

COMMENTS AND RESPONSES

Evaluation of Guidelines on Diabetes Medication

TO THE EDITOR: We were interested to read Bennett and colleagues' systematic review (1) on the evaluation of guideline recommendations on oral medications for type 2 diabetes mellitus. However, we were surprised by the omission of the 2010 update of the Scottish Intercollegiate Guidelines Network (SIGN) guideline on the management of diabetes (2). This guideline covers all aspects of diabetes, with a specific chapter addressing medication for type 2 diabetes, therefore meeting the review's main inclusion criteria.

In relation to Bennett and colleagues' other inclusion criteria, SIGN guidelines provide evidence-based guidance for the National Health Service in Scotland, a constituent part of the United Kingdom. Health care is one of the areas of public policy devolved from the U.K. government to the Scottish government, so any consideration of health provision in the United Kingdom as a whole has to take account of policies and advice on both sides of the border. We suggest that omission of SIGN 116 from this systematic review is substantial, affecting its completeness.

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Potential Conflicts of Interest: Dr. Petrie has provided consultancy or served on trial committees for pharmaceutical companies manufacturing products for the treatment of diabetes, including Bristol-Myers Squibb Pharma, Daaichi Sankyo, GlaxoSmithKline, Novo Nordisk, Pfizer, Roche, and Takeda.

References

1. Bennett WL, Odelola OA, Wilson LM, Bolen S, Selvaraj S, Robinson KA, et al. Evaluation of guideline recommendations on oral medications for type 2 diabetes mellitus: a systematic review. *Ann Intern Med.* 2012;156:27-36. [PMID: 22213492]
2. Scottish Intercollegiate Guidelines Network. Management of Diabetes: A National Clinical Guideline. Guideline no. 116. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network; 2010. Accessed 10 April 2012 at www.sign.ac.uk/guidelines/fulltext/116/index.html.

TO THE EDITOR: We read Bennett and colleagues' review (1) with interest. It is unfortunate that the authors restricted their research to the U.S., U.K., and Canadian databases because they "deemed these countries' guideline developers most likely to access and use the systematic review."

The Italian Standards for the Treatment of Diabetes Mellitus (2) represents a consensus document of the 2 Italian scientific diabetes societies (Società Italiana di Diabetologia and Associazione Medici Diabetologi) that provides specific recommendations for the diagnosis and treatment of diabetes and its complications. An original processing system was used to create these recommendations: The document prepared by the editorial team was published online for 20 days, and the suggestions and criticisms of all of the Società Italiana di Diabetologia, and Associazione Medici Diabetologi members were evaluated and integrated with those from a panel of dia-

betologists and members of other health care professions committed to diabetes care, as well as lay members, including patient representatives. These guidelines include recommendations on oral medications for type 2 diabetes mellitus.

In our opinion, the recommendation presented in the Italian Standards of Care for Diabetes Mellitus 2009–2010, which is an online appendix of the Italian Standards for the Treatment of Diabetes Mellitus, fulfills the 7-item rigor of development domain of the Appraisal of Guidelines for Research and Evaluation instrument (3). We believe that these standards, if taken into appropriate consideration, would probably earn the best score for appraisal according to the Appraisal of Guidelines for Research and Evaluation instrument in Bennett and colleagues' review.

The Italian Standards of Care for Diabetes Mellitus 2009–2010 (2), like all of the guidelines that Bennett and coworkers examined, proposes metformin as a first-line agent (upon and beyond lifestyle education) and acknowledges that most medications cause similar reductions in hemoglobin A_{1c} levels. This proposal suggests an accurate and personalized prescription behavior based on well-known, demonstrated adverse effects—rather than on intriguing but still hypothetical—pathophysiologic choices.

We would also like to specifically comment on the series of American Diabetes Association and European Association for the Study of Diabetes documents. These algorithms are based on expert opinion and generate consensus statements that deviate from evidence-based information that should be included in a guideline (4). This observation, for example, explains why the various versions of these statements had substantial changes in important medication choices over time and is also the main reason that they were probably not included in the American Diabetes Association's standards of care. Therefore, we are glad that Bennett and coworkers indirectly appreciated our work in establishing Italian guidelines for the oral management of type 2 diabetes and hope that a rigorous distinction between evidence-based guidelines and expert opinions will become more tangible.

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Potential Conflicts of Interest: None disclosed.

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1. Bennett WL, Odelola OA, Wilson LM, Bolen S, Selvaraj S, Robinson KA, et al. Evaluation of guideline recommendations on oral medications for type 2 diabetes mellitus: a systematic review. *Ann Intern Med.* 2012;156:27-36. [PMID: 22213492]
2. Bruno G, De Micheli A, Frontoni S, Monge L; Società Italiana di Diabetologia-Associazione Medici Diabetologi (SID-AMD) Working Group on the Standards of Care for Diabetes. Highlights from "Italian Standards of Care for Diabetes Mellitus 2009-2010". *Nutr Metab Cardiovasc Dis.* 2011;21:302-14. [PMID: 20851582]
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IN RESPONSE: We appreciate the letters by Dr. Brown and colleagues and Dr. Giaccari and colleagues. We have also received e-mails from guideline developers concerned about several missed guidelines related to oral medication treatment for type 2 diabetes. In response, our team carefully reviewed our search strategy and did an updated search of the National Guideline Clearinghouse (NGC); we identified guidelines that unfortunately were not captured in our original search.

We discussed our concerns with NGC staff members and identified several problems with our broad search ("type 2 diabete*"). Most important, the NGC Web site, including the search function, was modified during the summer of 2010, altering its translation of our search strategy and thus yielding fewer guidelines. Although the announcement was publicized on the NGC Web site, it had already been archived by the time of our search.

The NGC staff proposed solutions to improve the practice of conducting systematic, repeated searches of guideline databases. They advised us to use multiple search approaches, including a search for both the condition and medications of interest, and hand-searching the guidelines by using the Medical Subject Headings in the topic list.

To identify guidelines that we had missed in our original search, we used the methods proposed by the NGC staff members in the 3 guideline-specific databases: the NGC database (United States), the National Library of Guidelines (United Kingdom), and the Canadian Medical Association Infobase: Clinical Practice Guidelines (Canada) from July 2007 to August 2011 (our original search dates). We identified 9 additional guidelines that met our original inclusion criteria (Table) (1–9) but had been missed in the original search.

As Dr. Brown and colleagues noted, we missed the SIGN guideline (1) on the management of diabetes. This guideline's summary scores for quality were 97.6% for rigor of development and 100% for editorial independence (0% = lowest; 100% = highest), which were similar to the highest-quality guidelines that we previously reported. In addition, the U.S. Department of Veterans Affairs—Department of

Defense guideline (2) was notable for its consistently high quality scores and agreement with 6 of the 7 evidence-based conclusions from the 2007 evidence report (Table).

As Dr. Giaccari and colleagues noted, our searches were restricted to U.S., U.K., and Canadian databases; thus, the Italian Standards for the Treatment of Diabetes Mellitus (10) was not included, and we are unable to comment on its agreement with the 7 conclusions from the 2007 evidence review (11) or quality.

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Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-1625.

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10. Bruno G, De Micheli A, Frontoni S, Monge L; Società Italiana di Diabetologia-Associazione Medici Diabetologi (SID-AMD) Working Group on the Standards of Care for Diabetes. Highlights from "Italian Standards of Care for Diabetes Mellitus 2009-2010". *Nutr Metab Cardiovasc Dis.* 2011;21:302-14. [PMID: 20851582]
11. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med.* 2007;147:386-99. [PMID: 17638715]

Table. Clinical Practice Guidelines Missed in the Original Search

Sponsoring Organization, Year (Reference)	Guideline Scope	Basis for the Recommendations	Evidence-Based Conclusions With Which the Guideline Agreed, n*	Quality Summary Score for Rigor of Development, %†	Quality Summary Score for Editorial Independence, %‡
American Association of Clinical Endocrinologists, 2011 (3)	Comprehensive care for diabetes management	Systematic review or meta-analysis, single RCTs, cohort study, cross-sectional studies, case series or report, surveillance studies, expert opinion	7	76.2	100
British Geriatrics Society, 2009 (4)	Diabetes care for older adults	NICE; other guidelines, including the American Geriatrics Society	4	19.0	50
CADTH, 2010 (5)	Second-line therapy for diabetes inadequately controlled with metformin	Systematic literature review, pharmacoeconomic analysis, stakeholder input	4	83.3	91.7
CADTH, 2010 (6)	Third-line therapy for diabetes inadequately controlled with metformin and a sulfonylurea	Systematic literature review, pharmacoeconomic analysis, stakeholder input	2	83.3	100
Diabetes Coalition of California and the California Diabetes Program, 2011 (7)	Basic components of diabetes care	ADA-EASD guideline	1	40.5	50
National Health Service Quality Improvement Scotland, 2010 (1)	Management of diabetes	Systematic review, literature search for qualitative and quantitative studies on patient issues	5	97.6	100
University of Michigan Health System, 2009 (8)	Management of type 2 diabetes	ADA-EASD guideline, literature search, published evidence summaries, major RCTs, observational studies, expert opinion	5	66.7	100
VA and U.S. Department of Defense, 2010 (2)	Diagnosis and management of diabetes mellitus in adults	Systematic review or meta-analysis, single RCTs, observational studies, expert opinion	6	95.2	91.7
Wisconsin Diabetes Prevention and Control Program, Wisconsin Diabetes Advisory Group, 2011 (9)	Diagnosis and management of diabetes mellitus in adults	ADA, International Diabetes Federation guidelines, systematic review or meta-analysis, single RCTs, cohort studies, review articles	5	31.0	100

ADA = American Diabetes Association; CADTH = Canadian Agency for Drugs and Technologies in Health; EASD = European Association for the Study of Diabetes; NICE = National Institute for Health and Clinical Excellence; RCT = randomized, controlled trial; VA = Department of Veterans Affairs.

* Number out of 7 evidence-based conclusions related to oral medication treatment for type 2 diabetes mellitus. See our review for a list of the 7 conclusions.

† Appraisal of Guidelines for Research and Evaluation instrument domain summary scores are calculated by adding all of the item scores in each domain and dividing by the maximum possible score for that domain (0% = lowest score; 100% = highest score) (11). The basis for quality assessment included the guideline document, manuals for guideline development, and responses from corresponding authors.

Exposing Unethical Human Research

TO THE EDITOR: Gaw's report (1) of the Beecher–Pappworth correspondence deserves widespread discussion. Unless academic physicians discuss the sins of the past over and over again, how can we hope to prevent them in the future?

As a 1947 graduate of Harvard Medical School and intern at the Peter Bent Brigham Hospital in the 1940s, I remember learning of an unspoken though implicit medical compact between ward patients and hospital doctors: We took care of them for free, and in return they gave us their bodies to study.

Did I “learn” that—did someone say it out loud—or was it in the air? Too much time has passed for me to be sure, but somewhere in that developing academic scene, it became evident that our “laboratories” were not only rooms with benches and hoods, but also rooms with patients and beds. Patients could be our participants for study—therapeutic and more. How else could Minot and Murphy have won the Nobel Prize for treating pernicious anemia?

Another hint of this link between patient care and scientific study comes from an old plaque at Yale on the ground floor of the Hope Building, erected in 1901 as the “Dispensary” (Clinic) of Yale Medical School. It reads, in part, “This building has been erected by

her [Jane Ellen Hope's] daughter for the relief of the poor and the advancement of medical science.”

Almost all of my physician-teachers back in Boston were respectful of their patients, considerate, competent, and compassionate, and we learned how to care for our patients from their example. But we had no such idea as “informed consent,” burnished in the 1960s—I like to think—by Jay Katz at Yale Law School. When Pappworth published his reports, most of us resisted any suggestion that, in our studies, we were like the Nazi doctors who intended the death of their imprisoned subjects.

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Dr. Spiro passed away on 11 March 2012.

Potential Conflicts of Interest: None disclosed.

Reference

1. Gaw A. Exposing unethical human research: the transatlantic correspondence of Beecher and Pappworth. *Ann Intern Med.* 2012;156:150-5. [PMID: 22250147]

OBSERVATION

Successful Treatment of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis With Eicosapentaenoic Acid

Background: Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis is a life-threatening autoimmune disease that often causes inflammatory lesions in the kidneys and lungs. The current standard treatment combines steroids and cyclophosphamide to induce and maintain remission, but this treatment frequently causes adverse events that limit its efficacy (1).

Objective: To successfully induce remission of ANCA-associated vasculitis with an alternative treatment by using eicosapentaenoic acid (EPA) without steroids or immunosuppressants.

Case Report: An 80-year-old woman with aortic stenosis severe enough to cause syncope 1 year earlier presented with rapidly declining renal function. Her history included angina pectoris and myocardial infarction, and she was taking low-dose aspirin, 100 mg/d, to prevent further cardiac events.

Urinalysis revealed substantial hematuria (3+) and proteinuria (2+). Blood tests revealed anemia (hemoglobin level, 89 g/L) and elevated leukocyte count (6.0×10^9 cells/L with 64% neutrophils), erythrocyte sedimentation rate (107 mm/h), serum creatinine level (252 $\mu\text{mol/L}$ [2.8 mg/dL]), blood urea nitrogen level (20.1 mmol/L [56 mg/dL]), and C-reactive protein level (0.01 mg/dL [0.095 nmol/L]). Complement levels were not decreased.

Direct enzyme-linked immunosorbent assays found no cryoglobulin and no antibodies against streptolysin O, glomerular basement membrane, or proteinase 3. However, antimyeloperoxidase antibodies were present at a titer of 131 EU (normal, <10 EU). Cardiac ultrasonography showed an ejection fraction of 0.49, septal wall hypokinesis, and severe aortic stenosis with an estimated pressure gradient of 110 mm Hg. Results of the kidney biopsy revealed global sclerosis in one third of the glomeruli, prominent cellular crescents in 3 glomeruli, and a fibrocellular crescent in 1 glomerulus (Figure 1). An immunofluorescent assay showed little or no staining for immunoglobulins (pauci-immune pattern).

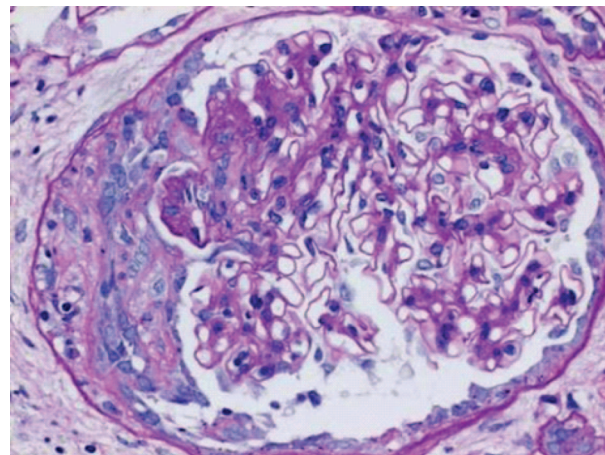
On the basis of these findings, we diagnosed ANCA-associated crescentic glomerulonephritis. Cancer was unlikely because results of imaging studies and tests for biological tumor markers were negative. Pathologic findings indicated that the glomerulonephritis would improve with steroids, but we were concerned that they might exacerbate the patient's heart disease.

We had already induced and maintained remission in 3 other cases of ANCA-associated vasculitis by using a combination of steroids and EPA.

Our laboratory was also working with anti-inflammatory lipid mediators derived from ω -3 fatty acids (including EPA). As a result, we knew that aspirin increased production of these mediators (2), and we wondered whether this patient's aspirin use might facilitate the effects of EPA that we had seen in other patients. Therefore, we started therapy with EPA, 1800 mg/d, before conventional immunotherapy (3).

Renal function started improving in approximately 3 weeks, hematuria in 1 month, and proteinuria in 4 months. Antimyeloperoxidase antibody titers also began to decrease gradually without steroids or immunosuppressants (Figure 2), and this patient has had no cardiovascular events 1 year later.

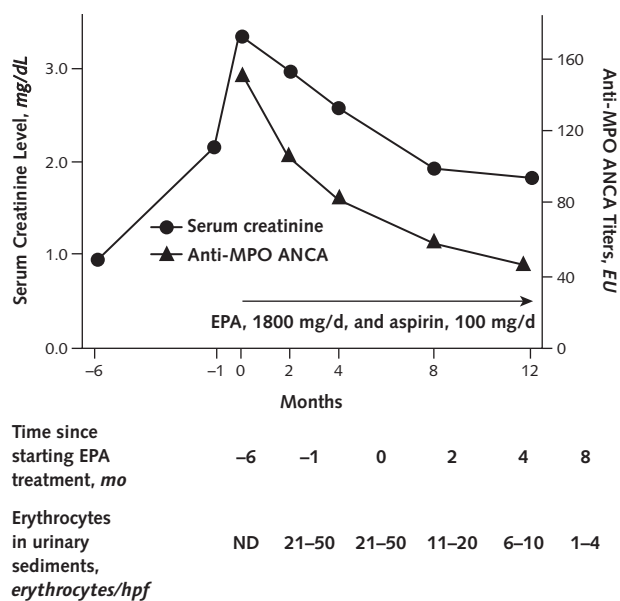
Figure 1. Renal biopsy specimen.



Glomerulus with a fibrocellular crescent (periodic acid–Schiff stain; original magnification, $\times 400$).

Discussion: Treatment of ANCA-associated vasculitis aims to control inflammation, limit organ damage, and decrease therapy-related toxicity. A recent study (4) showed that the greatest threat to patients in their first year of therapy is treatment-related adverse events rather than active vasculitis. Therefore, clinicians need an alternative strategy with less toxicity than steroids and cyclophosphamide for inducing and maintaining remission.

Figure 2. Clinical course of renal function.



To convert serum creatinine levels to $\mu\text{mol/L}$, multiply by 88.4. ANCA = antineutrophil cytoplasmic antibody; anti-MPO = antimyeloperoxidase antibody; EPA = eicosapentaenoic acid; ND = not determined.

Other researchers (5) recently showed that rituximab, which is an anti-CD20 monoclonal antibody, is as effective as cyclophosphamide in inducing remission, but rituximab can also cause adverse events that limit its efficacy. Dietary supplementation with EPA, which is a major component of fish oil, has diverse benefits in many inflammatory diseases. This case report highlights the anti-inflammatory and immunomodulatory potential of EPA for treating ANCA-associated vasculitis with fewer adverse effects than conventional treatment. However, controlled clinical trials are required to determine whether that potential can be realized.

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Potential Conflicts of Interest: The authors have applied for patents for the use of EPA to treat ANCA-associated vasculitis.

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CORRECTION

Correction: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

The first full sentence on page 224 of a recent guideline (1) should read as follows:

Metformin was also favored over sulfonylureas for cardiovascular mortality (low-quality evidence), as evidenced by 4 cohort studies (92, 94, 96, 101), although 1 prospective cohort study (94) showed slightly higher cardiovascular mortality rates for metformin than for sulfonylurea monotherapy. Also, ADOPT (A Diabetes Outcome Progression Trial) (89) reported only 1 fatal CHF event in patients treated with either metformin or glyburide (nonstatistically significant difference), but patients treated with glyburide generally experienced fewer CHF as well as cardiovascular events.

Reference

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