REVIEW ARTICLE

What's new in stroke? The top 10 studies of 2009–2011

Part II

Robert G. Hart[1], Wiesław J. Oczkowski[2]

1 Vascular Neurology, Department of Neurology, University of Texas Health Science Center, San Antonio, Texas, United States
2 Vascular Neurology, Division of Neurology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

KEY WORDS

atrial fibrillation, carotid stenting, clopidogrel, novel anticoagulants, stroke

ABSTRACT

Five studies published between 2009 and 2011 are reviewed that importantly inform stroke prevention for patients with atrial fibrillation (AF) or with cervical carotid artery stenosis. Two large, phase III randomized trials tested novel oral anticoagulants for stroke prevention in patients with AF: the direct thrombin inhibitor dabigatran 150 mg twice daily was superior to adjusted-dose warfarin (RE-LY trial) and the direct factor Xa inhibitor apixaban was far superior to aspirin in patients deemed unsuitable for warfarin (AVERROES trial). For both novel anticoagulants, major bleeding rates were similar to the comparator treatment. Clopidogrel plus aspirin was more efficacious than aspirin alone for prevention of stroke in patients with AF deemed unsuitable for warfarin, but major bleeding was significantly increased with dual antiplatelet therapy (ACTIVE A trial). Two large randomized trials (CREST, ICSS) provide the best available data on the short-term risks of carotid artery stenting vs. endarterectomy. In both trials, periprocedural stroke was more frequent with stenting than with endarterectomy, but the increased risk was largely confined to patients $\geq$70 years old. For younger patients, periprocedural risks were comparable with stenting or endarterectomy, but long-term outcomes are required to assess the relative merits of the two procedures.

Correspondence to:
Robert G. Hart, MD, Department of Neurology, University of Texas Health Science Center, 8300 Floyd Curl Drive, MC# 7883, San Antonio, Texas, USA, 78229-3900,
phone: +1-210-450-0530,
fax: +1-210-562-9371,
e-mail: hartr@uthscsa.edu
Received: May 2, 2011.
Revision accepted: May 3, 2011.
Conflict of interest: Robert G. Hart served on the stroke advisory and operation committees of the AVERROES trial and received compensation (<10,000 USD) from Bristol-Myers Squibb, the AVERROES trial sponsor, and of the ACTIVE A (no compensation).
Pol Arch Med Wewn. 2011; 121 (6): 200-207

Introduction We review our choices for the "top 10" studies published from 2009 to 2011 that influence our clinical management of patients with stroke and threatened stroke (TABLE 1).[1-11] Part I summarized 4 clinical trials concerned with management of acute stroke plus the first randomized trial assessing value of percutaneous closure of a patent foramen ovale (PFO) for stroke prevention.[12] Here we consider 3 recent trials of antithrombotic drugs to prevent stroke in patients with atrial fibrillation (AF) and 2 new trials comparing carotid artery stenting with endarterectomy.

By way of disclosure, one of us (RGH) served on the stroke advisory and operations committees of the AVERROES trial (Apixaban versus Acetylsalicylic Acid to Prevent Strokes)[8] and of the ACTIVE A trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events).[7]

6. Novel oral direct thrombin inhibitor dabigatran is as good or better than warfarin for stroke prevention in patients with atrial fibrillation Vitamin K antagonists, such as warfarin, have been the standard oral anticoagulants for more than 50 years, but the need for anticoagulation monitoring, frequent dosage adjustments, multiple drug interactions, and a relatively narrow therapeutic window have spurred the development of new oral anticoagulants that work by different mechanisms.[13] In the RE-LY trial (Randomized Evaluation of Long-term Anticoagulant Therapy), 18,113 AF patients with at least 1 additional stroke risk factor were randomly assigned to dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or adjusted-dose warfarin (target international normalized ratio [INR] 2–3) and followed for a mean of 2 years.[6] The 2 dabigatran dosages were administered double-blind, with warfarin given open-label. The trial was carried out at 951 sites in 44

TABLE 1 The top 10 stroke studies of 2009–2011

1. Pooled analysis of 8 randomized trials shows substantial benefit of i.v. tPA given 3 to 4.5 hours after stroke onset.[1]
2. Blood pressure lowering with candesartan may be harmful within the first days after acute stroke (SCAST).[2]
3. Thigh-length graduated compression stockings do not reduce venous thromboembolism in patients with acute stroke (CLOTS 1).[3]
4. Endovascular coiling is as good as neurosurgical clipping in the long-term for small, ruptured intracranial aneurysms (ISAT).[4]
5. Percutaneous occlusion of a PFO does not add to medical therapy in young cryptogenic stroke patients. (CLOSURE I).[5]
6. Novel oral direct thrombin inhibitor dabigatran is as good or better than warfarin for stroke prevention in patients with AF (RE-LY).[6]
7. Clopidogrel plus aspirin is superior to aspirin alone for preventing stroke, but with increased bleeding, in AF patients deemed unsuitable for warfarin (ACTIVE A)[7]
8. Novel oral direct factor Xa inhibitor, apixaban, is superior to aspirin for AF patients deemed unsuitable for warfarin (AVERROES).[8]
9. Complication rates of carotid stenting and carotid endarterectomy are equal (CREST).[9]
10. Carotid stenting has a higher complication rate than carotid endarterectomy (ICSS and pooled analysis of 3 European trials).[10,11]

Abbreviations: AF – atrial fibrillation, i.v. tPA – intravenous tissue plasminogen activator, PFO – patent foramen ovale

countries between 2005 and 2009. Average participant age was 71 years, 64% were men, half had previously used warfarin, 20% had prior stroke/transient ischemic attack (TIA), and 20% took aspirin (<100 mg daily) during the course of the trial. The time-in-therapeutic range for warfarin assigned patients averaged 64%.[6,14]

Dabigatran 150 mg twice daily was superior to adjusted-dose warfarin for the outcomes of all stroke or systemic embolism, of all stroke, and of all-cause mortality, and was associated with a similar risk of major hemorrhage (TABLE 2). Dabigatran 110 mg twice daily was associated with trends toward lower rates for these events compared with warfarin (not statistically different), but with a significantly lower rate of major hemorrhage (TABLE 2). Intracranial hemorrhage, the most feared complication of anticoagulation of elderly patients, was substantially and significantly lower with both dabigatran dosages. No serious hepatotoxicity was reported, but dyspepsia was twice as frequent in those assigned to dabigatran (TABLE 2).

Should dabigatran replace adjusted-dose warfarin for antithrombotic prophylaxis for patients with AF? This complex issue has several caveats.[15,16]

Dabigatran has important drug interactions with P-glycoprotein inhibitors such as verapamil, amiodarone, and quinidine, and the clinical importance of drug interactions is often not fully evident in selected participants in randomized trials. There is currently no accepted method to emergently reverse the anticoagulant effects of dabigatran in case of serious hemorrhage, although it has a relatively short half-life (averaging 12 hours) and can be partially removed by hemodialysis. It has been estimated that the effects of warfarin and dabigatran on preventing stroke in AF are about equal when the time in therapeutic range for warfarin is >70%,[17] but this level of warfarin anticoagulation control is infrequently achieved in clinical practice. From one editorialist: "... patients already taking warfarin with excellent INR control have little to gain by switching to dabigatran. In contrast, many other patients who have AF and at least one other risk factor for stroke

TABLE 2 Main results of the RE-LY trial: dabigatran vs. warfarin in atrial fibrillation patients[6,14]

	Dabigatran 110 mg twice daily n = 6015	Dabigatran 150 mg twice daily n = 6076	Warfarin n = 6022
stroke or non-CNS embolism[a], %/y	1.5[d]	1.1[c]	1.7
stroke[b], %/y (n)	1.4[d] (171)	1.0[c] (122)	1.6 (185)
myocardial infarct, %/y	0.8	0.8	0.6
major hemorrhage, %/y	2.9[c]	3.3	3.6
intracranial hemorrhage[b], %/y	0.2[c]	0.3[c]	0.7
all death, %/y	3.8	3.6[e]	4.1
dyspepsia, %	12[c]	11[c]	6

a the prespecified primary outcome
b stroke included ischemic strokes and primary intracerebral hemorrhages; intracranial hemorrhages included primary intracerebral hemorrhages, subdural hematomas, and subarachnoid hemorrhages
c $P < 0.01$ compared with warfarin
d $P < 0.01$ comparing the two dabigatran dosages
e $P = 0.05$ vs. warfarin

Abbreviations: CNS – central nervous system

TABLE 3 Main results of the ACTIVE A: clopidogrel plus aspirin vs. aspirin in atrial fibrillation patients[7]

	Aspirin, %/y n = 3782	Aspirin + clopidogrel, %/y n = 3722	Relative risk reduction (95% CI)	*P*
total stroke (n)	3.3 (408)	2.4 (296)	28% (17,38)	<0.001
all disabling/fatal stroke	2.1	1.6	26%	0.001
all intracranial hemorrhage[a]	0.2	0.4	–87%	0.006
major bleeding excluding intracerebral hemorrhage[a]	1.1	1.8	–57%	0.001
stroke or major hemorrhage	4.4	4.2	–	NS
all death	6.6	6.4	–	NS

a intracranial hemorrhages included intracerebral hemorrhages, subdural hematomas, and subarachnoid hemorrhages; intracerebral hemorrhages were also counted as strokes; subdural hematomas were counted as major bleeds, but not double-counted as strokes

Abbreviations: NS – nonsignificant

could benefit from dabigatran."[18] A recent American Heart Association/American College of Cardiology practice guideline endorsed dabigatran as an alternative to warfarin for AF patients.[19] Dabigatran has been approved by the European Medicines Agency for prevention of stroke in AF patients.

7. Clopidogrel plus aspirin is superior to aspirin alone for preventing stroke, but with increased bleeding, in atrial fibrillation patients deemed unsuitable for warfarin In AF patients deemed unsuitable for warfarin, the ACTIVE A investigators compared clopidogrel 75 mg daily plus aspirin (75–100 mg daily) with aspirin alone in a double-blinded randomized trials involving 7554 patients with at least 1 additional stroke risk factor entered from 561 centers in 33 countries (33% of participants were from Eastern Europe) between 2003 and 2008.[7] Reasons participants were deemed unsuitable for warfarin were an unacceptable bleeding risk if anticoagulated (e.g., predisposition to falling with head trauma, regular use of nonsteriodal anti-inflammatory drugs, uncontrolled hypertension, prior serious bleeding with warfarin) (23%), patient preference (26%), and physician recommendation based on the estimated balance of benefit/risk (inability to comply with INR monitoring, falling risk, alcohol habituation) (50%). Patients with high bleeding risk were excluded: active peptic ulcer disease within 6 months, prior intracranial hemorrhage, thrombocytopenia, ongoing alcohol abuse. Mean participant age was 71 years, 58% were men, 13% had prior stroke/TIA, and the average follow-up was 3.6 years.

All stroke (ischemic and hemorrhagic) was reduced by 28% (P <0.001) by dual antiplatelet therapy, but major hemorrhage was increased by 57% (P <0.001) (TABLE 3). Considering absolute rates, a 0.9% per reduction in all stroke (and 0.5% per year reduction in disabling/fatal stroke) was offset by a 0.7% increase in major hemorrhage. For the 992 participants with prior stroke/TIA (i.e., the highest risk for stroke), the stroke rate was 6.3%/y on aspirin and 4.5%/y on dual antiplatelet therapy (relative risk reduction 28%, P = 0.05, number-needed-to-treat for 1 year with dual antiplatelet therapy to prevent 1 stroke of 55).

In the companion ACTIVE W trial, combination antiplatelet therapy was substantially less efficacious than adjusted-dose warfarin in patients eligible for anticoagulation.[20] In summary, ACTIVE A demonstrated that combination antiplatelet therapy traded a reduction in all stroke for a similar absolute increase in major (mostly gastrointestinal) hemorrhage. The use of dual antiplatelet therapy for AF patients who cannot take warfarin but who are not at high bleeding risk has been approved by the European Medicines Agency, but it has not yet been considered by the European Stroke Organisation. Gastroprotective therapy with a proton-pump inhibitor (e.g., pantoprazol among many others) is recommended for patients taking antiplatelet therapy who are at special risk for upper gastrointestinal bleeding, including those receiving dual antiplatelet therapy.[21]

8. Novel oral direct factor Xa inhibitor, apixaban, is superior to aspirin for stroke prevention in patients with atrial fibrillation deemed unsuitable for warfarin For the millions of AF patients who cannot or will not take adjusted-dose oral vitamin K antagonists for stroke prevention, there has been an unmet need for well-tolerated, easy-to-administer, and safe antithrombotic prophylaxis that is more efficacious than aspirin for stroke prevention. While ACTIVE A demonstrated the combination of clopidogrel plus aspirin to be superior to aspirin alone, the increased bleeding associated with dual antiplatelet therapy lessens enthusiasm for combination antiplatelet therapy.[7]

Apixaban, a novel oral selective, reversible, direct factor Xa inhibitor, was compared with aspirin in the phase III randomized AVERROES trial involving 5999 AF patients with at least 1 additional stroke risk factor and who were not deemed candidates for warfarin (40% had previously received a vitamin K antagonist).[8] Participants were assigned double-blind to apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) vs. once daily aspirin (permitted dose range 81–325 mg daily) at 522 international sites between 2007 and 2010. Salient exclusion criteria were recent serious bleeding, active peptic ulcer disease, and severe renal insufficiency

TABLE 4 Main results of the AVERROES: apixaban vs. aspirin in atrial fibrillation patients[8]

	Apixaban, %/y n = 2808	Aspirin, %/y n = 2791	Hazard ratio	*P*
all first stroke (n)	1.5 (49)	3.3 (105)	0.46	<0.001
ischemic strokes (n)	1.1 (35)	3.0 (93)	0.37	<0.001
intracranial hemorrhage[a]	0.4	0.4	0.85	NS
major extracranial bleeding	1.1	0.9	1.23	NS
all major hemorrhage[b]	1.4	1.2	1.13	NS
all death	3.5	4.4	0.79	NS

a includes intracerebral bleeds, subdural hematomas, and subarachnoid bleeds
b Includes all first intracranial and major extracranial hemorrhages

Abbreviations: see TABLE 3

(about 25% of apixaban is excreted by the kidneys). Mean participant age was 70 years, 59% were men, 14% had prior stroke/TIA, and 9% in both treatment arms took additional non-study aspirin during follow-up. The trial was terminated at interim analysis after a mean follow-up of 1.1 years because of greater-than-anticipated efficacy of apixaban.[8]

Strokes (including ischemic and hemorrhagic) were sharply reduced by apixaban over aspirin (hazard ratio 0.46, 95% confidence interval [CI] 0.33 to 0.65, *P* <0.001) with an absolute decrease 1.8% per year. Major bleeding was not significantly increased in those assigned apixaban (44 (1.4% per year) with apixaban vs. 39 (1.2% per year) with aspirin, hazard ratio 1.13, 95% CI 0.74 to 1.75) (TABLE 4). Permanent discontinuation of medication was less frequent in those assigned apixaban vs. aspirin (*P* = 0.03). There were 11 intracranial hemorrhages with apixaban vs. 13 with aspirin.[8]

The strikingly positive results of the AVERROES trial should be considered in perspective. While there was no appreciable increase in major hemorrhage seen with apixaban over aspirin in the AVERROES trial, the CI around hazard ratio is relatively wide. Drug interactions with apixaban, particularly with those metabolized through the CYP450 system, have not been fully elucidated. Additional caveats that apply to any of the novel oral anticoagulants have been described.[22] Apixaban has yet not been approved by major regulatory agencies for AF patients. The ongoing companion ARISTOTLE trial (Apixaban for Reduction In Stroke and Other ThromboembboLic Events in Atrial Fibrillation) is comparing apixaban with adjusted-dose warfarin, with results anticipated in late 2011, and should contribute to a fuller picture of the role of apixaban in AF patients.[23] Preliminary results of a large randomized trial comparing another direct factor Xa inhibitor, rivaroxaban, with warfarin in AF patients reported comparable stroke rates with the two therapies.[24]

9 and 10. Complication rates of carotid stenting vs. carotid endarterectomy from 2 large randomized trials

The U.S. National Institutes of Health-sponsored CREST trial (Carotid Revascularization Endarterectomy versus Stenting Trial) compared carotid endarterectomy with carotid angioplasty/stenting in 2502 randomized patients from 108 US and 9 Canadian sites between 2000 and 2009.[9] The primary outcome was the composite of ischemic stroke, myocardial infarction, and all deaths within 30 days plus ipsilateral ischemic strokes up to 4 years post-procedure (the mean follow-up was 2.5 years). About half of participants (53%) had symptomatic carotid artery stenosis ≥50%, with the remainder asymptomatic stenosis ≥60%; overall, 86% of participants had ≥70% stenosis. A single type of stent and embolic protection device was used (RX-ACCULINK and RX-ACCUNET, Abbott Vascular Solutions), and cerebral protection devices were employed in nearly all participants (96%). Carotid endarterectomy was performed under general anesthesia in 90% of patients, and intraoperative shunts were used in 57%. There was a rigorous "lead-in" phase to document the proficiency of those performing the procedures. The mean participant age was 69 years, 65% were men, 30% had diabetes mellitus, 26% were current tobacco smokers, and the average blood pressure at entry was 141/74 mmHg.

The results of the CREST showed higher risk of perioperative myocardial infarction with endarterectomy and a higher risk of perioperative stroke with carotid stenting (TABLE 5). Of note, many of the myocardial infarctions were clinically silent, with the diagnosis based on electrocardiogram and troponin enzyme changes, whereas all strokes were clinically manifest. The ipsilateral stroke rate was low after the first 30 days with both treatments. Considering all strokes and death at 4 years, endarterectomy was superior (TABLE 5). There was no significant interaction of treatment effects with sex or symptom status, but there was a statistically significant interaction (*P* = 0.02) with age on the primary outcome: patients under age 70 tended to do better with stenting, and those over age 70 with endarterectomy.[9]

The CREST investigators concluded that the risk of the primary outcome composite did not differ significantly between the two interventions,[9] but, in our view, given the wide CI around the hazard

TABLE 5 Main results of the CREST: carotid stenting vs. endarterectomy[9]

	Stenting, % n = 1262	Endarterectomy, % n = 1240	Hazard ratio (95% CI)	*P*
primary outcome[a]	7.2	6.8	1.11 (0.81–1.51)	–
perioperative events				
ischemic stroke, myocardial infarct, or all-cause death	5.2	4.5	–	NS
all ischemic stroke	4.1	2.3	–	0.01
major stroke	0.9	0.6	–	NS
myocardial infarct[b]	1.1	2.3	–	0.03
ipsilateral ischemic stroke between 30 days and 4 years	2.0	2.4	–	NS
stroke or death by 4 years	6.4	4.7	1.5	0.03

a composite of ischemic stroke, myocardial infarction and all deaths within 30 days plus ipsilateral ischemic strokes up to four years post-procedure; mean follow-up was 2.5 years
b includes "silent" myocardial infarctions: troponin elevations and electrocardiogram changes, without symptoms

Abbreviations: CI – confidence interval, others – see **TABLE 3**

ratio for the primary outcome, the study was underpowered to assess whether the procedures are equivalent within a clinically meaningful range (i.e., stenting could be 19% better or 51% worse than endarterectomy). The accompanying editorial concluded that "until more data are available, endarterectomy remains the preferred treatment for most patients with symptomatic carotid stenosis; treatment for asymptomatic stenosis remains controversial. However, given the lack of significant difference in the rate of long-term outcomes, the individualization of treatment choices is appropriate."[25]

ICSS (International Carotid Stenting Study) was an international (50 sites in Europe, Australia, New Zealand, and Canada) randomized trial conducted between 2001 and 2009, which also compared carotid stenting with endarterectomy.[10] All participants had symptoms within 1 year (almost all were within 6 months) referable to a carotid with >50% stenosis (90% of had ≥70% stenosis). The primary outcome was disabling/fatal stroke (any arterial territory) during long-term follow-up, which was not reported pending additional observation, and only 120-day interim results were provided. The mean participant age was 70 years old, 71% were men, 22% had diabetes mellitus, 23% were current tobacco smokers, and mean blood pressure was 146/78 mmHg at entry. Several different types of stents and cerebral protection devices (the latter was used in 72% of cases) were employed. Centers were classified as experienced or supervised, depending on whether the investigator had previously placed >50 stents and/or performed >50 endarterectomies; 12% of participants were entered at centers designated as supervised, but outcomes were similar to those at centers designated as experienced.

Nondisabling stroke was the major difference in these 120-day results: 3% higher with stenting (P <0.001) (**TABLE 6**). In a substudy involving about 15% of participants, there was a large imbalance in new magnetic resonance imaging diffusion-positive abnormalities indicative of acute brain ischemia assessed 1 day after the procedures: 50% of 124 patients undergoing stenting vs. 17% of 104 patients undergoing endarterectomy (and not different for patients in whom cerebral protection devices were employed).[26] The 120-day stroke rates in the ICSS were higher in both treatment arms compared with the CREST, at least in part due to the symptomatic status of all ICSS participants, recognized to be associated with higher perioperative stroke rates.[9] The rate of perioperative myocardial infarction in the ICSS was only about 20% of the rate observed in the CREST

TABLE 6 Main results of the ICSS: 120-day outcomes with carotid stenting vs. endarterectomy[10]

	Stenting n = 853	Endarterectomy n = 857	*P*
stroke, death, or perioperative myocardial infarct, n (%)	72 (8.5)	44 (5.2)	0.006
disabling stroke or death	34 (4.0)	27 (3.2)	NS
any stroke, n (%)	65 (7.7)	35 (4.1)	0.02
disabling/fatal stroke, n (%)	26 (3.0)	22 (2.6)	NS
nondisabling stroke, n (%)	39 (4.6)	14 (1.6)	<0.001
all deaths, n (%)	19 (2.2)	7 (0.8)	0.02
perioperative myocardial infarct, n (%)	3 (0.4)	4 (0.5)	NS
cranial nerve palsy, n (%)	1 (0.1)	45 (5.3)	<0.001

Abbreviations: see **TABLE 3**

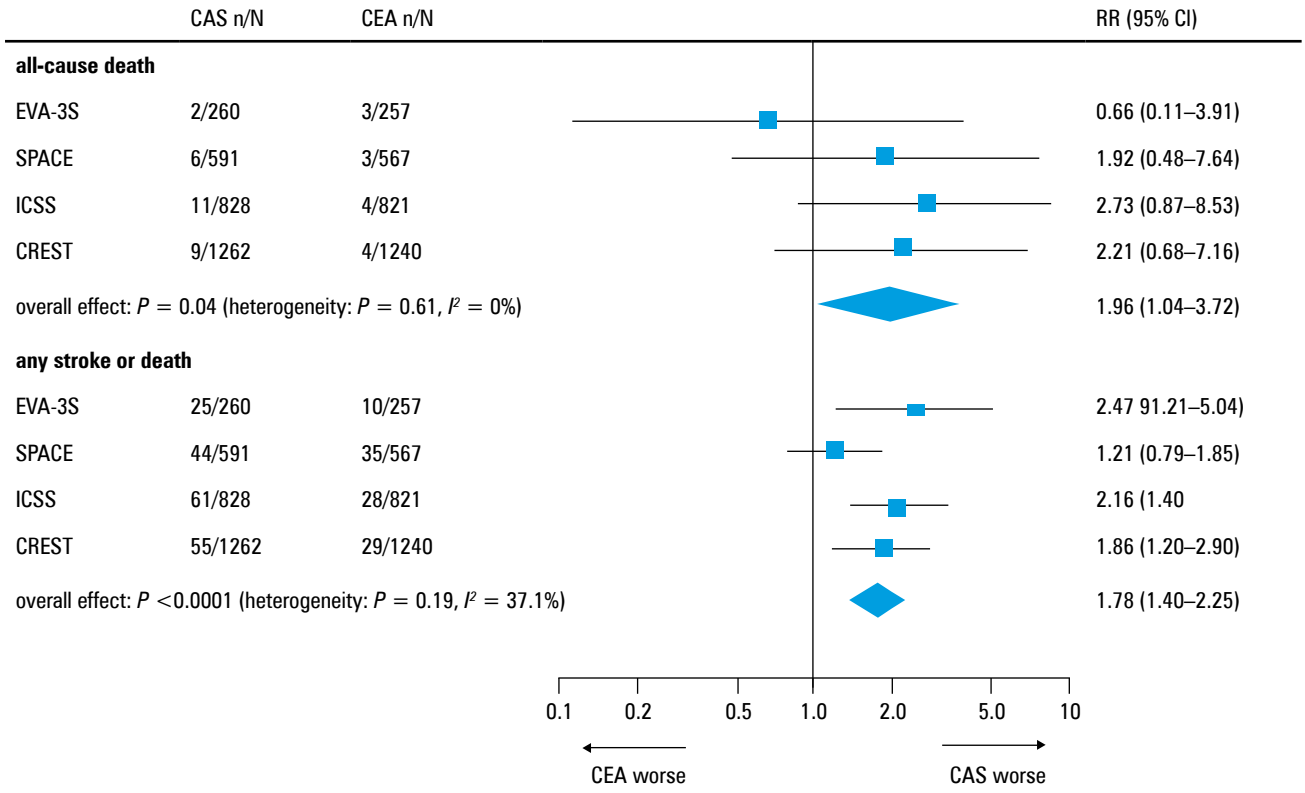

FIGURE Individual and pooled relative risks of death and combined stroke and death within 30 days of randomization in 4 randomized trials (see text for description of the trials)[27]

Abbreviations: CAS – carotid artery stenting, CEA – carotid endarterectomy, RR – relative risk, n – number of events, N – number of patients, others – see **TABLE 5**

(explained by inclusion of "silent" myocardial infarcts in the CREST). No subgroups were identified that had better results with stenting (including the absence of an age interaction). The ICSS investigators concluded that "our results are applicable to the current practice of carotid stenting" and that, pending long-term follow-up results, "carotid endarterectomy should remain the treatment of choice for patients with symptomatic carotid stenosis who are suitable for surgery."[10]

The Carotid Stenting Trialists' Collaboration pooled individual participant data from 3 European randomized trials of stenting vs. endarterectomy of symptomatic patients: EVA-3S (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis), SPACE (Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy), and the recent ICSS.[11] The two earlier trials had been criticized by some for lack of experience of those performing stenting (EVA 3S) and nonuse of cerebral protection devices (SPACE). Short-term results for 3433 randomized patients were generally consistent between all 3 trials (and also with the CREST) (**FIGURE**)[27] Considering any stroke or death, the 120-day risk was significantly lower with endarterectomy (6%) than with stenting (9%) ($P = 0.001$), but there was a statistically significant interaction with age regarding this outcome composite: the additional risk seen with stenting was confined to those ≥70 years old. The investigators concluded that "stenting for symptomatic carotid stenosis should be avoided in older patients (age ≥70 years), but might be as safe as endarterectomy in younger patients."[11] Updated recommendations regarding indications for carotid stenting vs. endarterectomy from the European Stroke Organisation[28] or other major national guidelines are not available since publication of these informative recent studies. Longer-term outcomes from these recent trials, especially the durability of stenting, are awaited. Of note, a randomized trial of stenting of symptomatic intracranial stenosis was recently stopped due to an unacceptably high periprocedural stroke rate.[29]

REFERENCES

1 Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 2010; 375: 1695-1703.

2 Sandset EC, Bath PMW, Boysen G, et al.; SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomized, placebo-controlled, double-blind trial. Lancet. 2011; 377: 741-750.

3 Dennis M, Sandercock PA, Reid J, et al.; CLOTS Trials Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet. 2009; 373: 1958-1965.

4 Molyneux AJ, Kerr RSC, Birks J, et al.; ISAT Collaborators Risk of recurrent subarachnoid haemorrhage, death, dependence and standardized mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. Lancet Neurol. 2009: 8: 427-433.

5 Furlan AJ. CLOSURE I Trial. Abstract presented at the 2010 American Heart Association meeting (Chicago, USA, November). In press.

6 Connolly SJ, Ezekowitz MD, Yusuf S, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361: 1139-1151.

7 Connolly SJ, Pogue J, Hart RG, et al.; ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009; 360: 2066-2078.

8 Connolly SJ, Eikelboom JW, Joyner C, et al.; AVERROES Steering Committee and Investigators. Effect of apixaban in patients with atrial fibrillation. N Engl J Med. 2011; 364: 806-817.

9 Brott TG, Hobson RW, Howard G, et al. Stenting vs. endarterectomy for treatment of carotid-artery stenosis. N Engl J Med. 2010; 363: 11-23.

10 Ederle J, Dobson J, Featherstone RL, et al.; International Carotid Stenting Study Investigators. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomized controlled trial. Lancet. 2010: 375: 985-997.

11 Bonati LH, Dobson J, Algra A, et al.; Carotid Stenting Trialists' Collaboration. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. Lancet. 2010; 378; 1062-1073.

12 Oczkowski WJ, Hart RG. What's new in stroke? The top 10 studies of 2009-2011: Part I. Pol Arch Med Wewn. In press.

13 Karthikeyan G, Eikelboom JW, Hirsh J. New oral anticoagulants: not quite there yet. Pol Arch Med Wewn. 2009; 119: 53-59.

14 Connolly SJ, Ezekowitz MD, Yusuf S, et al.; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. N Engl J Med. 2010; 363: 1875-1876.

15 Karthikeyan G, Eikelboom JW, Hirsh J. Dabigatran: ready for prime time? Pol Arch Med Wewn. 2010; 120: 137-142.

16 Douketis JD. Dabigatran as anticoagulant therapy for atrial fibrillation. Which patients should receive it, which patients may not need it, and other practical aspects of patient management. Pol Arch Med Wewn. 2011; 121: 73-80.

17 Wallentin L, Yusuf S, Ezekowitz MD, et al.; RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of INR control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010; 376: 975-983.

18 Gage BF. Can we rely on RE-LY? N Engl J Med. 2009; 361: 1200-1202.

19 Wann LS, Curtis AB, Ellenbogen KA, et al.; American College of Cardiology Foundation/American Heart Association Task Force. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran). Circulation. 2011; 123; 1140-1150.

20 Connolly S, Pogue J, Hart R, et al.; ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006; 367: 1903-1912.

21 Abraham NS, Hlatky MA, Antman EM, et al.; ACCF/ACG/AHA. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus doument on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol. 2010; 56: 2051-2066.

22 Sobieraj-Teague M, O'Donnell M, Eikelboom J. New anticoagulants for atrial fibrillation. Semin Thromb Hemost. 2009; 35: 515-524.

23 Lopes BD, Alexander JH, Al-Khatib SM, et al.; ARISTOTLE Investigators. Apixaban for Reduction In Stroke and Other ThromboembolLic Events in Atrial Fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J. 2010; 159: 331-339.

24 Executive Steering Committee on behalf of the ROCKET AF Study Investigators. Rivaroxaban – Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: the ROCKET AF study. Abstract presented at the 2010 American Heart Association Scientific Sessions, Chicago USA.

25 Davis SM, Donnan GA. Carotid-artery stenting in stroke prevention. N Engl J Med. 2010; 363: 80-82.

26 Bonati LH, Jongen LM, Haller S, et al.; ICSS-MRI study group. New ischemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). Lancet Neurol. 2010; 9: 353-362.

27 Amarenco P, Labreuche J, Mazighi M. Lessons from carotid endarterectomy and stenting trials. Lancet. 2010; 376: 1028-1031.

28 European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee Guidelines for management of ischaemic stroke and transient ischemic attack 2008. Cerebrovasc Dis. 2008; 25: 457-507.

29 National Institute of Neurological Disorders and Stroke. Neurological Clinical Alert Angioplasty Combined with Stenting Plus Aggressive Medical Therapy vs. Aggressive Medical Therapy Alone for Intracranial Arterial Stenosis: NINDS Stops Trial Enrollment Due to a Higher Risk of Stroke and Death in the Stented Group. http://members.asnr.org/misc/NINDS_Clinical_Alert.pdf. Accessed April 12, 2011.

ARTYKUŁ POGLĄDOWY

Co nowego w udarze mózgu? Dziesięć najważniejszych badań dotyczących udaru w latach 2009–2011

Część II

Robert G. Hart[1], Wiesław J. Oczkowski[2]

1 Vascular Neurology, Department of Neurology, University of Texas Health Science Center, San Antonio, Teksas, Stany Zjednoczone
2 Vascular Neurology, Division of Neurology, Department of Medicine, McMaster University, Hamilton, Ontario, Kanada

SŁOWA KLUCZOWE

klopidogrel, migotanie przedsionków, nowe antykoagulanty, stentowanie tętnicy szyjnej, udar mózgu

STRESZCZENIE

Przedstawiono 5 badań klinicznych opublikowanych w latach 2009–2011, które znacząco poszerzyły wiedzę o zapobieganiu udarowi mózgu u chorych z migotaniem przedsionków lub zwężeniem tętnicy szyjnej wewnętrznej. W 2 dużych badaniach III fazy z randomizacją oceniano nowe doustne antykoagulanty w prewencji udaru u chorych z migotaniem przedsionków: bezpośredni inhibitor trombiny dabigatran w dawce 150 mg 2 × dz. okazał się skuteczniejszy niż warfaryna w dawce dostosowywanej (badanie RE-LY), a bezpośredni inhibitor czynnika Xa apiksaban był znacznie lepszy niż kwas acetylosalicylowy (*acetylsalicylic acid* – ASA) u chorych niekwalifikujących się do leczenia warfaryną (badanie AVERROES). W przypadku obu nowych antykoagulantów częstość poważnych krwawień była podobna jak w grupie kontrolnej. Klopidogrel w połączeniu z ASA był skuteczniejszy niż sam ASA w prewencji udaru u chorych z migotaniem przedsionków niemogących przyjmować warfaryny, ale częstość poważnych krwawień była znamiennie większa w grupie otrzymującej podwójne leczenie przeciwpłytkowe (badanie ACTIVE A). Dwa duże badania z randomizacją (CREST, ICSS) stały się źródłem najlepszych obecnie danych na temat krótkoterminowego rokowania po zabiegu stentowania tętnicy szyjnej w porównaniu do endarterektomii. W obu badaniach okołozabiegowy udar mózgu występował częściej po stentowaniu niż po endarterektomii, ale zwiększenie ryzyka było w dużym stopniu ograniczone do chorych >70. rż. U chorych młodszych ryzyko okołozabiegowe było podobne w odniesieniu do obu procedur; do ustalenia, która daje większe korzyści, potrzeba danych o wynikach odległych.

Adres do korespondencji:
Robert G. Hart, MD, Department of Neurology, University of Texas Health Science Center, 8300 Floyd Curl Drive, MC# 7883, San Antonio, Texas, USA, 78229-3900,
tel.: +1-210-450-0530,
fax: +1-210-562-9371,
e-mail: hartr@uthscsa.edu
Praca wpłynęła: 02.05.2011.
Przyjęta do druku: 03.05.2011.
Zgłoszono sprzeczność interesów: Robert G. Hart był członkiem komitetów sterujących i doradczych ds. udaru mózgu przy badaniu AVERROES i otrzymał wynagrodzenie (<10,000 USD) od firmy Bristol-Myers Squibb, sponsora badania AVERROES, oraz przy badaniu ACTIVE A (bez wynagrodzenia).
Pol Arch Med Wewn. 2011; 121 (6): 200-207
Tłumaczył lek. Łukasz Strzeszyński