HIGHLIGHTS FROM THE 2016 M & M CARDIOLOGY MEETING: MERGING MEDICAL AND MECHANICAL MANAGEMENT

Fire and Ice Trials: Atrial fibrillation ablation procedures

Approximately 60% of patients with atrial fibrillation (AF) are symptomatic and will be considered for treatment. Although antiarrhythmic drugs are generally used as first line therapy, AF will reoccur in around 50% of patients within 6 to 12 months. Ablation is significantly more effective than drug therapy and improves quality of life. In the ThermoCool AF trial approximately two thirds of patients with symptomatic AF who had not improved with at least one drug remained free from symptomatic paroxysmal AF at 9 months after ablation in comparison to 16% treated with alternative antiarrhythmic drug therapy. Initial treatment with ablation therapy is also associated with significantly better outcomes than drug therapy and early referral as soon as possible after diagnosis improves the clinical outcome.

Current guidelines recommend catheter ablation of drug-refractory paroxysmal atrial fibrillation or as an alternative to initial drug therapy in symptomatic patients. Pulmonary vein isolation is the standard approach.

The most commonly used method of catheter ablation has been radiofrequency ablation, which requires only limited use of fluoroscopy, because catheter guidance is achieved with the use of an electro-anatomical mapping system. This approach is complex and requires extensive training. In contrast, cryoablation uses cryogenic energy applied with a balloon in a single-step mode, which leads to necrosis of the pulmonary vein antra by freezing. It is a faster and simpler procedure that uses more extensive fluoroscopic guidance to position the balloon catheter at the pulmonary veins.

The FIRE and ICE study was designed to compare radiofrequency ablation with cryoballoon ablation in a large population of patients with paroxysmal AF. It was a multicenter, randomised, noninferiority, parallel group, open-label trial including
762 patients with symptomatic paroxysmal AF that was refractory to class I or class III antiarrhythmic drugs or beta-blockers. The primary efficacy endpoint was the first documented clinical failure occurring more than 90 days after the ablation procedure, defined as documented recurrence of atrial fibrillation (lasting more than 30 seconds), documented occurrence of atrial flutter or atrial tachycardia, prescription of antiarrhythmic drugs (class I or III), or repeat ablation. The primary safety end point was a composite of death from any cause, stroke or transient ischemic attack from any cause, and serious adverse events considered to be related to the therapeutic intervention.

There were no significant differences in either the primary efficacy or safety endpoints. One-year Kaplan-Meier event rate estimates for clinical failure were 34.6% for cryoballoon and 35.9% for radioablation (hazard ratio, HR 0.96; 95%CI, 0.76 to 1.22; P<0.001 for noninferiority). The safety endpoint occurred in 10.2% and 12.8%, respectively (P=0.24). However, the sites of complications were different. Whereas groin-site complications were most frequent in the radiofrequency group (4.3% vs. 1.9%), phrenic nerve injury occurred in 2.7% of the cryoballoon patients and in none of the patients receiving radiofrequency ablation. Both the mean total procedure time (124 vs. 141 minutes; P<0.001) and left atrial dwell times were shorter in the cryoballoon group. Mean total fluoroscopy time was shorter in the radiofrequency ablation group (17 vs. 22 minutes; P<0.001).

In the long-term follow-up analysis (30 months), in comparison with radiofrequency ablation, there were significant benefits associated with the cryoballoon procedure.5 Patients treated with cryoballoon had significantly fewer repeat ablations (11.8% vs. 17.6%; P=0.03), direct-current cardioversions (3.2% vs. 6.4%; P=0.04), all-cause hospitalisations (32.6% vs. 41.5%; P=0.01) and cardiovascular rehospitalisations (23.8% vs. 35.9%; P<0.01). Quality of life scores were improved in both groups.

In comparison with radiofrequency ablation, cryoballoon ablation is a simpler and more cost effective procedure with better long-term clinical outcomes.

Innovation in anticoagulation care

Traditional vitamin K antagonist (VKA) anticoagulants may be reversed by administering vitamin K (oral or IV), fresh frozen plasma (FFP) and blood products, or more quickly by prothrombinase complex concentrates (PCC) or recombinant activated factor VII (rFVIIa).

Treatment protocols for bleeding in patients receiving non-vitamin K antagonist anticoagulants (NOAC) are similar to those for VKA and include NOAC discontinuation, supportive measures (e.g., mechanical compression, surgical haemostasis and fluid/blood replacement), FFP, platelets, PCC or rFVIIa. However, in comparison with bleeding on warfarin, a lower 30 day mortality was observed after bleeding in patients treated for venous thromboembolism (VTE) with dabigatran, because it has a short half-life and is rapidly cleared from the body. Even in the absence of a specific reversal agent, major bleeding occurs no more frequently with dabigatran in patients requiring urgent surgery or invasive procedures than it does with warfarin. Up until recently, despite improvements in convenience, efficacy and safety compared with warfarin, fears of bleeding risk and lack of a specific reversal agent has, for many prescribers, been a barrier to the use of NOACs. Consequently, anticoagulation is still widely underused for stroke prevention in patients with atrial fibrillation (AF).

Idarucizumab is a NOAC reversal agent, specific to dabigatran. It is a monoclonal antibody fragment that binds irreversibly to dabigatran with an affinity that is 350 times as high as that observed with thrombin. After intravenous administration, it produces immediate and complete reversal of the anticoagulant effects of dabigatran, with no intrinsic procoagulant or anticoagulant activity itself. The efficacy of idarucizumab remains constant in the presence of mild-moderate renal impairment, studies have revealed no clinically relevant drug-related adverse events and local tolerability reactions are comparable with placebo.

The efficacy and safety of idarucizumab in dabigatran-treated patients who present with serious bleeding or who require
urgent surgery or intervention is the subject of an ongoing study (RE-VERSE AD). It includes two groups of adults who are taking dabigatran and who reflect clinical situations in which a reversal agent would be required. Patients in group A are those with overt uncontrollable or life-threatening bleeding that is judged by the treating clinician to require a reversal agent. Patients in group B are those who require surgery or an invasive procedure that cannot be delayed for at least 8 hours and for which normal haemostasis is be required.

In an interim analysis including 90 patients (51 in group A and 39 in group B), dabigatran was completely reversed in all patients and laboratory results were normalised within minutes in 88% to 98%.

Among the patients who could be assessed, haemostasis in group A (n=35) was restored at a median of 11.4 hours. Among patients in group B who underwent a procedure (n=36), normal intraoperative haemostasis was reported in 33 (92%). No new safety concerns were identified.

Clinical implications of idarucizumab

In patients receiving dabigatran, the management of bleeding complications should be individualised on the basis of the location and severity of the haemorrhage. When it is available, idarucizumab is the treatment of choice for dabigatran reversal. However, clinicians should bear in mind that coexisting medical conditions may have a greater influence on prognosis than the ability to rapidly neutralize the anticoagulant effect of dabigatran.

In patients with a life-threatening bleed, coagulation tests may be of use to help identify the contribution of dabigatran to bleeding. Activated partial thromboplastin time (aPTT) approximates dabigatran levels in plasma and is a useful tool to quickly obtain anticoagulant status, whereas a normal thrombin time (TT) essentially excludes a contribution of dabigatran to bleeding. Due to the possibility of coagulopathy in the absence of anticoagulant treatment, abnormal coagulation tests in patients with liver disease or severe blood loss must be interpreted with caution. Furthermore, consideration of the time of the most recent dabigatran dose in a bleeding patient is important. Dabigatran is unlikely to be the major contributor to bleeding where more than 48 hours (normal renal function) or 72 hours (impaired renal function) has elapsed since the most recent dose was taken.

Where necessary, to avoid thrombosis after anticoagulation reversal, the short half-life of idarucizumab (terminal half-life = 4.4-8.1 hours) allows dabigatran to be restarted within 24 hours of its administration.

In patients requiring emergency surgery or an invasive procedure, the rapid onset of action of idarucizumab allows the procedure to be undertaken shortly after administration with reinitiation of anticoagulant therapy once haemostasis has been restored. Because idarucizumab is specific for dabigatran, it has no effect on the efficacy of alternative anticoagulants, which may need to be considered in patients with renal impairment requiring resumption of anticoagulation, and in whom the half-life of idarucizumab is prolonged.

Controversies in treatment of CAD

Intravascular ultrasound-derived minimal lumen area is frequently used as a surrogate marker of significant left main coronary artery stenosis. However, traditional cut-off values (4-6 mm²) may overestimate the functional significance of stenosis and thereby increase the rate of unnecessary percutaneous coronary intervention.

In patients where the indication for intervention is uncertain, correction of dyslipidaemias, and in particular LDL-cholesterol (LDL-C) reduction, has been shown to improve cardiovascular outcomes.

Irrespective of lipid profile and other characteristics, treatment with statins can reduce the 5-year incidence of major coronary events, coronary revascularisation and stroke by about 20% per mmol/L reduction in LDL-C. The size of the proportional reduction in major vascular events is directly proportional to the absolute LDL-C reduction achieved and there is no evidence of any threshold beyond which these risk reductions are diminished. Nevertheless, the ability of current statin therapy to reduce LDL-C is limited and the residual cardiovascular risk remains
high, even with the addition of ezetimibe. Pro-protein convertase subtilisin/kexin 9 (PCSK9) is a serine protease that is highly expressed in the liver and intestine and which regulates degradation of the LDL receptor. Expression of PCSK9 reduces the clearance of LDL cholesterol, while inhibition increases activity of the LDL receptor, which in turn increases clearance of LDL. Although statins upregulate the LDL receptor, they also increase the activity of PSCK9, which may attenuate cholesterol clearance. Therefore, PSCK9 inhibition is an attractive target to enhance the LDL-lowering efficacy of statin treatment and various PCSK9 inhibitors are currently under development.

In comparison to standard therapy alone, in two open-label, randomised trials enrolling 4465 patients who had completed a phase 2 or 3 trial of the PCSK9 inhibitor evolocumab, after 1 year of therapy LDL-C was reduced by 61%, and cardiovascular events were reduced by 53%. Another study with a different PCSK9 inhibitor, alirocumab, showed similar results. In comparison with placebo in patients at high risk for cardiovascular events and LDL cholesterol ≥1.8 mmol/l on maximum doses of statins with or without other lipid-lowering therapy, alirocumab reduced LDL-C by 62% and major cardiovascular events by 48%.

Ongoing cardiovascular outcomes trials will evaluate the impact of PCSK9 inhibition on clinical outcomes in distinct populations throughout the cardiovascular risk continuum.

Minimize right ventricular pacing to prevent AF and HF (MINERVA Study)

The MINERVA study evaluated whether atrial preventive pacing and atrial antitachycardia pacing (DDDRP) + managed ventricular pacing (MVP) reduces mortality, morbidity, or permanent AF compared with standard dual chamber pacing (Control DDDR). It was a multicentre (63 centres), international, randomized, single blind study with 3 arms enrolling 1,166 patients with class I or class II indications for dual chamber pacing, a history of atrial tachyarrhythmias and no history of permanent AF or third-degree A V block.

In comparison with Control DDDR, DDDRP + MVP was associated with reduced incidence of the primary endpoint (the 2-year incidence of a combined endpoint composed of death, cardiovascular hospitalizations, or permanent AF) (hazard ratio, HR = 0.74, 95% confidence interval 0.55-0.99, P = 0.04). DDDRP + MVP was associated with a relative risk reduction for permanent AF of 61% (HR = 0.39, 95% CI 0.21-0.75, P = 0.004). “Physiological pacing” demonstrated only a modest advantage, expressed by a reduction of AF, mostly limited to pts with sinus node disease (SND).

Most algorithms are strictly designed to eliminate ALL RV pacing, but VP 0% at ANY COST would be not beneficial, due to the concern about long AV delay.

Atrial antitachycardia pacing therapies may help in tailoring the proper programming in implanted patients.

4D Echocardiography and monitoring percutaneous interventions

Four-dimensional echocardiography is an innovative imaging technique allowing unprecedented imaging of the heart and cardiac flow in real time using volumetric datasets. Since 2007 it is also available for transesophageal imaging, which allows using higher frequency transducers and provides cleaner, less noisy signal of uniform quality resulting in improved three-dimensional data quality. Transesophageal echocardiography has become increasingly popular as a standard for noninvasive monitoring for cardiosurgical and cardiac catheter interventional procedures. Three-dimensional probes are also soon to be tested for this purpose. The benefits include less manipulation of the probe to obtain any desired cross-section, availability of simultaneous cross-sectional imaging (biplane or triplane imaging), as well as display of data from a three-dimensional perspective.
Regarding the currently used percutaneous interventional procedures, some of them require more detailed preprocedural quantification and understanding of anatomical relationships. Atrial septal defects can be thoroughly visualized to enhance preprocedural planning with precise planimetry. This allows for fully noninvasive device sizing, and 3D imaging can also provide otherwise unavailable real-time views, which contribute to the success of the procedure, especially in complex septal defects. Recently introduced advanced percutaneous valvular interventions require both complete preprocedural understanding of abnormal anatomy and unprecedented cooperation of interventionist and imager during the procedure. Morphological corrective treatments such as Mitraclip implantation in mitral regurgitation or implantation of occluders in minute perivalvular leaks benefit markedly from direct visualization of the intervention sites, both in multiplane and in en face “anatomical perspective” volume rendered images, which are useful for direct topographic guidance of device catheters. Finally, in any case of unexpected intraprocedural complications transesophageal three-dimensional probe is the ultimate imaging tool to rapidly explain the problem and guide corrections. A brief summary of possible therapeutic techniques which might benefit from a three-dimensional perspective and multidimensional imaging for pre- or intra-procedural planning are summarized in the table.

![Image](https://via.placeholder.com/150)

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4D Echocardiography: Added value through technological progress

Echocardiography has evolved for over 60 years to become a versatile, everyday-use advanced imaging technique for cardiac anatomy and flow. In the recent decade, a major technological step has been made to convert routine echocardiography from two-dimensional cross-sectional into the first cardiac routine, bedside volumetric imaging technique. The developments of more than 60 years delivered multiple varieties of echocardiographic examination and since 1974 efforts have been made to provide three-dimensional representation of cardiac structure and physiology. Currently three-dimensional echocardiographic probes are available as a clinically applicable commercial device on high-end echocardiographic systems allowing real-time volumetric scanning of the heart from precordial, transesophageal or intracardiac windows. The principal benefits of three-dimensional echocardiography lie in improved presentation of data, allowing understanding of complex spatial anatomy of the heart (presentation of nonplanar structures that do not fit in cross-sectional image planes) and improved quantification of distances, areas and volumes, as well as volume-based functional parameters, such as ejection fraction. Even the simplest applications of matrix three-dimensional transducers, such as multiplane modes, improve the quality of assessment of chamber volumes or valve planimetry. For most measurements, three-dimensional echocardiography offers 2-3 fold improved reproducibility (comparable to resonance imaging) and some of the available parameters, such as right ventricular quantification were previously not available using other ultrasound methods. These improved qualitative and quantitative features are supported by the use of three-dimensional color Doppler imaging.
Clinical examples include any distance measurements in unrestricted planes, robust, realistic planimetry for defects or stenotic sites or volumetry of cavities of tissue volume utilizing actual spatial outline. As regards cardiac valve disease, the method offers precise quantification of valvular orifices, detailed anatomical description of segmental valve lesions and approaches to quantify true three-dimensional volume of proximal isovelocity convergence zones. Improved assessment of segmental leaflet disease is facilitated by “anatomical perspective” of volume rendered images, and transesophageal window is often used to obtain ultimate image resolution and quality. Importantly, current echocardiographic systems are equipped with advanced dedicated quantification suites supporting the analysis of three-dimensional datasets and dedicated for specific clinically oriented pathways, such as quantification of the left or right ventricular function, assessment of mitral valve and automatic extraction quantification of the left ventricular outflow tract together with aortic valve functional complex. Expected developments of the technique are expanding everyday feasibility of large, high resolution, uniform quality datasets from single beat acquisitions, as well as improving quantification based on artificial intelligence and automated critical data extraction. Ongoing work is exploring potential of fusion of three-dimensional ultrasound datasets with other imaging modalities, such as computed tomography or real-time intraprocedural fluoroscopy, to guide and enhance performance during cardiac procedures.

Deep vein thrombosis and pulmonary embolism: acute treatment and prevention of recurrence

Venous thromboembolism (VTE) is a common chronic disease, being the third most common cardiovascular disorder after myocardial infarction and stroke. After the initial event, there is a high rate of recurrence - 11% within one year and up to 40% within 10 years. Complications are also common. After pulmonary embolism (PE), the cumulative incidence of chronic thromboembolic pulmonary hypertension is approximately 4% at 2 years, and post-thrombotic syndrome occurs in nearly one third of patients within 5 years of an initial deep vein thrombosis (DVT). Consequently, to help prevent recurrent events and complications, management requires prophylactic anticoagulation, which must be balanced with the risk of bleeding complications.

Clinical guidelines for the treatment of VTE have recommended initial parenteral anticoagulation with subcutaneous low molecular weight heparin (LMWH) or fondaparinux, followed by oral anticoagulation, both of which carry a risk of serious (and potentially fatal) bleeding. Until recently, warfarin has been the standard oral agent for prophylactic anticoagulation. However, it has limitations in that its anticoagulation activity is unpredictable, with considerable inter- and intra-individual variation, necessitating regular monitoring and dose adjustments.

Furthermore, it has potential for a number of serious drug-drug interactions. In contrast, the newer non-vitamin K oral anticoagulants (NOACs), dabigatran, edoxaban, rivaroxaban and apixaban provide efficient anticoagulation, are simpler to use and are associated with a similar or lower risk of bleeding complications. They have a rapid onset and short offset of action, fixed dosing, no known food effects, fewer drug interactions and do not require routine monitoring.

Unlike warfarin, heparin bridging is not recommended when using rivaroxaban or apixaban. However, the necessity for initial parenteral anticoagulation with the other NOACs has also been questioned, and it is uncertain which patients might benefit from this. In patients at low risk of complications, withholding parenteral anticoagulation allows earlier discharge from hospital.

All of the NOACs have shown superiority versus placebo in long-term prevention of DVT/PE recurrence, but there are no direct comparative studies of different NOACs in this setting.

In the RECOVER and RECOVER II studies, dabigatran 150 mg BID was compared to warfarin over 6 months in patients with confirmed acute symptomatic DVT of the leg and/or PE and who had received initial parenteral
anticoagulation. Dabigatran was non-inferior to warfarin for prevention of recurrent symptomatic VTE or fatal VTE (hazard ratio, HR 1.09 (95%CI 0.77-1.54). However, major bleeding events and clinically-relevant non-major bleeding events occurred significantly less frequently among patients treated with dabigatran (HR 0.56; 95%CI 0.45-0.71).

Dabigatran is the only NOAC to have long-term data versus warfarin in this setting. In the RE-MEDY study, over a treatment period of up to 36 months, dabigatran 150 mg BID was as effective as warfarin for prevention of recurrent or fatal VTE, but was associated with a 46% lower risk of major bleeding and clinically relevant non-major bleeds (HR 0.54; 95%CI 0.41-0.71). In the RE-SONATE study, 6 months continuation of dabigatran in patients who had received up to 18 months initial anticoagulant therapy was associated with a 92% reduction in the risk of recurrent VTE versus placebo. Recurrent VTE/VTE-related death occurred in 0.4% of dabigatran patients vs. 5.6% in the placebo group (HR 0.08; 95%CI 0.02-0.25). Any bleeding events occurred in 10.5% versus 5.9% of patients, respectively (HR 1.82; 95%CI 1.23-2.68).

In patients with PE, guidelines recommend risk stratification when deciding on course of therapy. Anticoagulation alone is recommended for patients at low or intermediate risk of early mortality (defined as in hospital or 30-day mortality), whereas reperfusion is recommended for those who are high risk (defined as suspected or confirmed presence of shock or persistent arterial hypotension).

Currently it is uncertain whether thrombolysis would be of benefit in haemodynamically stable patients considered to be at risk of early mortality. The Pulmonary Embolism Thrombolysis (PEITHO) trial compared thrombolysis with tenecteplase to placebo in normotensive patients with confirmed PE, an abnormal right ventricle on echocardiography or computed tomography, and a positive troponin I or T test result. Thrombolysis reduced the occurrence of haemodynamic decompensation and death within the first 7 days, but was also associated with a significant increase in extracranial bleeding and stroke (primarily haemorrhagic), suggesting that thrombolysis should not be administered to high-risk stable patients.

However, meta-analyses suggest that results may differ depending on patient age and absence of right ventricular dysfunction. Trials are ongoing to determine whether it is possible to improve the efficacy/risk ratio of fibrinolysis by selecting patients with a lower bleeding risk, using a safer (lower dose) thrombolytic regimen or, in the small group of patients who are suitable, using a catheter-based regimen.

In 2016, treatment guidelines for VTE were updated to include the following recommendations:8

- For proximal DVT or PE, long-term anticoagulation (3 months, or at least 3 months for unprovoked DVT) is recommended over no therapy.
- For VTE and no cancer, as long-term anticoagulant therapy, dabigatran, rivaroxaban, apixaban or edoxaban are recommended over vitamin K antagonist (VKA) therapy and VKA therapy is recommended over LMWH.
- For VTE with cancer, LMWH is recommended over VKA and NOACs.

Advancing anticoagulation care in your region: Selected topics in antithrombotic treatment for AF patients

Cardioembolic disease is the most important cause of stroke in patients over the age of 65 years. Consequently, providing effective and safe anticoagulation for people with atrial fibrillation (AF) is essential.

In this regard, the non-vitamin K antagonist anticoagulants (NOACs) represent a significant advance in therapy. Four NOACs are approved for use and are available worldwide. They include dabigatran, a thrombin inhibitor, and rivaroxaban, apixaban and edoxaban, which are FXa inhibitors. However, this is a relatively new class of drugs and questions still remain about the practicalities and safety of use, especially in patients with renal insufficiency and in those who require urgent surgical intervention or procedures where the risk of bleeding may be problematic. Furthermore, dabigatran is the only...
NOAC for which a reversal agent is now available and protocols are required to guide efficient and appropriate use of that. NOACs are not recommended in patients with creatinine clearance (CrCl) <30 ml/min. However, phase III trials have included patients with mild and moderate renal insufficiency and indicate that all 4 NOACs effectively reduce the incidence of stroke and systemic embolism in comparison with warfarin, without an increase in major bleeding events in patients with CrCl ≥30 ml/min.

In patients with a CrCl <50 ml/min and where the risk of bleeding is high, the dose of NOAC may be reduced according to the manufacturer’s prescribing information.

The BRIDGE study demonstrated that in patients with AF requiring interruption of warfarin for an elective invasive or surgical procedure, bridging with parenteral anticoagulation with low molecular weight heparin (LMWH) is unnecessary. In comparison with bridging, no bridging was non-inferior for the prevention of arterial thromboembolism, but decreased the risk of major bleeding.

The short half-lives and rapid onset of action of NOACs allow for short interruption of therapy without heparin bridging. In line with this, the European Heart Rhythm Association (EHRA) practical guide on the use of NOACs in patients with nonvalvular AF does not recommend heparin bridging when interrupting NOAC therapy.

In the RE-LY trial, which compared dabigatran with warfarin for stroke prevention in AF, with dabigatran interruption, in comparison to those who did not receive bridging, bridged patients had more major bleeding (6.5% vs. 1.8%, P=0.001) without a benefit in terms of thromboembolic events (1.2% vs. 0.6%, p=0.16).

Depending on the clinical situation and providing that adequate haemostasis has been established, dabigatran should be restarted as soon as possible after the procedure or surgery requiring interruption of anticoagulation. Guidelines recommend waiting ≥24 hours for patients with a low bleeding risk and 48-72 hours for those with high bleeding risk.

Because renal impairment may slow down elimination of NOACs and recent use of other oral anticoagulants may contribute to bleeding risk, assessment of renal function and coagulation tests are essential to support periprocedural decision-making. If possible, surgery or procedures may need to be delayed in patients with renal insufficiency or in those where use of another anticoagulant complicates the bleeding risk. A prolonged activated partial thromboplastin time (aPTT) indicates an anticoagulant effect of dabigatran, and a prolonged prothrombin time (PT) indicates an anticoagulant effect of the FXa inhibitors. However, because normal values with either test do not exclude clinically relevant NOAC plasma levels, the clinical utility of these tests is limited.

For patients on dabigatran, there is now a specific reversal agent that provides the option of immediate reversal when surgery is required. Administration of idarucizumab allows the patient to proceed to surgery without delay and with NOAC anticoagulation immediately reversed. Following idarucizumab administration, dabigatran can be restarted after 24 hours when it is clinically appropriate. If earlier anticoagulation is required, LMWH may also be initiated at any time after idarucizumab, allowing for minimal time without anticoagulation.

Idarucizumab is provided ready to use and is administered in a fixed dose regardless of the clinical situation. It has no known contraindications.

The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) is a large, international, observational registry designed to investigate patient characteristics influencing choice of antithrombotic treatment of stroke prevention in patients with newly diagnosed nonvalvular AF and to collect data on outcomes of antithrombotic therapy in clinical practice across different regions of the world. It will enrol up to 56 000 patients across nearly 50 countries. The study consists of three phases. Phase I includes patients before approval of NOACs. Phase II, beginning early after approval of dabigatran, monitors dabigatran safety and addresses potential channelling across treatment options based on propensity scoring to assess comparability of baseline characteristics of patients treated with dabigatran or VKA. Phase III entails analysis of large treatment groups, adjusting for differences in propensity score, to provide information about the relative effectiveness and safety of NOACs and VKA in routine clinical care.
In early analyses of patients in phase II, overall the data show a clear shift away from prescription of warfarin to a preference for NOACs after the introduction of these anticoagulants (64% vs. 0% in Phase I and 38% vs. 52% in Phase II). During the same period, the use of aspirin has decreased from 25% to 5%.

Conclusions

NOACs can be used in safely patients with renal insufficiency.

Because of their short half-life and quick time to onset, discontinuation and re-initiation of NOACs is straightforward for patients requiring an invasive procedure or surgery. The availability of idarucizumab, a specific reversal agent for dabigatran, further simplifies management of these patients and significantly reduces bleeding risk when there is no time to wait for dabigatran plasma levels to decline before surgery. Bridging is not required when restarting NOAC anticoagulation.

Accordingly, real-world registries demonstrate a worldwide move away from warfarin in preference for NOACs in patients with AF.

Arrhythmia treatment in Africa

Fifteen percent of the world’s population, some one billion people, live in the 54 countries on the African continent. Nevertheless, Africa remains the world’s poorest and most underdeveloped continent, with a gross domestic product (GDP) per capita in many countries being less than USD 2000. With the exception of North Africa and South Africa, African countries have few working doctors and even fewer specialist cardiologists. Although pacing remains one of the most cost effective treatments for relieving symptoms prolonging life, it is unavailable to most Africans. In the 2009 11th Survey of Cardiac Pacing, only 2 African countries submitted any data at all – South Africa, 60 pacemaker (PM) units per million population and Sudan 5 per million. By comparison, 2011 data indicated 938 PM units per million in Europe.

The 2014 PASCAR survey on pacing and electrophysiology in Africa surveyed 14 African countries and found a severe shortage of PM centers and doctors with appropriate skills in all. In South Africa, there has been a steady increase in PM implants over time, but rates are still very low in comparison with Europe – 173 PM doctors at 54 centers, distributed over 5 provinces, with no centers in 4 provinces. In contrast, with the exception of Tunisia, the other African countries surveyed had 6 or fewer centers and fewer than 20 PM doctors. Two countries have no PM doctors at all. The availability of skills and centers for implantable cardioversion devices (ICD) are even more scarce and with the exceptions of South Africa and Senegal, there are no electrophysiologists in SubSaharan Africa.

There is a desperate need for training centers, trained cardiologists and electrophysiologists. Training is also required for physicians in other medical specialities (e.g., obstetrics), and non-physician technicians who will be able to use hand-held echocardiography for early detection of cardiac disease, to facilitate early referral to a cardiologist or cardiothoracic surgeon.

The high cost of PMs is one of the most important barriers to the establishment of an effective cardiac pacing service in SubSaharan Africa. This may be overcome by re-use of PMs, which is safe and cost-effective.

The Pan African Society of Cardiology (PASCAR) Task Force on PM re-use has been convened to address the unmet needs of PM/ICD in SubSaharan Africa. The objectives of the task force are as follows:

1. Prevent and treat cardiovascular disease (CVD) in Africa (treat heart block and prevent sudden death): at least one pacing and ICD unit per African country.

2. Educate and train African healthcare professionals about CVD: PASCAR Fellowship in Clinical Cardiology and Cardiac Pacing.

3. Educate laypersons about CVD: Procurement, supply and regulatory issues of used PMs and ICDs to participating sites.

Cryptogenic stroke and atrial fibrillation - what is the link?

Stroke is a leading cause of mortality and serious long-term disability. Patients with atrial fibrillation (AF) are at especially high risk. In the presence of AF the risk of ischaemic stroke increases five-fold and in comparison to non-AF-related strokes, the risk of mortality doubles. In contrast, anticoagulation in patients with AF reduces the risk of stroke by 67%.

Cryptogenic stroke is defined as brain infarction not clearly attributable to a definite cardioembolism, large artery atherosclerosis or small artery disease, despite extensive investigation.

In the USA, approximately 200,000 cryptogenic strokes occur annually, accounting for approximately 30% of all ischaemic strokes. Most occur in patients who are receiving antiplatelet therapy for secondary prevention.

Long-term monitoring reveals atrial fibrillation (AF) in approximately 30% of patients with cryptogenic stroke - patients who would have benefitted from anticoagulant therapy. In these individuals, the risk of recurrent stroke is high, where up to 20% will have a second stroke within 4 years of the initial event.

Diagnosis of cryptogenic stroke is one of exclusion. Investigations include brain CT/MR, 12-lead ECG, precordial electrogram, extra- and intravascular imaging and cardiac monitoring for at least 24 hours. Nevertheless, unless the patient has an episode of AF during the assessment, that diagnosis is likely to be missed.

Conventional monitoring strategies may not be sensitive enough to detect AF, especially since up to 80% of AF episodes are asymptomatic. Patient compliance with holter monitors and event recorders is poor and, although it may be improved with mobile cardiac telemetry, given the paroxysmal nature of AF, a duration of monitoring limited to 30 days may not be sufficient.

Long-term monitoring with insertable cardiac monitors (ICM) may increase the detection of AF. The CRYSTAL AF study randomised 441 patients with a diagnosis of cryptogenic stroke and no evidence of AF during at least 24 hours of ECG monitoring to either an insertable (REVEAL™) cardiac monitor or conventional follow up. The primary endpoint was time to first detection of AF at 6 months. Secondary endpoints included time to first detection of AF at 12 months, recurrent stroke or transient ischaemic attack (TIA) and change in use of oral anticoagulant drugs.

By 6 months, AF had been detected in 19 patients (8.9%) in the ICM group and 3 patients (1.4%) in the control group (hazard ratio, HR 6.4; CI95% 1.9-21.7; P<0.001). Rates of detection at 12 and 36 months were 12.4% vs. 2.0% and 30.0% vs. 3.0% in the ICM and control groups, respectively.

In the ICM group, the median time from randomisation to detection of AF was 41 days (interquartile range 14-84 days) at 6 months and 84 days (interquartile range 18-265 days) at 12 months. Seventy nine percent of first episodes were asymptomatic during the first year.

By 12 months, 97% of patients in whom AF was detected were receiving oral anticoagulants. Ischaemic stroke or TIA occurred in 15 patients (7.1%) in the ICM group as compared with 19 patients (9.1%) in the control group.

Of 208 ICMs that were inserted, 5 (2.4%) were removed due to infection of the insertion site or pocket erosion. The device remained inserted in 98% of patients at 6 months and 97% at 12 months.

Numerous additional studies of ICM mirror these observations from the CRYSTAL AF study, with AF detection yields of up to 33% and median times to detection ranging from 48 to 161 days.

Similar observations have also been documented in real-world clinical practice. Using data from the de-identified Medtronic DiscoveryLink™ database, AF detection rates (episodes ≥2 minutes) were quantified using Kaplan-Meier survival estimates at 1 and 6 months for patients who received an ICM (Reveal LINQ™) for the purpose of AF detection following a cryptogenic stroke. Eighty five patients were monitored for a mean of 569 days and paroxysmal AF was detected by ICM in 16% at a mean of 109 days after stroke onset. In all cases, AF was asymptomatic and occurred in episodes lasting predominantly between 1 and 4 hours. Four patients suffered...
recurrent stroke, 3 of whom had AF and were on oral anticoagulation.

Overall, the message from these studies is clear: AF is common and the majority of first episodes are asymptomatic. Short- and intermediate-term monitoring may miss many patients with paroxysmal AF, whereas diagnosis is much more likely with long-term continuous monitoring.

In CRYS TAL AF, ICM reduced the incidence of stroke by approximately 40 per 1000 patients and improved quality-adjusted life years (QALYs). The probability that the ICM strategy would be cost-effective under a threshold of 30 000 Euros per QALY was 81%, and cost-effectiveness is likely to be greater in patients with higher CHADS score.

STEMI Management and Outcomes: Real World SA Practice

Unlike major centers in the USA and Europe, there is little or no data from coronary cath labs in South Africa. To address this, to assess how local performance compares with international standards and to maintain accountability in our own cath lab, in 2007 we started collecting data from every patient with ST elevation myocardial infarction (STEMI) admitted for percutaneous coronary intervention (PCI).

Full results are in preparation for publication. Our data however were very encouraging: in a small, low volume unit, we are able to produce door-to-balloon times and mortality outcomes in line with international standards. A key challenge that we face, however, is frequent staff changes in the emergency room, which are associated with delays in care. Much training of staff and constant input is required to maintain standards.

We believe that measuring our outcomes has helped to improve standards of care in our unit. Maintenance of these standards must be driven by clinicians and cannot be delegated to hospital management.

Diabetes and cardiovascular disease update

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. In addition to hypertension, smoking, obesity and dyslipidaemia, diabetes is a major risk factor for CVD and 75% of people with the disease will die from a CV-related event. In addition to insulin, there are numerous antidiabetic medications with different mechanisms of actions and safety profiles. Although few have studies that specifically address CV safety, metformin is considered to have probable CV benefit, while others are known to be associated with adverse cardiovascular outcomes. There is an increased risk of congestive heart failure with thiazolidinediones, saxagliptin and alogliptin, and observational studies and meta-analyses indicate an increased risk of CV events with sulphonylureas.

The sodium-glucose cotransporter (SGLT) 2 inhibitors are a new class of anti-diabetic drugs that have been approved for the treatment of type 2 diabetes. By decreasing glucose absorption in the renal tubule, they increase urinary glucose excretion and reduce plasma glucose concentrations. When administered either as add-on therapy or as monotherapy, these drugs reduce HbA1c in patients with type 2 diabetes, including those with renal impairment. In addition, treatment with SGLT2 inhibitors is associated with weight loss and a reduction in blood pressure, without an increase in heart rate.

The EMPAREG trial was a randomised, double-blind, placebo-controlled trial to assess the effect of once daily empagliflozin in addition to standard diabetes care on cardiovascular events in 7028 adults with type 2 diabetes and established cardiovascular disease (myocardial infarction, coronary artery disease, unstable angina, stroke or occlusive peripheral artery disease). Inclusion criteria included a body mass index ≤45 kg/m² and HbA1c 7.0-9.0% with no antidiabetic treatment in the previous 3 months or HbA1c 7.0-10.0% with stable antidiabetic treatment. The median duration of treatment was 2.6 years and median observation time was 3.1 years. The primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial
infarction (excluding silent myocardial infarction) or nonfatal stroke, occurred in 10.5% of patients treated with empagliflozin compared with 12.1% in the placebo group (hazard ratio 0.86, 95%CI 0.74-0.99; P=0.04 for superiority). Rates of myocardial infarction and stroke did not differ between groups, but in the empagliflozin group there were significantly lower rates of death from CV causes, hospitalisation for heart failure and all-cause mortality. Although the underlying mechanisms for these benefits are at present undetermined, EMPAREG suggests that empagliflozin may be a preferred medication for the treatment of type 2 diabetes in patients with established CV disease.

Recently published data from the EMPAREG study suggests that empagliflozin may also have renoprotective effects. In comparison with placebo, treatment with the SGLT2 inhibitor was associated with a slower progression of renal disease and lower rates of clinically relevant renal events.

The most common side effects that occur with this SGLT2 inhibitors include urinary tract infections and genital infections consequent to glycosuria. Hypoglycaemia is uncommon, with an incidence comparable with placebo.

Strategies in the management and prevention of complications in TAVI

Transcatheter aortic valve implantation (TAVI) is a management choice for patients with severe symptomatic aortic stenosis who are considered to be poor candidates for surgical valve replacement.

Successful TAVI, prevention of complications and management of complications that do arise requires a dedicated team approach. The TAVI program at the Vincent Pallotti Hospital was started in 2013 and has so far performed 55 implants using the CoreValve® (Medtronic) and, since 2015, Evolut™ R (Medtronic) transcatheter aortic valves. The team consists of 2 cardiologists, 1 cardiac surgeon, 1 anaesthetist and 1 radiologist. The procedural protocol is standardised so that it is done the same way every time.

Patients who are selected for the procedure must have a life expectancy >1 year after successful TAVI, be high surgical risk and inoperable, but the ultimate decision for eligibility remains with the medical team. Contraindications include inadequate annulus size, LV thrombus, subacute bacterial endocarditis, risk for coronary obstruction (short distance between the annulus and coronary ostium) and inadequate vascular or transapical access.

The complication rate during TAVI is significant, with a high morbidity and mortality. However, it can be minimised with careful patient selection. Possible complications include vascular injury, which when it occurs most frequently does so at the access site, difficulties with valve positioning, coronary obstruction, annular/root rupture, paravalvular leaks, AV block, cardiac perforation with tamponade, embolism and structural valve failure with poor expansion.

Paravalvular leaks are a common complication, and are reported to occur in 50% to 85% of patients. Most are mild or moderate. Nevertheless, long-term mortality outcomes may be significantly compromised by a leaking valve and the leak must be addressed by repositioning the valve, inserting a second valve or using a balloon to dilate a valve that is already appropriately positioned. Correctly positioned valves may continue to seal for a few days after the procedure. In the PARTNER 2A trial, two years after TAVI, mild and moderate paravalvular regurgitation was present in 27% and 8% of patients, respectively, in comparison with only 4% mainly mild regurgitation among patients after surgical valve replacement. Nevertheless, mortality at 2 years was similar between groups.

AV block has occurred in fewer than 10% of TAVIs at Vincent Pallotti. All patients with conduction disturbances receive a temporary pacemaker for 72 hours after TAVI and are monitored in ICU or with telemetry. Permanent pacemakers are inserted if the conduction problems persist.

There has been one episode of TAVI valve endocarditis that responded well to antibiotics.

Although cost constraints limit the
expansion of the TAVI program in our hospital, it has become an accepted treatment modality. Consequent to the awareness that the TAVI program has generated, total aortic valve replacements in our unit have increased since starting the program. Although the procedure is currently limited to surgical high-risk patients, a recommendation has been made to extend it to the intermediate-risk group.

Cardiovascular protection: A cornerstone in hypertension management

Despite optimal pharmacological and invasive therapies for acute coronary syndromes, the burden of recurrent ischaemic events and mortality remains high. The high cost of intervention programs means that they will not be sustainable in the future and emphasis on preventative strategies, comprehensive risk factor management strategies and less expensive effective (generic) medications is essential if the increasing burden of CVD is to be addressed.

Traditional approaches to cardiovascular (CV) risk reduction target lifestyle change (stopping smoking, moderation of alcohol consumption, physical activity) and reduction of risk factors, including blood pressure, blood glucose and lipids. Hypertension is the most important and most common risk factor for premature CVD.

However, risk reduction also requires comprehensive assessment and management of cardiovascular risk morbidities, including obesity, HIV, asthma, chronic inflammatory diseases, testosterone deficiency and sleep disordered breathing (SDB) that increase the risk of hypertension and the incidence of CV events. In particular, SDB is a common under-recognised and under-treated condition in South African patients, which significantly contributes to CV risk and treatment-resistant hypertension. Risk factors for obstructive sleep apnoea (OSA) include male sex, family history, menopause, craniofacial abnormalities, smoking and alcohol use, but perhaps most importantly, obesity. Sleep disorders, including OSA, upper airway resistance (UAR) and hypopnoea are present in almost 75% of obese individuals.

Sleep disorders are associated with increases biomarkers of inflammation and oxidative stress, hypercoagulable states and impaired endothelial dysfunction. Immune system activation plays an important role in the pathophysiology of CVD and is intricately linked to hypertension.

Recent studies indicate that hypertension treatment guidelines may also require revision in terms of recommendations for drug therapy. The PATHWAY-2 study, which sought to determine the optimal drug treatment for resistant hypertension, demonstrated that, in comparison to alternative antihypertensive pharmacotherapy, spironolactone is the most effective treatment and patients should not be defined as having resistant hypertension unless their BP remains uncontrolled on spironolactone.13

Blood pressure targets may also need to be reconsidered. The SPRINT study showed that, in patients at high risk for CV events, blood pressure targets lower than 120 mmHg vs. 140 mmHg were associated with lower rates of fatal and nonfatal major CV events and mortality.14 However, these targets were difficult to achieve and adverse treatment effects were increased.

Recommendations for hypertension management include following a healthy diet and moderate, but not excessive participation in regular exercise. For most patients drug treatment consists of mono- or combination therapy with a renin-angiotensin-aldosterone system (RAAS) blocker, calcium channel blocker and/or thiazide or thiazide-like diuretic. Due to their superior tolerability profile, patients are more likely to adhere to long-term treatment with an angiotensin receptor blocker (ARB) than an ACE inhibitor. ARBs provide good BP control over a 24-hour dosing interval, improve cardiovascular outcomes and reduce the risk of diabetes in comparison to placebo, beta-blockers and diuretics.
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