this agent. Alternatively, a similar meta-analysis was performed on available data using pioglitazone, and in 19 studies involving over 16,000 patients, pioglitazone reduced cardiovascular outcomes (hazard ratio, 0.82 [CI, 0.7-0.94]).

At this time, a definitive study has not yet been done. It is still reasonable to use TZDs in type 2 diabetic patients in whom other agents, that have a clearer safety record, have failed, such as metformin and sulfonylureas. If a TZD is used, pioglitazone is the preferred agent: It is has a favorable effect on lipids, compared with the slightly unfavorable effects seen with rosiglitazone, and no data suggested that pioglitazone increases cardiovascular risk. On the contrary, pioglitazone may reduce cardiovascular risk.

This study and the others that came after it, highlight the problems with using surrigeate markers in diabetes. Improvement in glycemic control, while desirable in theory, may not translate to improved outcomes. Future agents for diabetes should be scrutinized more carefully and not promoted for use without better outcome data over the long-term.

RELATED REFERENCES

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ASTHMA

Randomized comparison of strategies for reducing treatment in mild persistent asthma

The American Lung Association Asthma Clinical Research Centers.


AIM
To determine whether patients with mild persistent asthma that is well controlled by twice-daily inhaled corticosteroids can be managed with simpler treatment regimens.

METHODS
After receiving 6 weeks of twice-daily inhaled fluticasone, 500 patients with well-controlled, mild persistent asthma were randomly assigned to one of three treatment arms: 1) continued twice-daily inhaled fluticasone; 2) once-daily inhaled fluticasone plus salmeterol; or 3) once-daily oral montelukast. Outcomes focused on “treatment failure”, which included such metrics as the need for more intense management and physiologic deterioration and measurement of symptom scores, after 6 months.

RESULTS
Applying this broad definition of treatment failure, the authors found similar failure rates for patients continued on twice-daily inhaled fluticasone or managed with once-daily inhaled fluticasone plus salmeterol (20.2% and 26.4%, respectively) as well as a higher failure rate (30.3%) for patients treated with once-daily oral montelukast (hazard ratio, 1.6 [95% CI, 1.1 to 2.6]). The percentage of days during which patients were symptom free was similar across all three treatment groups (5.8%, 82.7%, and 78.7% [P > 0.10 for all comparisons]). By the end of the study, more patients assigned to receive twice-daily fluticasone (69.7%) or once-daily fluticasone plus salmeterol (78.4%) wished to continue their assigned treatment regimen, compared with those assigned to receive montelukast (56.4%) (P < 0.001).

CONCLUSIONS
Patients with mild persistent asthma that is well controlled with twice-daily fluticasone can be changed to once-daily fluticasone plus salmeterol. Once-daily montelukast proved to be inferior by the outcomes measures in this study but may be an acceptable regimen for some patients.

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KIDNEY STONES

A systematic review of medical therapy to facilitate passage of ureteral calculi

Singh A, Alter HJ, Littlepage A.

AIM
To determine whether medical therapy with $\alpha$-blockers and calcium-channel blockers (medical expulsive therapy) is effective in hastening passage of ureteral calculi.

METHODS
A systematic review and meta-analysis of 211 studies yielded 22 randomized trials involving nearly 2000 adult patients with radiographically confirmed ureteral calculi, to evaluate the benefit of $\alpha$-antagonists (tamsulosin) and/or calcium-channel blockers (nifedipine) compared with standard therapy.

RESULTS
While none of the included studies met all the criteria for a well-done, randomized control trial, the authors used the techniques of influence analysis to assure that no single study unduly influenced the results. For the $\alpha$-antagonist, tamsulosin, benefit was found in terms of likelihood of stone expulsion at 4 weeks (RR 1.59 [95% CI, 1.44 to 1.75]), with a number needed to treat of 3.3 (CI, 2.1 to 4.5). For the trials that reported time to expulsion, a 2- to 6-day average improvement was found. For the calcium-channel blocker nifedipine, stone expulsion rates were superior to standard therapy (RR 1.50 [CI, 1.35 to 1.68]) with an number needed to treat of 3.9 (CI, 3.2 to 4.6). Time to expulsion was improved in 7 of the 9 nifedipine trials. Minimal or no adverse side effects of either the tamsulosin (0.4 mg/day) or nifedipine (30 mg/day) were observed.

CONCLUSIONS
The results of this study were concordant with another recent meta-analysis and suggest benefit from medical expulsion of ureteral stone $\geq$ 5mm (but $<$ 10mm), both in terms of likelihood and time to passage. The implication is that patients treated with medical expulsive therapy experience fewer days of renal colic and are less likely to require interventions, such as lithotripsy or ureteroscopic procedures.

IMPLICATIONS FOR INTERNAL MEDICINE
The lifetime risk for urolithiasis in the United States is estimated at 13% for men and 7% for women, with a recurrence rate of 50% within 5 years. This accounts for 2 million office visits nationwide. Most ureteral calculi that are smaller than 5 mm in diameter pass spontaneously within 4 weeks of symptom onset.

Persistent ureteral stones are associated with stricture and renal damage. For the most part, open surgery to remove stone has given way to less invasive methods, including shock wave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy; however, these procedures are expensive and have side effects of their own.

Insofar as ureteral contraction is driven by an increase in intercellular calcium and is modulated by the autonomic nervous system and both $\alpha$-antagonist and calcium-channel blockers have been shown to inhibit ureteral spasm, it makes sense that these agents promote antegrade stone passage. Even more important is that this meta-analysis suggests that the benefits of these well-tolerated drugs outweigh the risks.

Recognizing the caveats associated with treatment decisions based on meta-analyses for patients with ureteral stone between 5 and 10 mm that are not passing quickly, it makes sense to use treatment with $\alpha$-adrenergic or calcium-channel blockers for a period of about 4 weeks to promote stone passage and to avoid more uncomfortable and costly procedures.

RELATED REFERENCE
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CERVICAL CANCER AND HPV VACCINATION
Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions: the FUTURE II study group

AIM
To determine whether a quadrivalent human papillomavirus (HPV) vaccine will reduce cervical cancer and its precursor lesions (CIN 2 and 3).

METHODS
This was a randomized, placebo-controlled, double-blind study done in 90 centers in 16 countries worldwide.