

TO THE EDITORS

McGarry and colleagues did an excellent job in providing an economic perspective on the effectiveness of thromboprophylaxis with a low-molecular-weight heparin versus unfractionated heparin in acutely ill medical inpatients.¹ Low molecular weight heparins (LMWHs) have gained wider acceptance as the drugs of choice in prophylaxis of venous thromboembolism (VTE) due to their superior efficacy and cost effectiveness to unfractionated heparin, and the reduced risk of heparin-induced thrombocytopenia and osteoporosis.¹

However, new developments in the realm of VTE prophylaxis in medically ill patients have provided us some valuable insights. The ARTEMIS trial demonstrated the efficacy and safety of fondaparinux in medically ill patients versus placebo.² Although there are no comparative trials between LMWHs and fondaparinux in medically ill patients, there have been a few head-to-head pharmacoeconomic studies in other patient types that have shown fondaparinux to be cost effective.^{3,4}

McGarry's study notwithstanding, we believe the current question to be addressed is how to choose between LMWHs and fondaparinux and which agent is a more cost-effective option in medically ill patients.

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TO THE EDITORS

Tinkelman and Wilson¹ have done a laudable job addressing some of the concerns around measurement of

return on investment of disease management programs, including seasonality and regression to the mean. However, their evaluation of the success of their program to diminish asthma expense in the Colorado Medicaid population has introduced substantial potential biases that diminish the strength of their conclusions.

Tinkelman and Wilson have chosen to have a "convenience" control group, as opposed to using a randomized control group. This control group is on average 4 years older than the intervention group, raising the question of overrepresentation of the disabled in the control group compared to the intervention group. There is substantial evidence that disabled and Temporary Assistance for Needy Families (TANF) Medicaid patients are very different populations,² and they should each be analyzed separately when reviewing efficacy of medical management programs. The need to eliminate 2.8% of the control group for "high use of nonasthma claims" also suggests that there were systematic differences between the intervention and control groups.

The control group was chosen because the researchers were unable to reach the provided home phone number. It is very likely that there is a systematic difference between those who researchers can reach and those who they cannot. The authors surmise that "those who were not at home were healthy and working, while those who were at home were sicker and not working." It is just as likely that those for whom the researchers did not have workable phone numbers were actually more impoverished, and therefore nonequivalent to the intervention group.

The authors also removed noncompliant patients from the intervention group, while they could not remove such patients from the control group. Clearly, those who had "lost telephone service" might have been at higher risk of adverse outcomes of their asthma. It would have been more appropriate to evaluate the intervention group on an "intention to treat" basis, since there was no similar elimination of members of the control group.

The authors acknowledge that their evaluation fails to consider the incremental cost of higher use of disease modifying inhalation agents in the intervention group. In fact, this additional cost might offset a considerable portion of the stated savings from this program.

Tinkelman and Wilson have done us a service to identify substantial regression to the mean (30.7%) in

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the control group of their population. More rigorous studies will be required to ascertain whether there was really substantially more decrease in cost in a comparable intervention group.

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TO THE EDITORS

The foundation of Tinkelman & Wilson's conclusion¹ on the effectiveness of an asthma disease management (DM) program is based on the assumption that the reference group was equivalent to the population that received disease management services. Unfortunately, the authors do not present sufficient credible evidence to support that essential assumption.

The authors do assert that answering the phone on the first call for both the participants and non-participants was a "random variable" and that the populations selected for DM and the comparison were "statistically and clinically well-matched as cases and controls." Yet, no supporting evidence from the literature is presented to back-up such a contention. Indeed, evidence available in the paper itself reveals that the 2 populations were quite obviously different.

First, the investigators state that "individuals with extreme non-asthma use" were present in the reference group and were removed from the analysis, but no such outliers were cited as being in the intervention group. This fact is an obvious contradiction to the idea that the "random variable" caused, by itself, a group of "well-matched" controls. Second, the evidence presented in Table 1 to show comparability on age, in fact shows just the opposite. A simple statistical test using the values presented on age (mean and standard deviation) calculates to a *t* statistic of 3.511 and a statistically significant difference on this important baseline characteristic ($P < .001$).

This study would have been far more persuasive if the authors had 1) presented credible evidence from the scientific literature suggesting that their selection method (answering the telephone on the first attempt) has been shown to produce equivalent comparison

groups elsewhere; and 2) if they increased the number of baseline metrics available in claims data (eg, comorbid conditions, inpatient and other utilization statistics, etc) in both the reference and intervention groups and offered appropriate statistical tests of their differences.

The "equivalence" principle is perhaps the most essential component of any study.² Like many before us, we recommend that investigators studying defined population interventions include a self-critical discussion of the "strength of evidence" supporting their conclusions,³ especially the degree to which selection bias was avoided.⁴ The extent to which a study achieved "internal validity" (and the extent to which it did not) should be supported by evidence from the literature and/or data produced by the study itself.

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IN REPLY

The correspondents have brought up some important points regarding the limitations of our study. So as to not "throw the baby out with the bath water," however, we would like to address some of these concerns. While acknowledging that both the methods and the data may not be perfect, at the same time we submit that some useful information can be garnered from these results.

We would argue that both Levin-Scherz and Wilson and Linden have perhaps overstated the likelihood of systematic differences between the treatment and control groups. While it is correct that the control group was not formally randomized and thus, could reasonably be construed as one of "convenience," at the same time, the manifest similarity of the 2 groups suggests that they likely were not systematically dissimilar in

with moderately to severely active rheumatoid arthritis and Crohn's disease treated with REMICADE in clinical trials with a median of 11.1 years of follow-up, 3 patients developed lymphomas, for a rate of 0.07 cases per 100 patient-years of follow-up in patients with rheumatoid arthritis and 0.12 cases per 100 patient-years of follow-up in the combined clinical trial data for rheumatoid arthritis and Crohn's disease patients. This is approximately 3-fold higher in the RA clinical trial population and 6-fold higher in the overall clinical trial population than expected in an age-, gender-, and race-matched general population based on the Surveillance, Epidemiology and End Results Database. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. An increased rate of lymphoma up to several fold has been reported in the Crohn's disease and rheumatoid arthritis patient populations, and may be further increased in patients with more severe disease activity. Other than lymphoma, 13 patients developed malignancies, which was similar in number to what would be expected in the general population. Of these, the most common malignancies were breast, colon/rectal, and melanoma. (See WARNINGS, Adverse Events.) Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving REMICADE during post-approval use. **Patients with Heart Failure** In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction <35%), 190 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends towards increased dyspnea, hypotension, angina, and edema in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II) (see CONTRAINDICATIONS and WARNINGS, Adverse Events). **Intracranial Infection** Treatment with REMICADE can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through one to two years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. The majority of antibody-positive patients had live tests. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see ADVERSE REACTIONS, Infusion-Related Reactions) than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA of MTX. The observed percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading. **Hepatic Injury** Severe liver injury including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving REMICADE (see WARNINGS, Hepatic Injury). Reactivation of hepatitis B has occurred in patients receiving REMICADE who are chronic carriers of this virus (i.e., surface antigen positive) (see WARNINGS, Hepatic Injury). In clinical trials in RA, Crohn's disease and ankylosing spondylitis, elevations of aminotransferase were observed (ALT were common than AST) in a greater proportion of patients receiving REMICADE than in controls, both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications. ALT elevations >5 times the upper limit of normal were observed in 1% of patients receiving REMICADE in rheumatoid arthritis clinical trials, 34% of patients who received REMICADE + MTX experienced transient mild (<2 times the upper limit of normal) or moderate (>2 but <3 times the upper limit of normal) elevations in ALT compared to 24% of patients treated with placebo + MTX. ALT elevations >3 times the upper limit of normal were observed in 3.9% of patients who received REMICADE + MTX compared with 3.2% of patients who received MTX alone (median follow up approximately 1 year). In Crohn's disease clinical trials (median follow up 54 weeks), 39% of patients receiving REMICADE-maintenance experienced mild to moderate elevations in ALT compared to 34% of patients treated with placebo-maintenance. ALT elevations >3 times the upper limit of normal were observed in 5.0% of patients who received REMICADE-maintenance compared with 4.0% of patients who received placebo-maintenance. In an ankylosing spondylitis clinical trial in which patients were not receiving MTX, 40% of patients who received REMICADE experienced mild to moderate elevations in ALT compared to 19% of patients treated with placebo. ALT elevations >3 times the upper limit of normal were observed in 12.6% of REMICADE-treated patients compared to none in placebo-treated patients. **Other Adverse Reactions** Safety data are available from 2620 REMICADE-treated patients, including 1304 with rheumatoid arthritis, 1108 with Crohn's disease, 282 with ankylosing spondylitis and 17 with other conditions. Adverse events reported in >5% of all patients with rheumatoid arthritis receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to pool to meaningful comparisons. The percentages of adverse events for placebo-treated patients (n=350), average weeks of follow-up 59) and REMICADE-treated patients (n=1128, average weeks of follow-up 66), respectively are: Gastrointestinal: Nausea: 20, 21; Abdominal pain: 8, 12; Diarrhea: 12, 12; Dyspepsia: 7, 10; Respiratory: Upper respiratory tract infection: 25, 32; Sinusitis: 8, 14; Pharyngitis: 8, 12; Coughing: 11, 12; Bronchitis: 11, 18; Herpes: 5, 8; Skin and appendage disorders: Rash: 5, 18; Pruritus: 2, 7; Scleritis: 3; Adverse general observations: Fatigue: 7, 9; Pain: 7, 8; Abnormal muscle enzyme elevations: Rose: 4, 7; Monoclonic: 3, 5; Central and peripheral nervous system disorders: Headache: 14, 16; Musculoskeletal system disorders: Back pain: 5, 8; Arthralgia: 7, 9; Urinary system disorders: Urinary tract infection: 6, 8; Gastrointestinal disorders: general: Hypertension: 5, 7. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice. The most common serious adverse events observed in clinical trials were infections (see ADVERSE REACTIONS, Infections). Other serious, medically relevant adverse events >0.2% or clinically significant adverse events by body system were as follows: **Body as a whole**: allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequelae, **Ear**: parotiditis, **Cardiovascular**: dromatory failure, hypotension, syncope, **Gastrointestinal**: constipation, gastroduodenal hemorrhage, gas, intestinal obstruction, ileus, ileocolitis perforation, intestinal stenosis, parosmia, peritonitis, proctalgia, **Central and Peripheral Nervous System**: meningitis, neuritis, peripheral neuropathy, dizziness, **Heart Rate and Rhythm**: arrhythmia, bradycardia, cardiac arrest, tachycardia, **Liver and Biliary**: biliary pain, cholecystitis, cholelithiasis, hepatitis, **Musculoskeletal**: tendon rupture, **Nutritional**: dehydration, **Musculoskeletal**: intervertebral disk herniation, tendon disorder, **Myo-, Endo-, Pericardial and Coronary Vascular**: myocardial infarction, **Platelet, Bleeding and Clotting**: thrombocytopenia, **Respiratory**: basal cell, breast, lymphoma, **Psychiatric**: confusion, **Salivary Gland**: sialadenitis, **Red Blood Cell**: anemia, hemolytic anemia, **Reproductive/Endometrial**: irregularity, **Respiratory**: **Nocardia** infection, **Urogenital**: cystitis, **Serum**: siderosis, **Respiratory**: adult respiratory distress syndrome, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency, **Skin and Appendages**: increased sweating, **Urinary**: renal calculus, renal failure, **Vascular** (Excludes): brain infection, pulmonary embolism, thrombophlebitis, **White Cell and Hematologic**: leukopenia, lymphocytopenia. The following adverse events have been reported during post-approval use of REMICADE: neutropenia (see WARNINGS, Hematologic Events), interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and ocular vasculitis, Guillain-Barre syndrome, transverse myelitis, and neuropathies (additional toxicologic events have also been observed, see WARNINGS, Adverse Events). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure. **OVERDOSAGE**: Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **REFERENCE**: 1. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2003;167:15221-3247.

several important ways. This methodology is consistent with that described previously by Haley.¹ We certainly agree, in accordance with that principle, "since the members of a convenience sample were not selected by a true random sampling method, one will not have the same degree of assurance that the results can be generalized to the target universe as one would have with a random sample. However, many convenience samples are free enough of obvious biases to provide accurate estimates of their target universes."^{1,p54}

Another issue raised in both letters relates to the age of the populations. While the ages were statistically different in the 2 groups (with the given group sizes and standard deviations, a difference of 2.1 years would have been statistically significant), the mean and range were very similar. This was also true for the other measured variables (sex, asthma utilization, and non-asthma utilization). We acknowledge it is possible that there were more disabled individuals in the control group or that the control group was more impoverished. However, it is difficult to conceive how these differences might not affect costs in the baseline year, but then go on to affect costs in the treatment year. Thus, we would argue that this supposition is possible but not likely.

Dr. Levin-Scherz makes an excellent point about using an intention to treat analysis, at least on the individuals who were excluded from the treatment group for reasons other than loss of eligibility for insurance. We would absolutely remedy this oversight in future studies. We also agree with his conclusion that replication of these findings is important step to further substantiating the benefits of asthma disease management. In addition, we agree with all of the valuable suggestions from Wilson and Linden, which indeed would have strengthened this paper significantly. We were constrained by space limitations by the journal and had to limit our presentation of these points in the Discussion. We thank both Drs. Levin-Scherz and Wilson for sharing their valued insights.

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