POEMs

Patient-Oriented Evidence that Matters

The POEMs for October are good for general practice because they provide evidence for what many of us already believe to be true. The first two POEMs, although adding to some of the confusion about lipid-lowering and longevity, question the benefits of these drugs in otherwise well patients. The second two POEMs support the use of PPIs as diagnostic agents in patients with non-cardiac chest pain. The final POEM for this month is a review of a New Zealand study that supports the use of antibiotics in women with symptoms of UTI even though there is no evidence of infection on dipstick or culture. Editor.

Clinical question

What methods of lipid lowering decrease overall mortality in patients with hyperlipidemia?

Bottom line

Only statin lipid-lowering drugs have been shown to decrease overall mortality in patients with high cholesterol but without evidence of heart disease. However, most patients treated with one of these drugs will not benefit: 228 have to be treated for 3.3 years to prevent one additional death during this period. In patients with known heart disease, statins and fish oil both have been shown to decrease mortality. Niacin, resins, and diet have not been shown to decrease mortality. Fibrates (gemfibrozil and others) actually increase overall mortality and at the same time decrease cardiac mortality. (LOE = 1a)

Reference

Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. Effect of different antilipidemic agents and diets on mortality. A systematic review. Arch Intern Med 2005; 165:725-30.

Study Design

Meta-analysis (randomised controlled trials)

Setting

Various (meta-analysis)

Synopsis

Do all lipid-lowering drugs make people live longer, on average? These researchers searched four databases to find randomised trials addressing this question. Two authors then independently determined whether each study was suitable for inclusion, only including studies that were randomised and were conducted over at least three months. They included studies that enrolled patients without evidence of heart disease – primary prevention as well as secondary prevention studies that enrolled patients with known heart disease. They included studies written in any language and ended up with 97 studies enrolling more than 275 000 patients. Only statins and n-3 fatty acids (fish oils or linolenic acid) decreased overall mortality and the effect of the n-3 fatty acids was only seen with patients with pre-existing heart disease. In primary prevention trials, fibrates (fenofibrate, clofibrate, gemfibrozil) increased mortality, with one additional death in every 132 patients treated for an average 4.4 years (number needed to treat to harm [NNTH] = 132; 95% CI, 69–662). Many patients have to be treated with a statin to prevent one additional death; the number needed to treat for 3.3 years was 228 (123–2958). In patients with known heart disease, 50 patients (38–78) would have to be treated with a statin to prevent one additional death and 44 patients (31–84) would need to be treated with fish oil to prevent one additional death, each over an average 4.4 years (excluding one low-quality study). Treatment with diet, resins (colestipol, cholestyramine), or niacin did not affect overall mortality.

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

Clinical question

What is the benefit of intensive lipid lowering in patients with stable coronary disease?

Bottom line

The benefit of intensive lipid therapy in patients with known heart disease is very modest: a number needed to treat (NNT) of 45 for five years to prevent any cardiovascular outcome. There was no difference in all-cause mortality between intensive and less intensive treatment groups (5.6% vs 5.7%), and the study was large enough and long enough to be able to detect such a benefit if one existed. Since the benefit of lipid lowering is greatest in patients with known disease, any benefit is certainly much less lower for patients without known disease who are at much lower risk. (LOE = 1b)

Reference

LaRosa JC, Grundy SM, Waters DD, et al., for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352:1425-435.

Study Design

Randomised controlled trial (double-blinded)

Allocation

Uncertain

Setting

Outpatient (any)

Synopsis

How low should we go? Recent guidelines have been urging us to lower the low-density lipoprotein (LDL) of patients at very high risk of coronary artery disease to 70mg/dL. In this study, 15 464 adults with a known coronary artery disease (angina with objective evidence of coronary artery disease, previous myocardial infarction [MI], or previous coronary revascularization) and an LDL between 130mg/dL and 250mg/dL were given 10mg of atorvastatin daily for eight weeks. Anyone with an LDL lower than 130mg/dL (n=10 003) at the end of this active run-in period entered the study and was randomised to atorvastatin at a dose of 10mg or 80mg per day. Patients were followed up for a median of 4.9 years. The higher dose of atorvastatin reduced the LDL cholesterol level more than the lower dose (to an average 77mg/dL vs 101mg/dL). The primary outcome was the usual cardiovascular combined outcome of death from coronary heart disease, nonfatal MI, resuscitation after cardiac arrest, or stroke. This outcome was slightly less common among patients receiving high-dose atorvastatin (8.7% vs 10.9%; P<.001; number needed to treat [NNT]=45 for five years), largely because of fewer nonfatal MIs. However, there was no difference in the likelihood of death from any cause (5.6% vs 5.7%). Both doses of the drug were well tolerated, which isn't surprising given the active drug run-in period. Adverse events were more common in the high-dose atorvastatin group (8.1% vs 5.8%; P<.001; number needed to treat to harm [NNTH]=43 for five years) as were discontinuation rates (7.2% vs 5.3%; P<.001; NNTH=52 for five years). There were only five cases of rhabdomyolysis – two in one group and three in the other – among the 10 000 participants. These findings are consistent with those of another recent article (Arch Intern Med 2005;165:725-30; see above).

Clinical question

How accurate is a trial of a proton pump inhibitor for the diagnosis of acid reflux, and how effective are PPIs for the treatment of noncardiac chest pain?

Bottom line

The use of a proton pump inhibitor (PPI) is useful in the diagnosis of gastroesophageal reflux disease (GERD) and an effective treatment for patients with noncardiac chest pain. Because some smaller studies with negative results may not have been published, the estimate of the degree of benefit of PPIs in this study may be on the high side. (LOE=1a)

Reference

Cremonini F, Wise J, Moayyedi P, Talley N. Diagnostic and therapeutic use of proton pump inhibitors in

non-cardiac chest pain. Am J Gastroenterol 205; 100:1226-32.

Study Design

Meta-analysis (other)

Setting

Various (meta-analysis)

Synopsis

This was actually two studies in one, and it did a good job of clarifying the accuracy and extent of benefit of proton pump inhibitors (PPIs) in the diagnosis and treatment of noncardiac chest pain. The authors performed an adequate search of the literature, including not only MEDLINE, but Embase, the Cochrane Controlled Trials Register, and a hand search of meeting abstracts. For the meta-analysis of the diagnosis of GERD using PPIs, acid reflux was diagnosed using 24-hour pH monitoring as the reference standard test and heart disease was excluded using appropriate tests (eight studies with 321 patients). Studies were not heterogeneous, and the pooled sensitivities and specificities for the outcome of 'greater than 50% response' were 83% and 75%. Given the overall prevalence of esophagitis using the reference standard test of 22%, this corresponds to positive and negative predictive values of 48% and 94%, respectively. The sensitivity was much lower (46%) when the outcome used was 'any response'. For the meta-analysis of treatment of noncardiac chest pain, only randomised trials that blinded patients to treatment assignment, used intention-to-treat analysis, and had a placebo control group were included (seven studies with 232 patients). Using the outcome of 'greater than 50% response' as the definition of success, the number needed to treat for PPIs in patients with noncardiac chest pain was three (pooled risk ratio=0.54; 95% CI, 0.41–0.71). There was no significant benefit if the stricter criterion of 'complete resolution' of chest pain was used. There was evidence of publication bias, with an absence of small studies that showed less benefit.

Clinical question

In patients with chest pain without cardiac origin, can a response to treatment with a proton pump inhibitor be used to confirm gastroesophageal reflux disease as the cause of the pain?

Bottom line

In patients with chest pain known NOT to be cardiac in origin, response to treatment with a stomach-acid reducing proton pump inhibitor will identify most patients with gastroesophageal reflux (GERD) and can be the first step in explaining the chest pain. (LOE=1b)

Reference

Wang WH, Huang JQ, Zheng GF, et al. Is proton pump inhibitor testing an effective approach to diagnose gastroesophageal reflux disease in patients with noncardiac chest pain. A meta-analysis. Arch Intern Med 2005; 165:1222-28.

Study Design

Meta-analysis (randomised controlled trials)

Setting

Various (meta-analysis)

Synopsis

Noncardiac chest pain (NCCP) is defined as retrosternal pain without a cardiac cause. In most cases, it is caused by GERD. This meta-analysis evaluated response to a proton pump inhibitor (omeprazole [Prilosec], lansoprazole [Prevacid], and others) as an indicator of GERD in patients without documented cardiac abnormalities. The researchers started by searching several databases, conference proceedings, and reference lists of retrieved articles for appropriate studies. Both the searches and the data abstractions were independently performed by three individuals. Endoscopy and/or 24-hour esophageal pH monitoring was used as the gold standard to diagnose GERD. The authors identified six studies enrolling a total of 200 patients. Five of the studies was double-blinded, and five of the studies were crossover studies, using the patients as their own controls. A one week trial of a proton pump inhibitor (four weeks in one study) with a greater than 50% decrease in chest pain had a sensitivity of 80% (95% CI, 71%–87%) and a specificity of 74% (64%–83%). In the individual studies, sensitivity and specificity varied with the prevalence of GERD in the population, making calculations of predictive values unwise. Another meta-analysis has shown similar results Am J Gastroenterol 2005; 100:1226-32).

Clinical question

In women with dysuria and frequency but a negative dipstick test result for nitrites and leukocytes, do antibiotics decrease symptoms?

Bottom line

No infection, no antibiotic, right? Maybe not. In women with dysuria and frequency but a negative urine dipstick result for nitrites and leukocytes, three of four women will respond to antibiotic treatment as compared with one of four taking placebo. The negative dipstick result correlated with culture 92% of the time. These results imply that some women have microbial infections that are not identified by dipstick or culture. Or, perhaps, the antibiotic is doing something other than killing bacteria. (LOE = 1b)

Reference

Richards D, Toop L, Chambers S, Fletcher L. Response to antibiotics of women with symptoms of urinary tract infection but negative dipstick urine test results: double blind randomised controlled trial. BMJ 2005; 331:143-46.

Study Design

Randomised controlled trial (double-blinded)

Allocation

Concealed

Setting

Outpatient (primary care)

Synopsis

The authors invited women between the ages of 16 years and 50 years to participate in this study if they presented to their New Zealand general practitioner with a history of dysuria and frequency but with a midstream urine specimen that was negative for nitrites and leukocytes using a standard urine dipstick. As a check on the validity of the dipstick, urine specimens were also cultured, though the results were not known until after the treatment and assessment had been completed. The 59 participants were randomised to receive, using concealed allocation, either placebo or trimethoprim 300mg daily for three days. At the end of treatment, 76% of the women treated with antibiotic had resolution of dysuria, as compared with 26% of women who were treated with placebo (P=.0005). By seven days, 90% of treated women had resolution of dysuria as compared with 59% of women receiving placebo (P=.02). One additional patient had resolution of symptoms by seven days for every four women who received treatment instead of placebo (number needed to treat = 4; 95% CI, 1.9–14.1). Urinary frequency was unaffected by treatment. It's not that the dipstick failed to diagnose infection: Culture of dipstick-negative urine grew organisms in only five of 59 women; therefore, the negative predictive value of the dipstick was 92%.

Naked

'The examination itself - the how and where of the touching - is, of course, the most potentially dicey territory. If a patient even begins to doubt the propriety of what a doctor is doing, something is not right. So what then should our customs be?

There are many reasons to consider setting tighter, more uniform professional standards. One is to protect patients from harm. About 4 percent of the disciplinary orders that state medical boards issue against physicians are for sex-related offenses. One of every 200 physicians is disciplined for sexual misconduct with patients sometime during his or her career. Some of these cases involve such outrageous acts as having intercourse with patients during pelvic exams. The vast majority of cases involved male physicians and female patients, and virtually all occurred without a chaperone present. About one third of cases studied in one state involved actual sexual intercourse with patients; two thirds involved sexual impropriety or inappropriate touching short of sexual contact. Another goal might be to reduce false accusations arising from misinterpretation.

Nonetheless, eliminating misconduct and accusations would be the wrong aim to guide medical care. The trouble is not that such acts are rare (though the statistics suggest they are), nor that total prevention - zero tolerance - is impossible. It is that, at some point, the measures required to achieve total prevention will approach the Talibanesque and harm care of patients.

Embracing more explicit standards for medical encounters, however, might actually improve relationships with patients - and that does stand as a worthy goal. The new informality of medicine - with white coats disappearing, and patient and doctor sometimes on a first-name basis - has blurred boundaries that once guided us. If physicians are unsure about what is appropriate behavior for themselves, is it any surprise that patients are, too? Or that misinterpretation can occur? We have jettisoned our old customs but have not bothered to replace them.'

Gawande A. Naked. NEJM 2005;353:645-648.