Conflicts of interest in medicine and science

Following the recent ESC initiative, Lois Rogers reports on this important topic

Doctors, medical institutions, and governments themselves have been forced to recognize that conflicts of interest are beginning to shake public faith in the medical profession.

Some of these conflicts have led to corruption on a gigantic scale, most notably the revelation that the fraudulent author of the scare over mumps, measles, and rubella vaccine which began in the UK was being funded by a firm of lawyers intent on proving the vaccine had caused autism in a small group of children.

Other less dramatic incidents include that of cardiovascular researcher Don Poldermans of Erasmus University, Rotterdam, himself an ESC official, who was last year found to have fabricated data, though his motive was unclear, and no patients were harmed.

Two American doctors have even set up a blog called Retraction Watch. They have not broken down reasons for research fraud by motive, so it is not clear how much malpractice is motivated by money, how much by the prospect of career advantage, and how much by a simple urge to bend the facts to make them fit a treasured hypothesis.

Heart disease along with cancer, diabetes, and obesity is, however, one of the most lucrative disease areas of this age. The rewards for skewing the agenda towards the use of particular treatments are considerable, and there are plenty of vested interests intent on doing so, some of which are undoubtedly of benefit to patients, and some of which are probably not.

The ESC has now set itself at the vanguard of professional medical bodies attempting to bring a new wave of transparency to the relationship between cardiologists, drug companies, and the manufacturers of medical devices.

It has declared that health-care providers, educators, professional associations, and industry must now take decisive and collective action to eliminate real or perceived bias.

It has published a white paper banning the presence of company staff on clinical guideline committees, the non-disclosure of company connections by authors of papers published in its journals, and the restriction of commercial input into continuing medical education.

Some outside observers might be dismayed, not to say astonished, that the influence of vested interests in the conduct of science has until now been so completely pervasive.

Those on the inside, however, point out it is inevitable. What they do acknowledge, however, is that if it is understood that interests are always declared, then conflicts will be transparent and much of the anxiety will disappear.

It is remarkable that only about half of the 40 000 scientific journals published around the world have any sort of policy covering the disclosure of vested interests.

Baroness Onora O’Neill, a Cambridge professor of philosophy and one of Britain’s leading authorities on issues of trust and transparency, points out that as a member of the House of Lords, the upper House of the British parliament, she has become entirely used to updating on a monthly basis her entry in the register of members’ interests.

She recognizes that most people in other fields are unfamiliar with the process, and if they try to do it at all, they often get lost in what relationships might represent a conflict and what might constitute a reasonable financial threshold to warrant declaration.

‘My experience is that most [scientific journals] are not trying to do it very actively, and for those that are, it is a disorganised cottage industry’, she said.

‘It would be most useful if the editors collaborated on a framework because then it would be transparent. If we had a standard form for declarations of interest then everyone would know what was expected and where they stood’.

It is a view shared by others. David Wood, professor of cardiovascular surgery at Imperial College, London, is the ESC board secretary who organized the meeting in Rome 2 years ago, which led to the development of the white paper. ‘In evaluating evidence for a drug or a device, it’s important that as scientists and clinicians, we are impartial’, he says. ‘If someone has a relationship with a company, then obviously there is a risk their advice will be biased. The drive towards disclosure of interests is an inexorable trend, and rightly so. Anyone not doing this is behind the times and will have to do so very soon’.

But should medical societies reject all industry subsidy and be funded by subscription only, thus excluding younger, impoverished scientists likely to have the best ideas, and should academic researchers boycott demands that they patent their discoveries and issue licenses to those undertaking commercial development, in favour of investigating areas of ‘pure science’ less likely to have a clinical application.

Regulatory authorities are increasingly requiring drug companies to disclose their expenditure on soft-soaping doctors. ‘As of this year, we have to account for every penny we spend on supporting doctors to attend conferences, and other related activities’, said a spokesman for the pharmaceutical giant Roche. ‘But if we don’t help them to go to meetings, who will. In the drive to clean
European health-care systems: a new CardioPulse series

National Cardiology Society leaders will discuss their nation’s health-care reforms in this era of increasingly available interventions and rising costs

Introduction

Nations around the world struggle to deliver the promises of modern medicine to their populations. No one knows the ‘right’ answer; yet, many challenges are remarkably similar across countries. For instance, we live in an era of extraordinary possibility and technological complexity in clinical medicine. This has led to better results for our patients, but also escalating costs and strain on our shared resources.

![Figure 1](http://eurheartj.oxfordjournals.org/)

Figure 1  Adopted from the OECD Health Care Systems: Efficiency and Policy Settings, 2010.

Although health-care reform has received greatest attention in the USA, it is no stranger to Europe. Despite sharing fairly consistent goals, Europe’s health-care systems remain varied and distinct (Figure 1). Each country’s approach differs as much as their history, culture, and geography. In the UK, global budgets and public providers are distinguishing characteristics. By comparison, the German health-care system is highly decentralized with a mixture of private insurance providing the bulk of basic coverage. Each of these reflects widely divergent choices that impact on

Everything up, we have to make sure we don’t go too far in the other direction and destroy the sharing of knowledge. Many others think it is unrealistic to think disclosure will make a big difference. ‘It’s a bit hypocritical to consider only financial conflicts of interest, and I think the importance of this is being overestimated’, said Tom Lüscher, editor in chief of the *European Heart Journal* and professor of cardiology at Zurich University. ‘If something is true it will be reproducible and survive the test of time’. Only time will tell if he is right.

Lois Rogers, international commentator on health science and social policy issues

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fundamental issues for their population, such as access to care and out-of-pocket costs.

We believe that lessons can be learned from this ‘natural laboratory’ of Europe, particularly in cardiovascular medicine where there has been simultaneous growth in evidence-based medicine and high-end services. Accordingly, we asked cardiovascular leaders from several European and non-European countries to briefly describe the greatest strengths and limitations of their health-care system, as well as its most important challenges for the next decade.

The UK is one of the oldest, economically developed nations in the world, consisting of the countries of England, Wales, Scotland, and Northern Ireland. The British National Health Service (NHS) was created in 1948 and is the largest single-payer health-care system in the world. It is funded from general taxation and is based on three core principles:

(i) It meets the needs of everyone.
(ii) It is free at the point of delivery.
(iii) It is based on clinical need and not the ability to pay.

These principles have guided the development of the NHS over more than 60 years and have made it one of the UK’s most cherished institutions.

In 1998, the UK government devolved power to elected assemblies in Scotland, Wales, and Northern Ireland. Although the powers of these political bodies differ, they all have important freedoms with respect to healthcare and have, to some extent, pursued different policies. Our answers to the following questions are based on an analysis of cardiovascular services in England and Wales unless stated otherwise.

1. What is the greatest strength of your country’s health system in tackling cardiovascular disease (e.g. prevention, acute treatment, long-term treatment)?

The UK has enjoyed a balanced approach to all aspects of cardiovascular health, partly because the NHS provides the vast majority of healthcare.

The most successful elements of our cardiovascular services include:

- The national audits and databases (see below).
- Primary Care, which provides excellent chronic disease management services and improved dramatically following the introduction of a performance management system known as the Quality Outcomes Framework (QOF). This has led to high rates of guideline-indicated, secondary prevention measures as well as effective identification of previously unrecognized hypertension and hyperlipidaemia in the general population.

Emergency services, deliver very good first-contact-to-balloon times for primary percutaneous coronary intervention (PCI), and excellent outcomes for all forms of myocardial infarction.

2. What is its biggest weakness?

In previous decades, the NHS has not provided timely, high-quality care for patients with suspected heart disease. However, there have been enormous improvements in the quality of care in the last 10 years. Age-adjusted cardiovascular mortality has fallen dramatically (50% decline in 10 years), waiting lists have virtually disappeared, and adherence to evidence-based guidelines (e.g. prescription of secondary preventive therapy after myocardial infarction) is now excellent. This has been driven by a programme of heavy investment initiated by the last government and the promotion of core standards or targets that were introduced through a National Service Framework (Scotland did not use the NSF but developed a similar strategy based on clinical networks).

Devolving decision-making and financial power to local bodies has helped to create a more responsive service, but has also led to increasingly important differences in local services. As a result, patients in some areas cannot access services that are available to those who live in nearby districts and vice versa (the so-called ‘postcode lottery’). Transcatheter aortic valve implantation (TAVI), for example, is currently not provided in Scotland. There is also growing concern over health inequalities related to socioeconomic status; thus, although patients from deprived backgrounds are at greatest risk of cardiovascular morbidity and mortality, they are still the least likely to access appropriate services.

3. What is being done to measure and improve quality in cardiovascular disease?

The Central Cardiac Database is a collaborative project, run by the Department of Health in England and a wide range of our professional societies, which oversees 12 national audits and registries. This includes comprehensive data for all forms of heart surgery, all cases of myocardial infarction, and all PCI procedures. There is good cross-linkage and the database is linked to the national death registry. The data are well validated and have proved to
be a powerful tool for both research and quality improvement. Scotland contributes to some but not all of these data sets.

A range of quality standards are being developed to help monitor and improve services. These are intended to be aspirational, but also achievable, markers of high-quality, cost-effective patient care, covering the treatment and prevention of different diseases and conditions. They address three aspects of quality: clinical effectiveness, patient safety, and patient experience. In England, these quality standards will be used to inform and set payment mechanisms and incentive schemes such as the Quality and Outcomes Framework (QOF). This has had a substantial impact on achieving guideline targets for hypertension detection and hyperlipidaemia treatment.

4. What is being done to control costs?

Services are commissioned by local bodies that have responsibility for obtaining value for money. The National Institute for Clinical Excellence (NICE—www.nice.org.uk) is an independent body that was created in 1999 with the remit of providing national guidance on the most effective use of health-care resources. The organization has developed a robust, evidence-based approach to its work and examines both clinical and cost effectiveness; it has already made 23 separate recommendations that if implemented might be expected to reduce costs and improve quality of care. The NHS has also been able to contain procurement costs through central purchasing and block contracts. As a result, costs of devices and drugs are much lower than in North America. Finally, there is currently a pay freeze for all but the lowest paid NHS workers in force.

5. How does your country address cardiovascular preventive services?

More than half of the fall in age-adjusted cardiovascular mortality is thought to be due to better prevention strategies. This has been approached at multiple levels. Our governments were among the first to introduce a ban on smoking in public places and have introduced schemes to encourage physical activity and healthy eating. Charities such as the British Heart Foundation (see below) and Action on Smoking and Health (ASH) have done a great deal to promote greater awareness of cardiovascular disease and better lifestyle choices. Health-care professionals identify at-risk individuals through opportunistic and routine screening and are charged with providing appropriate counselling and where necessary medication according to consensus guidelines drawn up by a group of interested professional societies (Heart 2005;91:1–52). These societies are about to publish new evidence-based guidelines that will recommend thresholds for intervention that are based on estimates of life-years gained and not just short-term absolute risk.

6. How are cardiologists in your country incorporating innovative drugs and devices (e.g., TAVI) into their practice?

The National Institute for Clinical Excellence (NICE) has been given the task of deciding which drugs should be made available through the NHS. The NHS in England and Wales has a legal obligation to fund drugs recommended by NICE: nevertheless, local decision-making bodies are still able to impose restrictions. The Scottish Medicines Consortium provides a similar service for Scotland. NICE also assesses medical technologies for the whole of the UK and makes recommendations on the safety and efficacy of a procedure. The guidance does not extend to whether or not the NHS should fund a procedure which is left to local NHS bodies. The UK’s professional societies have taken a leading role in developing methodology for introducing new technology. There is, for example, a TAVI steering group which has published consensus guidance on the introduction of TAVI and collects registry data on every case in the country.

7. What is the greatest challenge facing your country over the next decade?

Like many countries in the developed world, the UK faces a period of austerity with huge pressure on public finances. Although our government has promised to maintain health-care spending, there is no provision for the very high rate of health-care inflation or the need to fund new therapies that continue to cost more. We therefore fear that financial restrictions will limit the development of our cardiovascular services in the next decade and beyond, ultimately affecting patient care.

8. Additional comments that you believe would be of interest to readers, including any questions you would like to see answered by others.

The British Heart Foundation, which celebrated its 50th anniversary in 2011, has made a major contribution to the battle against heart disease in the UK. The charity now spends more than £80 million a year on research, prevention, and care; it currently supports 27 professors of cardiology and has played a pivotal role in promoting academic cardiology. The British Heart Foundation has also led the drive to collect high-quality data on the morbidity and mortality of heart disease in the UK. More information on the activities of the charity is available at www.bhf.org.uk.

Dr Nick Boon
Professor Keith Fox

Prior psychiatric hospitalization: an underappreciated risk factor for premature mortality among individuals with chest pain

Psychiatric disease, prevalent throughout Europe,1 is associated with an excess risk of premature mortality commonly from cardiovascular disease (CVD).2 Patients with psychiatric disease typically have less favourable cardiovascular risk factor profiles than the general population. Behavioural and lifestyle factors such as smoking, alcohol excess, sedentary lifestyle, and poor diet
contribute to this finding, as do the deleterious cardio-metabolic side effects of many modern anti-psychotic medications. Patients with psychiatric disease are also less likely to be offered cardiovascular risk screening and, where appropriate, subsequent intervention. Even taking these factors into account, major psychiatric disease is still associated with an excess risk of death, raising debate into the underlying mechanisms.

Often a first clinical presentation of CVD is with symptoms of chest pain. However, an overwhelmingly large proportion of the increasing number of patients who are admitted to hospital for assessment of chest pain are not experiencing an acute coronary syndrome (ACS) and are discharged from hospital following a period of intensive investigation using increasingly sensitive diagnostic tests. In many people, a definitive diagnosis is never reached. Such patients may be labelled as having non-cardiac chest pain (NCCP), a diagnosis of exclusion that, while often associated with ongoing symptomatology and psychiatric morbidity, has until now been considered a relatively benign condition. Yet, contemporary population level data on outcomes following an admission to hospital with NCCP are lacking.

In a recent study published in the European Heart Journal, we explored the influence of a previous psychiatric hospitalization on future all-cause and CVD-specific mortality. We used the Scottish Morbidity Record scheme which collates all hospital discharges in Scotland (population 5.1 million) to identify patients discharged from hospital between 1991 and 2006 with a diagnosis of NCCP and no prior history of coronary heart disease. Using data linkage, this group was followed for 1 year or until death with mortality statistics provided by the Registrar General Office, Scotland.

Our study included 159 888 men and women, of whom 4.4 and 3.9%, respectively, had been hospitalized for psychiatric disease (any cause) in the decade prior to their first NCCP hospitalization. Crude case-fatality rates following a first hospitalization for NCCP were higher among those with a previous hospitalization for psychiatric disease than those without: in men 6.3 vs. 4.3% and in women 5.4 vs. 3.6%. Following adjustment for year of NCCP hospitalization, socio-economic deprivation, and co-morbid diagnoses of hypertension and diabetes, the hazard of death (all-cause) was 3.71 (95% confidence interval 2.26–6.09) in men and 2.94 (1.60–5.41) in women under 40 years of age that had a previous psychiatric hospitalization compared with those that did not. The excess hazard associated with a psychiatric hospitalization was present in all age groups, although the effect was attenuated with advancing age such that in men over 60 years of age, the hazard ratio was 1.37 (1.12–1.67) and in women 1.70 (1.42–2.05). Similar trends were observed for CVD-specific mortality.

Why does such inequality exist and what should be done to address this? Several explanations are possible. Patients with psychiatric disease may find it difficult to report symptoms and atypical symptoms, particularly in younger patients, may lead to misdiagnosis of chest pain. A clinician’s priority during a first hospitalization for NCCP may be simply to exclude an ACS rather than to assess CVD risk, and as previously noted, patients with psychiatric disease are less likely to undergo CVD risk screening and less likely to receive evidence-based therapies to modify cardiovascular risk, even in the presence of established CVD. In addition, ongoing assessment and management of physical illness in patients with psychiatric disease often falls to a psychiatrist rather than an appropriate specialist. Perhaps then, a first hospitalization for NCCP should represent an opportunity to comprehensively assess cardiovascular risk and where appropriate intervene to modify risk. While this should arguably occur at the point of psychiatric diagnosis and be ongoing, patients with psychiatric disease can be difficult to reach; therefore each contact with a medical specialist must count. For the first time, the European Psychiatric Association (EPA), supported by the European Association for the Study of Diseases (EASD) and the European Society of Cardiology (ESC), has produced a position statement to assist psychiatrists, general practitioners, general physicians, and cardiologists in treating this population.

Acknowledging that anti-psychotic medications may worsen cardiovascular risk profiles in a group that already exhibit a greater CVD risk, the statement offers guidance on risk assessment and treatment. Annual cardiovascular risk assessment in those with normal risk factor profiles and assessment at 6 and 12 weeks after starting or changing second-generation antipsychotic medications is recommended. Perhaps more importantly, close communication between psychiatrists, primary care physicians, diabetes specialists, and cardiologists to fully optimize risk factor profiles is advocated.

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Reorganizing children’s heart surgery in England

Surgery for children with congenital heart disorders is being reorganized in England so that operations take place at fewer hospitals than at present. Helen Jaques looks at the new plans

Children’s heart surgery occupies an unusually high position in the public consciousness in the UK thanks to several scandals over the past 10 years or so. Between 1988 and 1995, 29 babies and toddlers died at Bristol Royal Infirmary following arterial switch operations or atrioventricular septal defect operations by two surgeons. Shortly after in 1999, The Royal Brompton and Harefield NHS Trust in London was investigated over claims of high death rates among children with heart defects. Then in 2010, children’s heart surgery was suspended at the John Radcliffe Hospital in Oxford after four deaths among infants with congenital heart problems over a period of 3–4 months.

A national inquiry into the deaths at Bristol, published in 2001, recommended that paediatric heart surgery should only take place at hospitals that conduct a minimum number of procedures, with those unable to meet this minimum forbidden from carrying out surgery. The report also suggested that surgeons should undertake four sessions of paediatric heart surgery a week to maintain their competence, or 40–50 open heart operations a year for surgeons who operate on neonates and infants.

Concentrating skills to improve safety

The logic behind these minimum volume thresholds is that having greater volumes of patients, albeit concentrated in fewer surgical centres, will make doctors better at spotting problems and treating them quickly, as well as help them keep up their skills. In addition, this approach will allow the latest equipment to be situated with a critical mass of expert clinicians. The overall effect, it is hoped, will be improved survival and recovery rates among children undergoing surgery for congenital heart conditions.

The evidence in the literature seems to back up these theories. A 2002 systemic review of 137 studies found that 71% of the studies of hospital volume and 69% of the studies of physician volume reported a statistically significant relationship between high volume and good outcomes, with a particularly strong association found for paediatric heart surgery. A 2007 systematic review agreed that high-volume hospitals had significantly better outcomes (association reported in 74% of the relevant studies), but this effect was limited in prospective studies (40%). Surgeon volume, however, was more equivocally associated with better outcomes (74%), in particular in cardiothoracic surgery (75%) and vascular surgery (73%). A 2009 study of data in the Society of Thoracic Surgeons Congenital Heart Surgery Database likewise reported an inverse association between paediatric cardiac surgical volume and mortality that became increasingly important as cases became more complex.

The change proposed for England

This year the Department of Health in England announced the outcome of a review of children’s congenital cardiac services, Safe and sustainable: a new vision for children’s congenital heart services in England. The review suggested stopping heart surgery in 4 or 5 of the 11 children’s heart surgery units in England and ensuring that each of the remaining institutions had at least four senior (consultant) surgeons and conducted at least 500 paediatric procedures a year. Specialist surgical centres in London, Leeds, Southampton, Newcastle, and Leicester were all put forward for ‘reconfiguration’, i.e. stopping surgery and changing into cardiology centres, providing initial diagnosis and continuing management.

The proposals were put out to public consultation and huge numbers responded: more than 75 000 parents, children, and health professionals from around the country. Most patients and the public agreed that paediatric congenital cardiac surgery should end in Leeds and Southampton, whereas most organizations including NHS trusts and heart charities backed closing surgical centres in Leeds and Leicester. The child heart surgery unit at the Royal Brompton Hospital in London will almost certainly be closed, although the hospital is currently in the midst of a judicial review to prevent the closure.

A bigger movement

The move towards centralizing services at fewer hospital sites is already underway in some other specialties. Earlier this year, the Royal College of Obstetricians and Gynaecologists suggested cutting the number of medically staffed maternity units to centralize complicated care at fewer institutions and to drive more care into the community, which it says will cut costs as well as improve safety. The Royal College of Paediatrics and Child Health similarly has suggested cutting the number of inpatient acute general paediatric services in the UK by nearly 50. Another example is stroke care in London, which since 2009 has been delivered at eight hyper acute stroke units instead of at most hospitals across the capital. NHS London believes that centralizing stroke care in these 24 h, highly specialized units could save up to 400 lives a year.
This all fits in with a push across the whole of the NHS towards ‘reconfiguration’ of hospital services, whereby acute services are concentrated in fewer hospitals and more care is delivered in the community. This plan is driven as much by money as by the more laudable goal of driving up quality and safety though, with the NHS in England under pressure to make £20bn worth of ‘efficiency savings’ by 2014–15. The fate of children’s congenital heart services now lies in the hands of the decision-making body for Safe and Sustainable review project, which is expected to announce its final decision by the end of 2011. It looks like the way in which children’s heart services are delivered in England is set for a major change, and not before time given the safety issues that have dogged paediatric heart surgery.

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Webinars: the future of online medical education?

A new online ESC educational programme for cardiology is discussed by Dr Nicholas Brooks.

With the launch of European Society of Cardiology (ESC) webinars, a new online programme in general cardiology, in October 2011, cardiologists are finding themselves right at the vanguard of a new concept in education. The ESC webinars, which are organized by the ESC, have been heralded as a revolutionary contribution to the future of medical training. Already more than 700 delegates have signed up to the programmes, which allow ‘real-time’ audience participation, and had access to world class teaching in the comfort of their own homes or offices.

‘Cardiology is a rapidly evolving field, creating an enormous need to deliver up to date information to health care professionals’, explains Dr Nicholas Brooks, a member of the ESC Educational Committee. ‘The idea behind the ESC webinars is to provide the audience with the basic knowledge required to be a cardiologist in the 21st century. It’s a cost effective approach allowing the delivery of education to large numbers of professionals, which is ideal for people who have neither the time or budget to travel to meetings’.

The approach, he adds, has the big advantage of creating a level playing field where health-care professionals throughout Europe receive equal access to high-quality medical education, delivered by key opinion leaders. ‘We’re finding that the webinar platform has raised educational opportunities in less developed European countries’, says Brooks from South Manchester Wythenshawe Hospital (Manchester, UK). An additional bonus, he adds, is that the webinars offer an extremely green approach that has resulted in a major reduction in air miles.

ESC webinars are targeted at both established cardiologists and trainees (including major content from the core curriculum), with the programme also proving popular with allied cardiology health professionals, such as technicians and nurses. All the webinars, which last for around 1 h, have been reviewed for accreditation by the European Board for Accreditation in Cardiology (EBAC).

The format of the sessions, which are most often scheduled in the evening, involves state-of-the-art talks, interwoven with clinical cases, live assessments in the form of MCQs (with anonymous results), and the opportunity for discussions with experts. ‘Delegates often feel less inhibited about asking questions online than when they’re sitting in big lecture theatres. The relaxed atmosphere can lead to more wide-ranging discussions’, says Brooks.

The ESC webinars provide a strong focus on guidelines, with many titles initiated by recent publication of new guidelines. ‘It’s a great way of improving everyone’s awareness of recent changes’, says Brooks.

To get involved, all participants need is a computer with a high-speed Internet connection and a head set or a telephone. They have the choice of paying a one-off fee to access individual ESC webinars or an annual subscription providing access to all the webinars as well as a ‘back catalogue’ of recordings. The QR-code provides direct access to information about ESC webinars with your smart phone.

Already ESC webinars have been broadcast in subjects such as hypertension, acute coronary syndromes, new guidelines on dyslipidaemia, congenital heart disease, and echocardiography evaluation of patients with multivessel disease. Forthcoming sessions for March include interventional cardiology, valvular heart disease, and pulmonary circulation; for April, heart failure, cardiomyopathies, and preventive cardiology; for May, endocarditis and syncope; and for June, thrombo-embolic venous disease.

Janet Fricker, medical writer

Link to the detailed programme: http://www.escardio.org/education/eLearning/webinars/general-cardiology/Pages/welcome.aspx
Heart disease in women: I: pathophysiology and symptoms

Helen Jaques looks at how the pathophysiology, risk factors, and symptoms of cardiovascular disease differ between men and women

Cardiovascular disease (CVD) is the leading cause of death worldwide—responsible for 29.0% (17.1 million) of deaths across the globe in 2004, a higher proportion than cancer (12.9%, 7.4 million deaths)—and causes nearly half of all deaths in Europe (48%). In particular, CVD is the number one killer of women worldwide, responsible for almost 32% of all deaths among women compared with 27% in men in 2004. There are various theories as to what is responsible for this higher death rate from CVD in women, the big factors being differences in how the disease develops in men and women, differences in risk factors, and differences in how women with symptoms of CVD are diagnosed and treated compared with men.

Pathophysiology

The biggest difference in the pathophysiology of CVD between men and women is that women are more likely to have a heart attack despite having open coronary arteries, says Dr C. Noel Bairey Merz, MD, FACC, director of the Women’s Heart Center and director of the Preventive and Rehabilitative Cardiac Center at Cedars-Sinai Medical Center in Los Angeles. The Women’s Ischemia Syndrome Evaluation (WISE) study, led by Bairey Merz, found that among women with chest pain or suspected myocardial ischaemia, more than a third (37%) had no stenoses on coronary angiography. In fact, between 10 and 25% of women presenting with acute coronary syndrome and ST-segment elevation myocardial infarction (STEMI) have ‘normal’ arteries at coronary angiography, compared with 6–10% of men. This is because women with chest pain are more likely to have diffuse stiffening and narrowing of the small vessels that supply the heart—a phenomenon known as microvascular dysfunction—which causes chest pain that can be similar to that of people with stenosis or occluded coronary arteries. However, it is ‘a myth’ that all women with MI have open arteries, counters Professor Eva Swahn, MD, PhD, director of the Linköping Academic Research Centre (LARC) in the Division of Cardiology at Linköping University, Sweden. ‘If you take a population you will find more women with angina pectoris or chest pain who have normal coronaries compared with men’, she says. ‘That means if around 10% of men have open arteries, 20% women do. But you still have around 90 and 80% who have atherosclerosis in their coronary arteries’.

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Women do also get atherosclerosis in the larger coronary arteries, but in a slightly different way to men. The progression of atheromas into vulnerable plaques occurs more slowly in women than in men, and women tend to have a lower atheroma burden and more stable plaques than men. Also, younger women are more likely to have plaque erosion rather than plaque rupture, which is seen in older women and men. Women and men do deposit the atherosclerotic plaque differently in the arteries’, confirms Bairey Merz. ‘In addition, women seem to do more positive remodelling and therefore the angiogram is less diagnostic because the angiogram then looks normal’.

It is possible that inflammation plays a role in the development of microvascular coronary dysfunction in women. The WISE researchers found that elevated levels of C-reactive protein, interleukin-6, and serum amyloid A were associated with greater risk of a coronary event or death within 5 years in women, even though these patients were only slightly more likely to have coronary artery blockages. The concentration of inflammatory markers such as high-sensitivity C-reactive protein starts to increase in women at puberty but does not change in men, explains Bairey Merz. As a result, women are more likely to have autoimmune diseases such as lupus and rheumatoid arthritis. ‘Are these diagnosed and subclinical autoimmune diseases

Eva Swahn

Bairey Merz
that are much more common in women impacting the heart and perhaps causing microvascular dysfunction, and are even low levels of inflammation that are not diagnosed as autoimmune disease but just chronically elevated levels of inflammation also having a similar effect? she asks.

**Risk factors**

Many of the classic risk factors in men are also implicated in women who have CVD. The massive INTERHEART case-control study indentified nine factors that accounted for 90% of the attributable population risk in men’s coronary heart disease and 94% in women. Abnormal lipids, smoking, abdominal obesity, diet, and psychosocial stress were all similarly associated with MI in men and women. However, hypertension, diabetes, physical inactivity, and moderate alcohol intake were more strongly associated with MI in women than in men. And although smoking is a strong risk factor for both genders, several studies have shown that smoking is a more powerful risk factor in women. Age is a big risk factor: on average, women tend to experience their first MI 9 years later than do men. The younger age of onset of acute MI in men is largely explained by the fact that their risk factors, including abnormal lipids and smoking, are higher at an earlier point in their lives. Ethnicity is another traditional factor that seems to affect the risk of heart disease in women. African American women have less obstructive coronary artery disease on angiography than do Caucasian women. ‘African American women also have a higher risk of sudden death that I don’t think anyone fully understands’, says Dr Bairey Merz.

Oestrogen is thought to act as a risk factor in CVD, as women who undergo menopause later have a lower risk of CVD than women who have early menopause. Oestrogen is heart protective when naturally produced by the ovaries and is thought to delay the onset of atherosclerosis, but oestrogen from birth control pills or hormone replacement therapy (HRT) increases the risk of coronary heart disease and blood clots, respectively. Oestrogen and progesterone, and also testosterone, sex hormone binding globulin, and some of the other androgens, do appear to influence the atherosclerotic burden, but they do not seem to be big risk factors, says Dr Bairey Merz. ‘We can put them into multivariate models. For example, we demonstrated that women who go through a very rapid menopause, transition under three years, have more progression of atherosclerosis’, she says. ‘So yes they appear to be playing a role. Is it a big important role? No’.

**Differences in symptoms**

As far as symptoms go, men and women with CVD largely present with the same complaints. Between 80 and 90% of both men and women have the so-called typical symptoms, i.e. chest pain potentially radiating to the arm and shoulder. At the end of the day the thing to say about symptoms is ischaemia is ischaemia, if the blood flow is interrupted and you’re having a heart attack, there’s not a lot of reasons to think it should be different in men and women’, says Dr Bairey Merz. However, women are more likely to report atypical symptoms of CVD such as discomfort, exhaustion, and shortness of breath.

The idea that women always have markedly different symptoms to men can have negative consequences for patients, says Prof. Swahn. ‘My feeling is that women have tended not to seek help when they have typical symptoms because they have been told that they shouldn’t have typical symptoms when they have MI, they should have something else’, she says. Another problem that can affect the diagnosis of women with symptoms of heart disease is that women report pain sooner, and they report milder forms of pain, says Dr Bairey Merz. ‘While you would think that this should be good, actually I think it is probably a liability’, she says. On the other hand, ‘women will often say that they have had pain for hours, so the doctor will think that it can’t be a heart attack because if you’ve had pain for hours you should have died by now’.

**Conclusions**

It seems that the differences in disease processes and symptoms of CVD between men and women are perhaps more subtle than is sometimes appreciated. The big message is that although some women will have ‘atypical’ pathophysiology and symptoms, a majority will have the same sort of disease and symptoms as men. The assumption that women with suspected CVD always present differently to men can have some dangerous implications for diagnosis and treatment.

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