Advances in Stroke
Emerging Therapies

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Over the past 2 years, the results of large clinical trials have fundamentally changed the clinical practice of stroke care in several different ways. Perhaps the greatest advances have occurred in stroke prevention, where we now have a wider array of anticoagulants to reduce the risk of stroke in patients with atrial fibrillation and we have confirmation from 2 large studies that medical therapies are more effective at stroke prevention than endovascular and surgical procedures for patients with intracranial atherosclerotic disease and internal carotid occlusion, respectively. However, new technological improvements have advanced endovascular techniques for acute ischemic stroke (AIS) to the point where we are on the verge of determining whether intra-arterial treatments may actually improve outcome. We discuss the highlights of several important articles during the past 2 years that have advanced the field in emerging therapies for stroke.

Acute Ischemic Stroke

Although no major advances have yet led to the approval of novel thrombolytic agents for AIS, the long awaited placebo-controlled IST-3 trial on IV t-PA for AIS was finally completed. IST-3 is the largest thrombolysis trial ever involving >3000 patients, confirming once again the benefits of IV t-PA and that, in unselected patients, alteplase is most effective in the 3-hour time window. The study supports the long-held notion that selected criteria are needed to identify patients who would benefit in time windows beyond 3 hours from symptom onset. In this respect, Parson et al. conducted a phase IIIB trial in which alteplase was compared with tenecteplase in patients who had a large artery occlusion and a perfusion lesion at least 20% greater than the infarct core on computed tomographic perfusion. Tenecteplase was associated with better reperfusion and better clinical outcomes compared with alteplase. This study not only supports the use of advanced imaging to identify patients likely to benefit from intravenous thrombolytic agents but also raises much hope that agents better than alteplase may be on the near horizon for clinical use in AIS.

Because of the limitations of IV t-PA for large artery occlusions, mechanical devices are widely used as alternative treatment options to achieve recanalization and reperfusion, often with variable results. Higher rates of recanalization using these devices have not consistently translated to better outcomes, necessitating the development of next-generation equipment. The application of stent retrievers represents a technological advancement in endovascular approaches for large artery occlusion. In the SWIFT and TREVO trials, investigators compared the Merci Retrieval System, a device in current practice, with 1 of 2 stent retrievers: the TREVO Retriever and Solitaire Flow Restoration device, respectively. Both studies enrolled patients with large artery occlusions within 8 hours of symptom onset and included patients who did not respond to IV t-PA. SWIFT was terminated early after meeting a prespecified efficacy stopping rule. In both studies, there were no major differences in device or procedural events or in the rates of symptomatic intracranial hemorrhage, and both stent retrievers achieved better rates of reperfusion on prespecified primary end points compared with the MERCI retriever. The results from these studies are highly encouraging and have helped to finally set the stage for pivotal phase III efficacy trials testing endovascular therapy against standard medical treatment both in comparison studies and in studies testing complementary treatment with t-PA.

Stroke Prevention

Although we await more definitive efficacy studies testing newer thrombolytics, such as tenecteplase or desmoteplase, and endovascular approaches for AIS, the greatest strides in emerging therapies for stroke during the past 2 years have occurred in prevention. For decades, we have had uncertainty how best to prevent stroke in several high-risk conditions, including atrial fibrillation, intracranial atherosclerosis, patent foramen ovale (PFO), and carotid artery occlusion. Clinical trials have now been completed during the past 2 years for all these conditions, yielding high-quality data that have and will impact clinical practice.

For atrial fibrillation, a growing list of novel direct thrombin and factor Xa inhibitors, which do not require monitoring, have reached the market as alternatives to warfarin. In the most recent, double-blind, randomized trial, ARISTOTLE, involving 18 201 patients, the factor Xa inhibitor apixaban was superior to warfarin in preventing strokes (ischemic and hemorrhagic), causing less hemorrhage and reducing mortality. Overall, newer oral anticoagulants seem to have better safety profiles than warfarin and may be preferable in some cases as first-line agents for stroke prevention. Postmarketing data will be important to better understand the safety and efficacy of these drugs compared with warfarin.

Apart from atrial fibrillation, patients with reduced left ventricular function are also at increased risk for stroke because...
of predisposition to left ventricular thrombosis. The WARCEF investigators addressed the question whether warfarin or aspirin is better to decrease cardiogenic emboli in patients with reduced left ventricular ejection fraction and sinus rhythm. There was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage.6

Another cause of cardioembolic stroke is PFO, especially in conjunction with atrial septal aneurysm. Whether endovascular closure of PFOs for patients with cryptogenic strokes is more effective than medical therapy alone to reduce recurrent stroke is unknown. To address and perhaps settle this issue, 3 large randomized trials comparing endovascular PFO closure with medical therapy have been completed. In the CLOSURE trial, 909 patients with cryptogenic stroke or TIA were randomized to PFO closure (STARFlex Septal Closure System) or medical therapy (aspirin or warfarin). There was no difference in recurrent stroke or TIA between the 2 groups, but there was an increased incidence of atrial fibrillation in the closure group.7 In contrast, the RESPECT trial randomized 980 patients only with cryptogenic stroke (no TIsAs) to the Amplatzer PFO Occluder device or to medical therapy and followed them up to 9 years.8 Although the trial was neutral in an intention-to-treat analysis, there was a significant reduction in recurrent stroke in those patients who underwent closure in the per-protocol analysis.9 A third trial (the PC Trial) did not show superiority of PFO closure with the Amplatzer device, but there were 5 strokes in the medical arm and only 1 in the closure group.9

Although the data from PFO studies may suggest a possible role for endovascular devices in stroke prevention, the opposite has been found in patients with intracranial atherosclerosis. Based on the WASID trial, patients with severe intracranial atherostenosis are at high risk for stroke. In the follow-up study, SAMMPRIS, involving 451 patients with recent TIA or stroke attributed to 70% to 99% stenosis of a major intracranial artery, aggressive medical therapy was superior to the use of the Wingspan stent in reducing recurrent stroke or death. The rate of periprocedural strokes was higher than expected in the stenting group, and the rate of stroke in the medical group was much lower than expected.10 Based on these results, many neurologists are now recommending the medical regimen adopted in SAMMPRIS for patients with severe intracranial atherostenosis. Such a regimen includes a lifestyle modification program and pharmacological prevention with aspirin and a short-term course of clopidogrel, anti-hypertensive agents, and low-density lipoprotein lowering. Dual antiplatelet agents in the short term after stroke might be effective when the risk for recurrent stroke is high. We await the results of clinical trials formally testing this hypothesis in these patients. However, the recent SPSt3 trial testing the long-term effect of clopidogrel added to aspirin showed that the combination causes significantly more bleeding and confers no added benefit in patients with recent lacunar stroke.11

Similar findings favoring medical therapy over surgery were also reported for patients with internal carotid artery occlusion. In the Carotid Occlusion Surgery Study (COSS), extracranial-intracranial (EC-IC) bypass for symptomatic carotid occlusion (COSS) was tested again, but this time in patients with hemodynamic cerebral ischemia at high risk for subsequent stroke; 195 patients were randomized to EC-IC bypass or best medical therapy. Similar to SAMMPRIS, patients in the medical arm had lower than expected event rates, and consequently EC-IC bypass, despite improved cerebral hemodynamics, failed to show clinical superiority to medical therapy alone.12

Overall, several well-designed clinical trials have been conducted, which have impacted clinical practice. The SAMMPRIS and COSS trials have shown that medical regimens are far more effective in preventing strokes than previously known, and we anticipate based on data from the PFO trials that closure may emerge as a therapy for stroke prevention in selected patients with cryptogenic stroke.

Disclosures
Dr. Mattle is on the steering committee of the PC Trial. The other author has no conflicts to report.

References
新しい脳卒中治療
Emerging Therapies

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急性虚血性脳卒中：2012年には、急性虚血性脳卒中に対する新規の血栓溶解薬の使用認可に至るほどの大きな進歩は得られなかったが、急性虚血性脳卒中での経静脈t-PA投与の長期観察プラセボ対照試験であるIST-3が終了した。1 IST-3は3,000例以上の症例を含む血栓溶解療法の最大の試験であり、経静脈t-PA投与の有効性を再度証明し、3時間以内の投与が最も有効であることを示した。主幹動脈閉塞患者においてアルテプラーゼとテンテクレプルを比較した第IIB相試験では、テンテクレプルはアルテプラーゼと比較して、より良好な再開通率と臨床的転帰を示した。主幹動脈閉塞に対する血管内治療の技術の進歩としては、ソリタールとTREVOステントリトリーバーが挙げられる。MERCIリトリーバーとソリタールリトリーバーを比較したSWIFT試験と、TREVOリトリーバーを比較したTREVO2試験では、デバイスによる手技上の合併症や症候性頭蓋内出血の割合に大きな差はなかったが、両者ともMERCIリトリーバーと比較して再開通率でより有効だった。

脳卒中予防：心房細動を有する患者に対して、モニタリングを必要としない直接トロンビン阻害薬やXa因子阻害薬がワルファリンの代替薬として上市された。二重盲検無作為試験であるARISTOTLE試験では、18,201例の症例が登録され、ワルファリンと比較してXa因子阻害薬であるアピキサバンが有意に脳卒中（虚血性および出血性）を予防し、出血性合併症の発症率が低く、死亡率を低減させることを示した。3 新規経口抗凝固薬はワルファリンと比較して安全性が高く、症例によっては脳梗塞予防の第一選択薬となる。卵円孔開存（PFO）を有する原因不明の脳梗塞患者に対して血管内PFO閉鎖術の効果を検討した3つの臨床試験が発表され、一部の患者では脳梗塞予防の治療法となる可能性がある。SAMMPRIS試験では、70〜99%の頭蓋内主幹動脈狭が原因となったTIAまたは脳梗塞を発症した41例が対象で、血管内治療群と比較して再発脳梗塞や死亡において優位性を示した。症候性内頭動脈閉塞患者に対する頭蓋外頭蓋内（EC-IC）バイパス術の有効性を検討したCarotid Occlusion Surgery Study（COSS）の結果が報じられた5。195症例が無作為にEC-ICバイパス群と薬物治療群に分けられたが、SAMMPRIS試験と同様に薬物治療群で想定よりもイベント発症率が低く、その結果EC-ICバイパス群は脳の血行動態は改善したものの、薬物治療単独群に対する臨床的な優位性を示さなかった。これらの結果は、薬物療法が脳梗塞予防において従来考えられていたよりも有効性が非常に高いことを示したと言える。

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代表的な引用文献


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