Intensive glucose lowering treatment in type 2 diabetes
The effect on microvascular disease seems to be modest at best

The recognition that diabetes is an independent risk factor for cardiovascular disease has led to trials of different glucose lowering strategies in an attempt to reduce the risk of such disease. The effect of glucose lowering on cardiovascular disease outcomes is one of the most contentious in recent history, as indicated by the class llb recommendation from the joint American Diabetes Association, American Heart Association, and American College of Cardiology guidelines. In the linked meta-analysis, Boussageon and colleagues assess both microvascular complications and cardiovascular events related to the intensity of glycaemic control and the quality of randomised studies.

Before considering individual trials several factors warrant consideration. For example, it is possible that glucose lowering is a much weaker intervention than previously envisaged so that individual trials may be underpowered to detect changes in a chosen end point. Also, current treatments may partly negate any benefit of glucose lowering by exchanging one risk factor for another—for example, weight gain, which has concomitant effects on blood pressure and lipids.

The largest study to date, which compared the effects of intensive glucose lowering with standard treatment on cardiovascular outcomes, reported data from five randomised controlled trials on 33,040 patients in whom 1,497 non-fatal myocardial infarctions, 2,318 coronary events, 1,127 strokes, 2,892 deaths, and 1,391 cases of new or worsening heart failure occurred. It found that a 0.9% lowering of glycated haemoglobin (HbA1c) 7.5% v 6.6%) was associated with a 17% reduction in non-fatal myocardial infarctions, 15% reduction in coronary events, and a trend towards lower stroke risk with no statistical evidence of heterogeneity. Mortality and heart failure did not differ significantly between intensive and standard treatment arms. These data are consistent with literature based analyses that excluded PROactive, and a meta-analysis of four major trials with individual participant data, which also suggested that cardiovascular benefit after intensive glucose lowering was limited to people without known cardiovascular disease.

Boussageon and colleagues’ meta-analysis adds eight extra studies with information on a further 1,493 participants in whom 54 additional non-fatal myocardial infarctions, 209 deaths, and 187 cases of new or worsening heart failure occurred. The cardiovascular data are broadly consistent with earlier reports, showing a 15% reduction in non-fatal myocardial infarctions but no clear effect on other cardiovascular disease events. This is despite inclusion of some small studies with incomplete randomisation (UGDP), studies that lack end point adjudication (Kumamoto study, HOME trial), and trials of agents that are now withdrawn because of safety concerns (UGDP). The authors provide sensitivity analyses based on trial quality (Jadad score >3 for high quality, v ≤3 for low quality). However, the supposedly high quality studies provide data for only 6,465 subjects with 323 non-fatal myocardial infarctions and 195 strokes, thereby reducing the available data by more than 80%. Also the sensitivity analysis of intensive glucose lowering and heart failure events is dominated by the PROActive study, in which pioglitazone was the active treatment under investigation. It seems unlikely that there would be any clear significant difference between low and high quality studies for the various cardiovascular outcomes on the basis of conventional statistical interaction analyses.

The meta-analysis is consistent with earlier evidence 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 (figure). A combined approach that targets glucose lowering, lipid lowering, and blood pressure control seems to be most beneficial, and available data also suggest a long lasting beneficial effect on diabetes related clinical events many years after an intensive regimen. The authors rightfully say that an improvement in surrogate markers (such as HbA1c) is not conclusive evidence of clinical benefit. This was highlighted by the Food and Drug Administration in guidance published in December 2008, which includes specific targets for investigators to satisfy the cardiovascular safety of new glucose lowering drugs.

Boussageon and colleagues’ study provides large scale quantification of the effect of intensive glucose lowering on microvascular disease. Intensive glucose lowering reduced new or worsening microalbuminuria, with a trend towards a reduction in new or worsening retinopathy, but it had little
Diet and risk of diverticular disease

Vegetarians and people who consume high fibre diets may have a lower risk

Colonic diverticular disease causes a substantial healthcare burden, which is likely to increase as the elderly population grows. Little is known about who is affected by the disease, how often it occurs, and what the consequences are for patients. Nevertheless, the causes of diverticular disease, and the role of dietary fibre and a vegetarian diet, have been the focus of some small epidemiological studies. For example, in a study of 264 patients from the general population compared with 56 vegetarians, the vegetarians were less likely than the non-vegetarians to have radiologically confirmed diverticulosis (12% vs 33%).

Furthermore, in a cross sectional study of 264 patients with confirmed diverticulosis, those with a vegetarian diet were less likely to have diverticulosis than non-vegetarians (12% vs 33%). A cohort study of American healthcare professionals found that the insoluble component of fibre was associated with a decreased risk (relative risk 0.63, 95% confidence interval 0.36 to 0.75) of diverticular disease.

The linked study by Crowe and colleagues used data from the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) to assess the associations between vegetarianism and dietary fibre intake and the risk of diverticular disease. The authors found that vegetarians had a 31% lower risk of hospital admission or death from diverticular disease compared with meat eaters (0.69, 0.55 to 0.86). This translated into a cumulative probability of hospital admission or death caused by diverticular disease in 50-70 year olds of 4.4% for meat eaters and 3.0% for vegetarians; this represents a 1.4% excess absolute risk in non-vegetarians over a median of 11.6 years of follow-up. The authors also reported an inverse association between dietary fibre intake, with those in the highest fifth of fibre intake having a 41% lower risk (0.59, 0.46 to 0.78) of diverticular disease compared with those in the lowest fifth.

The main challenge in assessing whether these findings represent a true association between diet and occurrence of diverticular disease comes down to three factors: the choice of outcome measure, the amount of bias inherent in the study population, and the extent of unmeasured confounding.

The main outcome was based on a “first hospital diagnosis” of diverticular disease defined by ICD-9 and ICD-10 (international classification of diseases, 9th and 10th revisions) using linked hospital episode statistics data from England, data from the Information Services Division of Scottish Mortality Records, or a cause of death from a death certificate. When considering this the terminology of colonic diverticular disease and how a diagnosis is acquired must be clear. Colonic diverticulosis is the presence of outpouchings from the colon, diverticular disease is the presence of diverticulosis with attributable symptoms, and complicated diverticular disease is the presence of a complication (perforation, abscess, fistula, stricture, or bleeding) associated with diverticular disease. Unfortunately, both ICD-9 and ICD-10 are limited in their coding of such detail, so a positive outcome in this report would have included all of the above diagnoses, some of which are acquired through elective endoscopic or radiological investigations. Hence the overall incidence reported of 148 per 100 000 person years contrasts greatly with that
Chemotherapy in elderly patients with resected stage II-III A lung cancer

Age alone is not a contraindication to treatment

As a result of increasing life expectancy, the number of lung cancers in elderly people is rising—most cancers occur in patients over 65 years, with a median age at diagnosis of about 70 years. In the linked study, Wisnivesky and colleagues compare outcomes in elderly patients with stage II-III A non-small cell lung cancer (NSCLC) treated with and without postoperative platinum based chemotherapy.1

Lung cancer remains the leading cause of death from cancer worldwide. In 2008, 391 000 cases of lung cancer were diagnosed in Europe, and lung cancer was responsible for a fifth of the total number of deaths from cancer.2 Despite the declining use of cigarettes in many Western countries, lung cancer rates continue to rise in women. In several European countries, including the United Kingdom, lung cancer has become the most common cause of cancer related deaths in both sexes.2 The treatment of elderly patients with NSCLC presents special challenges for clinicians. The development of comorbid conditions and the proportion of patients who present with poor performance status increase notably between 70 and 75 years of age. Despite accumulating evidence that healthy elderly patients can benefit from effective anticancer treatment at all stages of NSCLC, concerns about their ability to tolerate treatment related toxicity lead to treatment disparities and undertreatment. Wisnivesky and colleagues’ study provides useful answers to the question of whether or not elderly patients with resected stage II-III A NSCLC should be offered adjuvant chemotherapy in routine practice.3

The management of NSCLC has changed over the past decade, since phase III randomised controlled trials and meta-analyses demonstrated a five year survival benefit of 5% with adjuvant platinum based chemotherapy in patients with resected NSCLC.4 5 The benefit is even greater in stage II-III A disease. Current evidence based practice guidelines therefore recommend adjuvant chemotherapy that combines a third generation agent and a platinum based drug for these patients. However, no solid evidence is available from phase III trials to guide treatment decisions in older age groups. Specific trials have focused on questions posed by advanced disease in elderly people. The under-representation of older patients in randomised controlled trials of stage II-II A disease and the selection of study participants by age and comorbidities may limit the generalisability of results to routine care.

Using data from a population based cancer registry and Medicare files, Wisnivesky and colleagues show that adjuvant platinum based chemotherapy is associated with improved survival in patients aged 65 and older with perforated diverticular disease, for example, which at 2.7 per 100 000 is 55 times less common, and the results should be interpreted in that light.7

The potential bias in the study population is important because by design the study selected mainly health conscious people and targeted those who were likely to have a vegetarian diet. Consequently, more than 82% of participants in this study were under 60 years of age at recruitment, and among the self declared vegetarians most were women who were younger and “healthier” than the meat eaters. Given these differences it seems plausible that the vegetarians in the cohort will have had less contact with the healthcare system in general (through other illnesses, comorbidities, and behaviour), which would have restricted their opportunity to be diagnosed with diverticular disease. In addition to this potential ascertainment bias, residual confounding is a problem. Potential confounding through the use of prescribed drugs previously linked to diverticular disease is one example, although the chance of this is probably small.

If we accept that the findings of this study represent a true effect of both a vegetarian and a high fibre diet on the occurrence of diverticular disease what are the implications for the health of the population and the individual? At a population level, if the available absolute risks are converted into a number needed to treat, about 71 meat eaters would have to become vegetarians to prevent one diagnosis of diverticular disease as measured in this study. As this cohort ages, the development of the complications of divertulosis, which increase in frequency and are associated with a high rate of mortality, can be studied. Such investigations would probably provide the best opportunity to make improvements in the treatment of this disease.8 9 Overall the opportunity for preventing the occurrence of diverticular disease and other conditions, such as colorectal cancer, probably lies in the modification of diet, at either a population or an individual level. However, far more evidence is needed before dietary recommendations can be made to the general public.

8 Humes DL, West J. The role of acute diverticulitis in the development of complicated colonic diverticular disease and one year mortality following diagnosis in the UK: population based cohort study. Gut 2011; online 6 May.

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bmj.com/archive
- Should we treat uncomplicated symptomatic diverticular disease with fibre?
- Diet and the risk of cancer

bmj.com/blogs
- Tauseef Mehrali on eating animals
- Juliet Dobson on eating animals

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EDITORIALS

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Pressure to work through periods of short term sickness

Can have long term negative effects on health and productivity

Recent research shows that during a period of four weeks a third of doctors and nurses have worked when they should have taken sick leave, and that, on average, this nearly halves their working capacity. Presenteeism is the phenomenon of workers turning up to work despite medical conditions that should prevent them from attending. Although it has been associated with negative health effects and with loss of productivity, it is only in recent years that presenteeism has gained some focus in research. In July 2003 a word search for absenteeism in Web of Science produced 1262 hits, whereas presenteeism produced only 11 hits. The same search in May 2011 scored 3388 hits for absenteeism and 287 for presenteeism.

Around 26% of healthcare workers report presenteeism in the past seven days and about 85% of general practitioners and hospital workers report being sick at work some time. Research has identified many risk factors for presenteeism, and much more work is needed to determine what factors are modifiable and what sort of impact successful modifications would have.

Presenteeism is more strongly noted in certain occupations, particularly those that involve caring and teaching. For health professionals hospital culture plays a role, and variations among health professionals report being sick at work some time. Research has identified many risk factors for presenteeism, and much more work is needed to determine what factors are modifiable and what sort of impact successful modifications would have.
workers who lack back-up and for whom work accumulates while they are absent are more inclined to practise presenteeism. 3 Other work related factors that foster presenteeism include working in teams where expectations to be present are high, 4 limited sick leave entitlements, 5 high job demands (which also correlates with burnout), 7 low levels of job satisfaction, 8 fear of dismissal, and concerns about promotion opportunities. 9 But stimulating work environments can also promote presenteeism. 7 Factors external to the workplace include financial problems and high unemployment rates. 6 Female workers may practise presenteeism more, 4 particularly as they are more likely to be in caring and teaching occupations, but in some occupations women resist the pressure to work when sick more than men do. 3

Certain medical conditions are likely to predispose to presenteeism. Psychological problems, particularly depression, may do so because they are not seen as legitimate reasons for absence. 3 Migraine is also associated with presenteeism, 3 and the phenomenon is also more common in workers with poorer health, probably because of concerns about finding other employment in the event of redundancy. 5

Certain individual traits, such as difficulty in resisting other people’s wishes, have also been associated with presenteeism. 6 Presenteeism may be higher in people whose self esteem is dependent on their individual performance—for example, young adults. 10

Presenteeism increases morbidity, 5 8 including musculoskeletal pain, fatigue, depression, 4 and serious coronary events. 11 It leads to exhaustion, and in a spiralling fashion exhaustion leads to more presenteeism. 9

In healthcare settings presenteeism poses a particular concern because of the spread of infections, 5 so preventive measures have been instituted. Less attention has been paid to presenteeism and its prevention in other occupations, however.

Presenteeism should be taken seriously if we are concerned with occupational health or workplace productivity. Presenteeism is a complex phenomenon that needs to be approached from several different levels including workplace culture, workplace policies, and carefully considered interventions from health practitioners.

Work related factors have a bigger effect on presenteeism than personal circumstances, although these are still important. 1 Health promotion at the workplace could emphasise the control that workers have over their work processes and the capacity of workers to resist hazardous demands from management. 12 Senior staff can model behaviour that does not promote presenteeism 4—for example, by discouraging over-commitment to work and encouraging workers to allow sufficient recovery time from sickness, which may require provision of back-up, particularly in the caring occupations. 10 Workers with poor health should receive special attention to avoid presenteeism because they are likely to have fewer resources to call on to resist its negative impact.

Occupational physicians should avoid “standardised” responses to return to work. The worker must be placed within the workplace context and the influences on absenteeism and presenteeism in that workplace, and how the person responds to them. 1 Manual labourers and clerical workers may have to be discouraged from attending work for different kinds of medical conditions. For example, some musculoskeletal problems may be more problematic for one group than for the other.

Occupational physicians should consider developing indices of workplace presenteeism that would help them when advising both employers and employees. Managers and occupational physicians need to be alert to the findings that even though presenteeism may have some positive effects in the short term—particularly for healthy workers with high job satisfaction—it is likely to be negative in the long term. 3 Workers with chronic conditions, who by some definitions will always be sick at work, provide an important contrasting consideration. However, evidence suggests that for many the pressure to work when sick is intense, and more effort is needed to prevent this health debilitating behaviour.

WikiProject Medicine
Could become a trusted resource if it is assisted not shunned

In January 2011, members of WikiProject Medicine published an article about the intricacies, strengths, and weaknesses of Wikipedia as a source of health information and compared it with other medical wikis. The article poses some interesting challenges and opportunities for the global community as Wikipedia’s seven year old WikiProject Medicine reaches an estimated 150 million viewers every month.

The claimed usage of Wikiproject Medicine is just under half of the 362 million monthly viewers of its parent Wikipedia, which is now the sixth most popular site on the internet. This seems set to rise if search engines such as Google continue to show this site at the top of search results and with an upcoming iPhone application that will make it even more convenient and accessible.

The WikiProject Medicine group within Wikipedia has developed systems that make this project superior to many other health wikis and provide the potential for future improvements. These systems include grading of article quality and importance, a set of referencing guidelines for authors, and links to PubMed Plus and PubMed from article pages. Impressively, of the more than 25,000 medical articles published, all but 304 have been assessed, according to the WikiProject article quality grading system, by one of the 206 group members. A grade is “subjectively” assigned by a project member after an author’s request. Unfortunately, only around 70 articles have been graded as suitable for a “feature article or listing,” which means the article is well written, comprehensive, well researched, neutral, stable (not subject to edit wars), and follows particular style guidelines. Most articles are graded as either incomplete or a “stub,” providing “little meaningful content.” With the exception of a small star given to “feature articles” the grade is publicised only to readers who register for that specific feature.

Improving this quality grading process could be a key step towards improving the overall quality of the information. Ideally all articles would achieve a featured article grade, but authors and readers are not provided with any feedback from the WikiProject Medicine reviewer that could help them to revise and improve their article and aspire to this level.

As with any open source document there is a risk that information will be tampered with and that harmful information may be posted. The group has introduced anti-vandalism features, such as page protection and blocking, and has attempted to flag “unreliable” and “unstable” pages. However, this kind of monitoring requires commitment by trusted administrators and editors. This is a key factor in whether the project truly has the potential to become a sustainable and effective resource.

Given that Wikipedia is run by a charitable organisation, Wikimedia Foundation, authors and reviewers need to continue to provide and revise content without compensation or recognition. It is laudable that Wikipedia creates a virtual community of authors that includes professionals and laypeople, and that articles written by laypeople have been shown to be trustworthy. However, the group will have to tackle the tension between promoting a free speaking virtual community of authors that publishes exclusively under pseudonyms and the need to declare conflicts of interest and allow greater transparency for readers. It is currently difficult to detect commercial and other conflicts of interest, although such conflicts are likely in articles where particular treatments are over-represented compared with current clinical practice guidelines. Some would argue that authors (and reviewers) should be named for ethical reasons in peer reviewed journals and other publications, although it is uncertain what effect this would have on the quality of content and reviews in Wikipedia.

The quick, easy, and free access to Wikipedia makes it attractive to many people, particularly those in developing countries, where internet access remains slow and costly. It is also promising that non-English articles are appearing, although they are rare compared with English ones; 129 articles are published on hypertension in English but only six in Bahasa Indonesian. Chinese contributions are non-existent, which is a pity given the burden of disease from hypertension in that nation. If WikiProject Medicine truly is to become a resource for informing healthcare in non-English speaking countries there are real challenges in harnessing experts in these nations to write, review, and update content. Also, it could provide an excellent opportunity for authors to publish in their own language, reflecting health practices in their own health systems and cultures. The same quality checks and balances outlined above will still need to apply.

WikiProject Medicine promotes itself as an information source for healthcare providers and students. One qualitative study reported that 70% of junior doctors used Wikipedia for health information at least once a week. With time constraints continuing to be a major barrier for clinicians trying to access evidence based information, the simplicity and speed of the Wikipedia format is appealing. Clinicians have continually stated that they want simple summaries of evidence rather than lengthy detailed technical items that require access to complex and sometimes expensive databases. If we really want to see the dissemination of evidence based information and facilitate putting evidence into practice, perhaps we need to start writing articles for Wikipedia.