Viewpoint: Megatrials and the Development of Antithrombotics

Gilles Montalescot, MD, PhD, is professor of cardiology at the Institut de Cardiologie, Centre Hospitalier Universitaire Pitié-Salpêtrière in Paris. He expresses his concerns about new drug development to Monika Polak, PhD.

Huge, multicentre international trials help drive cardiology practice and patient care forward, but they also have their downsides, according to Gilles Montalescot, MD, PhD, a professor of cardiology at the Institut de Cardiologie, Centre Hospitalier Universitaire Pitié-Salpêtrière in Paris.

Dr Montalescot, an interventional cardiologist with an interest in thrombosis and antithrombotics, acknowledges the major role played by large trials, and especially so-called megatrials, in answering important clinical questions that affect recommendations and clinical practice. However, he remarks that the inclusion criteria for many of these megatrials focus on the same highly selected patient populations. Dr Montalescot says “In reality, there are many more patients who could benefit and who do not fit into the select subset outlined by trial recruiters.”

Dr Montalescot fears that patients with certain characteristics will never be studied. For example, many new anticoagulant drugs have been tested in patients with acute coronary syndromes (ACS), atrial fibrillation, or venous thromboembolic disease, but not in those with prosthetic heart valves. “Despite being a limited group of patients, they are of great importance because they require lifelong treatment and deserve the drugs with the best risk/benefit ratio,” explained Dr Montalescot.

He feels that the pharmaceutical giants that run multicentre trials write off these peripheral groups of patients as representing too small a market share, and therefore view interventions for them as not profitable and not worth pursuing.

Dr Montalescot argues that exclusion of certain patient groups in key trials can make it difficult to apply guidelines in daily practice. “There is a need to question the relevance of general guidelines that are based on big trials performed on homogeneous populations, rather than on the heterogeneous population of daily practice. The latter have specific issues that are not addressed in the trials, such as, for example, renal failure, or patients at a high risk of bleeding.”

Although he has been involved in carrying out large trials himself, Dr Montalescot believes it is vital to initiate smaller trials in order to capture these peripheral patients. In addition, it is important to investigate treatment strategies as well as specific drugs.

His research team had to secure public funding for a randomised study (the ABOARD study) that is now in process and is investigating outcomes following immediate catheterisation compared with delayed intervention in patients with ACS. He argues that this trial is important as it may show that if catheterisation is carried out quickly, complications, length of stay, and, therefore, costs are reduced.

Dr Montalescot suggests, “There might be a role for governments to encourage such trials by funding them directly. Limiting health expenditure is a big issue in many countries, including France, which has recently suffered reductions in hospital beds and nursing staff. Therefore, duration of treatment should also be a key issue for trials. It is essential to know how long patients are likely to need treatment, and when drugs are no longer beneficial.” This information would benefit patients and also the health system in terms of fewer wasted medicines and lower costs, but Dr Montalescot says that such “withdrawal from treatment” trials are rarely seen.

Another small-scale trial about to be published, the ALBION study, has investigated high loading-dose clopidogrel in patients with ACS. Even though the drug has been around for a decade or so, this question had never been taken on by the industry. Dr Montalescot says, “Funding was forthcoming from the industry, but it took some convincing, and the trial was actually designed by myself and my team.” The results revealed that clinicians had probably been using too low a dose of clopidogrel in ACS patients.

“These smaller trials are obviously not trials for obtaining data in order to get a drug licensed,” he says. “They are trials to tweak clinical practice, provide information on subsets of the patient population that are not necessarily the norm, understand the disease better, or to generate new hypotheses for improved care.”

The field of antithrombotics is rapidly expanding, with a new drug “almost every morning,” says Dr Montalescot.
Such fervent development activity can make it difficult to keep practice right up-to-date. He points out, “Large industry-sponsored trials tend to test new drugs on top of what is already standard care, and this layered approach filters into guidelines, which then advocate using 3 or 4 drugs in combination.” He believes that modern practice should now try to replace several drugs with a single, new, more potent drug, and then build newer and safer treatment strategies.

More powerful antithrombotics are needed, Dr Montalescot feels, and suggests that the screening stage of drug development might be where the problem lies. Antithrombotics that appear too potent give drug developers too much cause for concern in terms of the potential risk of bleeding.

Dr Montalescot believes that one potent oral drug, with a rapid onset of action, that both inhibits platelets and combats coagulation, would be effective in emergency and secondary prevention, and would also increase compliance and reduce the risk of drug interactions. “While I am hopeful this may happen eventually, it is unlikely in the short term,” he says.

Dr Montalescot thinks cardiology is a “fantastic” specialty, in which much of current practice is driven by pharmaceutical or device industry-sponsored megatrials. Although he recognises that patients benefit from the advances in treatment made possible by these trials, he comments “Megatrials directly drive up healthcare costs, as more and more new treatments become recommended and available.”

He points out that to keep our healthcare systems viable, new ideas, the merging of facilities, better stratification of patients and optimisation of care, as well as new treatment strategies, are necessary to avoid restrictions in beds, prescriptions, staff, or limited access to medical care. Dr Montalescot warns, “Medical progress could potentially lead to real differences in patient care across Europe, as countries with varying reimbursement systems struggle in different ways to manage escalating healthcare costs.”

Monika Polak is a freelance medical writer.

Reference


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A National Cardiovascular Disease Screening Programme

The National Screening Committee in the United Kingdom has announced plans for a national screening programme for heart disease and stroke. Mark Nicholls canvassed opinion at home and abroad on the proposal.

The National Screening Committee (NSC) in the United Kingdom has said it wishes to implement a national screening initiative — the Vascular Disease Risk Factor Assessment and Management Programme — that could help detect patients at risk of cardiovascular disease (CVD) as early as April 2007. The NSC was set up by the UK government in 1996 to advise on the merits of screening for particular diseases and health problems. The programme proposes that just under 2 million patients of middle age be invited into general family practitioners’ (GPs) surgeries every year to have their serum cholesterol, blood pressure, and blood glucose levels measured. Lifestyle factors, ethnicity, and clinical tests would also be incorporated.

The UK Department of Health has broadly welcomed plans for the initiative. Roger Boyle, CBE, FRCP, FESC, national director for heart disease and stroke at the Department of Health, said, “The committee has raised this issue as an area for further exploration. Though at an early stage of consideration, we are interested in this idea.”

Eminent cardiologists from England, Scotland, The Netherlands, and Italy are also interested, and expressed varying opinions.

Alison Calver, MA, MD, FRCP, consultant cardiologist, Wessex Cardiothoracic Unit, Southampton University Hospital.

Dr Calver welcomed the initiative. “In principle, I think this is an idea that merits close consideration, as hypercholesterolaemia, early hypertension, and deranged glucose handling can all be asymptomatic,” she said. “Intervention in patients found to have abnormalities would be likely to prevent disease, and this could certainly have an impact on the incidence of cardiovascular events.”

But, Dr Calver cautioned, “There will need to be a careful health economic analysis to determine whether such a programme is cost-effective in terms of numbers screened in order to pick up one abnormality that requires treatment, and the cost of subsequent treatment required to prevent events.” She continued, “I suspect that it would be most successful at identifying more patients in need of treatment than are currently identified. Thus in the short term it may actually produce an increase in the amount of work that needs cardiology input and referral.

“In the long term one would hope that treatment of the hypercholesterolaemia and hypertension identified would reduce the incidence of cardiovascular events. I think it
likely that the number of patients requiring treatment for asymptomatic hypertension and hypercholesterolaemia would be considerable. Such a screening programme would undoubtedly increase the workload of GPs considerably, and so has resource implications for primary care personnel, as well as the increase that would be required in the drugs budget.

“Overall, I think it likely that such a programme would be cost-effective, but whether we choose to afford it will remain a political decision.”

Dr Packard said any initiative such as this will help reduce cardiovascular disease is a positive step. But he warned that for it to be most effective in terms of costs and benefits to patients there needs to be a carefully structured approach. He said, “This is not the first time people have suggested this (national screening), but usually it is we as cardiologists who suggest, and the politicians who veto it on the basis of cost, so this is an interesting turn up for the books.”

“I welcome it, but it has to be structured and implemented in a way that allows for waves of appropriate survey with waves of appropriate follow-up treatment. It is no good to just survey everybody in sight.”

He said that the danger of surveying a whole population is that it can create the worried well. “People know when they are unwell and they know when they are well, but people do not understand what it is to be at risk. We need an appropriate educational policy to address that.”

There needs to be a case-finding element to the survey so that it will look deeper into finding those at risk, such as working with GPs and looking to find those with inherited cholesterol problems, for example those with familial hypercholesterolaemia (FH).

“It is one of the things we have not done well. A GP will have about 2000 patients, of which 4 will have FH and they will represent 4 families. Finding those will be one of the more cost-effective things we can do,” he said. He believed that the blood sugar element of the screening was also a significant positive step.

Dr Packard said that such a survey will lead to disease diagnosed earlier, and rather than preventing CVD, we will see it eventually compressed into appearing later in life where people will live healthier for longer. That will be a health gain for society and a huge benefit for economic output, he said, but added, “We would not need fewer cardiologists — they would just be dealing with older patients. A structured survey would prevent disease happening in the first place and might at least highlight those at risk of diabetes and myocardial infarction.” He concluded, “Selective screening would be more cost-effective than screening on an indiscriminate scale, and would improve the cardiovascular health of individuals most at risk.”

Freek W.A. Verheugt, MD, FACC, FESC, chairman of the department of cardiology at the Heartcenter, University Medical Center, Nijmegen, The Netherlands.

Dr Verheugt believes a national screening programme is a good initiative and will have a significant impact on future CVD. He said, “The benefits will be clear in that risk factors for heart disease are detected early in life and may have a strong impact on cardiovascular morbidity and mortality in the future.”

At present, he added, there are no such national screening initiatives in The Netherlands except for a few epidemiological studies in certain areas. He says that often cardiologists do not think a lot about screening and primary prevention, usually only seeing patients who already have symptoms.

Dr Verheugt said, “Such a national cardiovascular health screening programme may especially apply to healthy individuals because they will participate. The highest risk individuals are not usually seen in such a programme, because they are not notified in the proper way, or are not willing at all to manage their health risks.”

But he went on, “I surely back such an initiative and I would like to see something like this in my country or elsewhere across Europe.”

Silvia Priori, MD, PhD, FESC, associate professor of cardiology, director of molecular cardiology at the University of Pavia, Fondazione Maugeri, Italy.

Dr Priori said, “Such a national screening programme would have clear benefits in the United Kingdom. I think it is a great idea. I am very much a supporter of education and public medicine, and this is very important. In Italy we have a very strong programme of monitoring children and adolescents when they start being active in sport.”

The Italian national programme conducts checks on children when they get to the 8-to-10 age group, and provides invaluable data, through which tests such as ECGs and blood pressure checks can start to identify those who are at risk of cardiovascular disease.

“Although somewhat different, a programme such as this taking place in the UK will be very effective in identifying those at risk,” said Dr Priori.

Mark Nicholls is a freelance medical journalist.
History of Medicine: The Wenckebach Phenomenon

Karel Frederik Wenckebach, MD, made his name in the study of cardiac arrhythmias. Diana Berry tells his story.

Dr Wenckebach was born in The Hague in The Netherlands. He attended the University of Utrecht, receiving his medical degree in 1888. He then worked at the same university in the physiology department of Theodor Wilhelm Engelmann, MD, whom he greatly respected. In Dr Engelmann’s department, Dr Wenckebach became familiar with the latest techniques in kymographic recordings, and in experimental work he was able to observe rhythm disturbances in frog hearts.

He left Utrecht in 1891 to work in a country practice but returned to work with Dr Engelmann again in 1896. It was here that he carried out some of his most important work on arrhythmias, where he is best remembered for his studies on the periodically dropped beats — the “Wenckebach periods,” or, as he called them, the “Luciani’s periods,” after the Italian physiologist Luigi Luciani, MD, (1840–1921).

It was in 1898 on examining a female patient in her early 40s that Dr Wenckebach first encountered a pattern of pulse irregularity that made him determined to decipher what would become his eponymous rhythm disturbances. His analysis of the radial arterial pulse curves using sphygmograms and a tuning fork to measure time proved puzzling, but with the help of Dr Engelmann, who had some 5 years earlier made some interesting polygraph tracings of a frog’s heart, Dr Wenckebach noted a gradual increase in the intervals between atrial and ventricular pulses. These intervals became progressively longer, until a complete absence of atrial contraction resulted in a delay of the next heartbeat. The first atrioventricular pulse interval after the dropped beat was the shortest, and then the cycle was repeated (see figure).

Interestingly, both Dr Wenckebach and the English physician Sir James Mackenzie, MD, were both working in the 1890s to unravel what lay behind arrhythmias that could be both felt in the pulse and recorded. Sir James used the venous pulse with arterial tracing, but Dr Wenckebach studied the arterial pulse, eventually adding other tracings such as the cardiogram that could show auricular as well as ventricular contractions.

The primary concern of both physicians lay with extrasystoles. It became possible to analyse their clinical significance after the French physiologist Étienne-Jules Marey, MD, discovered in 1876 the refractory period in the cardiac cycle and the compensatory pause after the extrasystole. The identification of extrasystoles and their differentiation from auricular fibrillation was important, because at that time an irregular pulse invariably meant a poor prognosis.

In 1906, after the development of Willem Einthoven’s string galvanometer, Dr Wenckebach had the technology to demonstrate the lengthening of the PR intervals before the dropped beat. This confirmed his earlier findings regarding second-degree atrioventricular block in frog experiments. Undoubtedly his work on arrhythmias and the publication of his book Die Arhythmie als Ausdruck bestimmter Funktionsstörungen des Herzens: Eine physiologisch-klinische Studie greatly enhanced his reputation, and in 1911 he was appointed professor of internal medicine at Strasbourg University, France, where he remained until 1914, finally moving to a corresponding post at the University of Vienna, Austria, where he remained until his retirement in 1929.

After his retirement, Dr Wenckebach went to the Dutch East Indies, where he studied heart disease associated with beri-beri, and then somewhat by chance discovered the usefulness of the drug quinine as an antiarrhythmic. Its effectiveness was brought to his notice by a Dutch merchant from Java who took the drug to prevent malaria, but claimed that it was also beneficial in interrupting attacks of arrhythmia. Dr Wenckebach used the drug because of “its quieting influence on the heart, quite apart from whether there is auricular fibrillation or not.”

Electrocardiogram showing the Wenckebach phenomenon.

Dr Wenckebach, or “Vencky,” as he was known by his colleagues, was a modest man much liked and admired by all who came into contact with him professionally and socially. He was enthusiastic in his life and work, charming, and of a humorous disposition. His comment, “No, I am not a great man; I am a happy man,” perhaps best portrays his character and outlook on life.

Diana Berry is a medical historian and freelance writer.

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