Authors' reply

We are pleased to respond to the comments on our Article.[1]

In their Comment in *The Lancet*,[2] Ajith Thomas and Christopher Ogilvy stated that we reported the outcome contingent on survival rather than modified Rankin alone. We would like to draw attention to the fact that there were different denominator numbers for death (complete ascertainment) and returns from the survivors (90% of the cohort), which is fully explained in the methods. Also, being alive and independent is what matters to patients and their families, and this was statistically significant at 10 years; 68·2% endovascular coiling group versus 61·7% in the neurosurgerical clipping group (odds ratio 1·34, 95% CI 1·07–1·67).

Thomas and Ogilvy also suggested that the convergence of the Rankin scores is due to rebleeding. This is not the case; the number of dead or dependent patients, after rebleeding from the treated aneurysm, was similar in the two groups (six patients in the endovascular group *vs* four in the neurosurgery group).

The premise that patients who undergo coiling should be followed indefinitely is not supported by any systematic data. This aspect should be the subject of a further analysis.

ISAT is the only study that has been able to properly compare cognitive outcomes of a randomised population. In those patients who were independent at 1 year, patients in the coiling group had significantly less cognitive impairment.[3]

Both Thomas and Ogilvy and Nicolaas Bakker and colleagues suggested that we exclude the patients who died before treatment or who were not treated from our analysis. This would breach the trial protocol and intention-to-treat analysis and is not a valid way to report the results of a clinical trial.

Nicolaas Bakker and colleagues have attempted to re-analyse the mortality data without access to the individual patient data and redefine the population for the primary outcome by omitting patients dying before treatment. Major methodological flaws are associated with this attempt at re-analysis. First, the decision to omit the 26 patients who died without treatment is arbitrary. Second, it is a retrospective analysis carried out after the results of the primary analyses are available. Third, Bakker and colleagues assume that the pretreatment deaths were caused by a delay in treatment. They have no evidence to make this assumption and that patients would have survived with earlier treatment, nor do they know the exact timing of the deaths without access to individual patient data.

Miika Korja suggests that the trial design is unsuitable for long-term follow-up. We would naturally disagree. First of all, the tertiary objective, set out in the protocol in 1994, was specifically designed to address the long-term durability of treatment. Second, the methodology, with a prospectively enrolled cohort with complete ascertainment for causes of all deaths up to 18 years, is the only way to provide reliable data on the long-term durability of both clipping and coiling and the outcome of subarachnoid haemorrhage. This method was only feasible for the UK cohort. Third, the protocol excluded overseas patients from long-term follow-up. It is incorrect to state that only 59% follow-up was achieved. Fourth, the assertion that sudden deaths outside hospital were not identified is wrong. There was complete ascertainment for all deaths, whether in hospital or in the community, because of returns from the Office for National Statistics, which records all UK deaths and the certified cause. Sudden unexplained deaths must be reported to the coroner and a post-mortem examination performed to establish the cause. Fifth, the suggestion that the survival analysis is more valid is incorrect. Because patients were enrolled in the trial over a 7·5 year period, only the 10 year data can be complete. As readers will know, all survival analyses will converge eventually. Finally, the assertion that clipping provides lifelong protection from subarachnoid haemorrhage is also incorrect. The results showed that there were 12 patients with recurrent subarachnoid haemorrhages in the clipping cohort, of whom four were from the treated aneurysm, six de novo, and two were pre-existing.

The only logical conclusion, based on sound methodological analysis, is that the clinical outcome after coiling allocation remains better at 10 years.

AJM is a consultant for Sequent Medical (clinical case adjudication and clinical study advice) and provides expert witness evidence in cases of subarachnoid haemorrhage. RSCK provides expert witness evidence in cases of subarachnoid haemorrhage. JB declares no competing interests.

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1 Molyneux AJ, Birks J, Clarke A, et al. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). *Lancet* 2015, **385:** 691–97.

2 Thomas AJ, Ogilvy CS. ISAT: equipoise in treatment of ruptured cerebral aneurysms? *Lancet* 2015, **385:** 666–68.

3 Scott RB, Eccles F, Molyneux AJ, Kerr RS, Rothwell PM, Carpenter K. Improved cognitive outcomes with endovascular coiling of ruptured intracranial aneurysms: neuropsychological outcomes from the International Subarachnoid Aneurysm Trial (ISAT). *Stroke* 2010; **41:** 1743–47.

Multimorbidity: health care that counts "past one" for 1·2 billion older adults

In his Comment (Feb 14, p 587)[1] Sube Banerjee describes, in real terms, the need to adapt health-care systems to meet the ongoing needs of people ageing and of those surviving to older ages. In response to ageing

populations, an economic case[2] has been made for immediate action by health-care systems to address the growing complexities of people who might present with several physical or mental health disorders. In addition to this urgency, evidence suggests that the onset of non-communicable diseases (NCDs) might be at a younger age (during peak economically-active years) in low-income and middle-income countries than in high-income countries,[3] meaning that the care of patients with multimorbidity (two or more long-term disorders) poses an imminent challenge for all countries.

Previously, NCDs and risk factor data needed to inform policy and guide system changes were scarce from low-income and middle-income countries, but this is changing. In a pooled sample of 42 489 people from six middle-income countries during 2007–10, multimorbidity was shown to range from 12% in people aged 18–49 years, to 61% in people aged 70 years and older; in China 20% of people and 35% in Russia had multimorbidity.[4] The probability of a person having a disability and depression increases significantly with multimorbidity, even without accounting for dementia (table). Furthermore, prevalence of dementia is high and increasing in developing countries; by 2050, 71% of people with dementia will be living in low-income and middle-income countries.[5] Comorbidities with dementia are high[6] and are much less likely to be diagnosed in people in lower-income countries and lower-resource settings than in those in higher-income countries and greater-resource settings. 21st-century health systems worldwide should start counting "past one"[1] now, to be ready for the 1·2 billion adults aged 50 years and older who are living in low-income and middle-income countries.

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1 Banerjee S. Multimorbidity-older adults need health care that can count past one. *Lancet* 2015; **385:** 587–89.
2 Bloom DE, Chatterji S, Kowal P, et al. Macroeconomic implications of population ageing and selected policy responses. *Lancet* 2015; **385:** 649–57.
3 Hunter DJ, Reddy KS. Noncommunicable diseases. *N Engl J Med* 2013; **369:** 1336–43.
4 WHO. WHO Study on global AGEing and adult health (SAGE). http://apps.who.int/healthinfo/systems/surveydata/index.php/catalog/sage (accessed May 19, 2015).
5 Alzheimer's Disease International. Policy brief for G8 heads of government. The global impact of dementia 2013–2050. London; Alzheimer's Disease International, 2013.
6 Poblador-Plou B, Calderón-Larrañaga A, Marta-Moreno J, et al. Comorbidity of dementia: a cross-sectional study of primary care older patients. *BMC Psychol* 2014; **14:** 84.

	≥1 ADL		Depression*	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
None†				
One	2·07 (1·93–2·22)	1·51 (1·38–1·65)	1·77 (1·57–2·01)	1·62 (1·42–1·84)
Two	4·08 (3·78–4·39)	2·47 (2·26–2·72)	2·80 (2·48–3·18)	2·44 (2·14–2·82)
Three	7·28 (6·66–7·92)	3·81 (3·42–4·26)	4·74 (4·12–5·46)	4·05 (3·47–4·75)
≥Four	15·18 (13·58–16·83)	7·21 (6·33–8·17)	8·75 (7·53–10·12)	7·33 (6·24–8·61)

Multilevel logit models were used. Adjusted ORs are controlled for background characteristics (eg, age, sex, living in urban or rural areas, and marital status) and health risk factors (eg, tobacco and alcohol use, physical activity levels, waist-to-hip ratio, and obesity). p<0·01 for all values. Data are from the WHO study on SAGE wave 1 (2007–10).[4] ADL=activities of daily living, in which one or more (≥1) deficiency in an ADL suggests dependence or disability. OR=odds ratio. SAGE=Study on global AGEing and adult health. *Depression was self-reported by patients. †Reference group.

Table: **Effects from the number of diseases on disability and depression in adults**

Author's reply

Paul Kowal and colleagues make three important points. First, they clearly illustrate that non-communicable diseases and multimorbidity are not just issues for developed countries, but are an emergent worldwide challenge for low-income and middle-income countries (LMICs) too. Data from WHO's Study on global AGEing and adult health (SAGE) are valuable, showing this emerging challenge and the resulting negative effects on health and wealth in LMICs as well as in developed economies.

Second, their letter reminds us that biological ageing does not happen at the same speed for all. Kowal and colleagues stress that the negative effects of multimorbidity can happen at a young age in LMICs. Strikingly, the same is also true in developed countries for some groups of people, such as those of a low socioeconomic status[1] and those with severe mental illness.[2] Older people are one of several groups that have a high likelihood of multimorbidity and poor outcomes from health care. Older people are an important group because of population ageing, but people of any age with multimorbidity might receive poor health care, particularly if they are in a group that is associated with stigma or low expectation of recovery—such as people with dementia, schizophrenia, or living in deprivation.

Finally, Kowal and colleagues remind us that dementia (a powerful exemplar of the challenges posed by multimorbidity) and population ageing, if anything, is a greater challenge for LMICs than it is for high-income countries. From 2013 to 2050, a 246%