Preface

At the 12th European Stroke Conference, which was held in Valencia, Spain between 21 and 24 May 2003, attendees had the opportunity to attend two important symposia – a Satellite Symposium entitled *Exploring new antiplatelet strategies in stroke prevention* and an Educational Symposium entitled *Imaging: upcoming techniques and implications for treatment*. This supplement to *Cerebrovascular Diseases* is based on the presentations made during these sessions.

In the opening article of this supplement, Dr Ángel Chamorro describes our growing understanding of the role of inflammation in ischaemic stroke (IS) and atherothrombosis. The onset of brain ischaemia is accompanied by a cascade of proinflammatory events, the strength of which influences stroke outcome. Looking at the pathophysiology that precedes IS, current data indicate that inflammation is a driver of atherosclerosis and can act as the bridge between atherosclerosis and atherothrombosis. Moreover, platelets play a central role in the inflammatory component of these disease processes by means of the CD40–CD40 ligand (CD40L) signalling system. Of note, the expression of CD40L in platelets from healthy volunteers is inhibited by clopidogrel alone or clopidogrel plus acetylsalicylic acid (ASA), but not by ASA alone. This article also raises the prospect of increased use of inflammatory biomarkers such as C-reactive protein for improved identification of patients at high risk of atherothrombosis and for monitoring the effectiveness of drug therapy.

In the first of two articles relating to new antiplatelet strategies for stroke prevention, Dr Philip Teal reviews data on major studies of the benefit of clopidogrel on top

of ASA in patients presenting with coronary manifestations of atherothrombosis. The CURE study in patients with unstable angina or non-Q-wave myocardial infarction (MI) showed that clopidogrel on top of standard therapy (including ASA) reduced the composite of cardiovascular death, MI or stroke by 20% ($p < 0.001$), with an absolute risk reduction of 2.1%. Although CURE did not have statistical power to demonstrate a significant reduction in stroke, this outcome was reduced by 14% in the clopidogrel group. PCI-CURE, a prospectively planned substudy of CURE patients who underwent percutaneous coronary intervention (PCI), provided further evidence of the early and prolonged benefit of clopidogrel observed in the entire CURE population. More recently, the CREDO trial in patients undergoing PCI showed the benefit of continuing clopidogrel on top of ASA for 12 months rather than the more usual one month after intervention. Dr Teal concludes that these data suggest important implications for the use of an early clopidogrel loading dose in patients undergoing carotid stenting, and if confirmed in ongoing or future trials, the use of clopidogrel loading doses followed by prolonged maintenance dosing with clopidogrel and ASA in other high-risk conditions such as transient ischaemic attack (TIA) and IS.

Dr Graeme Hankey then provides an overview of ongoing and planned trials of antiplatelet therapy in stroke prevention. In the setting of acute brain ischaemia, FASTER and ATARI are planned to compare clopidogrel plus ASA versus ASA alone, whereas AbESTT is a Phase II, placebo-controlled evaluation of abciximab. Six trials are evaluating clopidogrel plus ASA in subacute disease. A landmark trial that is close to completion is MATCH,

the first major study to investigate the potential role of clopidogrel plus ASA in patients enrolled on the basis of symptomatic cerebrovascular disease. MATCH is testing the hypothesis that 18 months of therapy with clopidogrel and ASA is superior to clopidogrel alone for the prevention of IS, MI, vascular death or rehospitalization for acute ischaemia in high-risk patients with recent TIA or IS. Another groundbreaking study among this group is CHARISMA, which is evaluating the effectiveness of long-term, dual antiplatelet therapy with clopidogrel and ASA in a broad spectrum of patients at high risk of atherothrombosis. Further trials are enrolling patients with small-artery disease (SPS3), symptomatic carotid stenosis (CARESS), and atrial fibrillation (ACTIVE).

Turning to the importance of advanced imaging techniques in the diagnosis and management of cerebrovascular disease, Dr Michael Hennerici considers current issues in the imaging of unstable atherosclerotic plaque. Recent studies have identified plaque properties that may indicate a high risk of vulnerability and rupture, such as outward plaque remodelling, inflammation, plaque cap thinning and ulceration, and abnormal plaque motion. Vulnerable plaques, even if asymptomatic, place affected individuals at risk of unpredictable ischaemic events. This highlights the importance of risk-factor management, together with pharmacological approaches, such as long-term antiplatelet therapy, to minimize the incidence of atherothrombotic events.

Drs Stephen Davis and Geoffrey Donnan describe new advances in ischaemic penumbra imaging and their potential application in trials of neuroprotection. Recent studies using perfusion-weighted MRI (PWI) and diffusion-weighted MRI (DWI) indicate that: (1) the periphery of the ischaemic core as imaged by DWI is potentially salvageable with early reperfusion; (2) the rim of the region identified by PWI represents a region of benign oligoemia; and (3) the PWI–DWI mismatch area plus the rim of the DWI core can be regarded operationally as the penumbra. On this basis, current prospective, randomized trials are being conducted to confirm preliminary indications that penumbral imaging using MRI can be used to predict which patients will benefit from thrombolytic therapy

beyond the 3-hour window. Penumbral imaging may be useful in predicting the opportunity for tissue salvage with neuroprotection approaches and is being used in surrogate-endpoint stroke trials, which can be performed with sample sizes that are approximately 10% of those needed for a Phase III study.

Dr Reto Meuli considers new advances in imaging viable brain tissue with perfusion CT. This technique has the advantages of rapidity, lack of requirement for specialized computer hardware, and the ability to exclude cerebral haemorrhage. Perfusion CT generates perfusion maps whose accuracy compare favourably with those obtained using xenon-CT, and perfusion CT offers comparable utility to DWI/PWI for the selection of acute stroke patients for thrombolytic therapy. Perfusion CT-generated maps of the infarct and penumbra can be used to obtain a potential recuperation ratio (or Lausanne Stroke Index). This Index has been shown to correlate with the improvement in the National Institutes of Health Stroke Scale (NIHSS) score in patients undergoing arterial recanalization.

Finally, Drs Nick Ward and Richard Frackowiak describe powerful brain imaging methodologies such as functional MRI and voxel-based morphometry that provide new opportunities to study brain pathology and plasticity. A major recent finding has been the dynamic plasticity of function in both normal brains and the brains of patients with neurological (and neuropsychiatric) disorders. Although in its early stages, the study of brain plasticity and its modulation by drugs and other therapies indicates a novel approach to rehabilitation after brain damage, including damage resulting from cerebral infarction.

This collection of articles highlights some of the exciting future prospects for improved acute and long-term management of stroke patients. We hope that you find it to be a valuable resource.

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