pathology findings might contradict those obtained intraoperatively. This technique thus requires a very close partnership between surgeons, pathologists, radiation oncologists, and physicists. Indeed, in TARGIT-A, 14% of patients received targeted intraoperative radiotherapy plus external-beam radiotherapy. Mixed-modality 3D-conformal accelerated partial-breast irradiation with opposed mini-tangent photon fields and en-face electrons is a promising alternative.[11]

We still await long-term follow-up and the results of another randomised trial from the National Surgical Adjuvant Breast and Bowel Project B-39.[12] Nevertheless, in elderly patients, we are already convinced that accelerated partial-breast irradiation is the new standard and intraoperative radiotherapy an excellent approach.

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Preventing type 2 diabetes with low-dose combinations

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The past decade has seen major advances in clinical trial evidence to support improved care in diabetes. One important area is prevention of type 2 diabetes. Several trials have tested single interventions for their ability to reduce the incidence of diabetes in high-risk individuals.[1–6] Lifestyle interventions aimed at reducing bodyweight, and use of metformin, thiazolidinediones, acarbose, and orlistat, reduce the risk of diabetes by 25–60% over 3–6 years. Generallly, interventions aimed at reducing body fat or its adverse metabolic effects show the best evidence for slowing or stopping progression to diabetes.[7] Indeed, the insulin secretagogue, nateglinide, had no effect in reducing diabetes risk.[8] Despite the positive outcomes of these trials, it remains unclear whether prevention is superior to early treatment in terms of long-term health. Additionally, concerns about cost and side-effects have limited recommendations for use of drugs to prevent type 2 diabetes.

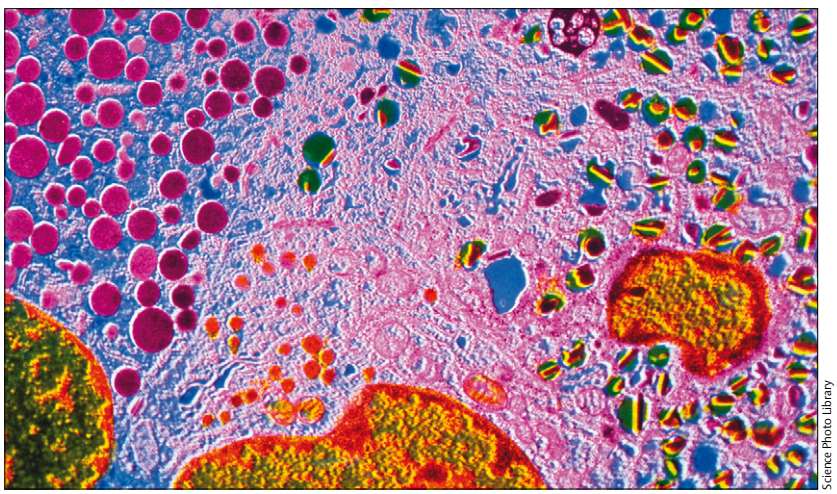
In *The Lancet* today, Bernard Zinman and colleagues[9] report the CANOE trial, the first to test low-dose combination drug therapy for diabetes prevention. During a median follow-up of 3·9 years, metformin and rosiglitazone at about half-maximum doses caused a 66% reduction in the risk of diabetes compared with placebo. Importantly, the treated group had no increase in weight gain, heart failure, fractures, or myocardial infarction. Diarrhoea was infrequent, but occurred more often in the treated group. Circulating concentrations of LDL cholesterol, C-reactive protein, and serum alanine aminotransferase fell more, while HDL cholesterol rose more, in the treated group. The investigators concluded that combination treatment with low-dose metformin and rosiglitazone could

be effective in preventing type 2 diabetes, with few of the side-effects associated with the two drugs at higher doses.

What does this new study tell us about diabetes prevention, and what is still missing? On the positive side, the concept of combining submaximum doses of effective drugs to maintain efficacy and reduce side-effects is an attractive one. Ideally, the CANOE trial should have included a high-dose group for each of the individual drugs to provide a rigorous test of the low-dose approach. Without those groups, comparisons need to be made with monotherapy in other studies. The reduction in diabetes risk in CANOE is in the ball-park previously reported with thiazolidinediones at submaximum (55% reduction[4]) or maximum (60% reduction[10]) doses, and more than twice the 31% reduction reported with metformin at a near-maximum dose.[2] Thus the low-dose combination seems to be effective.

The side-effect profile for the low-dose combination also looks favourable. However, that conclusion is not yet definitive, because side-effects of the two study drugs are not universal. In fact, only weight gain with thiazolidinediones and diarrhoea with metformin are so highly reproducible as to be expected in every study. Diarrhoea occurred in excess in the treated group in CANOE, but was rarely treatment-limiting. The clear side-effect benefit of the low-dose combination was mitigation of weight gain. CANOE's results suggest that the low-dose combination will be as effective as, but safer than, higher-dose monotherapy. However, definitive proof awaits future studies.

The larger issues that have cast doubt on use of drugs to prevent diabetes are not addressed by the CANOE trial. The report included no off-drug testing, so it is not clear that diabetes prevention represented any real slowing or arrest of metabolic deterioration. Surrogate measures of insulin resistance in today's trial suggest that treatment minimised worsening of insulin resistance and analogous measures of β-cell function failed to show a benefit, by strong contrast with other studies with thiazolidinediones.[4,11] Plots of the cumulative incidence of diabetes in CANOE diverged throughout treatment, a finding that suggests true slowing or arrest of progression.[7] In the end, it seems likely that treatment did slow progression significantly, but again proof is lacking. The issue of whether prevention provides better long-term outcomes than does early treatment remains unknown, because neither CANOE nor any other diabetes-prevention study has reported the requisite information yet.



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False-colour transmission electron micrograph showing cells of islet of Langerhans
At right in green, yellow, and brown are insulin-secreting β cells; in red at left are α cells, which secrete glucagon.

What is the take-home message here? We believe it goes back to the fundamental biology of type 2 diabetes in evolution. The disease is characterised by falling β-cell compensation for chronic insulin resistance, leading to rising glucose concentrations before and after diabetes develops. We must halt the progressive β-cell disease if we are to keep patients at low-risk glucose levels over the long haul. The intensity of intervention required to do so almost certainly varies between individuals. Some do fine with modest weight-loss but others require drugs to slow or stop their β-cell disease. Drugs that improve insulin resistance seem to be the most potent, whether used alone in high doses or in combination at lower doses. In either case, some patients will continue to manifest rising glucose concentrations. We need data on more intensive approaches, including high-dose combination therapy, to provide clinicians with a full range of evidence-based approaches to halt or reverse this progressive disease relatively early in its course.

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Reducing the global burden of stroke: INTERSTROKE

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Stroke is the second leading cause of death globally, with more than 85% of deaths from stroke occurring in developing countries.[1,2] However, there has been little research to identify the causes of stroke in low-income and middle-income countries. An understanding of the risk factors for stroke in these countries is crucial to determine priorities and strategies for reversing the rapidly rising rates of stroke mortality in developing countries. In *The Lancet* today, the INTERSTROKE investigators[3] report the initial findings from their phase 1 case-control study of risk factors for stroke in 22 countries worldwide. The findings suggest that ten key risk factors explain 90% of the population-attributable risk for stroke, and that the risk factors for stroke are similar to those previously identified for myocardial infarction in the related INTERHEART study (table).[4]

	INTERSTROKE (all stroke; 3000 cases, 3000 controls)[3]*	INTERHEART (acute myocardial infarction; 15 152 cases, 14 820 controls)[4]†
Hypertension	34·6% (30·4–39·1)	17·9% (15·7–20·4)
Smoking	18·9% (15·3–23·1)	35·7% (32·5–39·1)
Waist-to-hip ratio (abdominal obesity)	26·5% (18·8–36·0)	20·1% (15·3–26·0)
Diet		
Diet risk score	18·8% (11·2–29·7)	..
Fruits and vegetables daily	..	13·7% (9·9–18·6)
Regular physical activity	28·5% (14·5–48·5)	12·2% (5·5–25·1)
Diabetes	5·0% (2·6–9·5)	9·9% (8·5–11·5)
Alcohol intake	3·8% (0·9–14·4)	6·7% (2·0–20·2)
Psychosocial factors		
All psychosocial factors	..	32·5% (25·1–40·8)
Psychosocial stress	4·6% (2·1–9·6)	..
Depression	5·2% (2·7–9·8)	..
Cardiac causes	6·7% (4·8–9·1)	..
Ratio of apolipoproteins B to A1	24·9% (15·7–37·1)	49·2% (43·8–54·5)

Data are population-attributable risk (99% CI). *Adjusted for all stroke risk factors apart from ratio of apolipoproteins B to A1. †Adjusted for all myocardial infarction risk factors. ‡See original article for definition of risk factor and methods used to calculate population-attributable risk.

Table: **Comparison of the population-attributable risk (99% CI) for common risk factors‡ in the INTERSTROKE and INTERHEART studies**

The INTERSTROKE investigators classified participants into five regions: high-income countries, South America, southeast Asia (including China), India, and Africa. They found that a self-reported history of hypertension or acute blood pressure of higher than 160/90 mm Hg was the most important risk factor for both ischaemic and intracerebral haemorrhagic stroke. Whilst hypertension is well established as the most important cause of stroke in high-income countries, INTERSTROKE confirms that it is also the most important risk factor for stroke in developing countries.[5] This finding is particularly relevant because it highlights the need for health authorities in these regions to develop strategies to screen the general population for high blood pressure and, if necessary, offer affordable treatment to reduce the burden of stroke. It also provides an impetus to develop population-wide strategies to reduce the salt content in the diet of individuals in these countries.[6]

Smoking and abdominal obesity, as measured by waist-to-hip ratio, were also identified as important risk factors for stroke. Current smokers had a significantly