What future does the pharmaceutical industry have in the cardiovascular world?

Looking back over a long period of success in the medical treatment of cardiovascular diseases, Dr Eugene Braunwald, MD, Distinguished Hersey Professor of Medicine at Harvard Medical School, Boston, MA, takes a look at the future

There is nothing like a major international meeting to sharpen perceptions and focus on looming issues. Fresh from the annual meeting of the American Heart Association, held last year in Los Angeles, Dr Eugene Braunwald, who keeps an almost daily watch on the world’s cardiovascular literature to update his iconic textbook, Braunwald’s Heart Disease, recently shared his views on the pharmacological armoury that the cardiologist can expect to have in future years. It so happens that the two drugs that have commanded the greatest sales worldwide are both in the cardiovascular arena, namely, atorvastatin and clopidogrel. But the future is uncertain. According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), there will be near-zero growth in pharmaceuticals in the top five European markets through to 2016, compared with 3.8% for 2007–11. And patent expiry will reduce brand spending in Europe, the USA, and Japan by $127 billion.

There is no doubt that the pharmaceutical industry, even the select group of Big Pharma companies, is facing a multiplicity of challenges. The cost of getting a new medical entity (NME) to market is now reckoned to about €1.5 billion. Braunwald believes that the period of patent protection that remains after the 10 years or so needed to get an NME to market is too short. According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), there will be near-zero growth in pharmaceuticals in the top five European markets through to 2016, compared with 3.8% for 2007–11. And patent expiry will reduce brand spending in Europe, the USA, and Japan by $127 billion.

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Further addressing this issue, he said: ‘I think that the financial and business models of the industry are not working well at this moment. Of the drugs we all use – the statins, the ACE inhibitors, the ARBs, the beta blockers and clopidogrel – they’re nearly all off patent, and they are the “big winners”! In all of these areas the potential gains from more clinical trials are still there, but they are harder and harder to achieve. In the early TIMI trials we required 1000–2000 subjects to answer a relevant question. Now we need more than 20 000. In the future we might need 50 000 – this escalation can’t go on forever!’

‘The analogy I like the best is that of the “statin pyramid”. At the apex is the 4 S Trial [Scandinavian Simvastatin Survival Study] with patients who had had a myocardial infarction and had an elevated LDL [with about 2250 subjects in the treatment and placebo arms]. For statins it was the “home run”. One step lower on the pyramid was the CARE [Cholesterol And Recurrent Events] trial, which we began before the 4S trial ended, and which studied a similar number of patients with a previous MI, but now with average levels of LDL. We also found a statistically significant benefit, but not as dramatic as in 4 S. Then, moving further down the pyramid, there was the JUPITER [Justification for the Use of Statins in Primary Prevention] trial, a primary prevention trial on subjects without coronary disease, a normal LDL but an elevated hs-CRP [high-sensitivity C-reactive protein]. It required about 18 000 subjects to demonstrate significant benefit. We are now near the base of the pyramid. From a public health perspective, it is important to determine whether LDL lowering in normal subjects without a risk factor can provide primary prevention, but this could require 30 000 subjects followed for as long as 10 years. That’s clearly impossible.’

Dr Braunwald refers to statins as ‘the most important drugs that have been developed since the antibiotics.’ He believes that they are the key to a future in cardiovascular medicine that is firmly focused on prevention. Atorvastatin is now off-patent in Europe and the USA, but he suggests that the pole position it held in branded pharmaceutical league tables owes much to the way in which it was developed. He said: ‘The manufacturers had an
exceptionally good drug and managed it well. It succeeded because it is more powerful milligram for milligram than the other statins, and it is extremely well tolerated, with very low rates of side effects such as myositis and rhabdomyolysis. And they pressed their advantage by providing vast amounts of strong clinical trial results, e.g. in treating diabetics, patients with stroke and other important groups. Rosuvastatin is marginally more potent, but by the time it came along there had been many trials with atorvastatin and many physicians and patients were reluctant to change.

Two new classes of drugs for improving the cholesterol status are being actively investigated by several groups, including the Boston TIMI group, now chaired by Dr. Marc Sabatine. Inhibitors of cholesterylester transfer proteins (CETP) work by blocking the transfer of cholesterol from high-density (HD) to low-density (LD) and very low-density (VLD) lipoproteins, thereby increasing HD and hopefully reverse cholesterol transport and reducing LDL and VLD as well. The other promising class of NME is inhibitors of the enzyme PCSK9 (proprotein convertase subtilisin/kexin type 9) that binds to and inactivates LDL receptors.

The drug that comes second in the league tables of sales is clopidogrel, but its history is quite different, explained Dr. Braunwald. Faced with the problem of thrombosis secondary to coronary stenting, which was limiting its use for CHD, investigators first determined that the thrombi were rich in platelets. The search then started for an antiplatelet agent with acceptable side effects. He said: 'the first drug was ticlopidine, which blocks the platelet P2Y12 receptor – it was a terrific drug, and was responsible for the explosion of coronary arterial stenting. Its use spread rapidly, but it had some nasty side effects, including leukopenia, thrombocytopenia and thrombocytosis, but there was nothing else available at the time. Then clopidogrel came along -- it works on the same receptor, but doesn’t have the same side effects. A very important trial was the CURE study [Clopidogrel in Unstable Angina to Prevent Recurrent Events] published in 2001, that showed that clopidogrel [when added to aspirin] reduced events by 20%, though there was more bleeding.'

Thinking more internationally in the fight against CVD, Dr. Braunwald lends support to the concept of the ‘polypill’, a drug with multiple actions that could be an effective means of preventing CVD, though there are still issues of the target population and compliance to be settled. He said: ‘It would contain a statin, aspirin, and could have an ACE inhibitor, a thiazide diuretic and/or a beta blocker. I think it’s a great idea if we’re talking about bringing primary prevention of coronary disease to large populations in developing nations. Let’s see if we can put something together that is very inexpensive, using off-patent drugs, using safe doses, and keeping administration as simple as possible – 1 pill a day.’
A cardiovascular study that includes a million subjects

Cardiologist Prof. Salim Yusuf, Executive Director of the Population Health Research Institute at McMaster University, Hamilton, Canada, has directed some of the most frequently cited clinical and epidemiological studies in the world, but now looks to community leaders and politicians for future advances.

Clinicians and epidemiologists at McMaster University in the city of Hamilton, Ontario, have been making major contributions to advances in cardiovascular medicine for decades. It is no coincidence that it was here that the ‘evidence-based’ epithet first got attached to medicine (as opposed to ‘prejudice-based’ and ‘personality-based’). The powerhouse of these studies for the last 29 years has been the Population Health Research Institute (PHRI), located in the setting of Hamilton General Hospital, which serves a population of 1.8 million and carries out 8000 catheterization procedures and 1600 open-heart operations a year. Population Health Research Institute has a research staff of 250, including 35 principal investigators, two-thirds of whom are cardiologists.

Heading the research institute is cardiologist-cum-epidemiologist, Prof. Salim Yusuf, who, among other things, is President-Elect of the World Heart Federation (WHF).

As well as managing a huge research agenda, he is clinically active, overseeing care in a CCU for several weeks a year and holding clinics from time to time. He trained at St John’s Medical College, Bangalore, India—where he is now a visiting professor—and then cut his teeth at the University of Oxford, Oxford, UK, on a Rhodes Scholarship. In the late 1970s he co-ordinated the International Study of Infarct Survival (ISIS) studies, working with Sir Richard Peto FRS, now Professor of Medical Statistics, and Prof. Peter Sleight, who formerly held the British Heart Foundation Field Marshall Alexander Chair of Vascular Medicine. He has made PHRI one of the most productive centres for cardiovascular population studies in the world. It is funded mainly by industry, but with 10–15% from the Canadian government and ~5% from charitable and philanthropic sources.

He pointed to a few of the many clinical trials he has led: ‘HOPE [Heart Outcomes Prevention Evaluation], which showed that ramipril, and ACE-inhibitors reduced myocardial infarction, strokes and death, OASIS-5 [Optimal Antiplatelet Strategy for InterventionS], which showed that fondaparinux reduced mortality compared to low molecular weight heparin by reducing bleeding, CURE [Clopidogrel in Unstable Angina], which demonstrated the added benefits of clopidogrel in acute coronary syndromes, and the recent RE-LY trial, demonstrating the superiority and safety of dabigatran in reducing stroke compared to warfarin in atrial fibrillation.’

He also led INTERHEART, a study based on >29 000 subjects from 262 sites in 52 countries, which showed that 90% of global risk for acute myocardial infarction can be accounted for by nine risk factors. The two most important ones were an abnormal apo-lipoprotein B: apolipoprotein A-1 ratio and smoking. The paper announcing the main results of the study appeared in The Lancet in 2004 and was subsequently selected by the journal as one of the ‘100 vintage papers’ published in its 200-year-old history. In the pipeline at PHRI are two related studies, INTERSTROKE, with 22,000 subjects of 25,000 subjects already recruited, and the Prospective Urban Rure Epidemiology (PURE) cohort study of 154,000 people from developed and developing countries. There are also major studies of ‘neglected’ cardiovascular diseases in progress, including a trial in sub-Saharan Africa of a steroid/vaccine combination therapy for tuberculosis pericarditis, and another for heart disease related to the insect-borne Chagas disease.

The scale of the studies that PHRI run is a sign of the intellectual and organizational machinery it encompasses. It is one of its proud principles that all studies are run by the PI’s, rather than being outsourced under supervision. Currently it is recruiting 1 million people in a new surveillance study to document the prevalence of risk factors of mortality and morbidity in Kerala, a state in southwest India, in order to quantify the disease burden. Prof. Yusuf said: ‘We want to sample 3% of the total population of 34 million, to enable the authorities to develop an informed and rational approach to disease prevention.’

A major element of CVD prevention in this setting might involve combination therapy with a ‘polypill.’ Although the term was first coined by Sir Nicholas Wald, Director of the Wolfson Institute of Preventive Medicine in London, UK, the concept of combination...
pharmacotherapy for heart disease had been proposed earlier by Richard Peto in 2001 at a joint Wellcome Trust/WHO meeting held in London, and was followed up a year later by a commentary by Prof. Yusuf in The Lancet. In September 2012 PHRI hosted a global summit on combination therapy in CVD prevention attended by 90 delegates, including cardiologists, epidemiologists, and representatives from the pharmaceutical industry, WHO, and the WHF. One type of polypill has already been licensed in India, on the basis of The Indian Polycap Study (TIPS) and Prof. Yusuf is hopeful that a similar product will soon be considered by the Food and Drug Administration (FDA) in the USA and regulatory authorities elsewhere.

He said: ‘Even in developed countries, 5 years after an MI or stroke less than 40% of patients receive treatment with drugs such as aspirin, a statin, an ACE inhibitor or a beta-blocker. The situation is much worse in developing countries. A low-cost pill with 4 or 5 active ingredients would cost a fraction of each one separately. There is no need to titrate the dose – patients are put on a low dose first and receive the full dose if there are no side effects. It may not be ‘perfect’ but at the moment more than 80% of patients with CVD in developing countries and about 30% in developed countries are not getting anything.’

Major messages from PHRI studies for Europe and other developed parts of the world are, he believes, that physicians should, of course, reduce risk factors, but in addition community leaders and politicians should put more effort into reshaping the environment that people live in. He said: ‘The biggest impact will come from societal change. I’m always impressed by the Netherlands and Denmark, where it is so easy for people to bike to school or work. Getting people to walk for 30 min twice a week is better than nothing, but we really need to make it easier for people to be active in day-to-day life. I know changing policies is difficult and it always takes a long time. But you have got to start somewhere and in 20 years you will make a ‘dent’ if you do something. If we do nothing the epidemic of obesity and CVD will just get worse!’

Prof. Yusuf says his career has benefited greatly from ‘two of the most forward thinking institutions in the world’, the University of Oxford and the National Institutes of Health (NIH) Bethesda, MD, and also from the freedom and support his current institution has given him. At Oxford, cardiologist Peter Sleight showed him ‘the skills of bringing people together’—and they still collaborate—and Richard Peto demonstrated ‘innovative thinking focused on the big questions.’ Then he had the ‘staggeringly fantastic opportunity’ to work at NIH on Studies of Left Ventricular Dysfunction (SOLVD), taking ‘the ideas from Oxford and testing them in a new environment.’ In 1992 he was invited to McMaster, where he set up a preventive cardiology and therapeutic research programme which in 2002 evolved into PHRI as it is.

The research at PHRI could not be done without modern information and communication technology, but Prof. Yusuf, who lent his name to more than one peer-reviewed paper a week last year, admits: ‘I’m technology shy, not technically savvy at all. I have to be shown the basics of how to use a computer and e-mail. I just do the cerebral stuff’
More than 10% of global death and disability due to cardiovascular diseases

Ischaemic heart disease is the top cardiovascular disease, according to the latest findings of the Global Burden of Disease Study

Global Burden of Disease 2010
The GBD 2010 project began in 2007 and was primarily funded by the Bill & Melinda Gates Foundation with a wide variety of additional funding sources. It is a collaborative project led by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, Seattle, USA, working with six core collaborators:

- The University of Queensland,
- Harvard School of Public Health,
- Johns Hopkins Bloomberg School of Public Health,
- The University of Tokyo, Japan,
- Imperial College London,
- The World Health Organization.

The project has involved 302 institutions and 50 countries, including 26 low- and middle-income countries, and 486 authors. It is the largest scientific study to quantify levels and trends in the world’s health problems.

The first GBD study was published in the 1990s and funded by the World Bank. This new consortium of researchers has now revealed its 2010 results (GBD 2010) in The Lancet, 13 December 2012.

Ischaemic heart disease and stroke remained the two top causes of death between 1990 and 2010. But all other rankings in the top 10 causes changed. Diabetes, lung cancer and chronic obstructive pulmonary disease all moved up, while diarrhoea, lower respiratory infections, and tuberculosis moved down.

Dr Mohammad H. Forouzanfar, acting assistant professor at IHME, spearheaded the work on cardiovascular disease in GBD 2010. He says: ‘we found cardiovascular has been the most fatal disease since 1990.’

In 1990, cardiovascular disease was the top cause of death, but lower down the list as a cause of morbidity and disability. The total burden, which includes death and years lived with disability (YLD), was 9.6%. But in 2010 cardiovascular disease had a total burden of 11.8%, which was the biggest burden globally and for almost all countries. For some countries in sub-Saharan Africa, communicable diseases are the greatest burden.

The researchers found that ~15.6 million deaths or 29.6% of all mortality in 2010 was because of cardiovascular disease. This is an increase from 11.9 million in 1990, or 25.6% of all deaths. In 2010 for each 100 persons, 4.3 years were lost due to death and morbidity because of cardiovascular diseases.

But while the total number of deaths due to cardiovascular diseases has increased, because the population has increased in size and is older, individual risk has decreased by 21% from 1990. ‘It means that overall, the situation has improved,’ says Forouzanfar. ‘We have fewer deaths and fewer burdens from cardiovascular disease at the individual level and per capita when standardised for population size and age structure.’

Looking at the 11.8% total burden from cardiovascular disease in more detail, ischaemic heart disease was the most important and contributed 5.2% of the total burden. Haemorrhagic stroke ranked next, contributing 2.5%, followed by 1.6% from ischaemic stroke. Hypertensive heart disease and other diseases combined made up the remaining 2.5%.

Overall the burden from cardiomyopathy remained quite stable, peripheral vascular disease increased or remained stable, and hypertensive heart disease showed a very slight decline. As expected there was a significant decrease in rheumatic heart disease burden because of improved control of rheumatic fever.

These patterns are not homogenous throughout the world. In developed countries the total burden from cardiovascular diseases decreased by 31% between 1990 and 2010, while in developing countries it fell by just 16%.

The picture also differs in the countries and regions within developing and developed areas. Developed countries refer to Eastern, Western, and Central Europe; North America (USA and Canada); Australasia; and Asia Pacific high-income countries such as Japan and South Korea. All other countries and regions were classified as developing.

Taking a look at the developed countries, especially in Europe, there was no improvement in cardiovascular disease between 1990 and 2010 in Eastern Europe, particularly in Russia and Ukraine. This is because these countries experienced a significant increase in cardiovascular disease until 1995 and the level has changed downward since 2005. In contrast, Western Europe and Australasia, especially Australia, have achieved a very successful decrease in death and morbidity from cardiovascular disease.

Developing countries also show disparities. In the South of Latin America (Argentina and Uruguay), there has been a 36% reduction in the burden of cardiovascular diseases. But the burden (age...
standardized per capita) in South Asia has only changed very slightly, from 5.5/100 person in 1990 to 5.3/100 in 2010.

Forouzanfar says: ‘It means that cardiovascular disease is going to be a large problem in South Asia - in India, Bangladesh and many developing countries.’

The European Society of Cardiology: facts and figures

The European Society of Cardiology (ESC) comprises 54 National Cardiac Societies, 19 Working Groups, 5 Associations, and 5 Councils. It also includes the community of ESC Fellows and Nurse Fellows (Fellow, FESC; Nurse Fellow, NFESC). In terms of membership, the ESC represents over 75,000 cardiology professionals across Europe and the Mediterranean.

To fulfil its mission of ‘reducing the burden of cardiovascular disease in Europe’, the ESC undertakes an array of scientific and educational activities such as the production and continuous updating of ESC Clinical Practice Guidelines, the organization of educational courses and initiatives, pan-European surveys on specific disease areas and the largest medical meeting in Europe, the ESC Congress. The ESC is also proud to hold, in conjunction with its communities, eight subspecialty congresses, which are becoming increasingly popular within the profession. Additionally, the ESC edits and publishes eight of the world’s leading journals on cardiology.

http://www.escardio.org/journals/Pages/welcome.aspx

The official website of the ESC is www.escardio.org.

ESC Congress

The ESC Congress is an international meeting and one of the leading events in cardiology, officially the largest medical congress in Europe where the best recent scientific developments and novel research are presented. It is also an important platform for networking among peers and to exchange knowledge.

The ESC Congress is held in August/September every year and brings on average over 900 h of science and education with 10,125 abstracts submitted, 4,375 approved, 423 breakout sessions and workshops reflecting specialty subjects, and an exhibition of 25,000 m², making it the prime meeting platform for the profession. The European Society of Cardiology Congress last year (2012) registered over 30,000 participants in Munich, Germany.

ESC Congress 2012. Photo credit Sam C. Rogers

This year (2013), the ESC Congress will take place in Amsterdam, The Netherlands.

Past information on the ESC Congresses can be found at http://www.escardio.org/congresses/past_congresses/Pages/past-ESC-congresses.aspx.

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