For the **ICSS trial** see http://www.strokecenter.org/trials/TrialDetail.aspx?tid=86

The excellent Seminar by Geoffrey Donnan and colleagues[1] provides a comprehensive review of the epidemiology, pathophysiology, prognosis, and treatment of stroke. An issue that might prove different from Donnan and colleagues' analysis is the place of carotid angioplasty with stenting (CAS) in the treatment of symptomatic carotid artery stenosis.

Donnan and colleagues suggest that "carotid angioplasty with stenting... will probably replace carotid endarterectomy as the treatment of choice in most patients". The first randomised trial comparing the long-term results of carotid endarterectomy with those of CAS (median observation time 64 *vs* 66 months, respectively) has now been published.[2] Compared with carotid endarterectomy, CAS was associated with a higher rate of post-procedural ipsilateral stroke (0 of 42 *vs* four of 42 patients, respectively; p<0·05), a higher rate of more than 70% restenosis (0 of 29 *vs* six of 32 patients, respectively; p<0·05), and a higher reintervention rate for more than 70% restenosis (0 of 29 *vs* five of 32 patients, respectively; p<0·05).[2]

Verification of the above results might question the place of CAS in the treatment of symptomatic carotid artery stenosis.

I declare that I have no conflict of interest.

Kosmas I Paraskevas
paraskevask@hotmail.com

Department of Vascular Surgery, "Red Cross" Hospital, 24 Papagou Street, Athens 141 22, Greece

1 Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet* 2008; **371:** 1612–23.
2 Steinbauer MG, Pfister K, Greindl M, et al. Alert for increased long-term follow-up after carotid artery stenting: results of a prospective, randomized, single-center trial of carotid artery stenting vs. carotid endarterectomy. *J Vasc Surg* 2008; **48:** 93–98.

Authors' reply

Luca Mascitelli and colleagues suggest that the effect of statins in the secondary prevention of stroke is modest, associated with an increased risk of haemorrhagic stroke, and might protect mild strokes only. We would argue against this at a number of levels.

First, the relative risk reduction of 16% on intention-to-treat analysis (not 13% as suggested) from the SPARCL trial[1] ($NNT_{4.9}$ 45) is clinically important. Second, there was no difference in fatal haemorrhagic stroke between groups (17 in the treatment group, 18 placebo) and the absolute number overall was small at 55 in the atorvastatin group and 33 in the placebo group. Further, haemorrhagic strokes were included in the primary outcome measure of fatal and non-fatal stroke, so the net absolute benefit of 1·9% nicely takes the risks and benefits into account.

In other words, although we agree that there is an intriguing relation between low cholesterol and haemorrhagic stroke, this is more of academic than pragmatic interest since the benefits of cholesterol lowering with statins far outweigh the risks.[2]

Finally, the likelihood that statins protect only against mild stroke seems unlikely given that in the SPARCL trial there was a significant protection against fatal stroke (absolute risk reduction 0·7%, p=0·04), the most severe strokes of all.

Kosmas Paraskevas also addresses the very current and important issue in secondary stroke prevention of carotid angioplasty versus endarterectomy. We had quite conservatively suggested that angioplasty will probably replace endarterectomy in most patients but that further trials are awaited to confirm this view. With the exception of the EVA-3S trial,[3] the periprocedural risk profiles of both procedures have been clinically similar.[4,5] However, we do agree that long-term follow-up is important since comparative restenosis and vascular event rates are, as yet, poorly understood.

The study quoted by Paraskevas is an important initial contribution to this process although it should be noted that the sample size is somewhat small and the data come from a single centre. We await with interest for the results of follow-up data from trials such as EVA-3S, SPACE, CREST, and the ongoing ICSS.

We declare that we have no conflict of interest.

**Geoffrey A Donnan, Marc Fisher, Malcolm Macleod, Stephen M Davis*
gdonnan@unimelb.edu.au

National Stroke Research Institute, Austin Hospital, University of Melbourne, 300 Waterdale Road, Heidelberg Heights, Victoria 3081, Australia (GAD); Department of Neurology, University of Massachusetts Medical School, Worcester, MA, USA (MF); Department of Neurology, Stirling Royal Infirmary, Stirling, UK (MM); and Department of Neurology, Royal Melbourne Hospital, University of Melbourne, Melbourne, Victoria, Australia (SMD)

1 Amarenco P, Bogousslavsky J, Callahan A 3rd, et al; for the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High–dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; **355:** 549–59.
2 Thrift AG, McNeil JJ, Forbes A, et al, for the Melbourne Risk Factor Study (MERFS) Group. Risk factors for cerebral hemorrhage in the era of well-controlled hypertension. *Stroke* 1996; **27:** 2020–25.
3 EVA-3S Investigators. Endarterectomy *vs.* angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial. *Cerebrovasc Dis* 2004; **18:** 62–65.
4 Ringleb PA, Allenberg J, Bruckmann H, et al. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006; **368:** 1239–47.
5 CAVATAS investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001; **357:** 1729–37.

Hyperglycaemia as a cardiovascular risk factor in diabetes

In their Seminar (May 24, p 1790),[1] Ravi Retnakaran and Bernard Zinman argue, on the basis of the DCCT/EDIC Study,[2] that hyperglycaemia is an important cardiovascular risk factor, and that hyperglycaemia early in the disease course might exert particular harm through "metabolic imprinting/memory". Another study of intensive versus conventional treatment, in type 2 diabetic patients (Steno-2),[3] has also shown continuing divergence of cardiovascular events during follow-up, despite converging glycaemia,

lipidaemia, and blood pressure. In both studies, the cardiovascular risk reduction exceeded 50%.

However, these findings contrast strikingly with epidemiological observations on glycaemia. From observational UKPDS data,[4] DCCT/EDIC group differences in glycosylated haemoglobin would predict a maximum cardiovascular benefit of 9·6%, and for Steno-2 the predicted benefit is 6·5%.

Both studies involved random assignment to different packages of care, and not just glycaemia. In DCCT,[2] patients in the intensive therapy group were assigned multiple injection or pump regimens, blood tests four times daily, monthly multidisciplinary clinic visits, and more frequent telephone contact. In Steno-2,[3] the conventional treatment group was followed up by general practitioners, whereas the intensive intervention patients were seen every 3 months by a multidisciplinary team at a diabetes centre for advice on physical activity, smoking, and diet.

Gale has pointed out the relevance of the "Hawthorne effect" to clinical trials.[5] In DCCT/EDIC and Steno-2, intensive interventions by multidisciplinary care teams might have resulted in subtle changes in lifestyle that were more likely than metabolic imprinting to be responsible for the long-term benefit.

I declare that I have no conflict of interest.

John S Yudkin
j.yudkin@ucl.ac.uk

University College London, 28 Huddleston Road, London N7 0AG, UK

1 Retnakaran R, Zinman B. Type 1 diabetes, hyperglycaemia, and the heart. *Lancet* 2008; **371:** 1790–99.
2 The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; **353:** 2643–53.
3 Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358:** 580–91.
4 Stratton IM, Adler AI. Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321:** 405–12.
5 Gale EAM. The Hawthorne studies—a fable for our time? *QJM* 2004; **97:** 439–49.

Management of allergic rhinitis

We agree with *The Lancet* that the prevalence of allergic rhinitis has been increasing and that there is a need for more allergy specialists to manage those patients (June 21, p 2057).[1] Given the current shortage, the American College of Allergy, Asthma and Immunology (ACAAI) and the American Academy of Allergy, Asthma and Immunology (AAAAI) recommend better training of primary-care providers to manage milder forms of allergic disorders and to work closely with allergy specialists. However, your Editorial also states that pharmacists should "fill the cavernous hole of allergy knowledge, treatment, and management." We strongly disagree with this statement.

As you mention, the prevalence of allergic rhinitis is increasing. This presents serious cost and quality-of-life issues. Unless a proper diagnosis is made and appropriate environmental control measures are incorporated into a comprehensive management programme, patients are unlikely to achieve optimum control.

A task force of the AAAAI and the ACAAI has just released an updated practice parameter on allergic rhinitis,[2] keeping specialists current with the latest research to provide the most effective care for those with the disease.

Pharmacists remain an important component of the health-care system, but they should not be encouraged to take on a provider role. Allergy specialists working with primary-care providers remains the best option for provision of optimum care.

We declare that we have no conflict of interest.

**Jay M Portnoy, Hugh Sampson*
joannfaber@acaai.org

American College of Allergy, Asthma and Immunology, Arlington Heights, IL 60005, USA (JMP); and American Academy of Allergy, Asthma & Immunology, Milwaukee, WI, USA (HS)

1 The Lancet. Allergic rhinitis: common, costly, and neglected. *Lancet* 2008; **371:** 2057.
2 Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008; **122:** S1–84.

Thromboprophylaxis for patients at high risk of VTE


Science Photo Library

As Chair of the Guideline Development Group for the current Scottish Intercollegiate Guidelines Network (SIGN) guideline on prophylaxis of venous thromboembolism (VTE),[1] I wish to comment on the letter from Graham Mackenzie and colleagues (June 7, p 1911),[2] and the reply from Alexander Cohen and colleagues.[3]

Mackenzie and colleagues report that use of aspirin or compression stockings (but not use of heparin) was associated with lower 1-year mortality after hip fracture than was non-use. I agree that these findings from an observational study might be due to residual confounding, and highlight the need for large randomised controlled trials. I suggest that such trials might usefully include other relevant clinical endpoints (symptomatic non-fatal VTE) and also investigate combinations of these methods (in factorial design).[1,3]

In their reply, Cohen and colleagues correctly quote the SIGN guideline, which states that, although published evidence from a meta-analysis of all randomised controlled trials in surgical patients suggests that aspirin reduces the risk of fatal pulmonary embolism, aspirin does not reduce total mortality, and is associated with an increased risk of bleeding. However, the section on hip fracture surgery in this guideline[1] noted that, by comparison with its effect on symptomatic deep-vein thrombosis or fatal pulmonary embolism, the excess risk of bleeding is small in those who were not receiving concomitant heparin prophylaxis (for which there is limited evidence for clinical benefit in hip fracture patients).