Atherosclerosis: The 21st Century Epidemic
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Frustrations in Cerebrovascular Disease

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As we have made progress in the treatment of atherosclerotic stroke and related brain diseases, the problem of cerebral hemorrhage has remained largely unaddressed. There has been a modest reduction in the incidence of cerebral hemorrhage in many populations, mainly as a result of the treatment of chronic hypertension. However, most of the treatments and methods of control of risk factors for ischemic cerebrovascular and coronary disease may themselves be the cause of cerebral hemorrhage. The main risk factor for hemorrhage, increasing age, will become a larger issue in the future.

The term *cerebral hemorrhage* is roughly equated with 'hemorrhagic stroke'. It accounts for approximately 20% of all strokes among individuals of European origin, but closer to 45% of all strokes in those of Asian ethnicity. As a rule, the severity of hemorrhagic stroke is more severe than for ischemic stroke and a residual disability is correspondingly greater. The current conceptualization of the nature of cerebral hemorrhages comes from investigations by French neurologists early in the last century and elaborated by C.M. Fisher, published in 1971 in the *American Journal of Pathology*. Fisher found bulbous outpoutchings in the small penetrating lenticulostriate vessels. These 'Charcot Bouchard aneurysms' are situated in the same small blood vessels that are subject to the effects of chronic hypertension and hyperlipidemia. In the latter circumstances, the pathology occludes a vessel and causes a lacunar stroke.

While cerebral hemorrhage shares many risk factors with ischemic stroke, several appear to have an influence in the opposite direction. For example, greatly reduced LDL concentrations in the blood have been associated with an increased risk of cerebral hemorrhage in several studies of the widespread use of statins. It is also apparent that the increasing use of anticoagulants and t-PA for ischemic stroke have contributed to a resurgence in the incidence of cerebral hemorrhage.

With regard to the risk of cerebral hemorrhage with statins, the recent SPARCL trial (High Dose Atorvastatin After Stroke or Transient Ischemic Attack, NEJM 2006) is representative of many others. Several similar primary and secondary analyses of the effects of cholesterol-lowering drugs on cerebral hemorrhage have generally shown odds ratios of increased risk

for cerebral hemorrhage between two and four but with confidence intervals that barely cross one. Nonetheless, even if the risk is small, if a substantial population is exposed to drugs and severe reduction of LDL, preventative treatment for atherosclerosis may contribute to and to a increased incidence of cerebral hemorrhage.

The risk of cerebral hemorrhage has long been known to increase with the incidence hypertension but there are major covariates including smoking, low LDL, alcohol intake, and BMI. There has indeed been a reduction in the standardized mortality ratio from cerebral hemorrhage over the past several years in numerous populations, but there has been an even more impressive shift in the underlying causes of hemorrhage. Moreover, the reduction in hemorrhage rate that can be attributed to treatment of hypertension has varied widely between ethnic populations.

The Oxfordshire series by Lovelock *et al.* in *Lancet Neurology* 2007 has the advantage of studying a stable population over two well-defined epochs (Figure 1, see p. 198). In the appended figure, 'OCSP' refers to the population from 1981 to 1986 and OVASC refers to it from 2002 to 2006. It is evident that the incidence of cerebral hemorrhage has not changed appreciably between these two time periods.

Figure 2 (see p. 199) taken from the same study, shows that the causes of hemorrhage have changed during the last decade, with an increasing number due to anticoagulation.

Another instructive study in this regard is by van Asch colleagues in *Lancet Neurology* 2010 (Figure 3, see p. 200). The persistently high rate of hemorrhage in Asian populations is evident and scrutiny discloses that the incidence per 100,000 person-years stratified by race is as follows: white – 24.2, black – 22.9, Hispanic – 19.6, and Asian – 51.8. Increasing age continues to be the main risk factor for cerebral hemorrhage. From this same study, using ages 45 to 54 as a reference, the proportional incidences are 1.8 for the decade 55 to 64 years old, increasing to 9.6 for those over age 85.

The implication is that these types of strokes will be more frequent in the future in both developing and developed countries.

Several interesting recent findings in the genetics of stroke may shed light on the origin or propensity to have cerebral hemorrhage. First, the genome wide association study (GWAS) of stroke by Ikram and colleagues in NEJM 2009 suggests that polymorphisms on chromosome 12 confer a 30% increased risk of stroke in both black and white people. This is the first of several attempts to look at stroke and its risks from a new perspective. It would be hoped that for spontaneous cerebral hemorrhage in particular, which is a somewhat more homogeneous group than ischemic stroke, this

would offer special insights. Furthermore, the findings by Gould *et al.* in NEJM 2008 that link COL4A1 mutations to both small vessel disease and spontaneous hemorrhage are very provocative.

I suggest for your consideration that cerebral hemorrhage has been relatively neglected in comparison to ischemic stroke although it is more disabling and has a higher short-term mortality. There has been little if any successful prevention aside from the global treatment of hypertension and increasing caution with the use of anticoagulants. The aging population will result in an increase in the incidence of cerebral hemorrhage, almost certainly contributed to by amyloid angiography in the aged.

As we make progress in treating and preventing atherosclerosis, we should be aware of the overall management morbidity that may contribute to increased cerebral hemorrhage rates. The recent conceptions of antithrombin and anti-factor Xa drugs should contribute to a future reduction in cerebral hemorrhage.

	OCSP		OXVASC		Rate ratio	p
	Number of cases	Standardised incidence	Number of cases	Standardised incidence		
All intracerebral haemorrhages						
<75 years	28	0·10 (0·07–0·14)	18	0·06 (0·03–0·08)	0·53 (0·29–0·95)	0·03
≥75 years	27	1·55 (0·96–2·13)	34	1·44 (0·95–1·92)	0·91 (0·55–1·51)	0·72
Overall	55	0·21 (0·16–0·27)	52	0·16 (0·12–0·20)	0·72 (0·49–1·05)	0·08
Fatal intracerebral haemorrhage						
<75 years	11	0·04 (0·02–0·07)	10	0·03 (0·01–0·05)	0·74 (0·31–1·74)	0·49
≥75 years	15	0·86 (0·42–1·30)	19	0·81 (0·44–1·17)	0·91 (0·46–1·81)	0·79
Overall	26	0·10 (0·06–0·14)	29	0·09 (0·05–0·12)	0·87 (0·51–1·46)	0·59

Data are cases per 1000 per year (95% CI) or rate ratio (95% CI).

Figure 1. Incidence of intracerebral haemorrhage per 1000 per year in OXVASC and OCSP standardised to the 2001 population of England and Wales. Reprinted with permission from Lovelock C.E., Molyneux A.J., Rothwell P.M., *et al.* Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurology* 2007;6:487-93.

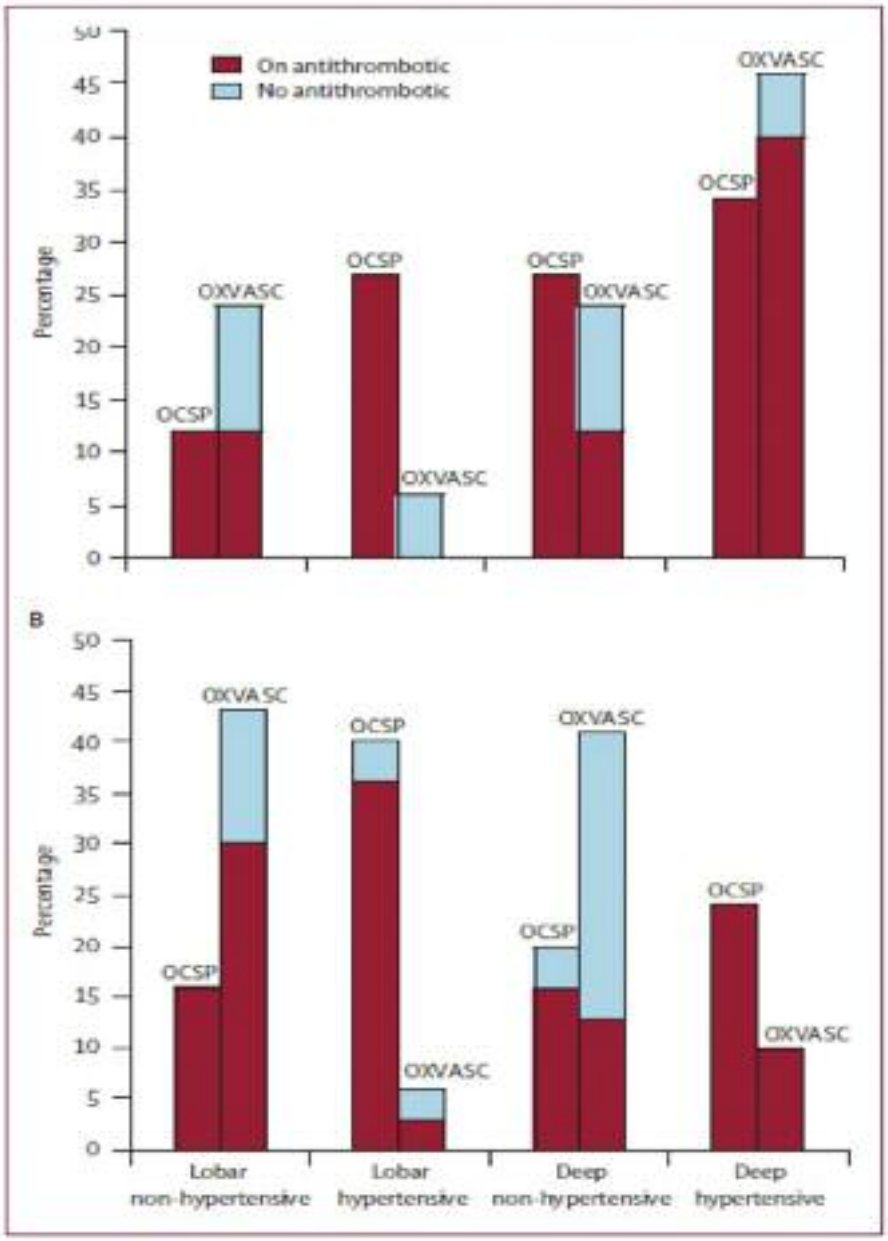

Figure 2. Proportions of hypertensive and non-hypertensive deep and lobar intracerebral haemorrhages in OCSP and OXVASC. Reprinted with permission from Lovelock C.E., Molyneux A.J., Rothweil P.M., *et al.* Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurology* 2007;6:487-93.

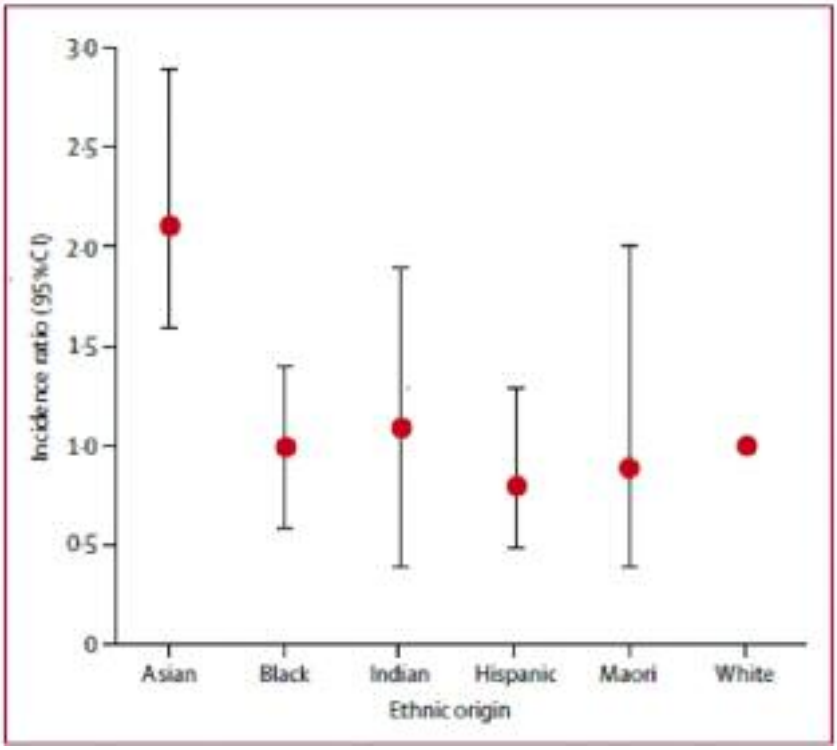

Figure 3. Intracerebral haemorrhage incidence rations in ethnic groups. White ethnic origin was taken as reference because it was the ethnic group with the largest number of patients with intracerebral haemorrahage. Circles are means and bars are 95% CI. Reprinted with permission from van Asch C.J.J., Luitse M.J.A., Rinkel G.J.E., *et al.* Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurology* 2010;9:167-76.