COMMENTS AND RESPONSES

Is Patient Cost-Sharing the Best Way to Protect the Medical Commons?

TO THE EDITOR: Wharam and colleagues (1) reported that a high-deductible insurance plan providing first-dollar coverage for fecal occult blood tests (FOBTs) but not colonoscopies did not change colorectal cancer screening rates but did result in somewhat higher use of FOBTs and lower use of colonoscopies. The article and accompanying editorial (2) imply that it might be unsound to cover FOBTs but not colonoscopies. However, clinical practice guidelines at the time of the study recommended both tests. These guidelines did not consider either method to be unequivocally superior, but pointed out that they had different characteristics that might matter to individual patients. Very recent guidelines judge colonoscopy and other structural examinations of the colon to be preferable to stool tests because they can better detect adenomas and so prevent cancer.

In their editorial, Mahajan and Brook (2) wonder whether Harvard Pilgrim Health Care (HPHC) gave careful consideration to the consequences of providing first-dollar coverage for FOBT, the less expensive test, but not colonoscopy. Since 1996, an ethics advisory group has advised HPHC on ethical issues, including tough allocation decisions and confronting contemporary health plans (3). Two dozen participants represent a range of stakeholders, such as HPHC staff, community physicians, consumers, purchasers, and ethicists. At a time of national backlash against insurer- and physician-led managed care, the ethics advisory group was asked to explore the ethical dimensions of insurance that was more affordable and included deductibles that encouraged greater consumer participation in their own health care decisions. The group devoted 6 meetings to these issues and did take into account research evidence of test effectiveness as well as evidence that, in some settings, deductibles reduce care without regard to its effectiveness. Harvard Pilgrim Health Care also encouraged studies of the effects of its policies, and the study by Wharam and colleagues is a result.

We agree that it would be wonderful if "patient cost-sharing were not needed to control costs and patients and physicians instead worked together to eliminate waste and equivocal . . . or ineffective services" (2). But the cost of heath care is an urgent, practical problem with widespread consequences. For example, Emmanuel (4) has argued that cost is the underlying cause of so many uninsured Americans. So pipe dreams are not enough. Harvard Pilgrim Health Care believes that one of its most important obligations is "protecting the medical commons" (5). Should we not applaud, rather than criticize, efforts to live with less-expensive care at a time when there was not evidence-based consensus that more-expensive care produced better outcomes?

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Disclaimer: The authors are affiliated with Harvard Pilgrim Health Care, whose policies were studied in the article (1) and commented on in the editorial (2).

Potential Financial Conflicts of Interest: None disclosed.

References

1. Wharam JF, Galbraith AA, Kleinman KP, Soumerai SB, Ross-Degnan D, Landon BE. Cancer screening before and after switching to a high-deductible health plan. Ann Intern Med. 2008;148:647-55. [PMID: 18458277]
2. Mahajan AP, Brook RH. High-deductible health plans and better benefit design [Editorial]. Ann Intern Med. 2008;148:704-6. [PMID: 18458284]
3. Sabin JE, Cochran D. Confronting trade-offs in health care: Harvard Pilgrim Health Care's organizational ethics program. Health Aff (Millwood). 2007;26:1129-34. [PMID: 17630456]
4. Emanuel EJ. The cost-coverage trade-off: "it's health care costs, stupid". JAMA. 2008;299:947-9. [PMID: 18314437]
5. Hiatt HH. Protecting the medical commons: who is responsible? N Engl J Med. 1975;293:235-41. [PMID: 1143304]

IN RESPONSE: We thank Dr. Fletcher and colleagues for their thoughtful letter describing HPHC's decision-making process and rationale for providing first-dollar coverage of FOBT, but not colonoscopy, in its high-deductible health plan. The HPHC's ethics advisory group, which engages a range of stakeholders, is laudable.

Dr. Fletcher and colleagues defend HPHC's decision to provide first-dollar coverage for FOBT but not colonoscopy by citing evidence-based guidelines, from the time when the coverage decision was made, that regarded the 2 screening interventions as equally effective. In light of new consensus guidelines recommending colonoscopy over FOBT because of the added benefit of early detection and removal of polyps (1), we reviewed the high-deductible health plan information available to potential enrollees on HPHC's Web site and found that colonoscopy is still subject to the deductible (2). Given the plan's goal to design benefits in a way that encourages the use of high-value preventive services, we hope that the HPHC is in the process of changing its high-deductible health plan policy to provide first-dollar coverage for colonoscopy.

Citing the need to control rising health care costs, Dr. Fletcher and colleagues justify the use of cost-sharing to promote use of less-expensive care that produces outcomes equivalent to those of more-expensive care. Although "protecting the medical commons" is indeed an important obligation that we share, it is not clear from existing evidence that an isolated focus on promoting preventive screening will achieve significant cost reductions in the long run. The HPHC high-deductible health plan does not provide first-dollar coverage for highly effective care, such as prescription medications for chronic disease (2); increased cost-sharing for medications reduces their use for such conditions as hypertension, diabetes, asthma, and depression (3). In addition, cost-sharing reduces the use of clinically effective services and less-effective or ineffective services in roughly equal proportions (4). If HPHC is interested in protecting the medical commons, why resort to a cost-sharing policy that will adversely affect the well-being of some patients? Wouldn't it be better to first attempt to eliminate wasteful and inappropriate care (in which risks to the patient exceed the potential benefit) (5) by implementing appropriateness criteria and methods (4, 5) and systematically educating its providers and enrollees in how to use the criteria?

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Disclaimer: Dr. Brook's wife, Dr. Jacqueline Kosecoff, is CEO of Prescription Solutions.

Potential Financial Conflicts of Interest: None disclosed.

References

1. Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. American Cancer Society Colorectal Cancer Advisory Group. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin. 2008; 58:130-60. [PMID: 18322143]
2. Harvard Pilgrim Health Care. Six Facts About the HPHC Insurance Company Best Buy HSA PPO—Massachusetts. Accessed at https://www.harvardpilgrim.org/pls/portal/docs/PAGE/MEMBERS/COVERAGE/BESTBUYHSAPPO/CC2389_MA_PRE.PDF on 5 August 2008.
3. Goldman DP, Joyce GF, Escarce JJ, Pace JE, Solomon MD, Laouri M, et al. Pharmacy benefits and the use of drugs by the chronically ill. JAMA. 2004;291:2344-50. [PMID: 15150206]
4. Newhouse JP. The Insurance Experiment Group. Free for All? Lessons from the RAND Health Insurance Experiment. Cambridge, MA: Harvard Univ Pr; 1993.
5. Schuster MA, McGlynn EA, Brook RH. How good is the quality of health care in the United States? 1998. Milbank Q. 2005;83:843-95. [PMID: 16279970]

Monitoring Cholesterol Levels: Understanding Variance and Finding the Most Useful Data

TO THE EDITOR: I read with great interest the article by Glasziou and colleagues (1), which provided useful variance parameters for a simulation study I am currently conducting. I believe the authors made 2 errors, however, and although neither error alters the conclusions of their study, researchers using the reported estimates for other work might come to erroneous conclusions depending on which estimates they use.

First, the variance estimates reported on page 659 (column 2, paragraphs 3 and 4) are in the wrong units. The units should be $mmol^2/L^2$ (mg^2/dL^2) and not mmol/L (mg/dL).

Second, the variance estimates given on page 658 (column 2, paragraph 4) are incorrect. To convert a variance estimate from $mmol^2/L^2$ to mg^2/dL^2, one must take the square of the conversion factor because variance is not a linear operator: $Var(cX) = c^2 \times Var(X)$. Thus, the variation in initial response to treatment is not 21.8 mg^2/dL^2, but: $(1\ mg/dL \div 0.02586\ mmol/L)^2 \times 0.56\ mmol^2/L^2 = 837\ mg^2/dL^2$.

The same error applies to the variance estimates reported on page 659. The authors report the correct estimates for the SD of changes in low-density lipoprotein cholesterol throughout the paper, probably because the authors made the conversion from mmol/L to mg/dL on the scale of SDs (and not variance), in which squaring the conversion factor is not needed. For this reason, any reader interpreting the study's conclusions by using the SD estimates will be correct regardless of the units, but when interpreting the variance estimates, will be correct only for the variance estimates reported in $mmol^2/L^2$.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Glasziou PP, Irwig L, Heritier S, Simes RJ, Tonkin A. LIPID Study Investigators. Monitoring cholesterol levels: measurement error or true change? Ann Intern Med. 2008;148:656-61. [PMID: 18458278]

TO THE EDITOR: The study by Glasziou and colleagues (1) finds that "noise" random variations during serial cholesterol level monitoring may be greater than the change in cholesterol levels due to a therapeutic effect. This points to the importance of what exactly has been tested in cholesterol-lowering studies. Although guidelines and clinical practice often focus on titrating lipid treatment to obtain specified goal levels (2), the intervention that has actually been tested in many of the important statin trials is the administration of a fixed medium or high dose of a cholesterol-lowering medication. For example, the WOSCOPS (West of Scotland Coronary Prevention Study) and LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) studies compared pravastatin, 40 mg/d, with placebo (3, 4), and the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) and REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) studies compared fixed high-dose atorvastatin with fixed medium-dose pravastatin (5, 6). Thus, the treatment that has been evaluated in each case is a fixed dose of a cholesterol-lowering medication, not titration to a specified goal. Evidence-based cholesterol treatment should then focus on providing patients with an appropriate statin dose based on trial data rather than on a less-studied dose-titration strategy.

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Potential Financial Conflicts of Interest: None disclosed.

References

1. Glasziou PP, Irwig L, Heritier S, Simes RJ, Tonkin A. LIPID Study Investigators. Monitoring cholesterol levels: measurement error or true change? Ann Intern Med. 2008;148:656-61. [PMID: 18458278]
2. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. National Heart, Lung, and Blood Institute. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227-39. [PMID: 15249516]
3. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation. 1998;97:1440-5. [PMID: 9576423]
4. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349-57. [PMID: 9841303]
5. Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/l: an analysis of the PROVE-IT TIMI-22 trial. J Am Coll Cardiol. 2005;45:1644-8. [PMID: 15893181]

6. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005;352:29-38. [PMID: 15635110]

TO THE EDITOR: As Glasziou and colleagues (1) report, after the initial decrease in cholesterol level in response to treatment, subsequent cholesterol level monitoring may be much less frequent than is currently recommended. They show that much of current testing will detect only false-positive results, which are related to either short-term biological variation or analytic error (1). However, they don't clearly show the factors inducing false-positive results or a way to decrease variation.

We would like to ask some questions. First, what are the statistical factors that induce the differences observed? Except for pravastatin treatment, the variation in cholesterol levels may result from other factors, such as other medications, level of physical activity, eating habits, smoking status, depression, and others (2). For example, the patients may receive another medication that may affect cholesterol levels and enhance (or weaken) the effect of pravastatin. Second, did the authors try to avoid controllable biological variation, such as not allowing the patients to drink alcoholic beverages when detecting serial cholesterol concentrations? Third, what methods did the authors use to decrease false-positive results in their study? Finally, this study is based on participants from Australia and New Zealand, so the results may not be applicable to Asians. Could the authors comment on the effect of racial diversity on the variation in cholesterol levels?

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References

1. Glasziou PP, Irwig L, Heritier S, Simes RJ, Tonkin A. LIPID Study Investigators. Monitoring cholesterol levels: measurement error or true change? Ann Intern Med. 2008;148:656-61. [PMID: 18458278]

2. Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, et al. BMI-CHD Collaboration Investigators. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Arch Intern Med. 2007;167:1720-8. [PMID: 17846390]

IN RESPONSE: We thank Dr. Timbie for the 2 corrections. All our calculations and writing were done in mmol/L, but we added the U.S. units (mg/dL) in our revision and did this incorrectly for variances (although SDs and means are correct).

Dr. Cayley points out that most of the statin trials have used a fixed dose (4S [Scandinavian Simvastatin Survival Study] is an exception) rather than monitoring-based titration or adjustment. As our work demonstrates, trials with a fixed dose allow the opportunity to assess how cholesterol values increase over time. In patients who truly have a substantial increase, a change in treatment can be considered. Inferences can then be made about monitoring-based titration or adjustment, but we do not believe practice must exactly echo the trials, which are designed for maximum power rather than optimal practice.

Like Dr. Hong and colleagues, we would like to understand the factors that could explain and reduce the variability. Some of the variation is irreducible, such as the analytic variation from the laboratory, which has a coefficient of variation of 2.7% compared with the within-person coefficient of variation of 7.8% (1). Only some of the short-term biological variation is explained by the other factors Dr. Hong and colleagues mention.

Unfortunately, we generally do not know what these factors are. In the LIPID trial analysis, this variability was minimized by both the design (run-in periods and fixed-dose therapy) and analysis methods that accounted for patients changing therapy. In clinical practice, the variability may be greater. Therefore, our results may not hold if a patient changes medication or substantially changes diet.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

1. Choudhury N, Wall PM, Truswell AS. Effect of time between measurements on within-subject variability for total cholesterol and high-density lipoprotein cholesterol in women. Clin Chem. 1994;40:710-5. [PMID: 8174241]

Clinical Observation

Sildenafil-Induced Thrombocytopenia

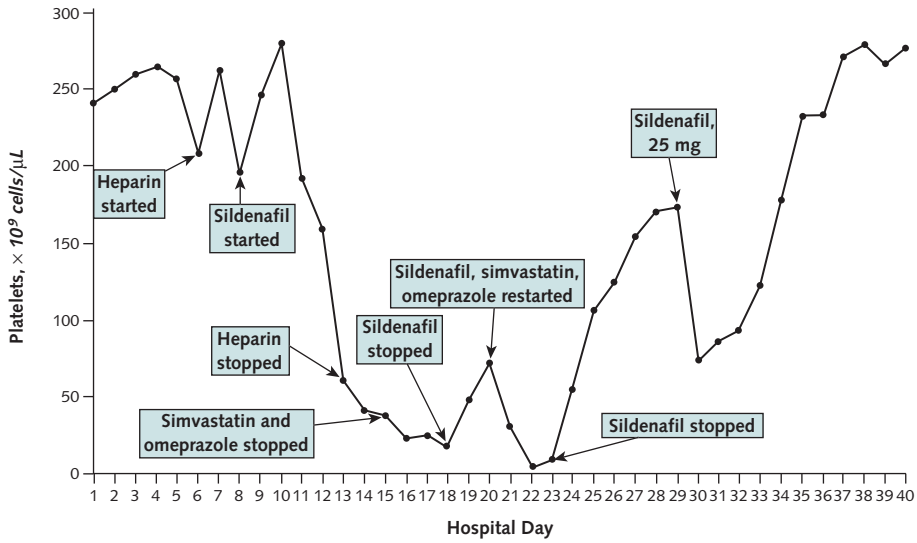
Background: Drug-induced thrombocytopenia is a serious side effect that is typically due to platelet destruction caused by drug-induced antibodies (1, 2). Sildenafil is an approved treatment for both erectile dysfunction and pulmonary arterial hypertension and has not been previously associated with thrombocytopenia (3). Reports of any adverse reaction to this medication may have important consequences because more than 23 million patients were prescribed sildenafil from 1998 to 2005 (4).

Objective: To describe a case of sildenafil-induced thrombocytopenia.

Case Report: A 53-year-old woman was admitted with dyspnea and volume overload. Her medical history included coronary artery bypass surgery that resulted in recurrent pleural effusions and fibrothorax. Other previous conditions included pulmonary hypertension, diastolic dysfunction, hypertension, diabetes, chronic kidney disease, and obstructive sleep apnea.

On admission, we administered furosemide and metolazone as well as the patient's home medications of lisinopril, atenolol, aspirin, simvastatin, omeprazole, acetaminophen, and insulin. We administered deep venous thrombosis prophylaxis with unfractionated heparin. Her clinical condition continued to deteriorate, and she developed respiratory distress. We transferred her to the intensive care

Figure. **Daily platelet count and the relationship to dosing of medications administered during hospitalization.**



unit. Because of the severity of her condition, we started empirical treatment with sildenafil, 25 mg 3 times daily, even though the patient did not meet established indications for this therapy (3).

One week into her hospitalization, we found that the patient had acute thrombocytopenia with a decrease in platelet count from 158×10^9 cells/L to 61×10^9 cells/L over 24 hours. She had no history of thrombocytopenia, and a peripheral smear revealed no platelet clumping or schistocytes. We discontinued all heparin products and ordered both heparin-induced thrombocytopenia (HIT) antibody and serotonin-release assay testing. Platelet count decreased further, and we stopped other medications previously reported to cause thrombocytopenia (acetaminophen, simvastatin, furosemide, and omeprazole).

Four days after the initial diagnosis of thrombocytopenia, the patient's platelet count continued to decrease to 17×10^9 cells/L. We did not inadvertently give any heparin products to the patient. We then discontinued sildenafil, a new medication started during the admission. The next day, her platelet count increased to 72×10^9 cells/L and her HIT antibody result was positive. We then treated the patient as having an atypical case of HIT and started argatroban therapy (5).

We restarted sildenafil, simvastatin, furosemide, and omeprazole treatments. Forty-eight hours later, the platelet count decreased to 4×10^9 cells/L. We again confirmed that no heparin products were given. At this time, the HIT serotonin-release assay result was negative, bringing into question the diagnosis of HIT. Repeated HIT antibody and serotonin-release assay tests at this time yielded negative results.

Her respiratory status transiently improved while taking sildenafil, but we again discontinued the medication because of her recurrent thrombocytopenia. The patient's platelet counts normalized during the next 4 days, but her respiratory status worsened. Without the confirmed diagnosis of drug-induced thrombocytopenia, we rechallenged the patient with a 25-mg dose of sildenafil. Her platelet count subsequently decreased from 174×10^9 cells/L to 74×10^9 cells/L over 24 hours. We permanently discontinued sildenafil, and her platelet count again normalized. This confirmed the diagnosis of sildenafil-induced thrombocytopenia, and we eliminated the continued use of sildenafil in this patient.

Discussion: This case of sildenafil-induced thrombocytopenia meets standardized criteria established for drug-induced thrombocytopenia (2). Sildenafil was the only medication started before the development of thrombocytopenia, and withdrawal resulted in sustained recovery of platelet levels (**Figure**). Sildenafil-induced thrombocytopenia has not been previously described, possibly because sildenafil is infrequently used with sustained daily dosing. The relatively small number of participants in studies of sildenafil for pulmonary arterial hypertension makes it possible that a rare side effect could be missed; we note that our patient did not meet criteria for pulmonary arterial hypertension, which would have fully justified use of the drug. Furthermore, no data are available on platelet counts in patients using sildenafil regularly for erectile dysfunction. Some of these patients may develop undetected thrombocytopenia after recurrent use.

Conclusion: Sildenafil therapy was the likely cause of this patient's thrombocytopenia. Whether this is a class effect of phosphodiesterase type 5 inhibitors cannot be determined. However, these medications should be considered as a possible cause in patients being evaluated for new-onset thrombocytopenia.

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Potential Financial Conflicts of Interest: None disclosed.

References

1. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med. 2007;357:580-7. [PMID: 17687133]
2. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med. 1998;129:886-90. [PMID: 9867731]
3. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353:2148-57. [PMID: 16291984]
4. Jackson G, Gillies H, Osterloh I. Past, present, and future: a 7-year update of Viagra (sildenafil citrate). Int J Clin Pract. 2005;59:680-91. [PMID: 15924597]
5. Arepally GM, Ortel TL. Clinical practice. Heparin-induced thrombocytopenia. N Engl J Med. 2006;355:809-17. [PMID: 16928996]

CORRECTIONS

Correction: Sequential Therapy Appears Superior to Standard Therapy for *Helicobacter pylori* Infection in Patients Naive to Treatment

The Results section of the meta-analysis of trials comparing sequential and standard triple therapies for treatment of *Helicobacter pylori* infection contained errors (1). Data regarding clarithromycin-resistant strains derived from the study by De Francesco and colleagues (2) included 22 patients treated with sequential therapy (instead of 81) and 16 patients treated with standard triple therapy (instead of 75). Pooling these data with pertinent data from the study of Vaira and colleagues (3) showed eradication rates of 83.9% and 35.1% with sequential and standard triple therapy, respectively (difference between treatments, 48.7% [95% CI, 25.7% to 64.8%]).

References

1. Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. Ann Intern Med. 2008;148:923-31. [PMID: 18490667]
2. De Francesco V, Margiotta M, Zullo A, Hassan C, Troiani L, Burattini O, et al. Clarithromycin-resistant genotypes and eradication of *Helicobacter pylori*. Ann Intern Med. 2006;144:94-100. [PMID: 16418408]
3. Vaira D, Zullo A, Vakil N, Gatta L, Ricci C, Perna F, et al. Sequential therapy versus standard triple-drug therapy for *Helicobacter pylori* eradication: a randomized trial. Ann Intern Med. 2007;146:556-63. [PMID: 17438314]

Correction: Seeding Trials: Just Say "No"

In a recent editorial on seeding trials (1), Drs. Sox and Rennie said that they received a letter to the editor from Dr. Amos Egilman. The doctor's name was actually David Egilman. The online version of the editorial has been corrected.

Reference

1. Sox HC, Rennie D. Seeding trials: just say "no" [Editorial]. Ann Intern Med. 2008;149:279-80.