injections experienced a modest improvement in pain but that this was not significantly different from the improvement in patients who underwent physical therapy plus pharmacotherapy or patients who underwent a combination of physical therapy, pharmacotherapy, and epidural steroid injections over a 6-month period.

In this study, Cohen et al randomly assigned 169 consecutive subjects with cervical radiculopathy from 7 treatment facilities to 3 equal groups. The first group received cervical epidural steroid injections only; the second group underwent physical therapy plus pharmacotherapy; and the third group underwent a combination of physical therapy, pharmacotherapy, and epidural steroid injections. All patients were >18 years old, had a history of cervical radicular pain that was no less than 1 month and no more than 4 years, rated their arm or neck pain ≥4, and had magnetic resonance imaging demonstrating an anatomic correlate to their symptoms. Patients with myelopathy and patients who had undergone prior surgery were among those who were excluded. The patients in the epidural steroid group received an interlaminar injection of a 3-mL solution containing 60 mg depomethylprednisolone and normal saline at either the C6-7 or C7-T1 interspace under fluoroscopic guidance. The injection could then be repeated at 3 months and again at 6 months if the patient experienced only partial improvement or if symptoms initially resolved but later recurred. The patients in the pharmacotherapy plus physical therapy group were started on gabapentin and/or nortriptyline. The medication and dose were determined at the treating physician's discretion, and the doses were uptitrated over 16 to 24 days to reach a therapeutic range. Physical therapy began within 1 week of the initial evaluation, but patients who had previously tried and failed physical therapy could opt out of parts of the regimen that had not worked before or could even opt out of the entire regimen altogether. The patients who were in the third combination group received epidural steroid injections, pharmacotherapy with gabapentin and/or nortriptyline, and physical therapy according to the same standards as patients in the other 2 groups.[6]

The results of this study showed that all 3 groups experienced a modest reduction in both arm and neck pain. Although the largest improvements were seen in the combination group, the difference was not significant. The authors did find, however, that at 3 months patients in the combination therapy group were significantly more likely to have a positive "categorical outcome," meaning that the patient responded positively to a questionnaire about pain and satisfaction and had a 2-point improvement in arm pain. When this same outcome measure was taken again at 6 months, however, a significant difference was no longer appreciable.[6]

However, the authors speculate that perhaps their study was underpowered because the beneficial effect of combination therapy was less than expected during the design of the study. It seems more likely that there truly is not a statistical significance between the 3 treatment groups and that the nonsignificant trend toward subjectively better outcomes in the combination group may be explained simply by the placebo effect of receiving a shot. This is concordant with previous studies that have not shown a lasting benefit of epidural steroid injections over conservative treatment in the lumbar spine.[7,8] This study therefore suggests that the use of epidural steroid injections in the treatment of degenerative neck pain and cervical radiculopathy should be limited to a smaller group of patients who are also receiving physical therapy and pharmacotherapy. Additionally, given that there is no proven benefit to this procedure, which does carry risk, it may be that there is no role at all for epidural injections in the treatment of cervical radiculopathy. Rather than receiving multiple rounds of epidural injections, patients may benefit from referral to a spine surgeon for definitive decompression when conservative measures fail within the appropriate time period.

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Long-term Follow-up of the International Subarachnoid-Hemorrhage Aneurysm Trial

The International Subarachnoid Aneurysm Trial (ISAT) has been an ongoing landmark study that has firmly established endovascular coiling as an effective alternative therapy.

In 2002, investigators reported the initial results of 2143 subarachnoid hemorrhage (SAH) patients randomized to neurosurgical clipping (n = 1070) or endovascular treatment with detachable platinum coils (n = 1073). At the planned interim analysis, 23.7% of patients allocated to endovascular treatment were dependent or dead at 1 year compared with 30.6% allocated to neurosurgical treatment.[1] The risk of rebleeding from a ruptured aneurysm was higher in the coiled cohort. Results at 1 year were similar, with patients experiencing decreased death, dependence, and epilepsy in the endovascular cohort, but requiring an increased number of treatments and having an increased risk of rebleeding.[2] At a minimum of 6 years and a maximum of 14 years (mean follow-up, 9 years), rates of rebleeding were again higher in the endovascular group, but the risk of death was significantly lower in the coiled group. If the data are analyzed according to the primary outcome of the first two studies,[1,2] 241/867 (27.8%) in the endovascular group and 273/857 (31.9%) in the neurosurgical group had an mRS score of 3 to 6 at 5 years. The proportion of survivors at 5 years who were independent did not differ between the two groups: endovascular 83% (626 of 755) and neurosurgical 82% (584 of 713).

Recently, the authors report the results of 1644 patients in 22 UK neurosurgical centers with 10.0 to 18.5 years of follow-up (Figure).[3] The primary outcome could not definitively be ascertained, as death was assessed from the Office for National Statistics, and disability and outcome events were reported by questionnaire. At 10 years, 674 (83%) of 809 patients allocated to endovascular coiling and 657 (79%) of 835 patients allocated to neurosurgical

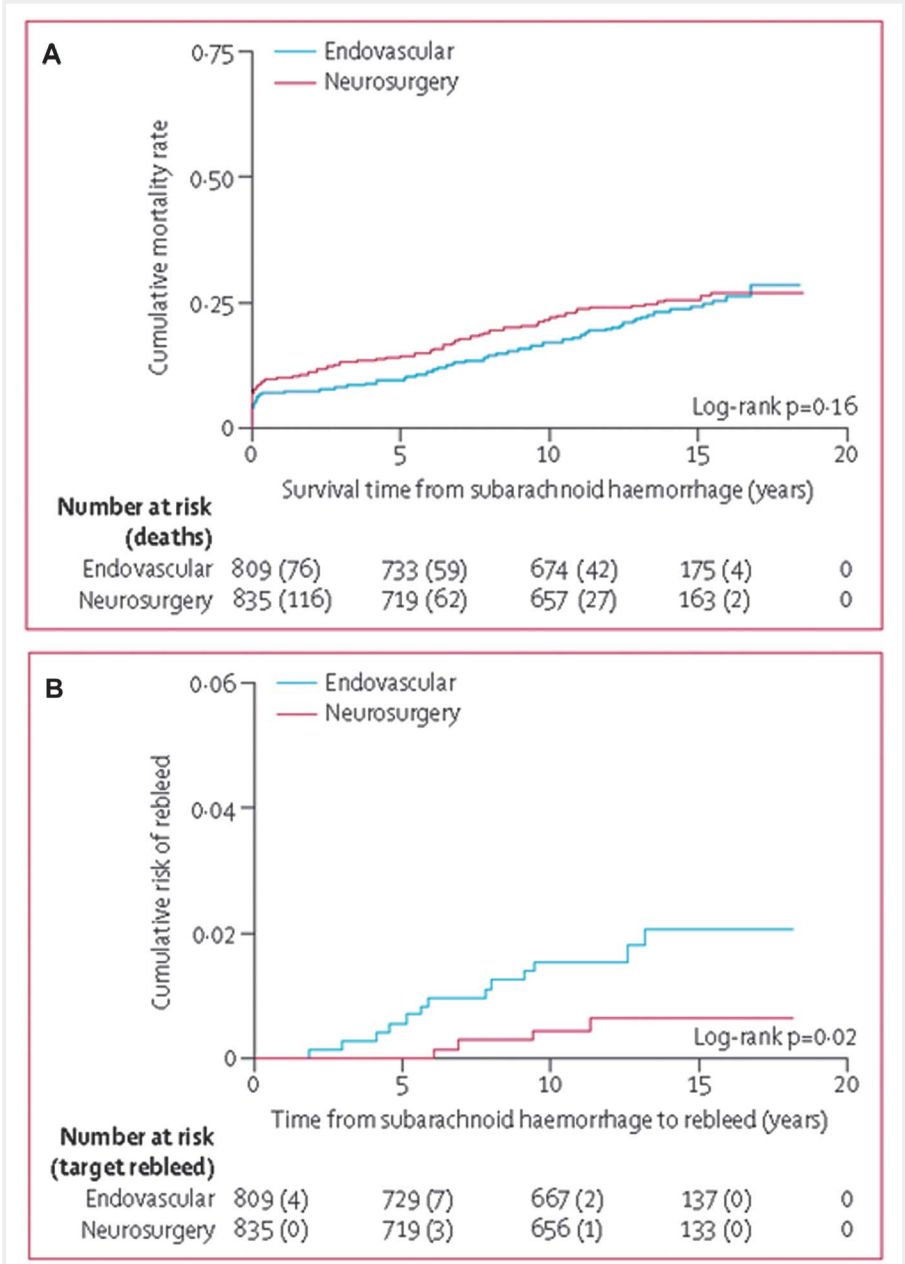

Figure. **A**, *Kaplain-Meier plot of cumulative mortality.* **B**, *Kaplan-Meier plot of cumulative risk of rebleeding from target (treated) aneurysm later than 1 year after subarachnoid hemorrhage.* From Molyneux et al.[3]

clipping were alive (odds ratio [OR] = 1.35, 95% confidence interval [CI], 1.06-1.73). Of 1003 individuals who returned a questionnaire at 10 years, 435 (82%) patients treated with endovascular coiling and 370 (78%) patients treated with neurosurgical clipping were independent (modified Rankin scale score 0-2; OR = 1.25; 95% CI, 0.92-1.71). Patients in the endovascular treatment group were more likely to be alive and independent at 10 years than were patients in the neurosurgery group (OR = 1.34, 95% CI, 1.07-1.67). Again, rebleeding was higher in the endovascular cohort.

The study cohorts and prior limitations of the ISAT have been previously reviewed. Eighty-eight percent of patients were of good clinical status, 93% of the target aneurysms were 10 mm or smaller in diameter, and 97% of target aneurysms were in the anterior circulation. The external validity is also limited by the fact that only 80% of screened patients with aneurysmal SAH were randomized. Additionally, rates of complete aneurysm occlusion in the surgical group were lower than expected (82%) and could also be accounted for by surgeon experience.

Despite these limitations, ISAT have solidified endovascular therapy as a treatment option for ruptured aneurysms. These results have provided an impetus for coiling of aneurysms, which is often extended to aneurysms regardless of history of rupture, size, or location. This is reflected in audits that have recently demonstrated that 85% of ruptured aneurysms in the UK are coiled.[4] Despite these findings, significant equipoise remains, demonstrated by the severe practice variation in coiling of ruptured aneurysm in the United States, which ranges from 36.3% to 98.8% at different centers.[5]

This study underscores the progress made in the treatment of intracranial aneurysms. Mortality rates from SAH have significantly improved from the 1950s when they reached approximately 50%.[6] Still, a large number of patients are disabled following SAH. This study also demonstrates that following aneurysmal SAH, patients are significantly more likely to die earlier than a general age-matched population.[3] Patients were most likely to die from cancer and cardiovascular disease and approximately 40-times more likely to die from another cause than from the treated aneurysm.

These long-term follow-up results also demonstrate the durability of endovascular coiling in preservation of neurological function. Although prior ISAT publications have demonstrated a significantly higher retreatment rate in the endovascular cohort, this information is not presented in the current publication and frequency and duration of imaging follow-up is unknown.

Improvements have been noted in the microsurgical clipping of cerebral aneurysms,[7] but endovascular therapies have arguably undergone significantly greater technology improvements since the first patients enrolled in ISAT in 1994. Despite these improvements, novel technologies have also been associated with an increased incidence of complications.[8] A number of studies have noted improved clinical outcomes over time following coiling of ruptured aneurysms along with decreasing rebleeding rates.[9,10] Thus, the present disparity in outcomes between patients treated with microsurgery and coiling remains unclear.

Remaining questions are not whether coiling or clipping is preferred, but for select aneurysms,

is there a benefit for clipping or coiling. A recent meta-analysis of three randomized clinical trials including ISAT did not show a significant difference in outcomes between patients treated with these two options.[11]

Despite limitations of ISAT, this is a well-executed trial that highlights the necessity of long-term follow-up in aneurysmal SAH patients. The increased rate of rebleeding in untreated and de novo aneurysms underscores that clipping or coiling does not eliminate the underlying pathogenesis of cerebral aneurysms and that aggressive management of secondary risk factors is essential.

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Mammalian Target of Rapamycin (mTOR) Activity Promotes Neuronal Survival in Stroke With or Without Ischemic Postconditioning

Ischemic postconditioning (IPC), a concept derived from myocardial ischemic models, confers neuroprotection in various models of experimental stroke.[1] Following a series of occlusion and reperfusion periods after the initial ischemic insult, IPC improves glucose uptake, reduces free radical generation, inhibits inflammation, and promotes protein activity in the phosphatidylinositol 3-kinase/Akt pathway.[2,3] Although the exact relationship between mammalian target of rapamycin (mTOR), a member of the phosphatidyl 3-kinase–related kinase family, and IPC is still unclear, it is known that modulation of mTOR through IPC promotes cell metabolism, growth, differentiation, development, and cell survival.[4]

Xie et al[5] created an in vivo stroke model incorporating IPC by generating focal cerebral ischemia through bilateral common carotid artery occlusions and permanent distal middle cerebral artery occlusion in male Sprague-Dawley rats. IPC was performed immediately after bilateral common carotid artery occlusions with 30 seconds of reperfusion followed by 10 seconds of temporary reocclusion. This sequence was repeated 3 times. Because Xie and colleagues were unable to clone the mTOR gene in a plasmid backbone, they constructed a lentiviral vector expressing S6K1, a downstream protein of mTOR and indicator of mTOR activity. To inhibit mTOR activity, the authors used rapamycin and a lentiviral vector containing mTOR short hairpin RNA (shRNA) to reduce mTOR expression. Rapamycin (5 μL, 1 mmol/L) was infused into the ventricular space ipsilateral to the ischemic side 1 hour before occlusion with a microsyringe pump. Lentiviruses were injected into the left cortex 5 days before occlusion, and infarct size was measured 2 days after ischemia.

The authors went on to subject mixed neuronal cultures derived from rat fetal brains to oxygen-glucose deprivation (OGD). Nine to 11 days after preparation, 6 hours of OGD was induced in a hypoxic chamber, followed by in vitro hypoxic postconditioning (HPC). HPC was achieved through 3 cycles of 15-minute restoration of glucose and oxygen and 15 minutes of OGD. Lactate dehydrogenase levels were used to quantify cell death 18 hours after OGD.

Initial experiments demonstrated that IPC promotes the phosphorylation and activation of mTOR and other mTOR-related proteins (S6K1, S6, and 4EBPI). The authors showed reduced levels of protein phosphorylation in stroke models without IPC. In the penumbra, phosphorylation of such proteins was elevated in IPC models and reduced in non-IPC models. Furthermore, rapamycin, a known mTOR inhibitor, was found to exacerbate infarct volumes and to lower phosphorylated proteins in common carotid artery occlusion models with or without IPC. Likewise, transfection of shRNA worsened ischemic injury and reversed the protective effects of IPC, whereas gene transfer of S6K, a downstream protein of mTOR, inhibited neuronal death. In vitro, rapamycin worsened cell death induced by OGD and abolished the protective effects of HPC (Figure).

Postischemic neuronal injury occurs through multiple mechanisms, including the disruption of cell growth, a decrease in protein activity, and the creation of a proinflammatory state. Since the discovery of the protective benefits of IPC after myocardial ischemia, neuroscientists have tried to obtain equally positive results and to understand which proteins are affected by IPC in the setting of cerebral ischemia. The ability to successfully promote mTOR phosphorylation and to accelerate its downstream protein production may ultimately represent a novel therapeutic strategy for patients with stroke.

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