declining in many countries. Elevated lipids and diabetes are also important contributors, with the rates of diabetes increasing in many parts of the world.

While we have effective treatments for many of these conditions, they are not being implemented as widely as they should be. At the same time, heart attacks and strokes are declining in most Western countries and many middle-income countries, but may be increasing in poorer countries due to urbanisation and changes in lifestyle.

Heart failure is also increasing, partly because we are now saving people who would previously have died from heart attacks.

Overall, although patterns are changing, cardiovascular disease remains the number one cause of premature death worldwide.



Q2 You have led more than 50 large international trials across over 100 countries. What have these global collaborations taught you about the similarities, and striking differences, in cardiovascular risk and care between high-, middle-, and low-income countries?

The underlying causes of heart disease and stroke are broadly similar across most parts of the world, although their relative contributions vary. There are still many unanswered questions. For example, why does China have a high rate of stroke, yet better survival and less disability after a stroke, compared with other regions? We don't fully understand this, despite ongoing research.

Similarly, tobacco smoking appears to affect heart attacks more strongly than strokes, and, again, we don't understand why. These remain open questions.

At a high level, the major causes can be grouped into around eight to 10 key factors, though their relative importance varies by

region. At the individual level, we think of causes such as smoking and diet. However, we are increasingly recognising broader societal and environmental influences. Air pollution, climate change, and socioeconomic status all play important roles.

We don't fully understand the mechanisms that underlie the above risk factors, but it is clear that poorer populations are more prone to disease and also tend to have worse outcomes, partly due to limited access to prevention and treatment. There are also emerging community-level factors that are only beginning to be explored.

This creates something of a paradox: individual risk factors explain much of disease within populations, but they do not fully explain differences between countries or communities.

We are also increasingly recognising the substantial impact of medical management. About 50 years ago, Thomas McKeown hypothesised that medical care had only a small effect on

population health, but that is not true. Both prevention and treatment have a major impact. How health systems are structured and how care is delivered matters a great deal.

Q3 Your early trials on beta-blockers after myocardial infarction and later work on angiotensin-converting enzyme inhibitors and antithrombotic combinations changed practice. When you design large clinical trials, what methodological principles do you prioritise to maximise the likelihood of generating evidence that shifts guidelines and bedside care?

In the 1970s, there were no proven treatments for preventing heart attacks or strokes. The main intervention was defibrillation for cardiac arrest, which could be effective in cases of ventricular fibrillation. We were just beginning to understand that lowering high blood pressure could prevent strokes.

However, for heart attacks, there were no established

preventive measures, either for first or recurrent events. There was suspicion that smoking was harmful, and beta-blockers were emerging as a potentially promising therapy.

As part of my DPhil (PhD), working with Richard Peto and later Rory Collins, both from the University of Oxford, UK, we reviewed all available studies on beta-blockers in heart attacks. While few individual studies were definitive, many showed a consistent trend. We developed what is now called meta-analysis, but what we called systematic overview, combining results across studies in a systematic and valid way. This demonstrated a clear 25% reduction in mortality and reinfarction with beta-blockers after a heart attack.

At the time, our methods were questioned, as combining data across studies was unfamiliar. However, this approach is now widely accepted in medicine.

We also realised that trials needed to be much larger. To achieve this, they had to be simplified so that many centres could participate. This concept was outlined in our paper, 'Why do we need large, simple trials?' in the 1980s. Today, large trials are standard practice.

Our first large beta-blocker trial (ISIS-1) showed a modest 15% reduction in mortality, with borderline statistical significance, but it demonstrated that treatment could work. Other groups subsequently confirmed these findings.

A major breakthrough came with the ISIS-2 trial, which showed that thrombolytic therapy with streptokinase, combined with aspirin, reduced mortality by about 40%. This was a dramatic finding. Streptokinase had been available for over 20 years, but earlier studies were too small and inconclusive. Our systematic overview had already suggested a 25% reduction in mortality, but this was not widely accepted until the large trial confirmed it.

Aspirin also showed substantial benefit. These findings transformed the field. Importantly, positive results not only demonstrated effective treatments, but also validated the methods used to generate evidence.

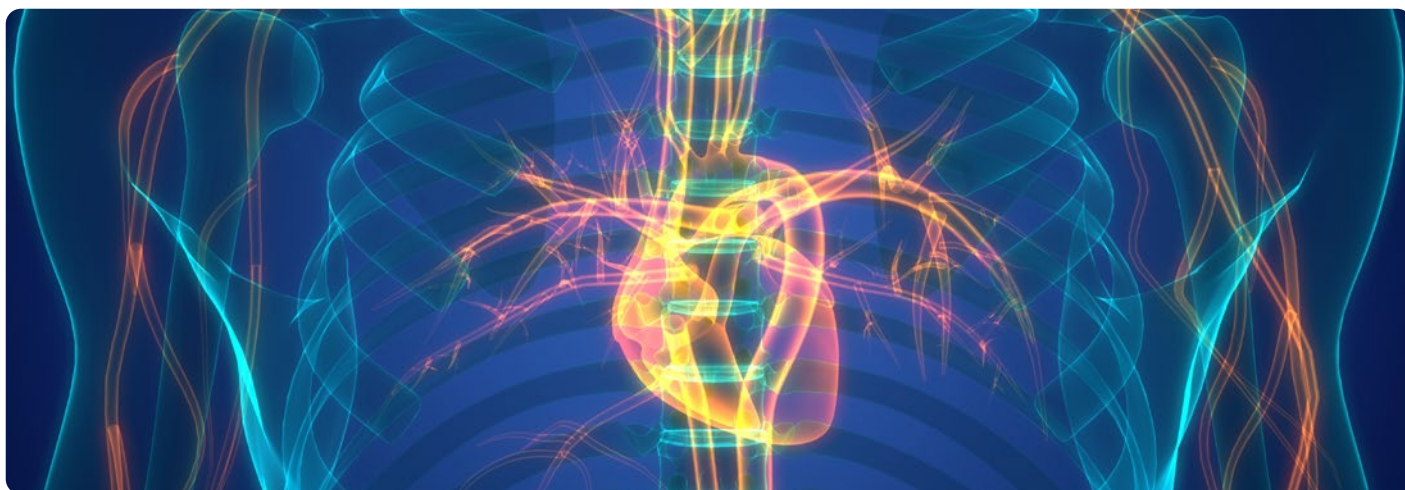
Since then, many trials have been conducted. Some treatments have shown modest benefit, while many have been neutral. Without these large studies, clinical thinking would have remained driven by theory rather than evidence.

Around this time, the concept of evidence-based medicine emerged. The term was formalised by David Sackett and Gordon Guyatt at McMaster University, Ontario, Canada, but part of its roots lie in these large trials and meta-analyses.

Today, we have multiple treatments that improve outcomes after a heart attack, and the field of antithrombotic therapy has advanced significantly, including its use in atrial fibrillation. The work from the late 1970s and early 1980s laid the foundation for a global shift in how we generate and apply evidence.

Q4 Global trials such as INTERHEART demonstrated that a handful of modifiable risk factors explain most myocardial infarction risk across populations. Two decades on, what lessons from that work remain under-implemented in routine practice, and which findings have proven more complex than originally anticipated?

Our work showed that smoking is a universal risk factor. Elevated cholesterol, particularly low-density lipoprotein and its component apolipoprotein B, is also important, as are high blood pressure and diabetes. These factors are relevant worldwide.



Diet has been one of the most controversial areas, and it remains so today. Early research focused on saturated fats, but those initial studies may not have been robust. More recently, attention has shifted towards high intake of refined carbohydrates as being harmful, while some fats in the diet may be protective.

Diet remains a contentious area. Recent USA dietary guidelines have moved away from simply recommending reduced fat intake and now emphasise overall dietary patterns, including increased protein and dairy consumption. However, trans fats (industrial products) should be avoided.

Fruits and vegetables have consistently been shown to be beneficial worldwide. Overall, our understanding of diet is evolving.

Physical activity is almost certainly beneficial, although it is difficult to obtain definitive proof. Observational studies suggest it matters globally, but there are nuances. Occupational physical activity may have different effects compared to leisure-time activity, possibly due to confounding by socioeconomic status.

Social connectivity is another emerging factor. Strong family and community ties may improve resilience, although the mechanisms are not fully understood.

Stress is increasingly recognised as important. Acute stress, such as bereavement or financial crisis, is clearly associated with increased cardiovascular events. Chronic stress, particularly related to lack of control at work, may also play a role, again potentially linked to socioeconomic status.

Environmental factors are also gaining attention. Air pollution has emerged as a significant risk factor and climate change has clear effects. Both extreme cold and extreme heat increase mortality, particularly among older individuals. This is evident during heatwaves and cold spells in Europe and in many other parts of the world.

These environmental hazards are an area of growing importance.

Q5 You have championed scalable prevention strategies, including dual antithrombotic regimens and fixed-dose combination therapy (the polypill). Do you believe the next frontier in prevention is further simplification and population-level deployment, or greater individualisation of therapy, and how should guidelines balance these aims?

Both individual-level treatments and population-level strategies are important. However, population-level approaches have historically been neglected, partly because they fall outside traditional medical practice.

Better treatments will always help individuals. For example, taking a statin reduces risk at the individual level, but two major gaps remain.

First, we are not fully implementing what we already know works. Treatments such as statins, aspirin, and blood pressure control are underused, even in high-risk individuals.

Second, we need to explore and implement population-level strategies, such as reducing air pollution and addressing climate change. We also need adaptive measures, such as improving housing, to protect against

cold, and strategies to mitigate extreme heat.

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Q6 Nutrition remains one of the most contentious areas in cardiovascular prevention. Given your critiques of prevailing guidelines on sodium and saturated fat, how should researchers and policymakers reconcile heterogeneous epidemiological data with the need for clear public health messaging?

Diet is challenging to study, because most of the evidence comes from observational studies and we really need large observational studies. Diet is hard to measure, because the most common method is what's called dietary recall. You ask somebody what they ate in the last 24 hours, or even over the last year. Now, when I try to think about what I had for breakfast yesterday, I struggle, let alone over a year.

There are signals that come through and, in large populations, these errors tend to cancel out, but diets may change over time and that needs to be factored in. Diet is also highly confounded, because what people eat depends on culture, social circumstances, wealth, and affordability. So, what we call a 'healthy' diet may simply



reflect that someone is wealthier or more educated.

People try to adjust for these confounders, but these adjustments are never perfect. A group in Oxford are trying to bring together all the large observational studies of diet into a single analysis, but there is so much debate about the right way to do this that it has been ongoing for several years without results being published.

Salt is an important example. People often forget that sodium is essential for body physiology. Every beat of the heart, every cell, has an electrical potential, what we call the action potential, and that depends on sodium and potassium moving in and out of cells.

Some epidemiologists think of sodium like tobacco, the lower, the better, but that's not quite right. With tobacco, no level is safe, but with diet, there has to be a range that is optimal. If sodium is too low, that can be harmful. If it is too high, that can also be harmful, so the key issue is finding that sweet spot.

The original concern about salt came from populations with very high intake and high blood pressure, which is valid. The question is whether, in populations with moderate intake, like the UK or Canada, it makes sense to lower salt for everyone, or only for those consuming high amounts. That is where the debate lies.

Q7 Recent work across your group explores proteogenomics and novel biomarkers for early disease detection. In the next decade, what role do you foresee for multi-omics risk prediction in clinical cardiology, and what evidence thresholds must be met before such tools influence routine decision-making?

I think we are far away from coming up with proteomic predictions at the moment. It's a very important area of scientific investigation and exploration, and we ourselves are working on it.

If you think of the concept, people are born with a set of genes. The genes, per se, do not change over one's lifetime, but various factors

affect the genes and their ability to produce proteins. The common terms people use are methylation and epigenetics.

We have recently published one paper and are in the process of publishing a second, where a large amount of the risk is associated with an array of proteins (it is about 800 proteins that we measured). The genetic contribution is modest. The epigenetic contribution (whether the genes produce proteins and which proteins they produce) may be larger.

However, in the clinic, you can't sit down with 1,000 molecules and then say what to do, and, right now, we don't know how to modify them either, so measuring them and talking about risk alone won't do.

For the moment, for the majority of people, risk is best assessed through simple measures: history, physical examination, blood pressure, smoking, cholesterol, glucose, and weight. Extreme obesity matters, and modifying these are going

to remain the mainstays of prevention for a while.

That is fine in the clinic, where you see people one-on-one, but at a population level, because these risk factors are widely distributed, the majority of heart attacks actually come from people at average risk, not high risk, simply because there are many more people in that category.

We published a paper last year showing that about 80% of cardiovascular disease comes from the average-risk population, and only a minority from the high-risk group, but the focus has been on high risk, and high risk means individualisation, so I think we've emphasised the wrong path.

We do need to identify high-risk individuals and treat them more aggressively, but we also need to intervene in the average-risk population.

Q8 Through initiatives, such as the Emerging Leaders Programme, and global capacity-building efforts, you have emphasised implementation science. From your perspective, what are the biggest barriers to translating existing cardiovascular knowledge into population-level impact: scientific gaps, health-system constraints, or issues of policy and political will?

Well, there are many constraints.

The reason I initiated the Emerging Leaders Programme is that most cardiovascular disease occurs in poorer settings, low-resource countries, and low-resource communities, even within wealthy countries. We had to draw attention to that.

The second thing is that you have to train people very early on and nurture a lifelong way of thinking. Because 80% of cardiovascular disease is in low- and middle-income countries, we needed to train people from these countries.

If you try to train people earlier in their careers, you can have an effect, but many may go down different paths. If you take people in the middle of their careers, they have already declared what they want to do, so we train about 25 people every year.

At the moment, people from about 50 countries have been trained, around 250–300 individuals. They are kept connected through seminars and electronic communication. The idea is that they will initiate studies and, importantly, implementation work to overcome barriers. Even if 10% of them succeed, we will start to see a global impact.

These individuals are not being trained in molecular biology or genetics, but in how to transfer evidence into practice and how to generate and evaluate that evidence. That is a complex process: it involves health systems, social acceptability, and communication. The press can also be a powerful ally.

For something like this to have an impact, it will take time, at least 25 years. People need to be trained, mature, build their own programmes, and then influence governments to implement change.

We have done studies showing that better implementation strategies, even when not expensive, can have a large impact. For example, the HOPE study and a large

study in China. Simply improving implementation in around 1,000 communities in China reduced strokes by about 35%.

The challenge is getting governments to buy in and change systems. Implementation will not just involve doctors; it will include other healthcare professionals, including community-level workers.

Implementation science is one of the most neglected areas, and one of the key frontiers we need to focus on.