Intensive glucose lowering in type 2 diabetes

As shown by the spat between the German Diabetes Association and Germany’s drug evaluation agency (BMJ 2011;343:d6609), the controversy around intensive blood glucose control for type 2 diabetes is ongoing. Now Rémy Boussageon and colleagues have carried out an updated meta-analysis (p 244) to evaluate microvascular complications, cardiovascular events, and severe hypoglycaemia related to intensive glycaemic control and the level of evidence of the selected studies.

Their conclusions are not encouraging: no benefit of treatment on all cause mortality or death from cardiovascular causes; a 10% reduction in the risk of microalbuminuria, but without significant benefit on other important microvascular complications, and the favourable results on non-fatal myocardial infarction and microalbuminuria did not remain significant when the analysis was restricted to studies of high quality, whereas a 47% increase in the risk of congestive heart failure became significant. There was also a twofold increased risk of severe hypoglycaemia.

In their accompanying editorial (p 215), David Preiss and Kausik Ray write that the cardiovascular benefit of intensive glucose lowering seems to be modest at best, and that glucose lowering is probably less efficacious and more difficult to achieve than lipid lowering and blood pressure control. “

Adjuvant chemotherapy for elderly patients with lung cancer

Lung cancer remains a leading cause of death from cancer, predominantly in elderly people. Non-small cell lung cancer at stages I to IIIA is still potentially resectable and curable, but with a rate of recurrence of 40-65% in the more advanced stage II or III disease. So, evidence from clinical trials that adjuvant platinum based chemotherapy improves survival in such patients has been welcomed. Unfortunately, like most clinical trials, these studies have tended to exclude patients with comorbidities and have thus weed out many elderly patients—the group with most to gain from the treatment, but also most likely to be vulnerable to the toxic effects of chemotherapy. Using data from a nationally representative cancer registry, Juan Wisnivesky and colleagues (p 247) have shown that chemotherapy was associated with improved survival in 684 patients aged over 65 with resected stages II-IIIA lung cancer. However, the beneficial effects did not extend to the relatively few patients aged 80 or over, nor did the study look at patients’ quality of life.

The basic message for treating clinicians seems to be that although their concerns about adverse effects of adjuvant chemotherapy in elderly patients are not unfounded, they can afford to raise the cut-off point for age.

Diet and diverticular disease

Diverticular disease has been called a “disease of Western civilisation” because of its high prevalence in countries like the UK and United States compared with parts of Africa. Its prevalence in the UK has been rising and is expected to increase further, owing to its association with age. Dietary factors, including consumption of fibre and meat, are also thought to play a part in diverticular disease, but supporting evidence is scarce.

Francesca Crowe and colleagues’ prospective cohort study in England and Scotland shows a reduced risk of admission to hospital or death from diverticular disease among vegetarians and people with a high intake of dietary fibre (p 245). Vegans had an even lower risk of diverticular disease, but this finding was based on small numbers. There was no significant association between the amount of meat consumed and the incidence of diverticular disease among meat eaters.

Other studies have found that vegetarian diets and high fibre intake are correlated with rapid bowel transit times and more frequent bowel movements, which suggests a possible biological mechanism for this study’s findings. In the full length paper online (doi:10.1136/bmj.d4131) the authors discuss this and other explanations, such as the possibility that vegetarians might be less likely to undergo investigations and be diagnosed with the disease.

In an editorial (p 216) David Humes and Joe West say that modification of diet probably provides an opportunity for preventing diverticular disease at the population or individual level, although more evidence is needed before dietary recommendations can be made to the general public about the specific benefits discussed here. However, the findings lend support to existing public health recommendations about fibre intake.

LATEST RESEARCH: For these and other new research articles see www.bmj.com/research

Effect of pregnancy planning and fertility treatment on cognitive outcomes in children at ages 3 and 5

C Carson and colleagues’ UK cohort study showed no adverse effect of planned pregnancy, subfertility, or assisted reproduction on children’s cognitive development (doi:10.1136/bmj.d4473).

Patients’ and family members’ views on how clinicians enact and how they should enact incident disclosure

We give priority to articles reporting original, robust research studies that can improve decision making in this qualitative study, Rick ledema and colleagues investigated perceptions and experiences of how doctors communicate about serious healthcare incidents, and how the situation might be improved (doi:10.1136/bmj.d4429).
Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials

Rémy Boussageon,1 Theodora Bejan-Angoulvant,2,3,4 Mitra Saadatinia-Elahi,2 Sandrine Lafont,1 Claire Bergeonneau,13 Behrouz Kassai,2,3,4 Sylvie Erpeldinger,1 James M Wright,6 François Gueyffier,2,3,4 Catherine Cornu1

STUDY QUESTION
What are the benefits of intensive glucose lowering treatment on all cause mortality and deaths from cardiovascular causes in adults with type 2 diabetes?

SUMMARY ANSWER
This meta-analysis found limited benefits of intensive glucose lowering treatment on all cause mortality and cardiovascular deaths.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Glucose lowering treatments are widely used to treat type 2 diabetes to prevent long term cardiovascular complications as well as impairment of renal and visual functions. Such treatment should be considered with caution, and escalation of treatment should be limited.

Selection criteria for studies
Eligibility criteria were randomised controlled trials assessing the efficacy of intensive glucose lowering treatment (oral or insulin) versus a standard treatment, less intensive glucose lowering treatment, or placebo (intensive treatment could be defined either by a specified glycated haemoglobin (HbA1c) target or by treatment intensification); trials using clinically relevant outcomes; and participants aged 18 years or older with type 2 diabetes.

Primary outcomes
Primary endpoints were all cause mortality and death from cardiovascular causes.

Main results and role of chance
Intensive treatment did not significantly affect all cause mortality (risk ratio 1.04, 99% confidence interval 0.91 to 1.19) or death from cardiovascular causes (1.11, 0.86 to 1.43). Heterogeneity between trials was significant for all cause mortality (P=0.09, I2=0.42%) and for cardiovascular deaths (P=0.006, I2=0.61%). Over a treatment period of five years, 117 to 150 patients would need to be treated to avoid one myocardial infarction and 32 to 142 patients to avoid one episode of microalbuminuria, whereas one severe episode of hypoglycaemia would occur for every 15 to 52 patients. When only high quality studies were considered, no benefit was associated with intensive treatment and the risk of severe hypoglycaemia doubled.

Bias, confounding, and other reasons for caution
The benefit: risk ratio of intensive glucose lowering treatment in the prevention of macrovascular and microvascular events in adults with type 2 diabetes remains uncertain. The harm associated with severe hypoglycaemia might counterbalance the potential benefit of intensive glucose lowering treatment.

Study funding/potential competing interests
The meta-analysis was not supported by private or public funding. We have no competing interests.
**STUDY QUESTION**

Do individuals consuming a vegetarian diet and those with a high intake of dietary fibre have a lower risk of diverticular disease?

**SUMMARY ANSWER**

The risk of admission to hospital or death from diverticular disease was 30% lower among vegetarians compared with meat eaters and 40% lower among those with a high (>25 g/day) compared with a low (<14 g/day) intake of dietary fibre after taking into account factors like smoking and body mass index.

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS**

A low fibre diet is thought to be an important risk factor for diverticular disease and vegetarians might have a lower risk, but there is limited evidence from prospective studies to substantiate these hypotheses. Results from this prospective study suggest that participants who consume a vegetarian diet or have a high intake of dietary fibre are less likely to develop diverticular disease.

**Participants and setting**

Participants were health conscious men and women living in England or Scotland who took part in the EPIC-Oxford study, of whom 15 459 (33%) reported consuming a vegetarian diet.

**Design, size, and duration**

This prospective cohort study included 11 340 men and 35 693 women. Diet group was assessed at baseline and categorised as “meat eaters,” “fish eaters” (who ate no meat but some fish), and “vegetarians or vegans.” The intake of dietary fibre was estimated from a 130 item validated food frequency questionnaire. The main outcome was the relative risk of admission to hospital or death from diverticular disease (ICD-9 562 and ICD-10 K57) by diet group and fifths of dietary fibre intake adjusted for confounding variables.

**Main results and the role of chance**

After an average follow-up of 11.6 years, there were 812 cases of diverticular disease (806 admissions to hospital and six deaths). Vegetarians had a 31% lower risk (relative risk 0.69, 95% confidence interval 0.55 to 0.86) of diverticular disease compared with meat eaters. The cumulative probability of admission to hospital or death from diverticular disease between the ages of 50 and 70 for meat eaters was 4.4% compared with 3.0% for vegetarians. There was an inverse association with dietary fibre intake; participants in the highest fifth (≥25.5 g/day for women and ≥26.1 g/day for men) had a 41% lower risk (0.59, 0.46 to 0.78; P<0.001 trend) compared with those in the lowest fifth (<14 g/day for both women and men). After mutual adjustment, both a vegetarian diet and a higher intake of fibre were significantly associated with a lower risk of diverticular disease.

**Bias, confounding, and other reasons for caution**

A third of participants reported consuming a vegetarian diet, with most (>85%) maintaining this diet five years later, which allows for a reliable estimation of the association between vegetarianism and diverticular disease. Cases of diverticular disease were identified by record linkage with information from hospital admissions records; if there was a tendency for vegetarians to undergo fewer investigative techniques, this might bias the association between diet group and diverticular disease. Residual confounding or confounding by unmeasured variables might partially explain these results, although given the risk reductions of 30% to 40%, any effect of confounding would have to be substantial.

**Generalisability to other populations**

The finding of an inverse association between dietary fibre and diverticular disease is likely to be generalisable to other populations, but, as this was not a representative sample, the absolute rate of diverticular disease in the general British population might differ from that reported in this study.

**Study funding/potential competing interests**

The EPIC-Oxford study was funded by Cancer Research UK (grant No C570/A11691).
Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study

Jeffrey J Perry,1 Ian G Stiell,1 Marco L A Sivilotti,2 Michael J Bullard,3 Marcel Émond,4 Cheryl Symington,1 Jane Sutherland,5 Andrew Worster,6 Corinne Holt,7 Jacques S Lee,8 Mary A Eisenhauer,9 Melodie Mortensen,1 Duncan Mackey,10 Merrill Pauls,10 Howard Lesiuk,10 George A Wells12

STUDY QUESTION
Is modern third generation computed tomography sensitive enough to diagnose subarachnoid haemorrhage in neurologically intact patients?

SUMMARY ANSWER
Modern third generation computed tomography is extremely sensitive for subarachnoid haemorrhage, especially when done within six hours of headache onset and interpreted by a qualified radiologist.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
To exclude subarachnoid haemorrhage, traditionally lumbar puncture is recommended if initial results of computed tomography are negative. Modern multi-row detector third generation computed tomography alone, however, is highly sensitive for subarachnoid haemorrhage if performed within six hours of headache onset and if interpreted by a qualified radiologist.

Participants and setting
This study enrolled neurologically intact adults presenting to one of 11 tertiary care emergency departments within 14 days of a new non-traumatic headache peaking within an hour.

Design, size and duration
This prospective cohort study was carried out over nine years in 3132 patients.

Main results and the role of chance
Patients were young, most characterised the headache as being their worst ever, and a quarter arrived by ambulance. In total, 240 (7.7%) had subarachnoid haemorrhage, while 27 (0.9%) had other serious diagnoses (17 had other haemorrhagic strokes, nine had a brain tumour, and one had bacterial meningitis).

The sensitivity of computed tomography was 92.9% (95% confidence interval 80.0% to 95.5%) and the specificity was 100% (99.9 to 100). When computed tomography was performed within six hours of headache onset, the sensitivity was 100% (97.0% to 100.0%). When computed tomography was performed later, 17 of 119 patients with subarachnoid haemorrhage were not identified by unenhanced computed tomography (sensitivity 85.7%, 78.3% to 90.9%). The interval from headache onset to computed tomography ranged from eight hours to eight days.

Bias, confounding, and other reasons for caution
We accepted the local hospital’s laboratory detection of xanthochromia by visual inspection rather than using spectrophotometry, which has poor specificity and is rarely used in North America. Without a widely accepted standard criterion for subarachnoid haemorrhage, we used blood on computed tomography, xanthochromia, or the combination of erythrocytes in the final tubef of cerebrospinal fluid with abnormal cerebral angiography as the a priori definition of positive cases. We conducted telephone and medical record follow-up at one and six months to identify missed cases and so called sentinel bleeds.

Because we asked physicians not to alter practice, many lower risk patients with a negative result on computed tomography did not undergo lumbar puncture. Almost all of these patients were alive at six month follow-up, and no cases of sudden, unexpected death were reported to the provincial coroner.

We did not manipulate the time to imaging as an experimental variable nor perform serial scans. Many factors affect time to imaging, including patients’ and physicians’ perceptions of seriousness, ambulance transport, prioritised triage, and availability of imaging out of hours. Less than a third of patients, but half of those with subarachnoid, underwent imaging within six hours of headache onset. Confounding by severity (larger volume bleed) could therefore account for some of the observed difference in severity, in addition to the time dependence of erythrocyte diffusion and lysis within the subarachnoid space.

Generalisability to other populations
Our findings apply only to centres with modern, multi-row detector third generation scanners with thin slices and scans interpreted by a qualified radiologist. Healthcare systems with substantially different delays to emergency care and imaging access might also experience differences in sensitivity of computed tomography.

Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study

Jeffrey J Perry, Ian G Stiell, Marco L A Sivilotti, Michael J Bullard, Marcel Émond, Cheryl Symington, Jane Sutherland, Andrew Worster, Corinne Holt, Jacques S Lee, Mary A Eisenhauer, Melodie Mortensen, Duncan Mackey, Merrill Pauls, Howard Lesiuk, George A Wells

Sensitivity of computed tomography for subarachnoid haemorrhage in patients with acute headache stratified by timing of scan

<table>
<thead>
<tr>
<th>Time from headache onset to scan</th>
<th>No of patients</th>
<th>% Sensitivity (95% CI)</th>
<th>% Specificity (95% CI)</th>
<th>Likelihood ratio (95% CI)</th>
<th>Predictive value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>All patients</td>
<td>3132</td>
<td>92.9 (89.0 to 95.5)</td>
<td>100 (99.9 to 100)</td>
<td>Infinity</td>
<td>0.07 (0.05 to 0.11)</td>
</tr>
<tr>
<td>56 hours</td>
<td>953</td>
<td>100 (97.0 to 100.0)</td>
<td>100 (99.5 to 100)</td>
<td>Infinity</td>
<td>0.00 (0.00 to 0.02)</td>
</tr>
<tr>
<td>16 hours</td>
<td>2179</td>
<td>85.7 (78.3 to 90.9)</td>
<td>100 (98.8 to 100)</td>
<td>Infinity</td>
<td>0.14 (0.14 to 0.17)</td>
</tr>
</tbody>
</table>
Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIA lung cancer: observational cohort study

Juan P Wisnivesky,1 2 Cardinale B Smith,3 4 Stuart Packer,3 Gary M Strauss,5 Linda Lurslurchachai,1 Alex Federman,1 Ethan A Halm6

STUDY QUESTION
Does postoperative platinum based chemotherapy improve the survival of older patients after resection of stages II-IIIA non-small cell lung cancer?

SUMMARY ANSWER
Using propensity score methods to adjust for potential confounders we showed that chemotherapy was associated with improved survival (hazard ratio range 0.78–0.81) in older patients with stages II-IIIA non-small cell lung cancer treated in the community.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Randomised controlled trials have shown the efficacy of adjuvant chemotherapy for stages II-III A non-small cell lung cancer in selected patients. Using data from a population based cancer registry, we showed that adjuvant chemotherapy is associated with improved survival among older patients with lung cancer treated in the community.

Propensity score analysis of survival in patients receiving adjuvant chemotherapy for resected stages II-IIIA lung cancer

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard ratio (95% CI)</th>
<th>Not adjusted for radiation therapy</th>
<th>Adjusted for radiation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>Entire cohort:</td>
<td>Adjusting for propensity scores</td>
<td>0.80 (0.72 to 0.89)</td>
</tr>
<tr>
<td></td>
<td>Stratified by propensity score fifths</td>
<td>0.81 (0.73 to 0.89)</td>
<td>0.77 (0.69 to 0.85)</td>
</tr>
<tr>
<td></td>
<td>Matched analysis</td>
<td>0.78 (0.70 to 0.87)</td>
<td>0.74 (0.66 to 0.82)</td>
</tr>
<tr>
<td>Secondary analyses by age group</td>
<td>&lt;70 years:</td>
<td>Adjusting for propensity scores</td>
<td>0.74 (0.62 to 0.88)</td>
</tr>
<tr>
<td></td>
<td>Stratified by propensity score fifths</td>
<td>0.75 (0.63 to 0.90)</td>
<td>0.73 (0.61 to 0.87)</td>
</tr>
<tr>
<td></td>
<td>Matched analysis</td>
<td>0.76 (0.63 to 0.90)</td>
<td>0.72 (0.61 to 0.86)</td>
</tr>
<tr>
<td></td>
<td>70-79 years:</td>
<td>Adjusting for propensity scores</td>
<td>0.82 (0.71 to 0.94)</td>
</tr>
<tr>
<td></td>
<td>Stratified by propensity score fifths</td>
<td>0.83 (0.73 to 0.96)</td>
<td>0.78 (0.69 to 0.90)</td>
</tr>
<tr>
<td></td>
<td>Matched analysis</td>
<td>0.82 (0.71 to 0.93)</td>
<td>0.77 (0.67 to 0.89)</td>
</tr>
<tr>
<td></td>
<td>≥80 years:</td>
<td>Adjusting for propensity scores</td>
<td>1.33 (0.86 to 2.06)</td>
</tr>
<tr>
<td></td>
<td>Stratified by propensity score fifths</td>
<td>1.32 (0.84 to 2.05)</td>
<td>1.22 (0.78 to 1.90)</td>
</tr>
<tr>
<td></td>
<td>Matched analysis</td>
<td>1.46 (0.91 to 2.34)</td>
<td>1.29 (0.80 to 2.08)</td>
</tr>
</tbody>
</table>

Participants and setting
The study was carried out using data from patients aged more than 65 years with resected stages II-IIIA lung cancer included in the Surveillance Epidemiology and End Results (SEER) registry linked to Medicare files.

Design, size, and duration

Main results and the role of chance
Overall, 684 (21%) patients received platinum based chemotherapy. Analyses adjusted, stratified, or matched by propensity scores showed that chemotherapy was associated with improved survival (hazard ratio range 0.78–0.81). The beneficial effect of chemotherapy was also observed among patients treated with or without radiation therapy; however, chemotherapy was not beneficial for patients aged 80 or more.

Bias, confounding, and other reasons for caution
In observational studies, decisions about the use of adjuvant chemotherapy are influenced by patients’ preferences, doctors’ judgment, and practice patterns. These considerations can generate systematic differences in the distribution of prognostic factors among patients treated with and without chemotherapy, which act as confounders of the treatment effect.

Generalisability to other populations
The SEER-Medicare database is a comprehensive source of population based data on cancer. Thus our results should be highly generalisable to the US population of older people as a whole.

Study funding/potential competing interests
This study was supported by the National Cancer Institute (R01CA131348-02). CBS was supported in part by a research supplement to promote diversity in health related research programme award (R01CA131348-03S1). JPW has relationships with EHE International (member of research board), Novartis Pharmaceutical (lecture honorarium), and GlaxoSmithKline (chronic obstructive lung disease research grant) that might have an interest in the submitted work in the previous three years.