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Advances in Emerging Therapies 2009

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Stroke has multiple etiologies and presents in many forms. Therefore, it will continue to pose challenges in prevention, diagnosis, and treatment. 2009 has brought modest advances in terms of new acute stroke therapies but has provided encouraging preliminary reports of possible developments to come. The main progress of 2009 has been in the area of primary and secondary prevention, providing exciting new therapies that are likely to alter our practice significantly in the future. Prevention is better than cure.

Primary Prevention

Statins have a role alongside antithrombotic and antihypertensive agents for secondary prevention of stroke.[1] The JUPITER investigators recently demonstrated the efficacy of a statin for primary prevention.[2]

JUPITER was a randomized, double-blind, placebo-controlled trial of high-dose rosuvastatin (20 mg per day). The study population consisted of 17 802 apparently healthy men (>50 years of age) and women (>60 years of age) who, at screening, had low levels of low-density lipoprotein cholesterol (<3.4 mmol/L) and increased levels of high-sensitivity C-reactive protein (<2.0 mg/L). Nearly 90 000 patients had to be screened to attain this enrollment. The trial was stopped early after median follow-up of only 1.9 years of the planned 4 because of a striking reduction in the primary end point of first major cardiovascular event: 0.77 versus 1.36 events per 100 person years of follow-up, respectively (hazard ratio for rosuvastatin, 0.56; 95% CI, 0.46 to 0.69; $P<0.00001$). Of these major cardiovascular events, there were 33 strokes in the rosuvastatin group (n=8901) and 64 strokes in the placebo group (n=8901). This 48% reduction in stroke risk was found to be driven by a reduction in ischemic cerebrovascular events. There were similar numbers of hemorrhagic stroke in both groups. Subgroup analysis suggested that the patients who gained most benefit from rosuvastatin therapy were those with increased traditional risk factors, such as male sex, increasing age, and smoking. The treatment was well tolerated apart from a small but significant excess of new diabetes in the rosuvastatin group. This was not an adjudicated outcome measure and requires further examination.

Interestingly, JUPITER also reported a statistically significant reduction in deep venous thrombosis rates among patients treated with rosuvastatin (0.09 versus 0.20 events per 100 person years of follow-up, respectively (hazard ratio for rosuvastatin, 0.45; 95% CI, 0.25 to 0.79).[3] There was a reduction in venous thromboembolism as a whole, driven by statistically significant reduction in deep venous thrombosis and all "provoked" thromboembolism (ie, events occurring in the presence of malignancy, hospitalization, surgery, or trauma). The lipid-lowering effect of statin therapy alone does not readily explain this reduction in venous thromboembolism, but pleiotropic effects of statin therapy have been proposed previously. Anticoagulant or anti-inflammatory effects may be present.

With the results of JUPITER in mind, the question remains: at what point does the economic and clinical burden of primary prevention become worthwhile? The JUPITER reports may make us reconsider the scope of primary prevention, but relative costs and benefits must be carefully assessed before routine practice is changed.

Secondary Prevention

Embolic stroke caused by atrial fibrillation is associated with high rates of mortality and disability. Two large randomized control trials in atrial fibrillation appear likely to alter future practice.

Effective anticoagulation has achieved the most significant reduction in rates of atrial fibrillation–related stroke disease in recent decades, primarily using vitamin K antagonists. Warfarin prevents 64% of strokes in patients with nonvalvular atrial fibrillation.[4] However, it is an unsatisfactory drug in many respects. Most seriously, it is associated with increased hemorrhagic events that can be catastrophic. The narrow therapeutic index and susceptibility to interactions mandate regular laboratory monitoring with clear economic and practical implications. Despite best efforts, control of anticoagulation is suboptimal in a sizeable minority of patients, leaving them at increased risk of thromboembolism or major hemorrhage.

In the search for a novel approach to anticoagulation without the limitations of vitamin K antagonists, several drugs have been investigated. Some have similar efficacy to warfarin, at the expense of increased adverse effects. Ximel-

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agatran, a direct thrombin inhibitor caused unacceptable rates of liver toxicity comparable warfarin in the SPORTIF V trial.[5] The AMADEUS trial was stopped early because of increased rates of major bleeding in the group treated with subcutaneous idraparinux, a synthetic pentasaccharide that specifically inhibits activated factor X, compared with warfarin.[6]

The RE-LY study has revived hope that effective anticoagulation may be possible with a drug that is easy to administer and is free from significant interactions or adverse effects.[7] A total of 18 113 patients with atrial fibrillation and increased risk of stroke were randomized to receive either open-label dose-adjusted warfarin or one of 2 doses of dabigatran (110 mg twice daily or 150 mg twice daily, respectively) administered in a blinded fashion. Dabigatran is an oral prodrug that, once converted to its active form, inhibits thrombin. It has a favorable profile in terms of dietary and drug interactions because it is metabolized independently of cytochrome p-450. The trial found neither dose of dabigatran to be inferior to warfarin with respect to the primary outcome of systemic embolism or stroke. Instead, the rate of systemic embolism or stroke was significantly lower with the higher dose of dabigatran (1.11% per year) than with either warfarin (1.69% per year) or dabigatran at the lower dose regime (1.53% per year). In terms of safety, the performance of dabigatran was encouraging, especially when weighed against the inconvenience and risks of warfarin prescribed outwith trials. On the positive side, there were lower rates of hemorrhagic stroke at both doses (0.12% per year and 0.10% per year, respectively) compared with warfarin (0.38% per year) and comparable rates of extracranial hemorrhage in all 3 groups. The rate of hepatotoxicity, as defined by a rise in transaminase levels to >3 times the upper limit of the normal range, was similar in all 3 groups and well below the level seen in the SPORTIF trials. However, dyspepsia was noted with increased frequency in each dabigatran group (11.8% per year and 11.3% per year, respectively) when compared with warfarin (5.8% per year). Of greater concern, the rate of myocardial infarction was slightly higher with dabigatran (0.72% per year and 0.74% per year, respectively) than with warfarin (0.53% per year). Similar results were seen in patients treated with ximelagatran for acute deep venous thrombosis in the THRIVE Study.[8] A retrospective analysis in this study found a higher rate of serious coronary events in the group treated with ximelagatran (10 events in 1240 patients) compared with those treated with enoxaparin or warfarin (1 event in 1249 patients; $P=0.006$). These small effects may not outweigh the advantages of direct thrombin inhibition but deserve closer examination.

An attractive prospect to reduce stroke incidence in patients with atrial fibrillation would be suppression of the arrhythmia itself, a direct approach that has thus far proven ineffective. Maintenance of sinus rhythm may reduce symptoms and improve quality of life, but no antiarrhythmic drug has yet been shown to reduce the risk of stroke, arguably the most significant potential consequence of atrial fibrillation. The ATHENA investigators reported that dronedarone, a new class-3 antiarrhythmic drug, reduces the incidence of hospitalization resulting from cardiovascular events or death in patients with persistent or paroxysmal atrial fibrillation or atrial flutter.[9]

Dronedarone is a complex, multichannel blocking agent with a pharmacological profile similar to that of amiodarone but with different relative effects on ion channels. Structurally, there are important differences relative to amiodarone, rendering it more lipophilic, with a resultant reduction in half life to ≈24 hours, which successfully reduces tissue accumulation. Dronedarone has no iodine component, eliminating thyroid toxicity. Rates of thyroid- and pulmonary-related adverse events were not significantly different between groups in ATHENA; however, follow-up lasted one year only, whereas many of the expected side effects of traditional amiodarone therapy would be expected over a much longer time scale.

A post hoc analysis of ATHENA[10] suggested a reduction in stroke in patients receiving usual care including antiplatelet/anticoagulant therapy and rate control therapy. A total of 4628 patients were randomized to placebo or dronedarone with follow-up for a minimum of one year. There was similar use of antiplatelets and anticoagulants in each group. The reduction in the risk of stroke was from 1.8% to 1.2% per year (hazard ratio, 0.66; 95% CI, 0.46 to 0.96; $P=0.027$), and this effect was similar when adjusted for the use of oral anticoagulant therapy. A higher baseline risk of stroke, expressed by use of the $CHADS_2$ score, was associated with a greater effect of dronedarone. Patients with a $CHADS_2$ score ≥2 had a significantly greater effect of dronedarone than those with a $CHADS_2$ score of ≤1 ($P=0.03$).

There are obvious limitations to the post hoc stroke analysis. As an outcome, strokes were not adjudicated, possibly a reflection of the fact that an effect on stroke incidence was unexpected. This affects the quality of data collection regarding stroke incidence, but the trend is clear. The lack of an established mechanism for stroke reduction gives a focus for direction of further research. Improved maintenance of sinus rhythm, with reduction of arrhythmic burden, is an attractive explanation; however, dronedarone was also proven to have a modest antihypertensive effect and possible anti-ischemic effects. Could dronedarone have pleiotropic effects similar to those of statins?

The vision for management of patients with atrial fibrillation and increased risk of stroke, as defined by a $CHADS_2$ score of ≥2, would be to use a reliable antiarrhythmic drug free of significant toxic effects in conjunction with a predictable and safe oral anticoagulant medication that requires minimal monitoring. Perhaps the combination of dabigatran and dronedarone now offers a realistic prospect of this.

Acute Therapies

After the publication of ECASS III in 2008, guideline groups in several countries have recommended to increase the thrombolysis window to 4.5 hours, using recombinant tissue plasminogen activator (rt-PA). However, optimal recanalization therapy remains a challenge to us all, and we strive to

improve functional recovery in patients who present early enough to be eligible for treatment.

There have been limited advances during 2009 in the use of thrombolytic therapy, but this remains fertile ground. The relative benefits of intra-arterial over intravenous thrombolysis are intuitive but have yet to be proven given the inevitable complexities and delays with this method of delivery. Ongoing trials are investigating the relative benefits of novel thrombolytic agents (such as tenecteplase and desmotoplase) or the use of adjuvant therapy together with alteplase. Possible adjuvants are varied, including the addition of additional anticoagulant therapy (such as a direct thrombin inhibitors or glycoprotein IIb/IIIa inhibitors) or the delivery of transcranial sonolysis in conjunction with systemic microspheres, which have been shown in animal models to improve delivery of rt-PA and increase clot lysis.

Devices

Further information on endovascular mechanical clot retrieval comes from the final results of the Multi MERCI study. Recanalization of cerebral vessels is associated with good clinical outcomes.[11] However, large vessel occlusions are less responsive to conventional rt-PA therapy. Multi MERCI,[12] a single-arm prospective trial of 164 patients (131 of whom were treated with the newest generation L5 retriever), investigated the use of mechanical thrombectomy devices with and without adjuvant intravenous or intra-arterial rt-PA. Results of the trial are reassuring but difficult to translate to clinical outcomes in the absence of control data. Multi MERCI demonstrated that arterial canalization was achieved in 57% of patients treated with the L5 retriever alone and 69.5% in patients also receiving intra-arterial rt-PA. There was a 27% absolute advantage in mortality between the group that achieved recanalization and the group that did not. The safety and complication rates with the new device appeared favorable (5.5% procedural complication rate; 2.4% device-related serious adverse event rate), even in the context of previous IV rt-PA therapy. Marketing authorization for devices is predicated on demonstration that they function satisfactorily for their designed purpose (eg, to remove thrombus), and this may be apparent from uncontrolled studies. Widespread clinical use requires a higher level of evidence. Mechanical thrombectomy devices are still being evaluated in randomized trials (MR RESCUE and IMS III).

A novel device developed with the aim of reducing stroke in patients with atrial fibrillation has been granted expedited review status by the Food and Drug Administration for use in a clinical trial.[13] Evaluation of the Watchman Left Atrial Appendage Closure Device in patients with atrial fibrillation (Embolic Protection in Patients with Atrial Fibrillation–PROTECT-AF) is under way in a prospective trial. The left atrial appendage is thought to be a major source of emboli in patients with nonrheumatic atrial fibrillation, and this device, inserted percutaneously via femoral access and a transseptal technique, is designed to occlude the left atrial appendage, thereby removing this source of potential emboli. Options for patients with atrial fibrillation appear to be improving.

Summary

2009 was a year with little firm evidence for immediate change in practice but provided us with a large body of stimulating research showing promise for the coming years. Therapy for acute stroke is largely unchanged in the wake of the advances made with ECASS-III; however, much work is ongoing to optimize recanalization therapy.

The largest strides in 2009 were taken in the area of stroke prevention. The most exciting area of development is in the field of stroke prevention in atrial fibrillation, with what may develop into a 3-pronged attack of reliable and safe anticoagulation, improved rhythm control, and mechanical devices to reduce embolic risk. The possibility of extending preventative therapy with statins in appropriate healthy people merits further investigation.

The development of effective preventative strategies will always prove most efficient in terms of mortality, morbidity, and health economics, and we should celebrate the advances made by the stroke community. We can be confident that age-adjusted stroke incidence will continue to fall, and the outcome for patients who succumb will continue to improve with the ongoing design and conduct of high-quality clinical research.

Disclosures

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