Viewpoint: Oral Anticoagulation in Heart Disease

Freek W.A. Verheugt, MD, FACC, FESC, chairman, Department of Cardiology, Heartcenter, University Medical Center, Nijmegen, Holland, discussed with Mark Nicholls the benefits and risks of oral anticoagulation.

Close monitoring of patients in a tight net of laboratories has enabled countries such as Holland and Norway to use long-term anticoagulation effectively in coronary disease. These high standards of anticoagulation control and the clear benefits to patients have made long-term randomised trials possible in this area, explained Dr Verheugt, professor and chairman of the Department of Cardiology at the University Medical Centre, Nijmegen.

He said that there remains the risk of major bleeding with oral anticoagulation in heart disease, but in general the benefits of oral anticoagulation in, for example, atrial fibrillation or artificial heart valves, largely outweigh the bleeding risk. Dr Verheugt pointed to the benefits of oral anticoagulation in coronary heart disease, supported by major trials, and said, “Oral anticoagulation interferes with the coagulation cascade, and therefore limits the activation of coagulation through the intrinsic and extrinsic pathway. The latter is specifically important in the complications of atherosclerosis.

“In atherosclerotic vascular disease, oral anticoagulation was the standard of care in the 1960s and 1970s, and has been almost completely replaced by aspirin. Yet it has been shown that even in modern cardiology, oral anticoagulation plus aspirin is superior to aspirin alone in a number of major trials in patients surviving myocardial infarction,” he said. “Besides, it is the only effective antiplatelet strategy in patients with atrial fibrillation and in those with artificial heart valves.”

Dr Verheugt says that during the last 20 years the focus has been on the development of better antiplatelet drugs. He said, “Only clopidogrel has been demonstrated to equal aspirin in effectiveness, and the combination of aspirin and clopidogrel has been shown to be superior to aspirin alone in the management of acute coronary syndromes with or without stent implantation. These developments have overshadowed the improvements that have been seen with oral anticoagulation.”

He said that firstly, the development of an international normalised ratio (INR) has made the strategy of oral anticoagulation more reliable and has made large-scale studies possible. Secondly, these trials have shown that long-term oral anticoagulation is protective against cardiovascular death, stroke, and recurrent infarction in patients who have survived acute coronary syndromes but at a 2-fold to 3-fold higher bleeding risk.’ And finally, it was shown that this strategy only works if the achieved INR is > 2.0 (see Figure). Recently, Dr Verheugt said, the CHARISMA trial proved that double antiplatelet therapy (clopidogrel and aspirin) was not superior to aspirin alone in the long-term protection of these patients, but is associated with 50% more moderate-to-severe bleeding.

“This strongly suggests that long-term interference with the coagulation cascade is superior to antiplatelet therapy alone. However, oral anticoagulation is a laborious strategy and should be replaced by drugs that are simple to use,” he said. “Oral direct thrombin blockers or oral direct factor Xa inhibitors are the best candidates and are currently under investigation for this purpose.”

<table>
<thead>
<tr>
<th>INR &gt; 2.0</th>
<th>MORTALITY, (RE)INFARCTION</th>
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<tbody>
<tr>
<td>ATACS</td>
<td>(n = 214)</td>
</tr>
<tr>
<td>OASIS-2*</td>
<td>(n = 1,821)</td>
</tr>
<tr>
<td>APRICOT-2</td>
<td>(n = 300)</td>
</tr>
<tr>
<td>ASPECT-2</td>
<td>(n = 668)</td>
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<tr>
<td>WARIS-2</td>
<td>(n = 2414)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>n = 5417</td>
</tr>
<tr>
<td>OAC + aspirin better</td>
<td>3.8</td>
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<tr>
<td>aspirin better</td>
<td>6.1</td>
</tr>
<tr>
<td>p &lt; 0.0001</td>
<td>2.6</td>
</tr>
<tr>
<td>0.72 (0.62-0.82)</td>
<td>5.7</td>
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<td>15.0</td>
<td>20.0</td>
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Death and reinfarction in the postinfarction trials of oral anticoagulation plus aspirin versus aspirin alone in which the achieved INR was > 2.0.

Excellent monitoring facilities are available in countries such as Holland and Norway, with government-run thrombosis laboratories where patients can have their INRs checked. This facilitates the study of the optimal range of INR in the management...
of heart conditions such as atrial fibrillation and coronary artery disease, and in patients with artificial heart valves, it also helps the efficacy of long-term anticoagulation control.

Self-monitoring is at least as good as laboratory control, and is used more and more in Europe for patients with a hard indication for anticoagulation with thrombosis. Laboratories in Holland are currently instructing patients who apply for self-monitoring.

Asked how antiplatelet therapy compares with oral anticoagulation in atrial fibrillation, Dr Verheugt commented, “It is often stated that antiplatelet therapy is less effective than oral anticoagulation in atrial fibrillation. However, the meta-analyses in this field include the European Atrial Fibrillation Trial, which was a secondary prevention trial carried out in patients who had already experienced a thromboembolic event in atrial fibrillation. In primary prevention trials in atrial fibrillation, the benefit of oral anticoagulation over aspirin was not very strong and needed a conclusive trial.”

This, he said, has been accomplished in the ACTIVE-W trial, in which 6706 patients with atrial fibrillation were randomised to full intense oral anticoagulation (INR 2-3) or double antiplatelet therapy with aspirin and clopidogrel.

Dr Verheugt added, “The results clearly showed that oral anticoagulation is superior to antiplatelet therapy with regard to prevention of thromboembolism, whereas unexpectedly the bleeding risk of both strategies was similar. Many feel that oral anticoagulation is an unsafe treatment, whereas it was shown in ACTIVE-W that double antiplatelet therapy for this indication is at least as unsafe.

“So,” he continued, “good old warfarin is still the optimal antithrombotic protection in patients with atrial fibrillation.” The way forward, he believes, is for better oral anticoagulants to be developed. “Direct oral thrombin blockers and oral direct factor Xa blockers are currently under evaluation in patients with atrial fibrillation and in those who survived acute coronary syndromes. Optimal dosing is still unclear, and also liver toxicity and bleeding risk are not fully established. In the next 2 years, results of major trials will be available and will give the answer on these vexing questions,” he concluded.

Mark Nicholls is a freelance medical journalist.

References

The opinions expressed in Circulation: European Perspectives in Cardiology are not necessarily those of the editors or of the American Heart Association.

Emergency Cardiac Care in Turkey

Ulku Ergene, MD, an associate professor and president of the Emergency Care Specialists Association in Turkey, outlined recent developments in the field of cardiovascular-related emergency care in Turkey to Judy Ozkan, BA.

Important developments have been taking place in the field of general and cardiovascular-related emergency care in Turkey during the last 10 years. Pioneered by the universities, and backed by public sector nongovernmental organisations, these developments are part of a bigger drive to bring aspects of Turkey’s health sector in line with the European Union. The Turkish Ministry of Health, which has provided equipment and professional training for doctors, also supports these developments.

Training in emergency medicine as a postgraduate residency programme began at Dokuz Eylul University, Bornova-Yzmir, in 1994, where Dr Ergene worked as one of 2 faculty physicians, specialising in general internal medicine. By 1999, a total of 15 universities were providing this training, rising to 30 at present. These residency programmes take 5 years to complete and consist of practical, theoretical, and bedside training. One part of the program includes rotating internships through other specialties, including cardiology, internal medicine, surgery, neurology, and paediatrics.

There are currently 189 emergency medicine specialists in Turkey, with 96 working in university hospitals and 93 in different organisations, eg, state hospitals and private clinics.

Trained paramedic ambulance crews are not as common in Turkey as in other European countries such as the United Kingdom. However, since 1993, Dokuz Eylul University has been running a 2-year degree course to fill the paramedic gap. There are now 13 paramedic schools, and the training programme covers transport of patients, reception at emergency rooms, and general ambulance services.

Most emergency care patients in Turkey are treated at state hospitals. Only small numbers of emergency medicine specialist physicians work in these hospitals, and this means that
Iceland’s Genealogy Database

The genealogy of the entire Icelandic nation going back 1100 years is held on a computer database. Kári Stefánsson, MD, discussed how this is helping genetic research there with Jennifer Taylor, BS.

Dr Kári Stefánsson is now deeply involved in the study of genetics but in the past has been professor of neurology, neuropathology, and neuroscience at Harvard University, director of neuropathology at Beth Israel Hospital in Boston, Massachusetts, and has held faculty positions in neurology, neuropathology, and neurosciences at the University of Chicago.

His work is of great interest to cardiologists because preventing heart attacks could be several steps closer as scientists in Iceland mine the population’s genes for relevant information that may lead to innovative new treatments.

The work is being carried out by deCODE, a company cofounded in 1996 by Dr Stefánsson. The idea behind the company, says Dr Stefánsson, was to use genetics as a set of tools to help with drug discovery and development. He estimates that at the time there were around 10 or 20 companies of that sort, but deCODE is probably the only one left. The downfall of the other competitors was thinking that the rate-limiting...
step would be the technology. But instead, the stumbling block was access to populations.

“What matters is that you have access to a population that you understand, that has qualities that allow you to mine the genome for variants that are associated with disease,” said Dr Stefánsson. He added that during the past 5 years, deCODE has contributed between 50% and 75% of the publications on genes that have an impact on the risk of common diseases. While Dr Stefánsson says that Iceland is not unique, and there other places where the work could be done, he admitted there are some factors which make it a particularly good place for this work.

The fact that the genealogy of the entire Icelandic nation going back many years (see Figure) is held on a computer database allows scientists to study parallel flows of certain information, in order to isolate disease genes or genes that have an impact on complex phenotypes. Subjects may either give informed consent for the study of 1 disease, or they can give informed consent to work on any disease as long as the study is in keeping with the standards set by Iceland’s Data Protection Commission and Bioethics Committee.

About 95% of the subjects sign the latter agreement. “This gives us an opportunity to look for data on various diseases relatively systematically,” says Dr Stefánsson. Scientists at deCODE are studying the genetics of 50 of the most common diseases. The company has 9 drug discovery and development programmes based on its findings. It also has 3 compounds in clinical trials, and will have 5 before the end of the year. “These are the only programmes I know of in the world where people have gone from isolation of a disease gene to drugs in clinical trials,” says Dr Stefánsson.

This is what the company calls its population approach: using population information to help with isolation of a disease gene. So far, they have isolated 19 disease genes in 12 common diseases, and have mapped a great many more.

Dr Stefánsson says, “What matters when it comes to drug discovery is to have a gene in hand, because the gene gives you access to a biochemical pathway that you can manipulate for the purpose of curing or preventing a disease.” The method deCODE follows allows discoveries to be made more quickly than with traditional methods. It negates the need for a hypothesis and lengthy, expensive testing of that hypothesis. “We know from the beginning that the target we are working with is not only a part of the disease process, it is quintessential for the generation of the risk of disease,” says Dr Stefánsson.

Compound DG031, being developed by deCODE for the prevention of heart attack, is in Phase III clinical trials. DG031 is an inhibitor of 5-lipoxygenase activating protein (FLAP). The company has linked variants of the gene encoding FLAP, and the gene encoding leukotriene A4 hydrolase (LTA4H), to the risk of heart attack. These variants increase the risk of heart attack by increasing the production of leukotriene B4 (LTB4), a driver of inflammation produced in atherosclerotic plaques. DG031 reduces the production of LTB4. The HapK variant of the LTA4H gene confers a 250% increased risk of heart attack in African Americans. The phase II trial will focus on this group.

The drug has huge potential, and Dr Stefánsson compares its future with statins. He says, “I believe that we will, without any question, be giving drugs that contain the leukotriene pathway to a very large proportion of the population.” He adds that just as the level of blood lipids dictates the use of statins, LTB4 measurements will give the threshold for this new medication.

Dr Stefánsson says cardiologists today are keenly aware of the role of inflammatory pathways in the risk of heart attack. But over the past year or two it has emerged that when attempting to decrease the risk of heart attack, inflammation should not be inhibited in a non-specific manner, a recent example of this being COX-2 inhibitors.

“We have genetics to guide us, and that’s a privilege,” says Dr Stefánsson. “We feel that we have found exactly the right spot to influence the inflammation to contain the heart attack. Genetics still puts the fear of god in the hearts of some people,” says Dr Stefánsson. But, he adds, “I feel strongly that centralised databases in health care will become phenomenal discovery machines.”

Jennifer Taylor is a freelance medical writer.

References


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