

# An Evidence-based Approach to Stroke Prevention: Important Advances in the Last Decade

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**SIGNIFICANT ADVANCES IN STROKE HAVE BEEN** made in the last decade including TIA management, treatment of atrial fibrillation, and identifying unhelpful stroke treatments. This brief review will focus on these particular advances.

## RISK FACTORS FOR STROKE

Though there are some stroke risk factors which cannot be modified (e.g. age, family history, race, gender, and personal history of stroke or TIA), there are a number of modifiable risk factors. The INTERSTROKE study<sup>1</sup> found that 90% of all strokes were associated with ten causes including:

- hypertension
- current smoking
- elevated waist-to-hip ratio
- poor diet
- reduced physical activity
- diabetes
- increased alcohol intake or binge drinking
- psychosocial stress and depression
- cardiac causes, and
- ratio of apolipoproteins B to A1.

Modification of these risk factors could potentially lead to a dramatic reduction in incident stroke.

## TIA AND STROKE

In a large population-based study, Hackam and colleagues found that one out of eight stroke patients had a prior TIA.<sup>2</sup> A prior TIA was associated with a reduction in hospital mortality, in-hospital cardiorespiratory arrest, seizure occurrence, and a favorable outcome supporting the hypothesis of ischemic preconditioning.

Johnston and colleagues found that 10.5% of patients who presented with TIA returned within 90 days because of stroke, half of which were in the first two days.<sup>3</sup> Five factors associated with stroke risk included age greater than 60, diabetes mellitus, symptom duration longer than ten minutes, weakness, and speech impairment.

From this study and another in the United Kingdom, the ABCD2 score was developed [Age greater than 60 (one point), Blood pressure 140/90 mmHg or greater (one point), clinical feature of unilateral weakness (two points) or speech impairment without weakness (one point), Duration greater than 60 minutes (two points) or ten to 59 minutes (one point), and Diabetes (one point)]. Scores greater than four are associated with the greatest risk of recurrence.

Both the SOS-TIA study<sup>4</sup> conducted in France and the EXPRESS study<sup>5</sup> conducted in the UK showed an 80% reduction in expected stroke risk with rapid evaluation (e.g. carotid imaging, telemetry within 24 hours) and treatment (carotid stenosis repair, warfarin for atrial fibrillation within a few days, statins for elevated LDL).

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**Anticoagulation is generally recommended for an ABCD2 score of greater than two and no anticoagulation is recommended for a score of zero.**

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## ATRIAL FIBRILLATION

CHADS2 is a six-point score (range zero to six) in patients with atrial fibrillation with points assigned as follows: Congestive heart failure (one point), Hypertension (one point), Age greater or equal to 75 years (one point), Diabetes mellitus (one point), previous Stroke/transient ischemic attack (two points). Higher scores are associated with greater risk for stroke. Anticoagulation is generally recommended for a score of greater than two and no anticoagulation is recom-

mended for a score of zero. Uncertainty exists about anticoagulation of patients with a score of one.

The CHA2DS2VASc score was developed to help distinguish those with higher versus lower risk in the CHADS2 category of zero to one. The scores range from zero to nine with the following point assignment: [Congestive heart failure (one point), Hypertension (one point), Age greater or equal to 75 years (two points), Diabetes mellitus (one point), previous Stroke or transient ischemic attack (two points), Vascular disease i.e. CAD (one point), Age 65-74 years (one point), Sex category (one point for female gender). A CHA2DS2VASc score of zero to one predicts a lower risk of future stroke than does a CHADS2 score of zero to one.

Based on randomized trials, the risk of stroke following atrial fibrillation can be reduced by treatment with all of the following medications (approximate relative risk reductions noted with the caveat that there have been no direct trial comparisons between dabigatran, apixaban, and rivaroxaban): dabigatran 75%, apixaban 70%, rivaroxaban 60%, warfarin 60%, aspirin and clopidogrel 30%, and aspirin 20%. The absolute differences in clinical trials are as follows: dabigatran versus warfarin 1.11% per year versus 1.69% per year (Re-LY trial), rivaroxaban versus warfarin 2.1% per year versus 2.4% per year (ROCKET-AF trial), apixaban versus warfarin 1.27% per year versus 1.60% per year (ARISTOTLE trial), apixaban versus aspirin 1.6% per year versus 3.7% per year (AVERROES trial), clopidogrel plus aspirin versus warfarin 5.60% per year versus 3.93% per year (ACTIVE-W trial), clopidogrel plus aspirin versus aspirin 6.8% per year versus 7.6% per year (ACTIVE trial).

The different absolute annual risks in each trial reflect the different patient populations included (i.e. mean CHADS2 scores were higher in some trials) and different outcome measures (i.e. stroke versus stroke, myocardial infarction, and death). Intracranial hemorrhage is less

with dabigatran, apixaban, and rivaroxaban as compared with warfarin. Caution should be used with dabigatran in patients age greater than 80 years because of the risk of life-threatening gastrointestinal hemorrhage.

## UNHELPFUL STROKE TREATMENTS

### Long-term dual anti-platelet therapy

Not only does the combination of clopidogrel and aspirin for 18 months or more not reduce the risk of stroke, there is also an increased risk of major bleeding, as demonstrated in the MATCH and CHARISMA studies. At this time, the only solid evidence supporting combination treatment is for one year after cardiac stent and for at least six weeks after carotid stent placement.

### Immediate anticoagulation with heparin or heparinoid products for most stroke patients

A meta-analysis of trials by the Cochrane collaboration found no evidence that immediate anticoagulation reduced the risk of death or dependency at the time of follow-up.<sup>6</sup> Though there were fewer ischemic strokes, this result was offset by an increase in intracranial hemorrhage. The HAEST trial showed no benefit of immediate anticoagulation with dalteparin (a low molecular weight heparinoid) in patients with acute stroke and atrial fibrillation. The RAPID trial<sup>7</sup> enrolled 67 patients within a mean of 6.9 hours of stroke and found a suggestion of benefit for very early anti-coagulation but no additional studies have been performed. Patients with cerebral venous thrombosis probably do benefit from immediate anticoagulation (even in the setting of hemorrhage) based on small randomized trials.

### Intentional blood pressure lowering in the first week after stroke

The SCAST study compared candesartan with placebo in the first week after stroke.<sup>8</sup> After seven days, mean systolic blood pressure was 5 mmHg lower in the candesartan group (147 versus 152). At six months, there was no difference in the risk of stroke, myocardial infarction, or death but functional outcomes were about 17% worse in the candesartan group. Hypotension and renal failure were more common

with candesartan. Unless another medication that lowers blood pressure can be shown to improve outcomes, intentionally lowering the blood pressure in the first week after stroke should be avoided unless it poses a potential risk to the patient (e.g. systolic blood pressure greater than 180 mmHg in tPA patients and 220 mmHg in non-tPA patients). For patients known to be compliant with anti-hypertensives prior to stroke, it is reasonable to resume medications to avoid rebound hypertension.

### 100% oxygen therapy in acute stroke

A systematic review and meta-analysis of oxygen therapy in myocardial infarction concluded there was insufficient evidence to recommend routine supplemental oxygenation. In fact, one study showed a significantly increased risk of death. A quasi-randomized Norwegian study of acute stroke patients found that 100% oxygen therapy was associated with reduced survival at one year, particularly in mildly or moderately affected patients.<sup>9</sup> The SOS pilot study suggested more improvement at the end of one week in patients receiving 2L of oxygen by nasal cannula but there were baseline imbalances in the groups.<sup>10</sup> The pivotal Stroke O2 Study is now ongoing (<http://www.so2s.co.uk>).

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## Disclosure of Financial Interests

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