

ANTIPLATELET AGENTS, ANTICOAGULANTS: NEW MEDICAL STRATEGIES

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The pathogenesis of stroke

Stroke is a heterogeneous condition in which 85% is caused by arterial acute occlusion or ischaemic stroke and 15% blood vessel rupture or cerebral haemorrhage. Of those with ischaemic stroke, further heterogeneity is evident with cerebral ischaemia caused by artery-to-artery emboli, in situ small vessel disease or cardiac emboli. The underlying pathogenesis can usually be determined after considering the clinical phenotype and the results of this series of predominantly image-based investigations. This may result in a classification such as TOAST, whereby about 30% of ischaemic stroke is usually caused by artery-to-artery embolism, 20% by cardiac embolism and about 15% plus more artery disease. Regardless of the underlying cause of vessel occlusion, a common final pathway involves other platelet aggregation and/or stimulation of the coagulation cascade. Hence, preventative strategies are usually focused on these two basic mechanisms.

Secondary stroke prevention

There have been remarkable advances made in secondary stroke prevention beginning with the landmark Canadian co-operatives study in 1978 [1]. Then followed evidence that carotid endarterectomy was beneficial in 1991, anticoagulation in 1993, clopidogrel in 1996, blood pressure lowering in 2001, aspirin plus dipyridamole in 2006 and cholesterol lowering in the same year. For prevention of cardiac embolism strategies have involved anticoagulation, the use of anti-platelet agents or others such as anti-arrhythmics, antihypertensives or statins. We will discuss mainly anticoagulants which may be broadly divided into vitamin K antagonists such as Warfarin, the more recently developed Tecarfarin or the more novel anticoagulants. The latter include direct thrombin inhibitors such as xymelagatran, dabigatran or AZD 0387 or factor X inhibitors. The latter include Apixaban, betrixaban, Edoxaban, Idraparinux, Rivaroxaban and YM 150.

Stroke of arterial origin: as mentioned earlier, the final common pathway in artery-to-artery embolism or small vessel disease is most likely platelet aggregation. This commences with vessel wall injury followed by platelet deposition, platelet activation and recruitment, the development of a throm-

botic plug which in its own right then generates further platelet activation and recruitment. This process may be interrupted by blocking a number of pathways of platelet activation and aggregation which are well described. These include ADP, thrombin, thromboxane A₂, von Willebrand factor receptors or the final common pathway GP IIb/IIIa receptor. There have been numerous trials and of the secondary stroke prevention involving many of these agents. They may be categorised loosely to those involving aspirin versus controls, Trifusal or clopidogrel versus aspirin, clopidogrel versus aspirin, clopidogrel plus aspirin versus clopidogrel, clopidogrel plus aspirin versus aspirin or dipyridamole plus aspirin versus clopidogrel. By indirect comparison, the relative risk reduction versus placebo may reach as high as almost 30%. However, a sobering head-to-head comparison of aspirin plus dipyridamole versus clopidogrel (PROFESS), which showed no real difference between the two, would suggest that the real relative risk reduction for both approaches is only about 20% (see Hanky and Eikelboom, *Lancet Neurology* 2010 for review). Other approaches include the thromboxane A₂ inhibitor Terutroban (ceased 2010), aspirin plus clopidogrel in acute vascular events (POINT, FASTER), stronger ADP and antagonists (Prasugrel), reversible ADP antagonists (Ticagrelor), Factor Xa inhibition (Rivaroxaban, Apixaban), phosphodiesterase inhibition (Cilostazol) or thrombin receptor antagonists such as SCH 530348. In spite of the significant advances that have occurred with antiplatelet and anticoagulant therapy and this category of vascular disease over the last 20 years, the main problems are the sense that a ceiling effect may have been reached with the relative risk reduction of around 20 to 30% of vascular outcomes and the difficulty in balancing any further anticoagulant benefit against the risk of bleeding.

Stroke of cardiac origin

The most common cause of stroke in this category is the presence of atrial fibrillation. This rhythm disturbance sets up a change in flow dynamics with stasis seen in the atrial appendage particularly. This allows the generation of local clot and subsequent embolism to the periphery and brain. Atrial fibrillation is the most common rhythm disturbance and it is estimated that one in four individuals aged 40 years will develop this condition [2]. The prevalence of atrial fibrillation is likely to double within about 30 years [3]. Overall, stroke is increased by approximately 5 fold for those in Atrial fibrillation and this risk is similar for those in either paroxysmal or permanent fibrillation. Stroke due to atrial fibrillation has a 30-day mortality of around 25% and a 12-month mortality of about 50% [4]. There may be up to 3 million people who develop stroke due to atrial fibrillation worldwide each year.

The standard therapy for patients in Atrial fibrillation to prevent embolism has been the use of vitamin K antagonists such as warfarin. These are associated with significant disadvantages, including an unpredictable therapeutic response, a narrow therapeutic range, the need for routine INR monitoring, slow onset and offset of action, the need for frequent dose adjustments, a number of food interactions, numerous drug interactions and the presence in some patients of warfarin resistance. This has meant that the introduction of a more user-friendly therapeutic intervention for patients with atrial fibrillation would be met with some enthusiasm.

There have been a number of trials of vitamin K antagonists in stroke prevention (AFASAK, BAATAF, CAFA, SPAF, SPINAF), the aggregate of which has produced a relative risk reduction against embolism outcomes of around 70%. In spite of the undoubted biological efficacy of these agents, the difficulties of their usage outlined earlier has limited their uptake in a community setting. A number of community-based studies have placed the lack of uptake in the 30 to 50% range. This again emphasises the need for alternative interventions of at least similar efficacy but greater ease of use.

The Factor Xa and thrombin inhibitors appear as they may achieve this goal. These include particularly the Factor Xa inhibitors Rivaroxaban, Apixaban, Idaraparinux and the thrombin inhibitor dabigatran [5]. The latter has been the first to show clinical efficacy in the RELY trial published recently [6]. In this study warfarin was compared to dabigatran 110 mg or 150 mg twice daily in patients with atrial fibrillation plus one or more risk factors. The risk factors included a previous vascular event, left ventricular ejection fraction of less than 40%, aged 75 years or more or age of 65 years or more with diabetes, coronary artery disease or hypertension. With a follow-up of a mean of two years and primary endpoints of stroke or systemic embolism, dabigatran 110 mg was not inferior to warfarin while 150 mg was superior. The relative risk reduction of dabigatran 150 mg compared to warfarin was 34%. Somewhat surprisingly, life-threatening bleed-ing was significantly lower in both doses of dabigatran and Warfarin. Haemorrhagic stroke was also significantly lower with dabigatran at 0.12% for 110 mg, 0.10% for 150 mg but 0.38% for warfarin. This was significantly different at the .001 level.

The pharmacokinetic properties of the thrombin and Factor Xa inhibitors have differences in that the bioavailability of dabigatran is only about 6% while those of the Factor 1Xa inhibitors is 50 to 80%. Conversely, renal clearance is about 80% for dabigatran but only 35 to 65% for the Factor Xa inhibitors. Renal clearance issues may limit the use of dabigatran in patients with renal impairment.

There are a number of ongoing trials using novel anticoagulants such as ROCKET AF (Rivaroxaban), ARISTOTLE (Apixaban), AVERROES (Apixaban) and ENGAGE-AF (Edoxaban) in which these agents are being used to prevent embolism in patients, usually against the warfarin as the gold standard. The completion of these studies over the next few years should provide additional data about the use of novel anticoagulants in this clinical setting. Several issues which have been raised, which may also be answered with the entry of many of these compounds into standard clinical practice, include the maintenance of similar compliance rates to warfarin and the identification of asymptomatic patients with AF in the general community. With increased ease of use, presumably a greater number of patients will be able to be treated and with fewer side effects than is currently experienced with warfarin.

Summary

There are two main therapeutic approaches using anticoagulants in the secondary prevention of stroke. The first of these is the use of antiplatelet agents which are more appropriate for patients in whom artery-to-artery embolism is the most likely causal mechanism. Aspirin plus dipyridamole or clopidogrel are superior to aspirin alone. New combinations remained to be tested although a ceiling effect for antiplatelet agents at about 20 to 30% relative risk reduction probably exists. The novel anticoagulants such as thrombin and Factor Xa inhibitors are probably superior to warfarin in the prevention of stroke and systemic embolism due to atrial fibrillation. There may be a need to identify asymptomatic people with atrial fibrillation in the community as a public health initiative.

References

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