

The Future of Diabetes Disease Management: Integrating Lessons Learned from Clinical, Health Services, and Policy Research

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Our understanding of diabetes and its management is evolving rapidly based on information from researchers and the world of healthcare delivery about “what works” to improve outcomes. This theme issue of the *Journal* includes studies that can inform efforts to improve diabetes care on many levels, including more effective clinical decision-making, improvements in health systems that promote treatment quality, and health policies that encourage the best disease management practices.

Despite years of research on diabetes management and quality improvement, these new studies are worthwhile because, unfortunately, diabetes treatment processes and outcomes remain disappointing in many healthcare systems. The study by Godley and colleagues¹ highlights the gap between guideline recommendations and the care many patients with diabetes receive. Through a review of claims data and charts, the authors found that less than 20% of patients with diabetes achieved blood pressure goals, and many had additional cardiovascular risk factors. Perhaps most disturbing, 42% of patients with poor blood pressure control were on only 1 antihypertensive agent or no blood pressure treatment at all, suggesting significant room for improvement via appropriate medication intensification. The problem of “clinical inertia” in the context of poor physiologic outcomes has been documented in glucose management as well,² and may require system-level changes to ensure that patients are prescribed drug regimens that can reduce the risk of costly complications.

Fortunately, the quality of diabetes care in many healthcare systems is improving, and this is shown clearly in the study by McBean and colleagues.³ These researchers demonstrate that most Medicare benefici-

aries with diabetes now receive guideline-recommended services such as testing for regular hemoglobin (HbA_{1c}) and low-density lipoprotein (LDL) tests. However, rates of other recommended care processes remain unacceptably low. The investigators also found that treatment processes vary across racial groups and health plan types. This variation provides important clues about how to foster further quality improvements, and suggests opportunities for healthcare managers to learn from one another about how best to achieve goals set by the National Committee for Quality Assurance and other organizations.

Lessons about developing more effective models of diabetes care sometimes are best learned by examining healthcare systems that seem to have gotten it right. The US Department of Veterans Affairs (VA) healthcare system provides better diabetes care than many private managed care organizations,⁴ through a structure that promotes and rewards quality via information systems and management incentives. Jackson and colleagues⁵ linked organizational-level data from 177 VA clinics to patient outcomes and identified a number of organizational characteristics associated with improved diabetes control. Their study reinforces prior findings about the importance of system changes, such as electronic reminders, and identifies other provocative correlates of glycemic control, such as managerial autonomy and the

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INTRODUCTION

extent to which physicians as well as nurses participate in quality improvement efforts. These results should foster discussion within non-VA health systems (as well as in poorly performing VA facilities) about how they can adopt managerial practices that promote more effective diabetes management.

Much of the focus in chronic disease care has been on disease management programs, and Knight et al⁶ provide a systematic review of programs for patients with diabetes. These researchers report that overall, diabetes disease management can lead to modest improvements in patients' glycemic control, as well as improvements in related care such as retinal examinations. The authors also rightly caution readers against adopting programs without critically appraising their characteristics and goals. Publication bias may well lead to an overly optimistic picture of these programs' benefits, and even in the published literature, rigorous studies have not been uniformly positive.⁷ As the authors point out, many innovations in disease management are occurring without public evaluation of program effects.⁸ Nevertheless, the generally positive effects demonstrated by this review are encouraging. Health plans should continue to innovate in this area, taking what has been shown to be feasible and effective in other settings and adapting it to their own practices and patients.

Pharmaceutical researchers have developed a full menu of medications that can improve glycemic control, blood pressure, and lipid levels in patients with diabetes. Medication management is central to most patients' care, and pharmacists may play an important role in achieving physiologic targets. Choe and colleagues⁹ conducted a randomized trial of diabetes disease management delivered by a clinical pharmacist. After more than a year of follow-up, patients who received the service had greater improvements in blood glucose levels than those receiving usual care. Intervention patients also had more frequent LDL testing, retinal examinations, and monofilament foot screening, suggesting that the pharmacist fostered improved treatment quality that extended beyond medication use. This study illustrates 1 specific strategy for achieving improvements in diabetes care, even without more global changes in the way health systems are organized.

The study by Karter and colleagues¹⁰ also supports the need for greater attention to patients' medication management, demonstrating that many patients with diabetes need insulin plus insulin-sensitizing agents to achieve target blood glucose levels. The study was conducted within the Kaiser Permanente (KP) healthcare system, which (like the VA) has become a model of

how to evaluate and improve chronic illness care. Nevertheless, many patients with diabetes and poor glycemic control who were treated in the KP system received monotherapy with sulfonylureas (in agreement with current practice guidelines), which appears to be less effective in achieving glucose level targets. Karter and other KP researchers provide a valuable service to that system's patients, and their studies often provide the evidence base for quality improvement initiatives both within and outside of the KP system. Other health systems should consider encouraging health services research that leverages the enormous potential of their own data systems for improving the knowledge base available to their clinicians and managers.

Finally, the article by Herman and colleagues¹¹ adds to the growing body of evidence that appropriate medication use may not only improve the health status of patients with diabetes, but may also reduce their use of costly health services. The investigators compared outcomes for patients with type 2 diabetes who were randomized to either monotherapy with sulfonylureas or combination therapy with rosiglitazone. After 2 years of follow-up, patients in the combination therapy group experienced fewer emergency department visits and hospitalizations and lower per-patient treatment costs. In addition to the study's important clinical implications, findings such as these provide an important context for payer decisions about out-of-pocket drug costs and the influence they may have on the behavior of patients taking multiple medications. Too often, these costs inhibit appropriate adherence and foster poorer health outcomes.¹²

Collectively, these studies provide an exciting picture of where we have come in diabetes clinical and health services research. They also highlight the work that remains to be done in order to ensure that as many patients with diabetes as possible can lead healthy and productive lives. We must continue to develop new strategies for designing health systems that foster quality diabetes care. Given the demonstrated benefit of medication intensification for diabetes as well as other common chronic illnesses, future work should identify the barriers to appropriate prescribing, regimen adjustments, and patient adherence. Redesigning prescription drug benefits so that patients' out-of-pocket costs reflect their expected benefit from pharmacotherapy is an idea that has been championed by Fendrick and others for years.¹³ Studies such as those in this special issue add to the growing evidence supporting this innovative approach. The "business case" for effective disease management is growing. The challenge to researchers, health systems, and payers will be to take the bold steps

needed to redesign treatment and benefit structures in ways that foster the gains suggested here.

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Ezetimibe: The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended.

Simvastatin: Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses >40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, Pregnancy). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Geriatric Use: Of the patients who received VYTORIN™ (ezetimibe/simvastatin) in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See CLINICAL PHARMACOLOGY, Special Populations and ADVERSE REACTIONS.)

ADVERSE REACTIONS: VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerated.

Table 1 summarizes the frequency of clinical adverse experiences reported in ≥2% of patients treated with VYTORIN (n=1236) and at an incidence greater than placebo regardless of causality assessment from 3 similarly designed, placebo-controlled trials.

Table 1*
Clinical Adverse Events Occurring in ≥2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality

Body System/ Organ Class Adverse Event	Placebo (%) n=311	Ezetimibe 10 mg (%) n=302	Simvastatin** (%) n=1234	VYTORIN** (%) n=1236
<i>Body as a whole – general disorders</i>				
Headache	6.4	6.0	5.9	6.8
<i>Infection and infestations</i>				
Influenza	1.0	1.0	1.9	2.6
Upper respiratory tract infection	2.6	5.0	5.0	3.9
<i>Musculoskeletal and connective tissue disorders</i>				
Myalgia	2.9	2.3	2.6	3.5
Pain in extremity	1.3	3.0	2.0	2.3

* Includes 2 placebo-controlled combination studies in which the active ingredients equivalent to VYTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered.
** All doses.

Ezetimibe: Other adverse experiences reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: *Body as a whole – general disorders:* fatigue; *Gastrointestinal system disorders:* abdominal pain, diarrhea; *Infection and infestations:* infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders:* arthralgia, back pain; *Respiratory system disorders:* coughing.

Post-marketing Experience: The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:

Hypersensitivity reactions, including angioedema and rash; increased CPK elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasis; cholecystitis; and, very rarely in patients taking an HMG-CoA reductase inhibitor with ezetimibe, rhabdomyolysis (see WARNINGS, Myopathy/Rhabdomyolysis).

Simvastatin: Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: *Body as a whole – general disorders:* asthenia; *Eye disorders:* cataract; *Gastrointestinal system disorders:* abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea; *Skin and subcutaneous tissue disorders:* eczema, pruritus, rash.

The following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy. *Musculoskeletal system disorders:* muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Nervous system disorders: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances.

Ear and labyrinth disorders: vertigo.

Psychiatric disorders: anxiety, insomnia, depression, loss of libido. **Hypersensitivity Reactions:** An apparent hypersensitivity syndrome has been reported rarely which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal system disorders: pancreatitis, vomiting. *Hepatobiliary disorders:* hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma.

Metabolism and nutrition disorders: anorexia. *Skin and subcutaneous tissue disorders:* alopecia, pruritus. A variety of skin changes (eg, nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive system and breast disorders: gynecomastia, erectile dysfunction. *Eye disorders:* progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac fraction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

Concomitant Lipid-Lowering Therapy: In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

Adolescent Patients (ages 10-17 years)
In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with simvastatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, Pediatric Use).