Title

Correction: Effects of Varenicline on Smoking Cessation in Adults With Stably Treated Current or Past Major Depression

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COMMENTS AND RESPONSES

Observation Versus Initial Treatment for Prostate Cancer

TO THE EDITOR: In their cost-effectiveness analysis of treatment versus observation for low-risk prostate cancer, Hayes and colleagues (1) conclude that watchful waiting is less costly and more effective in terms of quality-adjusted life expectancy than the standard treatment of surgery or radiation. Their base-case results depend heavily on a hazard ratio (HR) for prostate cancer–specific death of 1.48 for treatment versus watchful waiting, which was obtained from an HR observed in the low-risk subgroup in PIVOT (Prostate Cancer Intervention Versus Observation Trial). However, the 95% CI on this HR was extremely wide (0.42 to 5.24) because only 10 deaths from prostate cancer occurred in PIVOT in this subgroup (6 in the treatment group vs. 4 in the watchful waiting group).

That such a pivotal parameter in the model was derived from such an unstable estimate should make readers cautious in interpreting the model's findings. Furthermore, the point estimate used, besides being unstable, lacks credulity. As the authors stated, it is already controversial that men with low-risk prostate cancer, who comprise up to 70% of men with clinically localized disease and have less than a 6% risk for prostate cancer–specific death through 15 years, are being routinely treated with radiation or surgery, given the fact that these treatments are known to greatly reduce quality of life (impotence and incontinence) and consume substantial health care resources. However, if it were widely accepted that such treatments also were associated with a 50% increase in the risk for prostate cancer death (or death from treatment for this condition) compared with observation only, this situation would move well past controversial—it would be one of the greatest medical scandals in the United States in recent decades. Solid evidence for such an increased risk is clearly not available yet.

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Potential Conflicts of Interest: None disclosed.

Reference

1. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Lee PA, et al. Observation versus initial treatment for men with localized, low-risk prostate cancer: a cost-effectiveness analysis. Ann Intern Med. 2013;158:853-60. [PMID: 23778902]

IN RESPONSE: We appreciate Dr. Pinsky's concerns about the HR for prostate cancer–specific death for treatment versus watchful waiting used in the base case of our study. We chose to use the results from the low-risk subset of men in PIVOT, despite the small number of deaths in both groups, in the absence of data from other randomized, controlled trials comparing watchful waiting with treatment in the era of prostate-specific antigen level testing (1).

The dearth of long-term data directing therapeutic choices in this context is one reason to perform decision analysis, which allows assumptions to be made and then varied over a wide range to determine their effect on results. We chose the best available data for our base case, then varied this HR over a wide range (HR, 0.42 [the lower limit of the 95% CI reported in PIVOT] to 2.96 [twice the base-case hazard ratio]) and performed threshold analyses to determine at what HR of prostate cancer–specific death would treatment be favored over watchful waiting in terms of quality-adjusted life expectancy (HR, 0.47 in men aged 65 years). Watchful waiting remained the least expensive strategy over the entire range tested (see our Appendix Table 2). Probabilistic sensitivity analysis was also performed to assess the effect of varying all key parameters over a wide range simultaneously, including the HR of prostate cancer–specific death, and our conclusions did not change.

We recognize the suboptimal nature of the HR of prostate cancer–specific death for men with low-risk prostate cancer provided by PIVOT. However, we used the best available data and then showed in multiple analyses that our results were impervious to changes in this estimate over a wide range. We hope that, with time, better data will be available for us to use in future models.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-0857.

Reference

1. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al; Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367:203-13. [PMID: 22808955]

Statin Toxicity From Macrolide Antibiotic Coprescription

TO THE EDITOR: We read Patel and colleagues' study (1) assessing statin toxicity and concomitant macrolide antibiotic prescription with interest. Although we commend the authors for performing this much-needed study, we have several concerns about the study design and interpretation of the results.

The investigators attempted to control for the cytochrome P450 isoenzyme 3A4 (CYP3A4)–inhibiting macrolides with azithromycin, stating that this agent has indications and patterns of clinical use similar to those of clarithromycin and erythromycin. Given the fact that the actual indications for antibiotic use are unknown in more than half of the participants, we believe that this comparison is fundamentally flawed, because the type, location, or severity of the infection could have affected the choice of antibiotic prescribed. In addition, the choice of azithromycin as the intervention in the comparison group implies that the investigators assumed that the in-

creased risks were due to CYP3A4 metabolism. Inclusion of a nondrug comparison group would have addressed these concerns.

Finally, we believe that all-cause mortality is too broad of an outcome in such a study and that to attribute its increase to statin toxicity is too presumptive. We caution against drawing such conclusions from a retrospective cohort. Although the authors acknowledge that these associations do not imply causation, they suggest that the concomitant prescription increases the risk for statin toxicity in older adults.

In conclusion, this study would have been strengthened by the inclusion of a nondrug control group, as well as knowledge about the indications for antibiotic prescriptions in the remaining half of the study population. Although the observed association in this study is strengthened by the study's large size, it is unclear whether the observed differences are due to the effect of the antibiotic itself or a result of the severity of the patients' illness and its effect on the prescriber's choice of medication.

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Potential Conflicts of Interest: None disclosed.

Reference

1. Patel AM, Shariff S, Bailey DG, Juurlink DN, Gandhi S, Mamdani M, et al. Statin toxicity from macrolide antibiotic coprescription: a population-based cohort study. Ann Intern Med. 2013;158:869-76. [PMID: 23778904]

IN RESPONSE: We disagree that inclusion of a nondrug comparator group would have been useful, because patients with infection who receive antibiotics would be expected to have a different risk for outcomes than those who do not receive antibiotics (and a comparison of the 2 groups would be heavily criticized for confounding by indication). Rather, we recently published another study to reassure readers that the associations that we reported in all probability reflect differences related to the type of macrolide antibiotic coprescribed with a statin (1).

In brief, this second study was also conducted using large health care databases in Ontario, Canada. We compared older patients who initiated treatment with clarithromycin (n = 52 251) versus azithromycin (n = 46 618) in the absence of other interacting drugs, such as statins (1). We showed that clarithromycin and azithromycin in Ontario are prescribed for similar infections (for example, respiratory, sinus, and oropharyngeal infections), by the same type of physicians (approximately 75% primary care physicians), and in patients with similar comorbid conditions. Furthermore, in the absence of interacting drugs, we found no significant differences in risks between clarithromycin and azithromycin in any of the 11 hospitalization outcomes assessed, including acute kidney injury (relative risk, 1.05 [95% CI, 0.71 to 1.58] in this study vs. 1.78 [CI, 1.49 to 2.14] in our study with concurrent statin use) (1).

Taken together with consistent, strong, and supporting pharmacokinetic data and warnings from such agencies as the U.S. Food and Drug Administration, everyone should agree that it is important to minimize preventable adverse events and avoid the combination of a CYP3A4-metabolized statin with clarithromycin or erythromycin when possible. We accept that the outcome of all-cause mortality, although universally used in many studies, is broad. Therefore, we prespecified hospitalization with rhabdomyolysis as our primary outcome (an outcome highly related to statin toxicity) and all-cause mortality as 1 of 3 secondary outcomes. We were convinced by the concordant associations suggesting statin toxicity observed across all outcomes, including those observed in the subpopulation with linked laboratory data.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-1300.

Reference

1. Fleet JL, Shariff SZ, Bailey DG, Gandhi S, Juurlink DN, Nash DM, et al. Comparing two types of macrolide antibiotics for the purpose of assessing population-based drug interactions. BMJ Open. 2013;3. [PMID: 23847265]

What Is Our Plan for Acute Unscheduled Care?

TO THE EDITOR: Kocher and Asplin's (1) discussion of acute unscheduled care in the United States resembles the debate on the same topic in England, where the National Health Service is conducting a comprehensive review of unscheduled care services (2). In England, general practice offices staffed by primary care physicians and hospital emergency departments (EDs) form the 2 "silos of acute care delivery" (1). Approximately 9% of patients who try but are unable to obtain a convenient appointment at their general practice office subsequently visit an ED (3). Consequently, recent national policies have attempted to improve access to general practice, using financial incentives to reduce demand for acute unscheduled care at EDs.

A national, observational analysis suggests that more timely access to general practice is associated with lower rates of ED visits in which the patient is self-referred and discharged (4). Therefore, the objective of these policies may be worth pursuing further in England and possibly in the United States as Kocher and Asplin suggest.

The National Health Service has also experimented with the provision of acute unscheduled care in alternative settings, such as "walk-in centers" and "urgent care centers." These services are designed for patients with low-acuity needs, are typically staffed by primary care physicians and nurses, and may have access to diagnostic facilities. Some are located in the same hospitals as EDs to prevent patients without the clinical need for investigation or treatment in an ED from contributing to ED workload (5).

A potential unintended consequence of expanding alternative care settings is that the "question of where patients with acute care needs should go for unscheduled care" (1) becomes more confusing for patients themselves, which has been observed in the National Health Service (2). An increase in the supply of acute unscheduled care services could also generate additional demand for unscheduled care, presenting another undesired result of this policy.

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Potential Conflicts of Interest: None disclosed.

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1. Kocher KE, Asplin BR. What is our plan for acute unscheduled care? Ann Intern Med. 2013;158:907-9. [PMID: 23778907]
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3. Ipsos MORI. The GP Patient Survey Overall Practice Report (July 2012-March 2013). 2013. Accessed at www.gp-patient.co.uk/results/latest_weighted/practice/ on 28 June 2013.
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5. Gnani S, Ramzan F, Ladbrooke T, Millington H, Islam S, Car J, et al. Evaluation of a general practitioner-led urgent care centre in an urban setting: description of service model and plan of analysis. JRSM Short Rep. 2013;4:2042533313486263. [PMID: 23885294]

TO THE EDITOR: We read Kocher and Asplin's (1) commentary about acute unscheduled care with interest. We recently confronted a decision about acute health care when a fall resulted in a wrist injury for one of us while visiting the United States. Rather than seek emergency care for what was almost certainly a fracture, we instead chose to splint and cool the wrist (about $35 for the wrist splint and cold packs at a pharmacy) until we returned to the Dominican Republic several days later.

The anteroposterior and lateral radiographs of the wrist ($14 retail cost in the Dominican Republic) confirmed fractures of the heads of the radius and ulna. We read the films ourselves (along with every physician and nursing colleague present at the time) and saved the cost of an official reading (about $5). Without a primary care physician or medical home setting available to us in the United States, we would have faced the inconvenience and expense of an ED visit. Our interest was "less about the provider and more about timely access" (1), as well as the out-of-pocket cost and the possible effect on our future health insurance premiums.

As physicians, we consider ourselves knowledgeable health care consumers and realize that we have more options available to us than the average patient. However, looking at the "challenge of acute unscheduled care" (1) from the patient's perspective, we opted for self-care and leaving the country.

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Potential Conflicts of Interest: None disclosed.

Reference

1. Kocher KE, Asplin BR. What is our plan for acute unscheduled care? Ann Intern Med. 2013;158:907-9. [PMID: 23778907]

Correction

Correction: Effects of Varenicline on Smoking Cessation in Adults With Stably Treated Current or Past Major Depression

On Annals.org, the URL to the authors' disclosure forms in a recent article (1) was incorrect. The correct URL is www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-0777.

This has been fixed.

Reference

1. Anthenelli RM, Morris C, Ramey TW, Dubrava SJ, Tsilkos K, Russ C, et al. Effects of varenicline on smoking cessation in adults with stably treated current or past major depression. A randomized trial. Ann Intern Med. 2013;159:390-400.