In 1976, when I went to Oxford from India to work with Professor Peter Sleight, he assigned me a project on the role of beta-blockers in reducing infarct size in acute myocardial infarction (AMI). Not much was known about how to treat patients with an acute heart attack at that time. The main approach was to keep people in bed for 4 weeks, and give them anti-arrhythmic drugs to suppress ventricular ectopic beats. The role of anticoagulants was controversial. Whether a coronary thrombus was the cause or the result of a myocardial infarction was debated. On one hand, pathologists like Georgio Baroldi and Bill Roberts claimed that the infarction came first and then the thrombus was formed. But William Fulton, in a series of elegant studies where he injected IV radiolabelled fibrinogen to people admitted with AMI, showed that in those who had died, the core or the thrombus was free of radiolabelled fibrinogen indicating that the thrombus occurred very early.

Coronary care units (CCUs) had just been organized by Desmond Julian, and defibrillation for VF was the only lifesaving therapy we had. The average stay in a CCU was as long as a week and patients were often in hospital for 2 weeks to a month. Mortality rates of hospitalized patients were as high as 30% at 1 month and 50% at 1 year.

The field was transformed over the next few decades by a series of related discoveries made by people with different perspectives in different continents. The role of pre-hospital ventricular fibrillation was recognized and that half of the patients with an AMI were dead in the first 2 h after the onset of symptoms was documented by several groups—through the work in Seattle of Leonard Cobb, in Brighton of Douglas Chamberlain, and many others worldwide. This lead to pre-hospital care systems being developed including the idea of mobile CCU ambulances, defibrillation by paramedics and early rapid admission to hospital bypassing seeing general practitioners. Mitchell and Hampton from Nottingham challenged much of the conventional wisdom and even questioned whether CCU’s were useful. In a randomized trial of 300 or so patients with AMI, they showed no benefit of CCU care vs. home care. These studies challenged conventional views because we did so little that was useful in a CCU and some that were likely harmful (such as perhaps prolonged bed rest and anti-arrhythmic drugs). I remember Richard Peto telling me that a CCU would only be of benefit if what we did in it was useful, and not harmful.

Mitchell and Hampton’s studies did science a huge favour. They questioned established dogma and conducted randomized trials to test common practice—the only problem was that their trials were too small.

Our work that we undertook in Oxford with beta-blockers were initially disappointing because they were too small (only 50–100 patients), the drugs were initiated too late, and we used oral beta-blockers which took too long to modify early myocardial damage. These studies were never published but are included as chapters in my doctorate thesis. Similar results were found in the Multicenter Investigation of Limitation of Infarct Size study lead by Eugene Braunwald. Through a series of visits to Gothenburg in Sweden to visit Ake Hjalmarsson, Lars Wilhelmssen, Karl Swedberg and others; to Heidelberg to visit Wolfgang Kubler’s group; and to Harvard to visit Peter Maroko, my ideas evolved and I learnt how to design our studies better. This taught me the value of learning from people at other centres with different ideas, but equally important that most scientists were trusting and collaborative and were willing to share their ideas.

The first thing that I did on returning to Oxford was to contact Richard Peto (at the urging of Peter Sleight), as he was recommended by many of the people I had met on my travels, as one of the world’s leading experts in clinical trials. The second was that with the visit of Robin Norris (who had done pioneering work in acute MI) from Auckland on a sabbatical to Oxford, we spent countless hours discussing the field—and that is when I learnt the next most important lesson—that discussions and reflections are one of the most important aspects of gaining a deeper insight into the issues and that was an essential part of good science. We then redesigned our trial to use IV beta-blockers early (within 12 h), and with the help of David Bennett and David Ramsdale at the Wythenshawe hospital in Manchester, we started a collaborative study which was initially planned for 200 patients with acute myocardial infarction, but soon grew to 477 patients.
benefitted from the statistical insights of Richard Peto, and the financial support organized by John Cruickshank from Imperial Chemical Industries. Peter Sleight was extremely supportive—he used all his clinical insights, generosity, and interpersonal skills to enable us to carry on the work. This was truly teamwork between statisticians and clinicians, senior and junior investigators, and selfless collaboration between hospitals. Equally, these early collaborators remain friends, some 30 years later. Another lesson learnt—one has to become friends to become good collaborators, and that everybody benefits from collaboration and nobody is diminished.

The results of our pilot study on 477 patients were exciting—we showed a reduction in infarct size (measured indirectly using ECG mapping techniques and by integrating levels of CK MB over 72 h), a striking reduction in deaths, and ventricular fibrillation and other arrhythmias with no significant side effects except for some bradycardia and some hypotension—both of which were generally reversible with atropine, volume replenishment, and stopping the beta-blockers. The work was published in the Lancet, the British Medical Journal, and in Circulation and I received my D Phil from Oxford and David Ramsdale received his MD.

Despite the striking results of our Oxford-Wythenshawe study, Richard Peto strongly encouraged us to do the ‘real study’—a study of 6000 people to detect moderate differences in mortality, as he did not believe that anything, including beta-blockers, could reduce mortality by 50 or 60% (which is what we saw in our pilot study). ‘Don’t believe large treatment benefits even if they are statistically significant’ he said, and this was one of the hardest, but truest lessons I learnt. The first ISIS trial was ultra-simple and relatively inexpensive by modern day standards—only 1 million pounds, but the grant was turned down by the British Heart Foundation twice before we were funded. The main criticism that we received from the reviewers was that we would only answer one question. We responded: ‘Yes, but one question reliably!’ The first ISIS study required developing an international collaboration of over 240 centres in over 12 countries in Europe and in Australia, with the help of John Varigos, and John Cruickshank from Imperial Chemical Industries and many national leaders across Europe including from Italy—Prof. Aldo Selvini, Gianni Tognoni, Maria Grazia Franzosi and Aldo Maggioni—all from Milan. It was in this city (where the award ceremony for this Prize has taken place) that the first Italian collaborative study network was born and this lead to the creation later of the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto (GISSI) group and the development of Associazione Nazionale Medici Cardiologi Ospedalieri, all of which led to the inclusion of community and non-academic hospitals in research—a national triumph that has not been replicated in many other countries. This was the renaissance of Italian cardiology. The ISIS 1 study expanded from the original of 6000 patients to 16 000 and showed that beta-blockers reduced mortality by 15%, re-infarction and VF. This was the first breakthrough, albeit a small step in retrospect, in the pharmacologic management of acute MI. ISIS-1 was also the first large and simple trial done at a relatively modest cost.

In parallel, Richard Peto, Rory Collins, Peter Sleight and I conducted a number of systematic overviews where we combined the results of many randomized controlled trials of the same question—the term meta-analyses was not commonly used at that time in clinical medicine, although it had been used in psychology (Figure 1). I believe that Tom Chalmers had performed a ‘pooled analyses’ of studies of anticoagulants in acute MI but the methods were rather rudimentary, and so were heavily criticized.—however, the concept was useful and important. Our two systematic overviews, one on β-blockers and then the one on fibrinolytic therapy (published in the second issue of a new journal—the European Heart Journal, under the editorship of Desmond Julian), both around 1985. These studies were notable in that the statistical and the clinical methods were more detailed and rigorous, they clearly demonstrated that both treatments reduced mortality by 20–25% and that much larger studies were needed to definitively prove this. This also led Rory Collins, Richard Peto and I to publish what I believe is one of the most important of our papers on clinical trials methods that we wrote—titled ‘Why do we need some large simple trials?’ Both these papers are the foundations of the large multicenter trials and the now widely used methods for meta-analyses—formalized by the Cochrane collaboration.

The ISIS-1 trial created an environment for collaboration. Our meta-analysis of fibrinolytic trials suggested benefit. The classic work by De Wood (a surgeon in Washington) documenting that coronary occlusion due to a thrombus was likely the cause of acute MI and the work by Peter Rentrop, that giving Streptokinase into the coronary artery would dissolve them, led to the GISSI 1 (led by Gianni Tognoni and Luigi Tavazzi) and ISIS 2 trials. This demonstrated that Streptokinase reduced mortality by 25% and that Aspirin nearly doubled the benefits, so that the two together reduced mortality by ~50%. These two studies transformed medicine and cardiology and patient care, and woke the world up—first we had treatments that really saved lives (Figure 2). Second we needed to do much larger and so collaborative international trials, in many countries, to detect these important, but moderate and plausible benefits. This launched the modern field of large collaborative international trials in cardiology and in other conditions. In parallel, the β-blocker studies in Scandinavia and in the USA consolidated...
**Figure 2** Results of ISIS-2 of aspirin alone, streptokinase alone, and both vs. placebo in AMI.\textsuperscript{21}

**Figure 3** Results of the HOPE trial showing the impact of ramipril in stable patients at high risk of future cardiovascular disease events.\textsuperscript{28}
the value of β-blockers post-MI and the meta-analysis of small trials of aspirin showed an added benefit.24

After moving to the National Heart, Lung, and Blood Institute in 1984, my own work focused on left ventricular dysfunction and heart failure—a condition with high mortality and morbidity; and severe symptoms. Little work had been done until then—mostly small studies with conflicting or unclear results. No treatment (other than diuretics given mainly for symptom relief) had been clearly shown to reduce mortality or morbidity have value at that time. The two studies of left ventricular dysfunction (SOLVD)25,26 studies were the first really large trials in this field (and along with the CONSENSUS27 from Scandinavia) and was ≏10 times larger than anything done until that time. These studies demonstrated the broad value of ACE-inhibitors in people with heart failure or systolic dysfunction. At the NHLBI, I was fortunate to work with wonderful, committed and generous people such as Curt Furberg, Larry Friedman, Jeff Probstfield, Ellie Schron, Jeff Cutler and Janet Wittes and her team of excellent statisticians; and in the SOLVD studies with Bertram Pitt and so many other wonderful people in the USA and Canada, from whom I learnt a lot. We changed the field of heart

Table 1  Potential cumulative impact of four simple secondary-prevention treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative-risk reduction (%)</th>
<th>2-year event rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Aspirin</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>25</td>
<td>4.5</td>
</tr>
<tr>
<td>Lipid lowering (by 1.5 mmol)</td>
<td>30</td>
<td>3.0</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>25</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Cumulative relative risk reduction if all four drugs are used is about 75% events = cardiovascular death, myocardial infarction, or strokes. To calculate cumulative risk-reduction, multiplicative scale was used—e.g. two interventions each reducing the risk of event by 30% would be expected to have about 50% relative risk reduction [1 – (0.70 × 0.70)]. No interactions in treatment effects are observed in trials suggesting that proportionate risk-reduction of specific drug in presence or absence of other effective interventions would be expected to be similar. Smoking cessation lowers risk of recurrent myocardial infarction by about one-half after about 2 years. So, in a smoker with vascular disease, quitting smoking, and use of four simple preventive strategies could theoretically have large potential benefit (say around 80% relative-risk reduction).

Figure 4  Baseline risk (upper panel) and 4-year cardiovascular disease events (lower panel) in 154 000 individuals from 17 countries in the Prospective Urban Rural Epidemiology Study.40
failure; and the SOLVD studies have influenced the design of future heart failure studies with β-blockers, spironolactone, devices, etc.

After moving to McMaster University in Canada, our group at the Population Health Research Institute (initially involving Jackie Bosch, Janice Pogue, Hertzel Gerstein, Eva Lonn, Gilles Dagenais and Terry Montague along with hundreds of other investigators from about 20 countries) later demonstrated that ACE-inhibitors were of value in people with vascular disease and no heart failure, and reduced deaths, MI and strokes in the HOPE study. In parallel, over 20 major studies conducted by numerous other collaborative teams have established the role of statins in both primary and secondary prevention (Figure 3). By now the field of cardiovascular disease (CVD) prevention had moved substantially—in acute MI we had many treatments for acute MI that collectively reduced mortality by over 60–70% (Table 1). We continued our efforts to reduce the risk of myocardial infarction and deaths through establishing the value of clopidogrel and fondaparinux (with Shamir Mehta, Keith Fox, and Susan Chrolavicius) in Acute Coronary Syndromes, and more recently the New Oral Anticoagulants in atrial fibrillation (with Stuart Connolly, Lars Wallentin, Mike Ezekowitz, and John Eikelboom).

In long-term secondary prevention, four simple drugs (antiplatelet drugs, β-blockers, ACE-inhibitors, and statins) along with a healthy lifestyle which included avoidance of tobacco, a healthy diet and moderate exercise could reduce subsequent deaths and reinfarction by over 80–90% (Table 1). The concept that a poly-pill with 4 or 5 pharmacologic components plus tobacco control and a healthy lifestyle could virtually wipe out heart failure had come a long way in 35 years, and it was due to the superb, dedicated, unselfish, and collaborative work of a lot of people from different backgrounds working on many different ideas and concepts across different continents—a few ideas worked, but many failed. But the only way to identify what worked and what did not, was through research that developed concepts and then testing them in very large randomized trials. These trials which are massive international team efforts have made a huge difference and benefitted several millions of people worldwide.

My own roots are from India. I have always been interested in discovering why people from India and other low income countries had higher rates of CVD. This led to the first case-control study identifying the causes of acute MI (with Prem Pais from India), which was followed by the INTERHEART study in 52 countries (with Stephanie Ounpuu) and the INTERSTROKE study in 36 countries (with Martin O'Donnell and Denis Xavier), and the PURE study now in 26 countries (with Martin McKee, and several others) examining not only the effects of risk factors but also the impact of the environment and health systems, on CVD and other non-communicable diseases. We have an agenda of questions and studies that will keep our teams busy for a decade or longer (Figure 4).

So, what are the challenges ahead?

First, even in rich countries we have yet to fully implement what we already know. Disappointingly, fewer than 50% of patients get evidenced based lifesaving cardiovascular care, even when they are inexpensive (Figure 5).

Second, this situation is even worse in low income countries, e.g. in Africa where under 3% of people after an MI receive aspirin and under 1% receive statins. The situation in most other parts of the world, especially in South Asia and China where about 40% of the world’s population live, is closer to Africa, than to Europe or North America.

Third, even the simplest generic treatments for CVD are not available or affordable in most low and middle income countries.

**Figure 5** Number of drugs taken by individuals by country economic status. Note the very low use of three or more drugs in secondary prevention especially in poorer countries.
in the world and we need to persuade governments to set up systems of health delivery and universal health care to provide low cost treatments for CVD and other common conditions.\textsuperscript{10} Can the poly-pill a fixed dose combination of 4 or 5 pills be an integral part of this?

An increase in health care investment by 1% of GDP in low and middle income countries, targeted at providing essential medicines for non-communicable diseases including CVD, combined with cost-effective healthcare systems, and avoidance of tobacco smoking can reduce CVD globally by over 50%. This can avoid 8–10 million premature deaths, heart attacks, and strokes every year.

If our collective efforts at reducing CVD globally are successful, this would rank as one of the greatest public health achievements of all time. We have the tools to make a big difference to the health of the world—it is time to act together, and the time to act is now. Let’s just do it!

Author contributions

S.Y.: drafted the manuscript. S.Y.: made critical revision of the manuscript for key intellectual content.

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