POEMs

Patient-Oriented Evidence that Matters

Two of the POEMs for June exemplify why practising evidence-based medicine can be difficult. They both consider whether actively treating patients who have glucose intolerance prevents the development of frank diabetes. One says yes and the other says no. One could argue about the strength of the evidence and the study design, but the bottom line is that the evidence for treatment is not strong. Having said that, it seems to me to make sense to advise patient who have impaired glucose tolerance to modify their diets and to lose weight! The other two POEMs add to the growing amount of evidence advising us to be wary of certain medical interventions, in this case the use of antioxidants and the use of aspirin in combination with warfarin (except in patients with mechanical heart valves). Editor.

Clinical question

Is the addition of aspirin to warfarin safe and more effective than warfarin alone?

Bottom line

Except for patients with mechanical heart valves, the addition of aspirin to therapeutic warfarin doses does not decrease the risk of death or of thromboembolism and does not increase the risk of a major bleed. (LOE = 1a)

Reference

Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease. A meta-analysis of randomized trials. Arch Intern Med 2007;167:117-124.

Study Design

Meta-analysis (randomised controlled trials)

Funding

Foundation

Setting

Various (meta-analysis)

Synopsis

The researchers conducting this study assembled and combined randomised studies of at least three months' duration that compared warfarin plus aspirin with warfarin alone, in which warfarin was administered to achieve the same target international normalised ratio (INR) or was given at the same fixed dose in both treatment arms. The authors conducted an appropriate search of three databases, reviewed reference lists, and contacted experts to find 10 studies of more than 4000 patients that met their criteria. Two authors independently evaluated the research using a modified version of the Jadad criteria and extracted the data. Five studies evaluated the use of the combination in patients with mechanical heart valves, and the other studies included patients with atrial fibrillation, with coronary artery disease, or at high risk for cardiovascular disease. Doses of aspirin ranged from less than 100 mg to 1000 mg per day; warfarin was dosed to obtain a target INR of at least 1.8 in eight studies and 2.0 or higher in two studies. Overall, major bleeding was more likely to occur when the combination was used (number needed to treat to harm = 100). Mortality due to any cause was not reduced by the addition of aspirin. In patients with mechanical heart valves, the addition of aspirin decreased the risk of thromboembolism (odds ratio = .27; 95% CI .15–.49), but also increased the risk of bleeding. In patients with heart disease or atrial fibrillation, the addition of aspirin did not decrease the risk for thromboembolism but also did not increase the risk of major bleeding. There was no evidence of publication bias and the result showed homogeneity among the studies.

** Patient-Oriented Evidence that Matters. See editorial (NZFP 2003; 30:150)*

Clinical question

Do diet and exercise delay the development of diabetes in high-risk patients?

Bottom line

Diet and exercise are effective in delaying the diagnosis of diabetes in patients at increased risk. (LOE = 2b)

Reference

Lindstrom J, Ilanne-Parikka P, Peltonen M, et al, for the Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 2006;368:1673-1679.

Study Design

Randomised controlled trial (nonblinded)

Funding

Industry + foundation

Allocation

Unconcealed

Setting

Outpatient (any)

Synopsis

In the Finnish Diabetes Prevention Study, 522 men and women, aged between 40 years and 65 years and at high risk for developing diabetes, were randomly assigned either to a tailored diet-and-exercise regimen or to usual care. To be eligible, the patients had to have a body mass index greater than 25 and have impaired glucose tolerance. The original study lasted a median of four years. The cumulative incidence of diabetes in the intervention group was 11% compared with 23% in the control group (number needed to treat = 8; 95% CI 6–16). In this report, the researchers provide three additional years of observations on the patients who had not developed diabetes by the end of the original study. No specific diet or exercise information was provided to the patients during this follow-up period. After a total of seven years of follow-up, 75 patients in the intervention group and 110 patients in the control group developed diabetes. The cumulative incidence rate was 4.3 per 100 person-years in the intervention group, and 7.4 in the control group. The authors estimate that one would need to treat 22 patients with diet and exercise to prevent one patient per year from developing diabetes.

Clinical question

Do antioxidant supplements reduce all-cause mortality for adults?

Bottom line

Current evidence suggests that regular supplementation with the antioxidants beta carotene, vitamin A, and vitamin E increases mortality risk in adults. This report found no evidence of benefit or harm from supplementation with vitamin C and selenium. (LOE = 1a-)

Reference

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention. Systematic review and meta-analysis. JAMA 2007;297:842-857.

Study Design

Meta-analysis (randomised controlled trials)

Funding

Government

Setting

Various (meta-analysis)

Synopsis

These investigators analysed the effects of antioxidant supplements (beta carotene, vitamins A, C, and E, and selenium) on all-cause mortality. They performed a thorough search of multiple databases including the Cochrane Registry, Science Citation Index, MEDLINE, and relevant references for randomised controlled trials evaluating these supplements, either singly or in combination. Two authors independently reviewed in-

dividual trials for quality. Disagreements were resolved through consensus discussion with a third individual. Assignment of individual trial quality scores occurred using standard methods. Overall methodological quality of the individual trials was good. From an initial list of 1201 references reporting approximately 815 individual trials, 68 met study inclusion criteria (n = 232 606). The mean age of participants was 62 years (18 years–103 years); follow-up occurred for a mean of 3.3 years (one month–14 years). When all the trials were combined, there was no significant effect of antioxidant supplements on mortality. An analysis of outcomes from only high-quality trials showed a significantly increased risk of mortality with beta carotene, vitamin A, and vitamin E, either singularly or combined. Selenium and vitamin C had no significant effect on overall mortality. Results of the individual trials did not meet standard criteria for heterogeneity (meaning that the findings from individual trials were generally consistent). No formal discussion of publication bias was reported. The majority of studies were funded by commercial sources (thus preferring not to publish negative trials), so it is likely that these summary results underestimate the true increased risks.

Clinical question

Does treatment of postprandial hyperglycemia in patients with early, asymptomatic diabetes delay progression to frank fasting hyperglycemia?

Bottom line

The jury is still out regarding the identification and treatment of patients with prediabetes. According to this study, a similar percentage of patients with early diabetes will develop frank diabetes whether or not they receive therapy to lower postprandial glucose levels. A larger, though shorter, study has shown a difference, but it looks like early benefit is lost over time. (LOE = 1b-)

Reference

Kirkman MS, Shankar RR, Shankar S. Treating postprandial hyperglycemia does not appear to delay progression of early type 2 diabetes. Diabetes Care 2006;29:2095-2101.

Study Design

Randomized controlled trial (nonblinded)

Funding

Industry + govt

Allocation

Uncertain

Setting

Outpatient (specialty)

Synopsis

Researchers conducting this US-based study enrolled 219 adults with obesity, a history of gestational diabetes, or a family history of diabetes. The patients did not have a diagnosis of diabetes but had a fasting plasma glucose level between 105 mg/dL and 140 mg/dL (5.5 mmol/L–7.8 mmol/L) and a two-hour postload of plasma glucose of at least 200 mg/dL (11.1 mmol/L). After a two-day admission for extensive testing, patients were randomly assigned, concealed allocation uncertain, to receive either placebo or acarbose (Precose) titrated to a maximum dose of 100 mg three times daily. The maximum dose was achieved by 91% of patients. The patients had their fasting glucose level measured every three months for up to five years. Approximately 43% of the patients did not complete the study. Since the dropout rates were similar in both groups, it is likely that the patients represent a highly motivated group of people. Additionally, given the frequent side effects of acarbose, patients receiving placebo were probably aware of that fact and may have been more rigorous with nondrug efforts to reduce the risk of diabetes. This increased effort might be responsible for the lower than expected development of diabetes in the placebo-treated patients. Though postprandial glucose levels were decreased by acarbose, over the five years of the study a similar proportion of patients in both groups developed frank fasting hyperglycemia, approximately 30% in both groups (29% vs 34%). The study was small and the results would only be significant if the treatment decreased the development of diabetes by half as compared with typical rates of development. The results conflict with the shorter-duration STOP-NIDDM study which found, after an average three years, that 32% of treated patients had diabetes as compared with 42% of placebo-treated patients (Lancet 2002;359:2072-2077). A nonsignificant difference in diabetes also occurred at three years in the current study, though the difference was lost by the end of the study.