The ESC goes global: Policies to prevent all chronic diseases

The alarming increase in global NCDs is stimulating efforts to tackle the burden at national levels.

Chronic non-communicable diseases (NCDs) account for 86% of deaths in the WHO European Region.¹ They include heart disease, stroke, diabetes, kidney disease, cancers, respiratory, and liver diseases. Four major health determinants—tobacco, poor diet, alcohol, and lack of physical activity—account for most of the chronic illness and deaths in Europe. All these factors need to be successfully addressed to prevent disease and promote health.

The scientific evidence for the adverse health effects of smoking is overwhelming, especially for common cancers, chronic obstructive pulmonary diseases, diabetes, and cardiovascular disease (CVD). About half of all continuing smokers will be killed by their addiction.²³

Poor diet can cause obesity, type 2 diabetes, CVD, hypertension, and common cancers.⁴⁻⁷ Increasing fruit and vegetable intake to 600 g/day could prevent over 135 000 CVD deaths each year.⁸

Alcohol excess accounts for over 7% of all ill-health and premature deaths in Europe, especially through liver damage, accidents, and addiction.⁹

Sedentary lifestyles promote osteoporosis, depression, type 2 diabetes, overweight and obesity, and some cancers.⁹⁻¹¹

The European Chronic Disease Alliance. Ten not-for-profit European organizations representing over 100 000 health professionals have formed the European Chronic Disease Alliance (ECDA) to combat chronic diseases. The ECDA mission is to reverse the alarming rise in chronic diseases by providing concrete evidence-based policy recommendations to lobby for immediate political action. The Alliance has produced very concrete recommendations for policy makers to address the four identified risk factors at both national and EU levels.¹²

Globally, NCDs represent a major cause of poverty and an urgent issue in developing countries. Worldwide, the chronic disease epidemic accounts for over 60% of deaths in low- and middle-income countries.

Global problems, global solutions: The UN high-level meeting

Non-communicable diseases are too big a problem to be solved by national governments alone. The World Heart Federation (WHF) and the NCD Alliance are now working to place NCDs at the top of the global agenda, by promoting a multisector response, to include the private sector.

The World Economic Forum, WHO Geneva, and the Harvard School of Public Health are currently working together on economic studies to quantify the health and social costs of NCDs. The report, expected in August 2011, will inform the participants at the UN High-Level Summit on NCDs.

This September 2011 Summit follows the UN General Assembly, in May 2010. It offers the best opportunity to put NCDs on the global agenda. The Summit aims to secure commitment from Heads of Governments for a coordinated global response and substantially increased financial resources for NCDs. It will recommend measurable targets for tobacco control, healthier diets, alcohol control, and increased physical activity. The specific targets will be used to produce commitments from governments to take action on NCDs, for which they can be monitored and held accountable through regular reporting.

These actions together could save millions from premature death and debilitating disease.

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References

A pioneer in cardiology, Professor Sir Salvador Moncada MD, PhD, FRS

Salvador Moncada, a pioneering scientist whose career has been defined by a series of ground-breaking discoveries, is director of the Wolfson Institute for Biomedical Research (WIBR), in London.

Salvador Moncada London 2010

As a pioneer, Moncada has crossed many scientific and geographic frontiers in his life. He moved from Central America to Europe and his discoveries surrounding aspirin, prostacyclin, and nitric oxide pushed back the scientific boundaries of the time. In 1995, he set up the WIBR as a body to foster paradigm-defying research.

Moncada grew up in Honduras, of mixed Central American and European parentage. From an early age, he wanted to study medicine. ‘I attended primary and secondary school in El Salvador and by chance went to a very good medical school there. It had been heavily influenced by the changes in medical education that took place in the United States in the 1950s, and was very research-orientated so we did a lot of basic training that gave me a strong background in medical sciences’.

Two influential teachers from these early years were Maria Isabel Rodriguez—a physiology teacher and experimental cardiologist—and pharmacology teacher, Augustos Campos, who helped fire an enthusiasm for research in the young Moncada, so much so that he spent much of his spare time during holidays working alongside him in the lab.

After qualifying, he practised medicine under fairly basic conditions in El Salvador. ‘There was no medicine, no proper facilities and no instruments, but it was immensely forming in terms of developing character and sensitivity to people’s suffering’.

A desire to pursue research in a more conducive environment, coupled with the first of many fortuitous events which Moncada believes have played a large role in his life and work, led him to London. ‘I had a connection who happened to have been a good friend of the late John Vane, and he introduced me to Sir John who was kind enough to accept me into his lab at the Royal College of Surgeons’.

For a budding researcher, it was a good place to be. ‘The conditions were wonderful and I started working with a very exciting group. One of the Profs in the group was Gustav Born, who invented the platelet aggregometer. The first project I worked was on aspirin and arachidonic acid metabolism. Within 8 months of my arrival we published one of three papers in Nature explaining that aspirin-like drugs act by preventing arachidonic acid metabolism.

We then discovered the enzyme that makes thromboxane A2, which is a pro-aggregating factor derived from arachidonic acid in platelets, thus explaining why aspirin prevents platelet aggregation. Our work was crucial for the later understanding of how and why a small dose of aspirin might be antithrombotic’.

The work around aspirin sparked an interest in vascular endothelium, and in 1975, Moncada followed John Vane to the Wellcome Research Laboratories near London embarking on a study with Stuart Bunting and others that would lead to what he describes as ‘one of the central discoveries we made’. This was the anti-aggregation agent prostacyclin, which was later developed for use in patients with primary pulmonary hypertension waiting for cardiopulmonary transplantation.

Moncada spent 20 years at the Wellcome Laboratories, first as head of prostaglandin research and later as head of research. It was a productive period and a place where ‘basic research and drug discovery existed in harmony’. During this time, lamotrigine (an anti-epileptic), atovaquone (an anti-malarial), and zomig (for migraine) were all developed, and the programme that led to the development of latanoprost (for treating breast cancer) was initiated. The Wellcome working environment is one that Moncada has tried to emulate at WIBR. ‘Balancing basic research and drug discovery has always been difficult for universities. What we have been aiming to recreate at the WIBR is a place where the best of industry and the best of academia come together’.

Moncada was busy working on the development of prostacyclin in the early 1980s when Robert Furchgott contacted him to ask for a reagent that might help him to determine the identity of his recently discovered endothelium-derived relaxing factor. ‘Those experiments did not work: however we started to develop a bioassay system for EDRF which became instrumental in testing its identity. It allowed us to identify EDRF as nitric oxide, thus confirming Furchgott’s hypothesis, and a year later to discover the mechanism of its biosynthesis from the amino acid L-arginine’.

Moncada is able to look back on his work with satisfaction: ‘I think that we have improved the understanding not only of the physiology but the pathophysiology of the cardiovascular system. Many people around the world have benefited from our work not only in terms of increasing knowledge but also in promoting drug discovery and development’.

The working life of a scientist is never easy and his work has been typical in this respect. He says: ‘There have been long periods of frustration with short but very valuable periods of elation. I am only interested in two aspects of science—the initial idea and working out the solution. Looking for the question is the first most exciting activity in science and imagining the answer is the second’.
He likens the learning of research to a medieval craft, to be acquired and honed to perfection by the apprentice researcher. The beauty of experimental research is that you can fly as much as you want with your imagination and at the same time you have to be the slave of your results. The results are the final arbiter of your ideas. Also, you often pursue roads that are empty for long periods, suddenly to discover that you missed something in the middle, which would have solved the problem. This is the nature of the adventure and I enjoy every second of it.

He created the WIBR in 1995 and has worked as a World Health Organisation advisor on Medical Education. He has interests in Latin American politics and works with Honduras Global, a charity that embraces a number of organizations trying to establish a network of global experts to help develop skills and training in his native country.

Moncada is currently investigating another fortuitous discovery, which came about when his team was looking into the role of nitric oxide in mitochondria. ‘The way cells feed themselves in order to proliferate has always been a mystery in biology. By chance, we have stumbled on the mechanism’. Although it’s too early to say, he suggests that this latest discovery might be bigger than nitric oxide.

In 2010, his discoveries were recognized with a knighthood for services to science.

Judy Ozkan, BA Hons

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**Book review**

**Key Questions in Cardiac Surgery**

Narain Moorjani, Nicola Viola, and Sunhil K. Ohri
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The field of Cardiac Surgery is undergoing tremendous change. As cardiac surgery is still a relatively young speciality, knowledge is constantly changing. This is occurring to accommodate higher expectations of our communities and technological innovations. Where in the old days, surgical experience through hour-long exposures in the operating theatre was the only path to success, currently incorporating theoretical knowledge of ‘evidence-based medicine’ and learning new technical skills, both contribute to obtaining better patient outcomes. These outcomes have become the fruit of interdisciplinary discussions based on consensus papers and modern guidelines. With the advent of catheter-based therapies, cardiac surgery has seen a massive shift towards minimally invasive techniques. In addition, our patient population has also experienced major changes; an increase in age and with a worse risk profile. It is true to say that the science of treating cardiovascular disease is changing.

With this aspect in mind, the new book *Key Questions in Cardiac Surgery* by Narain Moorjani, Nicola Viola, and Sunhil K. Ohri provides a fine tool for practical knowledge revision. The subjects covered are obviously cardiac surgery, but many aspects of cardiology and interventional therapies have been seamlessly integrated. As the title suggests, the authors have done a thorough job in distilling the broad knowledge necessary for cardiac surgeons into one concise manual. The question and answer format provides a much summarized depiction of this knowledge. Furthermore, the logical and clear constructions and classifications in different chapters allow the reader to use this book for many different purposes. Illustrations and tables are kept very simple and provide important additional information without confusing the reader. Even though this book is only in print form, the modern approach to practical didactics appears throughout the text and it is very interactive. Illustrations and up-to-date guideline interpretations add some ‘meat’ to the words. The practical Q&A approach makes for easy reading, thus ensuring that the lecturer will find his intellect stimulated. Preceding knowledge is not constantly repeated, but rather taken for granted. Reflection on subjects such as pathophysiology, diagnosis, etc. are spontaneous side effects to reading this book. As a sole limitation, an interactive CD-ROM or web-based extension of the book would allow even more interactivity. Maybe something for the future.

I recommend this book for cardiac surgery trainees, full-fledged surgeons, and also for other medical practitioners wanting a brief and precise overview into our speciality, without having to pick up heavy textbooks and spend precious time searching for information.

Dr Sacha Salzberg, Consultant Cardiac Surgeon, University Hospital Zurich
Nature, a scientific journal for all researchers with a high impact factor

Dr Philip Campbell Nature editor-in-chief, hopes that the iPad will spark a different relationship with individual readers

Nature was founded in 1869. John Maddox became editor in 1966 and stayed until 1973. He was editor for a second stint during 1980-95. During his editorship, Maddox instigated a system of peer review; previously, there had been more informal processes in place. The magazine function of Nature also took off and he instituted a strong tradition of journalism.

Dr Philip Campbell became editor-in-chief of Nature in 1995. He is also editor-in-chief of the Nature Publishing Group and has an oversight of the long-term quality in Nature-branded publications. During his editorship, the magazine component of Nature has developed further and the online dimension of Nature has also developed.

The online form of Nature exists in three versions. The digital edition mimics the print edition, with features such as turning pages. Online content also exists as standard PDFs and htmls. And there is an iPhone version of Nature every week.

'We're all eagerly waiting to see how the iPad affects us all', says Campbell. 'We would hope to have a slightly different relationship with individual readers of Nature as a result of the iPad'. As an interactive medium, it restores a print-like experience to some extent and he speculates that it may enable Nature to sell online only subscriptions in the long run.

Peer-review content and some commentaries are available by subscription only, while all of the journalism in Nature (which includes an online daily news service) is free of charge.

Nature’s content covers all of the natural sciences. The readership is primarily practising researchers from all disciplines, but also people with a real stake in research (policy makers, funders, industry), plus seriously interested members of the public.

Nature receives 11,000 submissions every year and publishes about 800 papers. Its impact factor is 34.480, and over the past 20 years, it has been ahead of the competition in the general scientific journals category. Campbell says: ‘Personally speaking, I’m happy to be ahead of the competition but the goal is to publish great science’. He points to the fact while some great papers receive 100 citations over a couple of years; others get just 4–5. ‘To me citations of an individual paper have never been a measure of its value’, he says. ‘It’s one measure of its value obviously, but there are other values that have nothing to do with citation’.

During Campbell’s editorship, the magazine has expanded and diversified. There is more externally authored comment and the journalism has become increasingly investigative as opposed to opinionated. Investigative stories are sometimes based on opinion polls, for example, on how animal researchers have been affected by protests. ‘Such stories get discussed much more and those types of stories tend to make an impact’, he says.

In the last year or two, Nature has specifically begun to focus more on the interests of researchers in particular. There was a time when the publication thought it would like to reach a much wider audience than researchers, not becoming a consumer publication, but going beyond researchers. But it concluded that the broader reach was diluting the impact on its core audience of researchers and has returned its focus to them. It hasn’t affected the topics Nature chooses but it has affected the way it writes about them.

The team has grown over the years. Today, there are 90 editorial staff on Nature of whom 60 are in the UK and the rest are in offices around the world. The hard core of decision-making about the papers it publishes is made by 25 editors of mixed disciplines based in the USA and London. The team of journalists comprises around 15 reporters and 12 editors.

The publishing strategy is to adapt to everything that the internet allows. ‘Print is still absolutely valued but there’s no question that in the future online offers so much more’, says Campbell.

That means thinking commercially about how to raise revenues that can replace revenues from the decline of print. Nature’s circulation in print has generally dropped but readership online has grown. Today, it has a circulation of ~52,000 in print and about 2 million unique users online every month.

The basic mission remains the same: to reflect, for the broadest possible scientific readership, whatever is important in and around science. But, says Campbell, ‘to do that in a way that is adventurous in our magazine. We like to challenge our readership as well as to stimulate it’.

Jennifer Taylor, MPhil
The Lancet, a controversial beginning

By making expensive medical lectures freely available, The Lancet was in some ways the first open access medical journal

The Lancet was founded in 1823 by the young surgeon Thomas Wakley to shine a bright light on the corruption in the London medical establishment. The great surgeons were making a fortune by collecting fees from students who attended their lectures. Wakley hired correspondents to go to the lectures and take notes and he would then publish the lectures in The Lancet. It destroyed the surgeons’ business and made him incredibly unpopular.

‘When he started The Lancet he immediately pitted himself against some of the most conservative forces in medicine of the time’, says editor Dr Richard Horton. ‘The journal almost died in the first decade because of this but because he was publishing material that people wanted to read, the journal survived’.

The Lancet has been a weekly journal since its inception, even during the First and Second World Wars when paper was in short supply. It has evolved from a journal focused on the UK and its colonies into a journal with an international perspective, and an equal interest in low-, middle-, and high-income countries.

Published articles originate mainly from the USA and the UK, with some from elsewhere in Europe and an increasing number from China.

The scope of topics covered has changed dramatically over the years. In the nineteenth century, it published lectures, not research, which was where the evidence of the day came from. Content gradually shifted to individual patient histories combined with some laboratory investigation. Today, The Lancet publishes very large-scale randomized trials, epidemiology, and basic science when it’s highly relevant to clinical medicine, especially in the genomics area.

It continues to publish one case report each week as a way of keeping the journal pages open to young clinicians. ‘That way hopefully the journal doesn’t become a place only for professors and leaders of research laboratories to get published in’, says Horton.

The Lancet covers all areas of medicine and has a diverse range of readers including doctors with a strong interest in medical research, doctors working in hospital-based specialties, physicians, and policy makers interested in international issues in health, and increasingly, younger doctors and medical students who are interested in global health and the politics of medicine.

In 2010, The Lancet received 4264 submissions and the acceptance rate was <5%. With rising numbers of submissions, they have had to raise the bar but they are careful not to make it so high that only research from high-income countries is accepted. It’s difficult for scientists in resource poor settings to do large randomized trials or epidemiological studies, so when considering papers, the editors take account of the importance of the question being asked for the locality. If the question is incredibly important for that region and the research has produced a highly informative answer, then even if the methodology is imperfect, they will work with the authors to produce the best possible paper for publication.

Horton says that editors do make mistakes and he hopes that authors will use the journal’s formal appeals process if they believe their paper has been wrongly rejected. He says: ‘Often it’s only at the appeals stage where you really can see why the authors think the paper is right for The Lancet because they make their case much more passionately second time around’.

The increase in submissions and quality of published papers has steadily pushed the impact factor up over the past 5 years, from 23.9 in 2005 to 30.8 last year.

The journal now has three daughter journals, The Lancet Infectious Diseases, The Lancet Oncology, and The Lancet Neurology, and there are plans to add The Lancet Respiratory Medicine and The Lancet Diabetes and Endocrinology over the next year or so. Having a family of journals enables The Lancet to keep more good papers under its umbrella and provides more opportunities for scientists to publish with the journal.

Horton joined The Lancet as a very junior editor in 1990 and became editor in 1995. His team of around 25 editors is a mixture of physicians and scientists.

His vision is for The Lancet ‘to be at the centre of the global conversation about the future practice of medicine’. Accomplishing that means they must do four things: publish the very best international medical research; focus on publishing clinical content that advances the knowledge and understanding of the practice of medicine; be the leader in global health research; and be a place for robust comment and opinion about the future politics and practice of medicine. ‘I think a medical journal, although its primary interest is science and knowledge, cannot do those in isolation of the politics’, says Horton.

Jennifer Taylor, MPhil
Cardiac centre of excellence

Thoraxcenter at Erasmus in the Netherlands

Felix Zijlstra head of cardiology at the Thoraxcenter, Erasmus MC, discusses expansion, transition, and innovation.

Erasmus MC: University Medical Centre Rotterdam is by any number of measures a leading international clinical research institution. In 2009, this included being ranked first in Europe for clinical medicine by the Times Higher Education Supplement on a scale calculated from the impact of published journal articles. It is this mix of first-class patient care and cutting edge research as well as some extremely eminent faculty members that puts one of its key departments—the Thoraxcenter—at the forefront of European cardiology.

Founded in 1971, the Thoraxcenter, which combines the departments of cardiology and cardiothoracic surgery, is part of the second largest hospital in the Netherlands; yet, it describes itself to potential employees as an ‘intimate organisation’ set within a large academic centre.

Prof. Felix Zijlstra, FESC/FACC, who took over from Prof. Maarten Simoons as head of cardiology at the Centre in September last year, further explains that while the Erasmus Medical Centre is a substantial community divided over several very large buildings, the Thoraxcenter stands alone in a moderately sized building creating an intimate and friendly working environment. However, by Dutch standards, it is fair to say that the hospital is a large one—at least compared with other university hospitals—and is soon set to expand even further. ‘In cardiology we have 14 intensive care beds and about 35 medium care beds, then there’s the surgical department with their own intensive care beds that is soon to be expanded. There are also four operating theatres with four catheterization labs and we’re building a fifth. We are currently rebuilding large parts of this building as well as renovating the cath labs and operating theatres’.

When asked to outline the areas that the Thoraxcenter excels in, it is clear that Zijlstra has a lot to choose from. He points to the ‘outstanding’ research in the interventional cardiology field which includes work looking at stereotaxis for positioning, improvements to percutaneous techniques including bioabsorbable scaffolds and stents, and the development of less invasive surgical techniques for the treatment of structural heart defects.

The international reputation enjoyed by the Thoraxcenter was recently highlighted by the lifetime achievement award presented to Prof. Patrick Serruys, who heads up interventional cardiology at the Centre, during this years’ American College of Cardiology meeting in New Orleans. Among his many achievements has been to carry out the first randomized trial on a stent. ‘It illustrates the outstanding quality of the Thoraxcenter research programs and the impact on clinical cardiology’, says Zijlstra. He also highlights the substantial innovations being made in biomedical engineering where work is largely focused on diagnosis and imaging. The department is also one of only four in the country managing congenital heart disease, one of three carrying out heart transplants and it boasts the biggest heart valve bank in Europe.

But despite these more than impressive credentials, when it comes to standing out from the crowd, it is the structure of his department that Zijlstra believes is the vital ingredient. ‘The extent of cooperation between our large preclinical laboratory facility and large clinical department is very important. At many institutions in the Netherlands, departments are not managed in the same way. The fact that it is integrated here facilitates bench to the bedside and vice versa, and that aspect is one of the key features, in addition to collaboration between cardiologists and surgeons which has big advantages in developing new coronary, vascular and valvular technologies. Close collaboration is the key to success’.

So, after his 6-month settling in period, what are Prof. Zijlstra’s goals for the future and what innovations can he see being important within the department in the next few years? ‘The management of this hospital ask me yearly where we will be in the near future but I’m not very good at that sort of prediction and I’m hesitant to play that game because when you look back at it, usually we pick the wrong things’. He adds: ‘One of the things we have learnt is that, at the start all new developments look promising but some of them don’t really grow up. For instance I’m quite certain that in the interaction between preclinical and clinical laboratories in terms of cell therapy there will be a number of breakthroughs but where exactly they’ll be is impossible to tell’.

He also points out that pinpointing the next big breakthrough is highly dependent on whom you ask as his staff are all, quite understandably, evangelical about the prospects for their specific areas of expertise. ‘If you asked the electrophysiology people, their answer would be trials with subcutaneous ICD devices and ongoing trials with novel ablation techniques. But if you go to the interventional cardiologists, their answer would be that it’s all about biodegradable scaffolds, and on-going innovations in the management of Acute Coronary Syndromes’.

Erasmus MC
Actually, breakthroughs aside, he believes his most important role over the next few years is to oversee a period of upheaval facing the department in terms of staff changes. There will be a number of years with a lot of transitions because some of the giants are now gradually leaving the department, so we’ll have a new generation to step in and take over that role.

These giants include the aforementioned Prof. Simoons, past president of the ESC, with 687 publications to his name and Prof. Serruys who has published inspiring 1704 articles over his career. Younger members of the faculty will certainly have their work cut out filling the void left behind as these eminent names in cardiology start to take a back seat. But Zijlstra is far from daunted and is upbeat about the road ahead. ‘It is a very exciting time and I’m glad that I’m here to see the department through that transition. That is my principle task’.

Emma Wilkinson, MA

Cardiology in Kosovo

Cardiology is making progress in the youngest state in Europe here discussed by Irfan Daullxhiu, MD.

Irfan Daullxhiu

Independent only since 2008, Kosovo has had little time for progress in medicine and cardiology in particular. Although the University of Prishtina and Faculty of Medicine opened in 1969 which was a landmark for medical education, currently, the nation has a very small budget of €79 million dedicated to medical services.

General medical education requires 6 years, internal medicine specialization 4 years, and then cardiology subspecialization another 2 years. Prior to independence, there was only internal medicine specialization with internists practising cardiology. This system must be aligned with the ESC Core Curriculum for General Cardiologists (2008 update) which recommends 6 years specialist training in cardiology. At present, the number of cardiologists in Kosovo is very low compared with Western European countries, with only two cardiologists per 100 000 inhabitants. More cardiologists are needed for the 2 million inhabitants with the highest population growth rate in Europe, at ~1.3% p.a.

The Kosovo Society of Cardiology (KSC) has 56 members, of which 32 are cardiologists. The Society was admitted to the ESC at the European Congress in Barcelona in 2009 and in 2010 opened its first stand at the ESC Congress in Stockholm. The KSC has organized two cardiology congresses in Kosovo and in the second had its first joint session with the ESC on ‘Acute Heart Failure’. In 2010, the first joint scientific meeting with the Turkish Society of Cardiologists was also organized. Currently, for the first time, the Society is involved in a multicentre survey for acute coronary syndromes (International Survey of Acute Coronary Syndromes in transitional countries, ISACS-TC) headed by Prof. Raffaele Bugiardini from Bologna.

In addition to non-invasive diagnostics, coronary care units, and implantation of permanent pacemakers, there has recently been some development in invasive cardiology. There is a need to create a network for primary percutaneous coronary intervention and develop cardiac imaging techniques. At the moment implantable cardioverter defibrillator implants, cardiac resynchronization therapy and electrophysiological studies and interventions cannot be performed in Kosovo. Similarly, there are no services for adult and paediatric cardiovascular surgery, for which the Society is campaigning. However, at a practical level through the efforts of Roberto Ferrari, the European Heart for Children Foundation has offered to create a paediatric cardiology and cardiac surgery centre in Kosovo. The matter is awaiting a decision by the Minister of Health. Another charity, the Mother Theresa Humanitarian Organisation, has enabled Albanian Physicians to work in small Primary Health Care offices in small communities.

There is still a long way to go until cardiology in Kosovo reaches European standards. In the meantime, The ESC Guidelines will be translated and applied in clinical practice. For the future, the KSC hopes to participate in registries, surveys, and multicentre clinical trials.

Irfan Daullxhiu, MD, FESC, FSCAI, President KSC, University Clinic, Kosovo
Systematic review and meta-analysis of pre-clinical research: the need for reporting guidelines

Animal studies should be reviewed more objectively before embarking on human clinical trials, hence the need for guidelines argues the NC3Rs

Animal studies are often used to inform clinical practice, but is the decision to conduct clinical trials supported by reliable laboratory evidence? One would expect that the answer to this would be yes and the decision to test a new treatment in humans to be based on clear evidence of efficacy in animal models. It would also be reasonable to expect pre-clinical evidence to be assessed in a comprehensive and objective manner to ensure an unbiased decision. Two recent systematic reviews—one of animal data and one of human data—of the effect of calcium channel blockers in stroke have however shown that this is not always the case, with the decision to perform clinical trials based on insufficient evidence.

Systematic reviews and meta-analyses of animal data are still rare compared with the clinical field. Those that have been conducted are usually from the CAMARADES group (the Collaborative Approach to Meta-Analysis and Review of Animal Data in Experimental Studies) which have focused on stroke, Parkinson’s disease, and multiple sclerosis. There are many obstacles to overcome before systematic review and meta-analysis of in vivo data become standard practice, the main ones being publication bias (studies with no significant results are less likely to get published) and the poor reporting quality of animal studies.

The latter is a particular problem. First, it prevents a rigorous quality assessment of the studies to be included in such reviews. While unrandomized studies would not be included in a meta-analysis of clinical trials, using such criteria in a recently published meta-analysis of the effects of anti-emetics in a ferret model of chemotherapy-induced emesis would have implied the exclusion of every single study! Very often, animal studies fail to report the steps taken to minimize the effects of subjective bias when allocating the animals to treatments or assessing the results for example. This was demonstrated in a survey carried out by the UK Government funded National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). The study reviewed 271 publications of publically funded in vivo research in the UK and USA and found that only 13% of studies reported randomization and 14% of studies using qualitative score reported blinding. These findings were echoed by other surveys carried out in various fields of research.

Secondly, failure to report features likely to be associated with heterogeneity, such as drug dose, route of administration, sex, and age of the animal used, greatly diminishes the potential of retrospective analyses and the potential to make maximum use of all of the data available. It creates the dangerously false assumption that results can be generalized when they might not be. It also prevents the investigation of sources of heterogeneity, which could reveal whether a treatment has a different efficacy in males and females, for example, or different adverse effects in young and old animals. This information should in turn inform the design of clinical trials or even the decision to start a clinical trial.

The NC3Rs has developed guidelines to improve the reporting of animal studies. The guidelines are called ARRIVE (Animal Research: Reporting In Vivo Experiments; www.nc3rs.org.uk/ARRIVE) and they describe the minimum information that should be included in a manuscript, ensuring that studies are reported in a clear and comprehensive manner, reflecting the study design and conduct. These guidelines are the animal research equivalent to the CONSORT statement, which has contributed greatly to improving the reporting quality of randomized controlled trials. The ARRIVE guidelines include advice on describing the background and objectives, methods, results, and interpretation of a study. They also recommend including information related to the ethical approval and funding sources, ensuring that the reviewers and readers are provided with all the information necessary to scrutinize and assess publications accurately. Specifically, the guidelines encourage a detailed description of the study design, a clear definition of the experimental outcomes, and the reporting of results with a measure of precision. They also prescribe a detailed account of the experimental procedures, characteristics of the animals used, and adverse effects. Altogether, this information will provide the means for future systematic reviews to inform the design of clinical trials accurately and improve the translation of animal findings into clinical results.

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