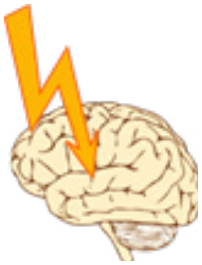
Stroke Medicine Bulletin July 2018



Welcome to the first edition of this newsletter. It is meant to be some light CPD for the busy stroke physician/neurologist as well as any other interested geriatricians, neurologists or acute physicians. We welcome content, articles, imaging and research and general feedback.

Contact: Declan.okane@nhs.net. Please email or send it to anyone who might find it useful. This will be stored at www.neurovascularmedicine.com. The newsletter may be printed but the online pdf version contains live hyperlinks that may be clicked.

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Stroke for Acute Medicine Physicians

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Stroke is unique in its subspecialty status and as a consequence benefits from the perspectives and insights of a truly multidisciplinary consultant workforce. Acute Internal Medicine (AIM) and Stroke Medicine have many parallels. Both:

- Are rapidly evolving, dynamic acute care specialties
- Deliver excellence in the diagnosis and management of challenging, undifferentiated, time critical conditions where a competent clinical decision maker at the front door is crucial
- Exemplify multidisciplinary team working and collaboration
- Face configuration challenges across their respective pathways necessitating innovative practice
- Require strong management and leadership qualities

For me, these parallels make them perfect professional partners and AIM training provides an excellent backdrop to fulfil many of the attributes required to become a stroke physician. I am lucky enough to enjoy a hybrid career in AIM and Stroke at North Bristol NHS Trust which provides a comprehensive stroke service that includes thrombectomy.

Working in two acute care environments can be intense, but I find that each role makes the other sustainable. Not only do I enjoy the hyperacute aspect of stroke and employing the exciting therapies we can now offer but I also relish having more time to spend with people and contribute to care far beyond the 72 hour AIM window.

Outside of work, I am a busy mum to 2 small children and have many interests. A career with varied shift patterns means I maintain a good work-life balance and have time to spend doing the things that matter outside work. If you would like more information about a career in AIM or Stroke please follow me on twitter@AIM4Stroke.

Latest Trial Research News

Wake up trial (link)

Some patients present without a clear time of onset, either a wake up stroke or dysphasia renders them unable to give a clear history. DWI shows early changes of Acute Ischaemic stroke (AIS) and changes with FLAIR come on later usually at around the 3-4.5 hours mark. DWI/FLAIR mismatch is seen in approximately 78-93% of strokes within 3-4.5 hours of onset. The Wake-up trial looked at the management of acute stroke in patients with an unknown time of onset. Those who had DWI changes but no changes on FLAIR were randomised to Alteplase or placebo. Overall, 1362 patients were screened and 503 of these were enrolled. The Alteplase group had a significantly better functional outcome (53.3% v 41.8%) but numerically more intracranial haemorrhages (2.0% v 0.4%) than placebo at 90 days. The benefit was comparable to thrombolysing patients known to be within 3-4.5 hours. This study should prompt a significant change in the choice of imaging in acute stroke care when time of onset is unclear.

POINT trial (link)

The aim of POINT was to determine whether clopidogrel plus aspirin started <12 hours after TIA or minor ischemic stroke (NIHSS <4) symptom onset was more effective in preventing major ischaemic vascular events at 90 days and safe compared to aspirin alone. The trial was carried out in an international population of patients. The results showed that those who received a combination of clopidogrel and aspirin had a lower risk of major ischaemic events (AIS/MI/Vascular death) (5.0 % vs 6.5 %) with the main benefit being reducing ischaemic stroke but at the cost of a higher risk of major haemorrhage (0.4% vs 0.9 %) at 90 days, than those who received aspirin alone. This meant 39 fewer ischaemic events for 13 more major haemorrhages. Interestingly, many of the ischaemic strokes were prevented within the first 30 days of treatment while haemorrhage occurred over a broader period.

CROMIS-2 (link)

CROMIS 2: a multicentre observational cohort study was a UK study. It looked at Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack. The symptomatic intracranial haemorrhage rate in patients with cerebral microbleeds was 9·8 per 1000 patient-years (95% CI 4·0–20·3) compared to 2·6 per 1000 patient-years (95% CI 1·1–5·4) in those without cerebral microbleeds (adjusted hazard ratio 3·67, 95% CI 1·27–10·60). What next? The authors suggest that large-scale, collaborative, observational, cohort analyses are needed to refine and validate intracranial haemorrhage risk scores by incorporating cerebral microbleeds to identify patients at risk of net harm from oral anticoagulation.

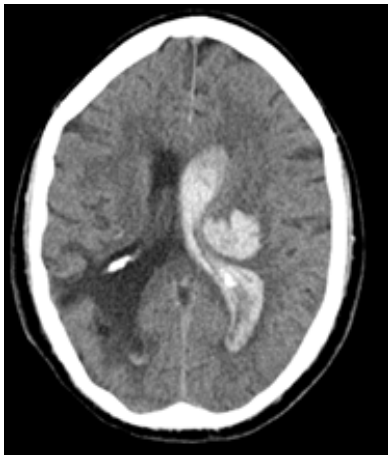
TICH-2 (link)

Another excellent UK trial, TICH 2, looked at the use of Tranexamic acid for hyperacute primary Intracerebral Haemorrhage (TICH-2). Tranexamic acid has proven effectiveness in reducing mortality from bleeding after trauma and post-partum haemorrhage and it seemed an obvious study to see if it could alter outcomes acutely in SICH. Unfortunately Functional status 90 days after intracerebral haemorrhage did not differ significantly between patients who received tranexamic acid and those who received placebo, despite a reduction in early deaths and serious adverse events. The authors suggest larger randomised trials are needed to confirm or refute a clinically significant treatment effect. The issue here is that Tranexamic acid may need to be administered much earlier after the onset of symptoms to reduce the bleeding in the first place or given to patients at very high risk of continuing to bleed (e.g. those with the spot sign).

Interesting Dilemmas: ICH and Mechanical Heart valves

Author: **Dr D O'Kane**, *Stroke Physician, Brighton.*

A 72 year old female with a metallic aortic valve on Warfarin presented with ICH and a GCS of 14. The patient had had a previous right parietal-occipital haemorrhage 18 months earlier and following recovery anticoagulation had been re-started. She had a 20 year history of hypertension but compliance with medications had always been an issue and control suboptimal. The haemorrhage was felt to be due to long standing hypertension but exacerbated by anticoagulation. Anticoagulation-related ICH is associated with a mortality of approximately 50% within the first 30 days.



Intracerebral haemorrhage is a dynamic process and the immediate concern was to achieve haemostasis. Her initial INR was 4.0. She was immediately given 4 Factor Prothrombin complex concentrate with IV Vitamin K without delay. Four-factor PCC includes coagulation factors II, VII, IX, X and anticoagulant proteins C and S. Prothrombin complex concentrate is preferred over fresh frozen plasma. The haemorrhage was complicated with intraventricular haemorrhage. This was the second such event that the patient had experienced. Changes from the previous contralateral bleed can be seen on the CT. A further repeat CT several hours later showed some early changes suggestive of obstructive hydrocephalus and neurosurgeons inserted an external ventricular drain once her clotting had normalised.

In some cases of life threatening haemorrhage, be they ICH or gastrointestinal haemorrhage in a patient with a mechanical heart valve there can be a momentary hesitation about reversing anticoagulation because of concerns about the valve and risk of thrombosis and thromboembolism. However, in almost all cases achieving haemostasis through reversing anticoagulation immediately to reduce the risk of further bleeding is the overriding priority. Reversal of anticoagulation also allows surgical remedies to manage the bleeding (such as craniectomy) or its secondary effects such as hydrocephalus with insertion of an EVD.

The patient was transferred to neuro ITU and then at day 7 was stepped down to the hyperacute stroke unit for further care. The decision then fell to us to plan for the current and future management of anticoagulation. In order to do this, we found that there were no national guidelines so we looked to see what evidence we could extract and extrapolate from the literature. First of all, we needed to get an idea of what were the real risks of thromboembolism and mechanical valve thrombosis with and without anticoagulation and see if they could give us some quantifiable measurements of risk.

Cannegieter and colleagues [1] looked at studies of both, embolic and bleeding complications, in patients with mechanical heart valves between 1970 and 1992 with regard to the choice of antithrombotic therapy, valve position, and valve type. The pooled data of over 13,000 patients studied for 53,647 patient-years showed that the risk of major embolism in the absence of Oral Anticoagulants was 4 per 100 patient-years. The risk in those on antiplatelet therapy alone was 2.2 per 100 patient-years, and with Warfarin was reduced to 1 per 100 patient-years. This risk varied with the type and the site of the prosthesis. A prosthesis in mitral position doubled the risk compared to the aortic position.

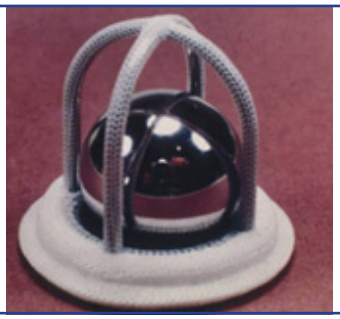
Generally, tilting disc valves and bileaflet valves showed a lower incidence of major embolism than the classical Starr-Edwards caged ball valves whose use was discontinued by their manufacturers in 2007. They do last lifelong so it is still possible to encounter such valves for the foreseeable future. If there is uncertainty, the chest x-ray shows their distinctive appearance.

When assessing for risk of thromboembolism, there are other additional additive risk factors such as previous thromboembolism, atrial fibrillation, mitral stenosis of any degree or a left ventricular ejection fraction <35%. Pregnancy and the post-partum state would pose another prothrombotic state but as mechanical valves are avoided in fertile females this should rarely surface as a problem. Dehydration, malignancy and infection can also add to the prothrombotic risks.

The holy grail of valve surgery is the bioprosthetic valve that lasts lifelong or the mechanical valve that requires no anticoagulation. The aim to try and design valves with very low thrombogenicity focuses on reducing the prothrombotic valve surface area and removing any design defects such as recesses or cavities that allow thrombi to form. Computer models and simulations can also help predict flow and potential sites of thrombus formation. Experimentally, new metal valves are assessed by being implanted in the mitral valve position in cows or pigs [6] on anti-platelets and embolic events are assessed over 6 months. When newer valves are introduced commercially they are regarded as having an unproven thrombotic status and should be placed in the 'medium thrombogenicity' category until sufficient long-term data is acquired.

With regard to our patient, she has a St Jude's Bi-leaflet valve which has a low risk thromboembolic profile in the aortic position which is regarded as lower risk. She is in sinus rhythm and has a normal ejection fraction. She has no previous valve related thromboembolism. The value of 4 per 100 patient years was based on an aggregate of multiple patients with different valves and positions and it is quite possible the rate is even lower for our patient with respect to valve type and position. This value is equivalent to AF and $CHADS_2$ score of less than 2 or CHA_2DS_2-VASc of 4. The study also showed that Aspirin had significant protective benefits.

The default anticoagulant of choice is warfarin and DOACs are not an alternative. A trial using Dabigatran was terminated early as there was a double negative hit of both increased ischaemic strokes and increased bleeding complications compared to warfarin [Eikelboom JW et al 2013]. Extrapolated as a class effect pending other studies, therefore, DOACs are not just ineffective but potentially harmful and are regarded as contraindicated.



1. Bileaflet valve
Low/Medium Thrombogenic

2. Tilting disc valve
Low/Medium Thrombogenic

3. Starr Edwards Cage valve. Highly thrombogenic.

Prosthetic Valve Thrombosis is uncommon. It is much more common with Mitral valve prostheses and those with a double valve replacement. It may cause a degree of circulatory obstruction. Consider it in any patient with any type of prosthetic valve, with new onset acute dyspnoea or an embolic event especially after a recent period of subtherapeutic anticoagulation or increased coagulability. The diagnosis can be made on echocardiography, either TTE and/or TOE. Surgery is emergent and high-risk. Fibrinolysis is preferred over surgery in right sided valves and the converse is true for left sided valves [7]. Neither would be appropriate in our patient. The baseline incidence of major bleeding complications in patients with MHV and taking oral anticoagulants has varied from 0.34% to 1.32% per patient-year [Akhtar RP et al. 2009].

Why not simply use biological (bioprosthetic) valves? The reason is that they have a shorter life span of 10-20 years needing further surgery and its inherent risks whereas metal valves last lifelong. Bioprosthetic valves deteriorate even more quickly in younger patients. They may, therefore, be preferred is an older patient who wishes to avoid anticoagulation. The other group is women of child bearing age who wish to avoid warfarin which is teratogenic and who may wish to become pregnant. They can later have elective mechanical valve replacement. In summary, the balance lies between the risk of teratogenicity or bleeding with long term anticoagulation against that of needing future valve replacement surgery.

In our patient, the risk of further bleeding on anticoagulation must be very high indeed. This is the second episode in 2 years. In one study, the strongest predictor of bleeding was previous bleeding (OR: 2.7; 95% CI: 1.4-5.3) [2]. She also has other risks factors including age and hypertension. One could easily argue that reintroduction of anticoagulation would risk a likely recurrence of ICH of greater than 50% over 2 years if the patient survives that long. In many ways, this is several times larger than the risk of thromboembolism or valve thrombosis. Long term decisions may need to be made on this patient dependent on recovery and prognosis which by all assessments is poor. Active management of hypertension and ensuring compliance with antihypertensive medication is also key in reducing bleeding risk.

I am not clear that further MRI imaging and identifying various stigmata of old haemorrhage and microbleeds will help in this case. Imaging after the first haemorrhage did not show any structural cause to chase. We already know that our patient is at high risk of repeat haemorrhage. In other cases, MRI SWI and other modalities might help guide risk and therapeutic decisions. There is an occasional misconception that MRI is contraindicated with metallic heart valves but available evidence to date, shows that all patients with prosthetic heart valves can safely undergo MRI at 1.5 Tesla and the vast majority at 3 Tesla too. The magnetic forces exerted on prosthetic valves are less than the forces exerted by gravity or the beating heart and resultant pulsatile blood flow [3].

A new paper has recently come out which looked at outcomes in 2504 patients with mechanical heart valves who had ICH on anticoagulants [4]. This study looked at outcomes based upon when therapeutic anticoagulation was restarted. Analysis showed that early re-initiation of anticoagulation was associated with increased rates of haemorrhagic complications until day 13 after the initial ICH. Even in the highest risk patients they advised avoiding anticoagulation before day 6 but for all others not before 14 days.

With warfarin anticoagulation, the risk of major bleeding increases considerably when the INR exceeds 4.5 and increases exponentially above an INR of 6.0. Current guidance suggests long-term VKA therapy for all mechanical valves with a target INR 2.5 for aortic only and 3.0 for mitral only or mitral & aortic valves which is lower than older recommendations. [7]. There are new trials suggesting a target INR of 1.8-2.0 may be adequate especially with a valve in the aortic position.

Our patient is at high risk of rebleeding but has a low risk valve. An individualised approach may opt for Aspirin in the short term which does have an evidence base suggesting reduced risk of valve thromboembolism. As time goes on we may also replace IPC stockings with prophylactic low molecular weight heparin. She is at a very high risk of VTE. If the patient survives the acute period then the plan will be low dose Warfarin strategy with a target INR of less than 2. This was shown to be safe with a low risk mechanical aortic valve in the recent study by Puskas and colleagues [9]. There are various reasonable options. Some case reports show the use of early therapeutic anticoagulation within the first week, however the current evidence does not support this. Each case needs an individualised multidisciplinary approach by those who understand the known risks. Cardiologists have already been involved with the discussion as well as family members. Finally, there is a growing evidence base to inform national guidelines that would give useful direction to clinicians.

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Inter-professional stroke education experience from Nottingham

Author: **Dr Sunil Munshi**, *Stroke Physician, Nottingham*

Inter-professional or multi-disciplinary(MDT) care is at the core of all health care and will be even more important in the future. Continuing education of the Stroke 'Multi-Disciplinary Team' (MDT) is vital. However, there is a lack of comprehensive educational opportunities for MDTs covering the entire stroke pathway. We would like to share the experiences of our nationally-acclaimed educational programme.

We have developed and delivered an educational programme to the multi–professional stroke staff from all stages of the stroke pathway – hospital and community. Three modules are delivered 4 times a year, consistently evaluated, with education provided by specialists in the following subject areas: vascular and clinical neuroanatomy, acute assessment and NIHSS, hyper-acute care, complications, all aspects of rehabilitation, TIA, palliative care, neuroradiology, research, national (SSNAP) audit, nutrition, discharge planning and stroke in the real world. The entire stroke pathway is covered and most of the teaching is interactive and workshop-based. Patients are also involved with the teaching programme. A 'Train the Trainer' programme helps to maintain high standards and in dissemination of the programme.

We have measured some parameters according to the Department of Health's QIPP agenda (Quality, Innovation, Prevention, Productivity), with qualitative and quantitative measures of improvement. Over a 10-year period more than 600 nurses and therapists have received education. There has been an improvement in mortality rates, readmission rates, falls, swallow screens, door-to-needle times, proportion of staff trained in thrombolysis, staff retention and confidence, communication skills, SSNAP results and an improvement in professional practice in general. This work has been ongoing now for ten-years and was shortlisted for the BMJ awards

Over the last three years we have delivered a similar programme to medical students at the University Hospitals of Leicester. Each cohort comprises approximately 200 students. We have introduced innovative measures of teaching, with involvement of patients and students. The students even participate in mock thrombolysis runs and enact roles of various MDT staff in mock case conferences. Statistical analyses of student feedback suggest excellent results. There is scope for improvement. We have presented the programme to BASP and there is a possibility of this being disseminated to various medical schools across UK, as a model, not just of stroke education, but also of inter-professional education. Author: Dr Sunil Munshi & The Nottingham Stroke Team.

The Editors

Declan O'Kane trained in Medicine in Belfast and gained an MD in cardiology. He then did Computer science at Cambridge and Geriatric/GIM in Leicester. He is a Stroke Physician in Brighton and has previously worked in acute medicine and geriatric medicine. He is the author of Acute Medicine 2nd edition and various online resources for students.

Anthony Pereira trained in Medicine in Cambridge and Neurology in London. He runs one of the largest training schemes in neurology and stroke medicine in the UK. He helped develop the 24/7 Thrombectomy Service based at St George's Hospital. He is the coauthor of the Oxford Handbook of Stroke Medicine pubished by OUP.

Please feedback thoughts and comments for this first edition to D O'Kane at *Declan.okane@nhs.net*