

Clinical use of evidence-based medicine: Searching

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Do ACE Inhibitors Delay the Progression of Renal Disease in IgA Nephropathy?

Patient

A 19-year-old hypertensive male with IgA nephropathy and nephrotic range proteinuria was admitted for worsening renal function.

Clinical Question

In a patient with hypertension, IgA nephropathy (IgAN), and nephrotic range proteinuria, do ACE inhibitors delay progression to end stage renal disease (ESRD)?

Search Strategy

1. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE) and ACP Journal Club using OVID interface (search performed May 1, 2006):
 - a. “nephropathy”
 - b. “ace inhibitor or angiotensin converting or ramipril or captopril or enalapril or lisinopril”
 - c. Combine (a) and (b)
 - d. Limit to systematic reviews and therapeutics
 - e. 45 matches, 1 applicable to our case:
Jafar et al - “Angiotensin-converting enzyme inhibitors and progression of non-diabetic renal disease: a meta-analysis of patient-level data.”¹

2. All years of MEDLINE (1966 to April Week 3 2006) using OVID interface (search performed May 1, 2006):
 - a. “IgA glomerulonephritis” (MeSH heading)
 - b. “angiotensin converting enzyme inhibitor” (MeSH heading)
 - c. Combine (a) and (b)
 - d. Limit (c) to human and English
 - e. Limit (d) “therapy (specificity)” under Clinical Queries
 - f. 24 matches, 1 applicable to our case:
Praga et al- “Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial”²

Searching—Focus on Clinical Queries

An efficient search strategy for a therapeutic question begins with searching high-quality, pre-appraised databases such as the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), and ACP Journal Club. The Cochrane Database of Systematic Reviews is the premier resource for high-quality, methodologically sound systematic reviews of the effects of health care interventions. Editorial teams oversee all aspects of the reviews’ preparation to ensure quality. Cochrane Database of Systematic Reviews should be considered the best initial resource for questions about therapy or prevention. DARE, one of the databases included in the Cochrane Library, contains structured abstracts of systematic reviews from the top medical journals. The structured abstracts highlight the strengths and weaknesses of the evaluated systematic reviews. ACP Journal Club evaluates articles from the top medical journals for clinical relevance and methodologic quality. The articles are presented as concise, structured abstracts. ACP Journal Club includes articles that answer a wide range of clinical questions including therapy, prevention, diagno-

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sis, prognosis, and economics. The OVID interface allows a simultaneous search of these 3 databases. If evidence that answers your clinical question is found in 1 of these 3 databases it may be sufficient to terminate your search. However, since these databases are small, evidence to answer your clinical question may not always be available. With respect to the aforementioned scenario, the search revealed a systematic review from 2001 on “ACE-Inhibitors and their utility on progression of non-diabetic renal disease,” which was abstracted by DARE. This review was not specific to our patient’s disease of IgA nephropathy. Therefore, MEDLINE was searched in an attempt to find a trial in patients more closely resembling our patient.

MEDLINE is an extensive database with over 15 million biomedical citations. Finding the specific evidence to answer a clinical question can seem overwhelming, time consuming, and frustrating. Clinicians need a way to find high-quality, relevant articles among this enormous number of citations. One way to effectively limit a MEDLINE search is by using filters or “hedges.” In the early 1990s, the Hedges Team, led by Brian Haynes at McMaster University, first developed filters based on clinical question type. These filters were updated by the same group in 2000. Haynes’s filters were designed for 3 possible outcomes: the most “sensitive” filter, which would miss as few relevant citations as possible; the most “specific” filter, which would have as few irrelevant citations as possible; and an “optimized” filter that would be a trade off between “sensitive” and “specific.” Haynes and colleagues evaluated how well these filters performed and discovered that the “sensitive” filter found 99.3% of the possible citations, while 97.4% of the citations found with the “specific” filter were clinically relevant.³ These filters are available under the heading of “clinical queries” in the OVID and PubMed MEDLINE interfaces.

Once the initial MEDLINE search generated a list of citations, pressing the “More Limits” icon on the main page of the OVID interface allows for the selection of filters within clinical queries. There are 9 categories including therapy, prognosis, diagnosis, cost, economics, reviews, clinical prediction guidelines, qualitative studies, and etiology. The emphasis may be sensitive, specific, or optimized as noted above. This strategy can also be performed in PubMed by choosing “clinical queries” from the left-side menu. In our search, we chose “therapy (specificity)” in an attempt to limit it to only rele-

vant citations. The number of citations was reduced from 103 to 24. This allowed us to save time by only looking at a small number of clinically relevant citations.

Study Characteristics

Jafar et al

- Systematic review and meta-analysis of randomized controlled trials.
- Non-diabetic patients with renal disease.
- Included studies that evaluated ACE inhibitors versus any anti-hypertensives other than ACE inhibitors.

Praga et al

- Prospective, single-center, randomized controlled trial.
- Patients with biopsy-proven IgA nephropathy, proteinuria ≥ 0.5 g/d and serum creatinine (SCr) ≤ 1.5 mg/dl.
- Evaluated enalapril versus anti-hypertensives other than ACE inhibitors.

Validity of Evidence

Jafar et al

- Pre-appraised by DARE.
- Some minor concerns that the search could have been more extensive.

Praga et al

- Appropriate randomization and concealment.
- The study was not blinded, which could introduce bias.
- Intention to treat analysis performed.
- Follow-up was 76 ± 36 months, which was sufficiently long to evaluate worsening of renal function.
- Two patients in each treatment group were lost to follow-up, which is reasonably complete.
- Patients appear to have been treated similarly during the trial except for the use of the experimental ACE inhibitors. Blood pressures were similar between groups.
- Patients were similar at entry into the study, but factors such as hyperlipidemia and tobacco use were not taken into consideration. These could affect progression of renal disease. Retrospective evaluation showed no differences in patients taking statins or proportion of smokers during the trial.
- Overall, this was a very small study of good methodologic quality.

Study Results

Study (Authors)	Jafar et al	Praga et al
Search Results	11 Randomized control trials met inclusion criteria	N/A
Patients	1860 patients, 941 in the treatment group, 919 in the control group	44 adult patients, 23 in the treatment group, 21 in the control group
Main Outcomes	RR (95% CI)	OR (95% CI)
50% increase in baseline SCr	N/A	0.62 (0.45-0.85)
Progression to ESRD	0.59 (0.47-0.74)	N/A
Doubling of SCr or progression to ESRD	0.18 (0.03-0.87)	N/A

SCr = Serum Creatinine; ESRD=End Stage Renal Disease.

Applying the Evidence to the Patient

- The patient in the scenario is very similar to the patients in the Praga et al study.
- The patients in the individual studies reviewed by Jafar et al are more diverse, but the evidence can probably be extrapolated to our patient since they all had non-diabetic renal disease with proteinuria.
- Treating with ACE inhibitors is feasible and our patient has no contraindications or concerns about taking the drug.

Summary

By simultaneously searching the Cochrane Database of Systematic Reviews, ACP Journal Club, and DARE, a well done systematic review by Jafar et al was obtained in a very time efficient manner. This pre-appraised review showed that ACE inhibitors significantly decreased the progression to ESRD in patients with non-diabetic renal disease. Clinical queries search filters allow clinicians to rapidly limit MEDLINE searches to relevant citations with minimal loss of potentially useful citations. Filters (or “hedged”) were used on this MEDLINE search, which found an article by Praga et al that was more specific to our patient. This small, high-quality study showed that ACE inhibitors might prevent a 50% increase in baseline SCr in the more select patient population that has proteinuria and IgAN.

Bottom Line

There is strong evidence that ACE inhibitors delay progression to ESRD in non-diabetic patients with proteinuria. In this clinical scenario, the benefits of

delaying progression to ESRD outweigh the risk associated with taking the medication, so the patient should be treated with an ACE inhibitor.

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Wisconsin Medical Journal

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