Understanding Risks – Assessing Therapeutic Options and Individualising Treatment According to Patient Needs

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Individualised Treatment Considerations in Stroke Prevention

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This article serves as an introduction to the problems and potential benefits of trying to target stroke treatments at individuals rather than simply prescribing a one-size-fits-all regimen. There are a range of opinions on whether it is possible to genuinely target treatments at individuals or if it will always be the case that doctors have to rely on group data from large clinical trials. Individualising treatment is not a new concept. In 1320 Henri de Mondeville wrote in his *Chirurgie*: "Anyone who believes that anything can be suited to everyone is a great fool, because medicine is practised not on mankind in general, but on every individual in particular." However, others have argued that "…it would be unfortunate if desire for the perfect (i.e. knowledge of exactly who will benefit from treatment) were to become the enemy of the possible (i.e. knowledge of the direction and approximate size of the effects of treatment of wide categories of patient)."[1] Nevertheless, there have been attempts to try to bring these extremes of view together to find the middle ground:[2]

"Some argue that when large randomised controlled trials are performed, the effects of most medical interventions are relatively modest, and that very large pragmatic trials with broad entry criteria are therefore necessary to have the statistical power even to quantify these modest overall effects reliably. Others argue that the effects of treatment are often so modest precisely because the trials are performed in such heterogeneous populations of patients, and that stratification into less heterogeneous clinical subgroups or risk groups is necessary."

There are several reasons why targeting treatments may be necessary. Differences in treatment effects between subgroups or individuals may be due to differences in the absolute risk of a poor outcome without treatment or to differences in risk of complications of treatment, differences in underlying pathology (stroke is a good example of a clinical syndrome with multiple underlying pathologies that do not all respond in the same way to treatment) and differences in severity of disease, natural history of disease, stage of disease (i.e. symptomatic versus asymptomatic), and treatment effect may depend on the timing of treatment in relation to clinical events.[3] However, while the theoretical benefits of targeting treatments in this manner may be accepted, reliable data on likely effects of treatment in subgroups or individuals are not always available. N-of-1 trials are not possible for most interventions and so clinicians must extrapolate from grouped data using either subgroup analysis or risk modelling. Rarely, multiple different trials are performed in different groups of patients with specific indications, as was the case with clopidogrel, in which case the overall trial results can be used to explore any heterogeneity of treatment effect.

Subgroup Analysis

Subgroup analysis is often criticised as it can produce chance findings with low reliability. An oft-cited example is from the Second International Study of Infarct Survival (ISIS-2), detailing the effect of acetylsalicylic acid (ASA) in acute myocardial infarction (MI) by birth sign. It would appear from this analysis that ASA is highly effective for people born under most birth signs, but ineffective in those born under Libra and Gemini (see *Table 1*).[4,5] However, this example is a little unfair. The researchers simply combined the two (non-adjacent) birth signs that happened to have the least treatment effect. A formal test of subgroup–treatment effect interaction across all 12 signs of the zodiac, which would be the only appropriate analysis, would show no statistically significant heterogeneity. However, there are genuine examples of subgroup analyses that were considered to be potentially genuine when first reported but that were shown not to be true. These include the findings that:[3]

- ASA is ineffective in women;
- antihypertensive treatment is ineffective for primary prevention in women and in the elderly;
- beta-blockers are ineffective after acute MI in the elderly and in patients with inferior MI;
- thrombolysis is ineffective more than six hours after acute MI and in patients with a previous MI; and
- tamoxifen is ineffective in women with breast cancer below 50 years of age.

However, although some of these subgroup observations did show a statistically significant subgroup–treatment effect interaction, none was pre-defined. *Post hoc* subgroup analysis is analogous to betting on a horse after the race has finished. If completed correctly with subgroups defined in advance and with appropriate tests of statistical significance, subgroup analysis is a reliable tool.

Subgroups in Stroke

Stroke is a very heterogeneous clinical syndrome. Using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification,[6] approximately 15% of stroke cases are cardioembolic, 15–20% are caused by large-artery disease (thromboembolic or haemodynamic), 20% by small-vessel disease, 5–10% are 'other' (dissection, venous, genetic or cerebral amyloid arteriopathy) and 40% are undetermined. There are many examples of treatment that affect the subtypes differently. For example, warfarin is a good treatment option for cardioembolic stroke or patients with atrial fibrillation (AF), but is harmful in patients with small-vessel disease. Even within particular subtypes there is evidence that treatment should be tailored to individuals. For example, there is the question of whether blood pressure should be treated in patients with severe carotid occlusive disease. For the majority of patients with symptomatic carotid stenosis, the risk of suffering a stroke increases with blood pressure. This relationship holds in patients with only unilateral severe carotid stenosis or occlusion, but is reversed in patients with bilateral >70% carotid stenosis or occlusion, suggesting that aggressive blood pressure lowering may be harmful in this group.[7]

More subtle physiological differences can also influence the effects of treatments. For example, there are differences between the sexes in the pathology of atherosclerotic plaques. Women tend to have smooth stenoses with fibrous caps and occasional endothelial erosion, whereas men are more likely to have thin fibrous caps and ruptured plaques. Therefore, the expectation is that carotid endarterectomy (CEA) for asymptomatic stenoses will be less effective for women then for men, and the data reflect that. Subgroup analysis of the Asymptomatic Carotid Surgery Trial (ACST) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) show that benefit of CEA at five-year follow-up is confined to men, with a statistically significant subgroup–treatment effect interaction (see *Figure 1*).[8]

> *There is increasing evidence that the risks and benefits of treatments used in stroke medicine do differ between subgroups and individuals.*

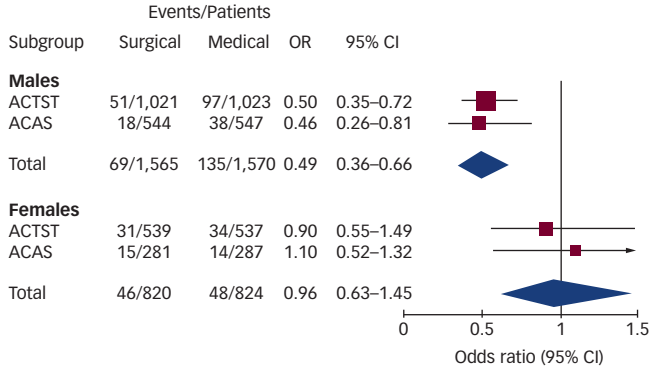
However, subgroup analyses do not usually show significant heterogeneity. In fact, they often disprove firmly held *pre hoc* hypotheses that a particular group will benefit more or less than others. For example, clinicians expected that CEA would be less effective in patients with lacunar stroke than in those with apparently thromboembolic events. However, a subgroup analysis of data from the Carotid Endarterectomy Trialists' Collaboration (CETC) showed a greater reduction in risk of recurrent stroke in patients randomised after a lacunar transient ischaemic attack (TIA) or stroke.[9] Therefore, subgroup analysis is often useful in preventing clinicians from targeting treatments too narrowly. Subgroup analysis is perhaps most useful not in identifying differences in responsiveness to treatment between different pathological or physiological groups, but in identifying more mundane interactions with factors such as the urgency with which treatment is given or the stage of disease at which it is used. For example, the benefits of CEA in patients with symptomatic carotid stenosis falls rapidly with delay from the presenting TIA or stroke to surgery.[10]

Table 1: Chance Findings in Subgroups

Astrological Birth Sign	Deaths		2P
	ASA	Placebo	
Libra or Gemini	150	147	NS
All other signs	645	869	<0.000001

ASA = acetylsalicylic acid; NS = not significant.

Figure 1: Effect of Endarterectomy for Asymptomatic Carotid Stenosis on the Risk of Any Stroke and Operative Death by Sex



ACTST = Asymptomatic Carotid Surgery Trial; ACAS = Asymptomatic Carotid Atherosclerosis Study; OR = odds ratio; CI = confidence interval. Adapted from Rothwell et al., 2004.[8]

Absolute Risk

It is a commonly held misconception that the overall result of a trial is a good measure of treatment in the average patient. In fact, the truth is sometimes diametrically opposite: the overall results are more often driven by the effect of treatment in a small number of high-risk individuals.[11] The average patient often provides very little information; they are often relatively low-risk and therefore contribute few events to the trial outcome. This effect is often seen when trial populations are stratified according to their predicted baseline risk. Such stratification is particularly helpful when the trial treatment itself has a risk of complications, such that treatment may not be justified in patients who have a low risk of a poor outcome without treatment.

By contrast, high-risk patients are most likely to benefit from more aggressive treatment, and there are several situations in stroke medicine in which it is possible to use validated risk scores to identify such individuals. For example, the ABCD2 score can be used to identify patients at high risk of stroke after a TIA.[12,13] A validated score is available to identify high-risk patients with symptomatic carotid stenosis,[11] and the CHADS score is widely used in patients with AF.[14] In primary prevention, the Framingham risk model is widely used to predict the 10-year risk of stroke. When trial results are stratified using such risk scores, it is sometimes possible to demonstrate increases in both relative and absolute risk reduction with increasing baseline risk.[11,15]

Summary and Conclusions

There is increasing evidence that the risks and benefits of treatments used in stroke medicine do differ between subgroups and individuals. More effort needs to be made to identify differences between pre-defined clinically important subgroups and to determine the effects of stratification of trial populations by predicted baseline risk of stroke and/or other important outcomes. ■

Clinical Assessment of Polyvascular Risk Patients

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REACH Registry Reveals High Event Rate with Cerebrovascular Disease

Based on the Reduction of Atherothrombosis for Continued Health (REACH) registry, the three-year event rate of stroke, MI and vascular death (VD) for patients with cerebrovascular disease is 15%, which is higher than many people expect. This is the highest rate of stroke/MI/VD for any disease bed, including coronary artery disease (CAD) and peripheral arterial disease (PAD). However, also according to REACH, patients with PAD have the highest rate of vascular disease hospitalisations for events other than stroke/MI/VD.[16]

Stroke – The Third Leading Cause of Death Worldwide

These data highlight the global burden of vascular disease. Coronary heart disease (CHD) and stroke kill millions of patients each year. CHD is the leading cause of death worldwide and is responsible for 13% of all global deaths, killing 3.8 million men and 3.4 million women each year. Stroke is the second or third leading cause of death worldwide, accounting for 10% of all deaths (3 million women and 2.5 million men each year).[17] There are limited interventions currently available for each of these conditions; therefore, the best strategy is prevention.

High Prevalence of Modifiable Risk Factors for Ischaemic Stroke in the General Population

There is a high prevalence of modifiable risk factors for ischaemic stroke in the general population. Hypertension is most common, with a prevalence of 25–40%, followed by elevated total cholesterol (>240mg/dl; 6–40%), smoking (15–20%), physical inactivity (25%), obesity (18%), asymptomatic carotid stenosis (>50%; 2–8%), alcohol consumption (more than five drinks per day; 2–5%) and AF (1–4% depending on age).[18] All of these factors carry a very high relative risk of stroke. This is the primary opportunity to intervene: to identify the patients with each of these risk factors and treat them.

High Incidence of Hypertension, Smoking and Diabetes Among Stroke Patients in the PRoFESS, ECASS-III and FASTER Studies

The importance of these risk factors can be assessed by their prevalence in some of the largest and most recent stroke studies. In the Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) trial, 74% of subjects had hypertension, 47% had hyperlipidaemia, 28% had diabetes and 16% had CAD with ischaemia.[19] In the European Co-operative Acute Stroke Study III (ECASS-III), 62% had hypertension, 29% were smokers and 15% had diabetes.[20] There is a similar profile of subjects in TIA studies. In the Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence (FASTER) trial, 50% of subjects had hypertension, 25% were smokers, 12% had diabetes, 9% had a history of MI or CAD and 8% had hyperlipidaemia.[21] In fact, typical TIA or stroke patients have high rates of these risk factors.

The Health Improvement Network Database Shows Diabetes, Hypertension and Blood Pressure Regimen Are Stroke Risk Factors

Within the general population there are also prevalent risk factors. The Health Improvement Network (THIN) is a large UK medical records database containing information from UK general practitioners. Data from 1983 to 2003 included 255 practices and 4.78 million patients, 2.26 million of whom were followed prospectively.[22] Within the THIN database, three conditions were found to be risk factors for stroke: diabetes, hypertension and being on a blood pressure regimen (see *Table 2*).

Other Vascular Beds

Ischaemic Stroke Patients Have a High Risk of Other Atherothrombosis Manifestations

A high percentage of patients with ischaemic stroke already have vascular disease in another bed. In the Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment (DETECT) survey, 753 patients admitted for ischaemic stroke were assessed for evidence of disease in other vascular beds: CAD, aortic atheroma or PAD. Of those admitted, 262 (34.8%) had one other manifestation of atherothrombosis, 81 (10.8%) had two other manifestations and 15 (2%) had three.[23] These other forms of vascular disease may not be immediately apparent; it behoves a physician to look for these other issues, particularly in high-risk individuals.

Ischaemic Stroke Patients Have an Increased Risk of Myocardial Infarction and Vascular Death

Ischaemic stroke patients are at an increased risk of MI and VD over time. The Northern Manhattan Stroke Study (NoMaSS) included 655 first-time ischaemic stroke patients. Cumulative rates of MI or VD were 8.2% after one year, 14.5% after three years and 17.4% after five.[24] Data concerning long-term mortality with vascular causes from three different populations in three different parts of the world are shown in *Figure 2*.

Stroke survivors are at an increased risk of dying following the incident stroke compared with the general population. Although the mortality risk is greatest during the first 30 days following a stroke, the risk persists for several years. The excess risk of dying has been attributed to vascular disease, specifically recurrent stroke and other cardiovascular conditions. In fact, stroke survivors are twice as likely to die from cardiovascular events (including MI) as from stroke events after the incident stroke. Therefore, they may also benefit from antiplatelet therapy.[25–27]

Myocardial Function Is Frequently Followed by Ischaemic Stroke

The reverse is also true and stroke is relatively common following an MI. A study of more than 2,000 patients hospitalised for MI and followed for a median of 5.6 years showed that the risk of stroke in the first month is 44 times higher than for the population as a whole. It remains two to three times higher for the three years after MI.[28] A meta-analysis investigated how common stroke is while in hospital following an MI. For all studies included, the rate was 14.5 strokes per 1,000 MI patients (95% confidence interval [CI] 11.7–17.9).[29] Given that millions of people are hospitalised worldwide each year for MI, this means that there is a risk of hundreds of thousands of strokes.

Stroke Risk Scores Predict One-year Risk of Recurrence and Cardiovascular Events

The Essen Stroke Risk Score (ESRS), developed by Joachim Röther, was derived from Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) population and validated in the European Stroke Prevention Study 2 (ESPS-2) population. The aim of the ESRS was to predict one-year risk of recurrent stroke and other cardiovascular events. It is calculated using age, presence of hypertension, diabetes, prior MI, cardiovascular disease (CVD), PAD, smoking status and prior TIA/stroke. The study showed that as the ESRS increases, so do the risks of suffering a stroke and all cardiovascular events combined. With the highest ESRS of more than six, the risk of having an event is 8–10% in one year.[30]

Extending the REACH Registry

Projections on REACH Data Provide an International Perspective on Vascular Disease, Risk and Management Methods

The primary objective of the REACH registry is to gain an international perspective of patients with or at risk of vascular disease and to see how they were managed: what their event rates are over time, what medications they take and what their outcomes are. It was designed to overcome limitations of previous surveys and be the most globally inclusive and geographically extensive registry of patients at high risk of atherothrombotic events, including a broad spectrum of patient types in a 'real-world' setting.[31] It started with 68,375 patients, with 95% retention at one year. At one year, the primary end-point of stroke, MI or VD had a rate of 4.2% for the whole population and 4.7% for the symptomatic population: double the rate for the group that only had multiple risk factors (see *Table 3*). If hospitalisation for an atherothrombotic event is included, this figure exceeds 14% in the symptomatic group (see *Table 3*).[32] Extrapolated over patients worldwide, this amounts to millions of events each year.

REACH Contrasts Event Rates in Single versus Multiple Vascular Beds

The REACH data can also be used to compare event rates in people with disease in one vascular bed with multiple vascular territories. Using the same end-points of stroke/MI/VD, the rates are 4.1% for a single bed and 7.1% for multiple beds. With hospitalisations added in, the event rate jumps from 12.6% in one bed to >21% in multiple beds. Overall, the risk of a major adverse cardiovascular event increases in line with symptomatic arterial bed involvement (see *Figure 3*).[32] Data from REACH[33] out to three years show event rates continuing to climb in the population, with approximately one-quarter of all subjects suffering a cardiovascular event or hospitalisation. Again, disease in more than one vascular bed was significantly more likely to lead to an event than disease in just one bed.[33] This is a tremendous public health burden that needs to be brought under control.

Summary and Conclusions

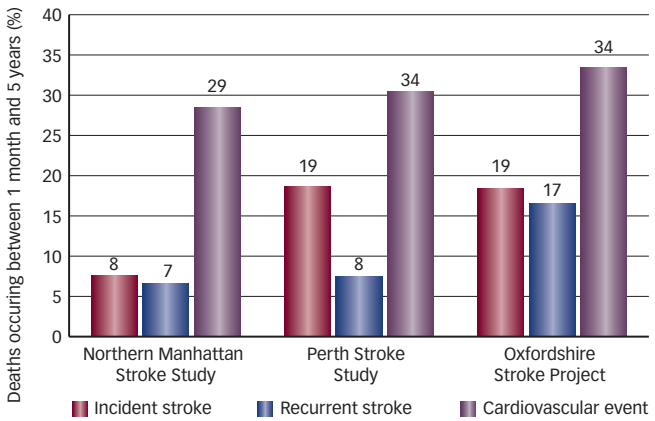
Patients with stroke and TIA have extremely high rates of vascular risk factors. Having symptomatic disease in more than one vascular bed significantly increases the risk of having subsequent events. Improved and more aggressive use of current medications – and continued investigation of new ones – is important if future vascular events are to be prevented. The best way to treat stroke is to prevent stroke. The prevention of vascular events is therefore the best approach to treatment. ■

Table 2: Stroke Factors in The Health Improvement Network Study

	Odds Ratio (95% CI)	
	Adjusted For Matching Variables	Fully Adjusted
Diabetes	2.06 (1.92–2.13)	1.90 (1.76–2.05)
Hypertension	1.59 (1.51–1.67)	1.46 (1.39–1.54)
BP medications	1.50 (1.43–1.58)	1.24 (1.18–1.31)

BP = blood pressure; CI = confidence interval. All The Health Improvement Network (THIN) practices combined n= 44,434: 20,172 males; 24,262 females; 22,217 cases with stroke. Adapted from Lewis et al., 2007.[22]

Figure 2: Long-term Mortality Due to Vascular Causes in Stroke Patients



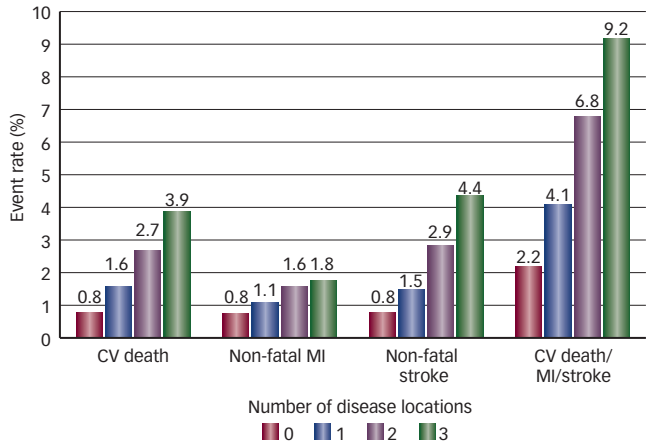
Adapted from Hartmann et al., 2007, Hankey et al., 2000 and Dennis et al., 1993.

Table 3: One-year Cardiovascular Event Rates in REACH

	Population (%)		
	Total (n=64,977)	Symptomatic (n=53,390)	Multiple RF Only (n=11,766)
Death (all-cause)	2.6	2.8	1.5
CV death	1.7	1.8	0.8
Non-fatal MI	1.1	1.2	0.8
Non-fatal stroke	1.7	1.9	0.8
CV death/MI/stroke	4.2	4.7	2.2
CV death/MI/stroke/ hospitalisation for atherothrombotic events	12.8	14.4	5.3

RF = risk factors; MI = myocardial infarction; CV = cardiovascular. Adapted from Steg et al., 2007.[32]

Figure 3: One-year Event Rates and Number of Disease Locations



MI = myocardial infarction; CV = cardiovascular. Adapted from Steg et al., 2007.[32]

The ACTIVE A Study – An Alternative to Warfarin for Patients with Atrial Fibrillation

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It is useful to put new therapies for cardioembolic stroke with AF in context alongside established therapies. A meta-analysis by Hart et al., which was initially published in 1999 and re-analysed in 2007, looked at all trials of antithrombotic therapies in AF with an end-point of ischaemic stroke, haemorrhagic stroke and subdural haematomas. There were three groups of studies: warfarin versus control, which showed a risk reduction of 64%; ASA versus control, which showed a 19% risk reduction; and warfarin versus ASA, with a 39% risk reduction (see *Table 4*).[34]

There are patients who for a variety of reasons cannot take warfarin, and ACTIVE A investigated whether clopidogrel plus acetylsalicylic acid is a reasonable alternative for these patients.

A number of guidelines have been published based on these studies. For example, the guidelines from the American Heart Association (AHA), the American College of Cardiology (ACC) and the European Society for Cardiology (ESC) on antithrombotic agents for AF were published in 2006. The message of these is that the therapy must be individualised depending on the risk–benefit patterns for each patient. The risk factors for stroke are the basis of the $CHADS_2$ risk factor score and include age >75 years, hypertension, heart failure, diabetes and previous stroke or TIA. Previous stroke or TIA contribute a score of two points, while the others contribute one point. In a patient having no risk factors, where the risk of stroke is small, ASA will suffice. In a patient with a $CHADS_2$ score of one, either ASA or warfarin is recommended. With a $CHADS_2$ score of two or more, or any other high-risk factor (mitral stenosis or prosthetic heart valve), warfarin is recommended.[35]

Dual Antiplatelet Therapy

Platelets are known to be involved in the thrombotic complications of AF. Platelet function studies in AF patients show increased platelet activation. ASA alone modestly reduces the risk of stroke in AF (by around 19%).[34] In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study,[36] the addition of clopidogrel to ASA was shown to suppress platelet activity more than ASA alone, and a combination of these two agents in patients with acute coronary syndrome (ACS) reduced future coronary events by 20%. ASA with clopidogrel is now the standard therapy for patients post-ACS and for patients with stents.

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) was a phase III multicentre, multinational, parallel, randomised, controlled evaluation of clopidogrel plus ASA with factorial evaluation of irbesartan for the prevention of vascular events in patients with AF. The study started after the CURE study ended. The ACTIVE study consisted of three separate but related trials: ACTIVE W (clopidogrel plus ASA versus warfarin; n=6,706), ACTIVE A (clopidogrel plus ASA versus ASA alone; n=7,554) and ACTIVE I (irbesartan versus placebo; n>10,000).

End-points of ACTIVE W were stroke, non-central nervous system (CNS) systemic embolism, MI and VD. Results were presented in 2006, and showed that patients on dual antiplatelet therapy have a worse outcome than patients on oral anticoagulant therapy, with a relative risk of 1.44 (p=0.0003). Owing to clear evidence of the superiority of warfarin, the trial was stopped early after 1.25 years. ACTIVE W concluded that, for patients who can take warfarin, it is a preferable therapy over clopidogrel plus ASA.[37] There are patients who for a variety of reasons cannot take warfarin, and ACTIVE A investigated whether clopidogrel plus ASA is a reasonable alternative for these patients.[38] The hypothesis is that in patients with AF who are unsuitable for warfarin, the addition of clopidogrel to ASA would reduce the risk of vascular events with an acceptable risk of bleeding.

The eligibility criteria for ACTIVE A were identical to those of ACTIVE W: documented AF, one or more risk factor for stroke and absence of major risk factors for bleeding. The assessment of a patient's suitability for ACTIVE W versus ACTIVE A was left to the investigators. Of those enrolled into ACTIVE A, half were deemed inappropriate for warfarin by the physician and 23% had a relative risk for bleeding (including predisposition to falling, persistent high blood pressure, previous serious bleeding on warfarin, severe alcohol abuse, peptic ulcer disease and thrombocytopenia), while the remainder of patients simply decided they did not want to take warfarin. All patients in ACTIVE A received ASA at a low level (75–100mg), then were randomised to receive either clopidogrel or placebo. Most of the baseline demographics were the same for ACTIVE A as for W, except the baseline use of warfarin and ASA. The mean age of the patients was 71 years and the mean $CHADS_2$ score was 2.0.

The hypothesis is that in patients with atrial fibrillation who are unsuitable for warfarin, the addition of clopidogrel to acetylsalicylic acid would reduce the risk of vascular events with an acceptable risk of bleeding.

Results

Over more than four years, the primary outcome (stroke, MI, systemic embolism or VD) was lower in the group assigned to clopidogrel plus ASA, with a relative risk/hazard ratio of 0.89 (p=0.014; 95% CI 0.81–0.98). This difference was driven primarily by a reduction in the incidence of stroke, with a relative risk of 0.72 (p=0.00002; 95% CI 0.62–0.83). The curves showing cumulative incidence of stroke for the two groups diverge before one year and are still separating at four years (see *Figure 4*).[38]

The addition of clopidogrel to ASA effectively reduces the primary event rate from 7.6% per year to 6.8%, and reduces the stroke rate from 3.3 to 2.4% per year (a 28% risk reduction). There is also a non-significant trend to a lower MI rate (from 0.9 to 0.7%; p=0.08). The rates of VD and non-CNS systemic embolism were unchanged.

Different types and severity of strokes were also investigated. The greatest reduction is in the number of ischaemic strokes (this category also included strokes of uncertain type), from 3.2% per year to 2.1%: a relative risk of 0.68 (p<0.001). Haemorrhagic strokes showed a trend to increase, but this was non-significant (p=0.27) (see *Figure 5*).[38] It should be noted that the reduction in stroke rates was seen in both non-disabling strokes and disabling or fatal stroke categories. Thus, this combination therapy is effective in all types of stroke.

As with any antithrombotic therapy, the advantage of a lower clotting risk is always balanced by an increased risk of bleeding; the question is, how much? In the ACTIVE programme, definition of major bleeding was either an overt bleed requiring ≥2 units of transfusion or a severe bleed, for example one that caused a drop in haemoglobin of ≥5 gm/dl or was fatal. Within ACTIVE A the addition of clopidogrel to ASA caused the major bleeding rate to increase from 1.3 to 2.0% per year, a relative risk of 1.57 (95% CI 1.29–1.92; p<0.001). The rate of severe bleeds had the same relative risk outcome. Both intracranial and extracranial bleeds increased, with relative risks of 1.87 (p=0.006) and 1.51 (p<0.001) respectively. The majority of the extracranial bleeds were gastrointestinal (GI)-based.

In terms of the overall risk and benefit, treating 1,000 patients for three years using clopidogrel plus ASA will prevent 28 strokes (including 17 fatal or disabling) and six MIs. By contrast, there will be an extra 20 non-stroke major bleeds, three of which will be fatal.

It is not possible to compare this regimen directly with warfarin, but using the results from a meta-analysis of warfarin trials it is possible to see the relative effects of the two therapies. Warfarin versus ASA has a relative risk reduction of 38% for stroke, but an increase of 128% for intracranial bleeds and 70% for extracranial bleeds (see *Table 5*). While clopidogrel plus ASA is less effective than warfarin in preventing stroke, with only a 28% risk reduction, it also causes fewer bleeds. This emphasises the need to individualise treatment to ensure that patients have the most effective therapy with the lowest risk for their disease.

Summary and Conclusions

For most patients with AF, the recommended antithrombotic therapy is warfarin. Nevertheless, for those unable or unwilling to take warfarin, there is now an alternative. The addition of clopidogrel to an ASA regimen does reduce major vascular events, primarily through reduction in stroke. There is an increase in major bleeding as a side effect, but as it is less than that with warfarin, this will be an acceptable risk for many patients.

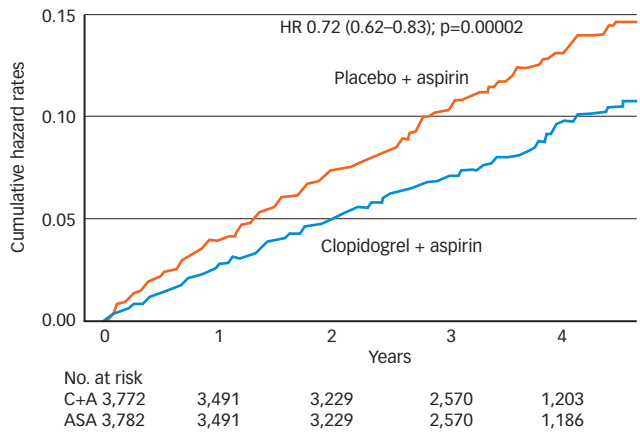
For each patient it is important that the physician make an individual risk–benefit assessment regarding choice of therapy. The results of the ACTIVE A trial will affect the way that cardiologists and other physicians prescribe antithrombotic therapy for AF. ■

Table 4: Meta-Analysis of Antithrombotic Therapy Trials to Prevent Stroke in the Atrial Fibrillation Population

	No. Trials	No. Patients	No. Strokes*	Relative Risk Reduction (95% CI)
Adjusted-dose warfarin versus control	6	2,900	186	64% (49–74)
ASA versus control	7	3,990	388	19% (1–35)
Warfarin versus ASA	9	4,620	330	39% (19–53)

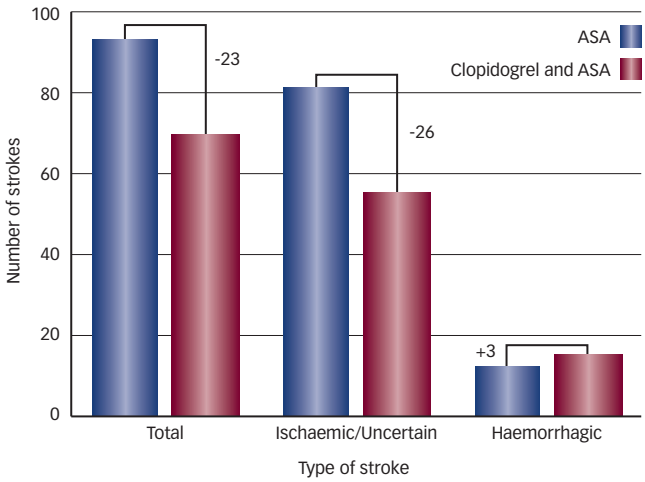
*ASA = acetylsalicylic acid; CI = confidence interval. *Ischaemic strokes, haemorrhagic strokes and subdural haematomas. Adapted from Hart et al. 2007.*[34]

Figure 4: Difference in Stroke Risk in ACTIVE A



ASA = acetylsalicylic acid. Adapted from Connolly et al. 2009.[38]

Figure 5: Number of Fatal Strokes Prevented



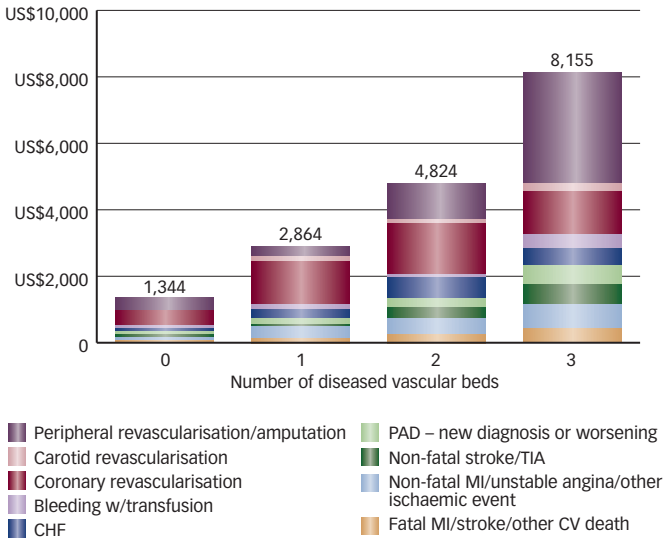
ASA = acetylsalicylic acid. Adapted from Connolly et al., 2009.[38]

Table 5: Safety Outcomes for Major Antithrombotic Comparisons by Treatment Regimen

Effects	Warfarin versus ASA Meta-analysis* (RRR)	Clopidogrel + ASA versus ASA ACTIVE A (RRR)
Reduction in stroke	–38%	–28%
Increase in intra-cranial bleed	+128%	+87%
Increase in extra-cranial bleed	+70%	+51%

RRR – relative risk reduction; ASA = acetylsalicylic acid. Adapted from Hart et al., 2007.[34]

Figure 6: One-year Hospitalisation Costs by Number of Vascular Beds



CHF = chronic heart failure; PAD = peripheral artery disease; TIA = transient ischaemic attack; MI = myocardial infarction; CV = cardiovascular. Adapted from Mahoney, 2008.[52]

Three Stroke Case Studies

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This article will present three clinical scenarios, each of which concentrates on a different aspect of the role of antithrombotic therapy in stroke prevention.

Acetylsalicylic Acid Resistance

The first patient is a 68-year-old male with sudden onset of dysphasia. He has a past history of TIA and hypertension, which he has been treated for, and has occasional falls. He is an ex-smoker. His current regimen is ASA 75mg daily and antihypertensive medication (angiotensin-converting enzyme [ACE] inhibitor, ramipril). His blood pressure is towards the high end of the acceptable range at 145/80mmHg.

One interpretation of these data are that this patient has ASA resistance. However, the definition of ASA resistance is controversial. It can be defined in two ways: clinically, e.g while taking ASA a patient has another cerebrovascular event; or empirically, by measuring biochemical, functional and genetic markers, e.g. by assessing bleeding time or platelet function.

Assessments of platelet function are quite difficult and there are a variety of methodologies. These different definitions and measurements for ASA resistance lead to a reported frequency in the range of 5–45%.[39]

Treatment Options

The treatment options for this patient include increasing his daily dose of ASA to 300mg, switching him to a regimen of dipyridamole or clopidogrel, either with or without concomitant ASA, or switching him to warfarin monotherapy.

A variety of studies have investigated adding dipyridamole to ASA, which according to meta-analyses leads to a relative risk reduction of 3–16%. The European Stroke Prevention Study 2 (ESPS-2) specifically set out to compare the use of ASA with or without dipyridamole in high-risk patients, and concluded that there is an additive effect of dipyridamole on top of ASA.[40] However, ESPS-2 used dipyridamole 200mg twice a day but only 25mg of ASA twice a day. A dose of only 50mg per day for ASA is considered to be quite low, thus throwing some doubt on the conclusions of the trial.

The Antithrombotic Trialists' Collaboration (ATTC) reviewed 25 studies of ASA in combination with dipyridamole conducted before 1997. The authors of the ATTC meta-analysis concluded that the addition of dipyridamole to ASA failed to clearly demonstrate additional reductions in serious vascular events.[41] This was also the conclusion of a later Cochrane review.[42] However, the data in these meta-analyses are largely from studies conducted with the standard-release preparation of dipyridamole. The modified-release preparation may reduce the frequency of headache, diarrhoea, nausea and vomiting, but there is a question as to whether the presence of these side effects still outweighs the therapeutic benefits. The UK's National Institute for Health and Clinical Excellence (NICE) is the only body to recommend this combination therapy.[43]

In an attempt to conclusively determine the benefit of this combined regimen, the European–Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) compared 1,363 patients taking ASA plus dipyridamole 200mg per day with 1,376 patients taking 30–325mg ASA per day alone. The mean follow-up was 3.5 years, and most of the patients were high-risk with a history of stroke or TIA. Results showed that primary outcomes (death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding) were less common with the combination regimen, with a hazard ratio of 0.8 (95% CI 0.66–0.98). When combined with meta-analysis of previous trials, the ESPRIT results lend weight to the conclusion that the combination regimen of ASA plus dipyridamole is preferred over ASA alone as antithrombotic therapy after cerebral ischaemia of arterial origin, with an overall hazard ratio of 0.82 (95% CI 0.74–0.91).[44]

Another aspect to consider is the number of side effects. Headache is a common side effect with dipyridamole. In ESPRIT at five years there were 470 drop-outs (33%) from the combination regimen compared with 184 (16%) from the ASA arm. The main reason for discontinuation was headache. In addition, once again, the dose of ASA given to subjects in ESPRIT was lower than standard recommendations: more than 50% of patients were taking less than 50mg.[44] Therefore, the issue of addition of dipyridamole to ASA is still not conclusively decided.

There is also the option of clopidogrel. The PRoFESS trial compared the twice-daily fixed combination of low-dose ASA 25mg and extended-release dipyridamole 200mg with a once-daily dose of clopidogrel 75mg in 20,332 patients over 1.5–4.4 years. The primary outcome of first recurrence of stroke occurred in 916 patients (9.0%) on the dual antiplatelet therapy compared with 898 (8.8%) on clopidogrel (HR 1.01, 95% CI 0.92–1.11). Many of the outcome measures were close or identical between the two treatment arms, and the authors concluded that the study did not show that either treatment regimen is superior to the other in the prevention of recurrent stroke. In terms of safety, there were more haemorrhagic

events with ASA plus dipyridamole (419 [4.1%]) than with clopidogrel (365 [3.6%]). Furthermore, a greater number of patients discontinued the dual treatment than clopidogrel (1,650 [16.4%] and 1,069 [10.6%], respectively), with headache accounting for the greatest disparity.[45] Therefore, clopidogrel may be considered as a suitable treatment for this patient.

Polyvascular Risk Patient

The second patient is a 67-year-old south Asian female from London. She has non-insulin-dependent diabetes, hypertension, a history of stable angina and some claudication. She has also had a TIA within the last 18 months and is taking ASA 75mg per day. Each of these can be considered to be an independent risk factor, and therefore she is a classic example of a multivascular high-risk patient.

The REACH registry confirms that, despite conventional therapy, the risk of experiencing a major atherothrombotic event or of being hospitalised within one year is much greater if more than one disease bed is involved: 12.6% for single disease bed versus 21.7% for multiple. The highest risk is for patients with CAD, CVD and PAD, at 26.3% (95% CI 23.8–28.7).[32] There is a linear relationship between the number of locations in which disease is present and the risk of subsequent vascular events (see *Figure 3*). Furthermore, within this risk hierarchy the presence of PAD doubles a patient's risk of subsequent vascular events.[32] In the US at least, and almost certainly worldwide, hospitalisation costs also increase with every vascular bed implicated (see *Figure 6*). Therefore, with this second patient it is important that her risk factors are aggressively managed.

Pharmacological Treatment

An aggressive treatment strategy for this patient includes statins to manage her cholesterol. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed that high-dose atorvastatin 80mg/day led to a 16% relative risk reduction in stroke/TIA. The authors of the paper added that stroke and TIA are 'risk equivalents' of CHD.[46] However, despite this, only around 17% of patients who are at high risk of ischaemic stroke are given statin therapy. Moreover, even in a wealthy city such as London, patients from an ethnic minority – in this patient's case, south Asians – are less likely to receive adequate statin treatment.[47] With diabetes, a 1% reduction in glycated haemoglobin (HbA_{1c}) is associated with a relative risk reduction of 21% for any related diabetes end-point.[48] Tight glucose control is likely to achieve good outcomes in stroke, with a target HbA_{1c} of <6.5%.[49] Similarly, there is a log-linear relationship between the relative risk of first stroke and the mean blood pressure. Even in the normotensive range of blood pressure of 75–85mmHg, this relationship holds.[50] Reducing blood pressure by 5mmHg leads to a 42% reduction in stroke risk.[51] Thus, by taking medication to control her cholesterol, glucose levels and blood pressure, this patient can reduce her stroke risk.

Atrial Fibrillation

The final patient is a more typical presentation. An 82-year-old man has a history of TIAs. An examination reveals hypertension and AF. The patient has a relative contraindication to warfarin.

Treatment

Considering the patient's relative contraindication to warfarin, the treatment options include ASA 75mg/day or 300mg/day, ASA plus clopidogrel or warfarin anyway, despite the relative contraindications. As determined in the ACTIVE W trial, warfarin is undoubtedly the recommended treatment for patients with AF who are at high risk of stroke.[37] Nevertheless, the ACTIVE A study showed that in high-risk stroke patients with AF who are unable or unwilling to take warfarin, dual antiplatelet therapy with ASA and clopidogrel is an effective alternative, with a 28% risk reduction for stroke.[37] Therefore, in this patient, the dual antiplatelet therapy would be the first choice of many physicians.

Summary and Conclusions

Several conclusions can be drawn from looking at these three clinical scenarios. First, ASA resistance is an important clinical phenomenon. In these cases it can be beneficial to add dipyridamole, although an alternative option is to use clopidogrel. Second, polyvascular risk patients need to be treated very aggressively in order to minimise their future event rate. Finally, warfarin is the treatment of choice in AF, but in a few patients where warfarin is a relative contraindication, combined antiplatelet therapy of clopidogrel plus ASA is appropriate. ■

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