Table 2. Change in Daytime Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Mean (SD, mm Hg)</th>
<th>With Daytime ABPM Mean Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>SBP &lt;135 mm Hg</td>
</tr>
<tr>
<td>Immediately after DOT</td>
<td>n = 48</td>
<td>-9.7 (17.3)</td>
</tr>
<tr>
<td>1 mo After DOT</td>
<td>n = 46</td>
<td>-11.0 (15.8)</td>
</tr>
</tbody>
</table>

Abbreviations: ABPM, ambulatory blood pressure monitoring; DOT, directly observed therapy; SBP, systolic blood pressure.

Results | A total of 60 consecutive patients (32 men [67%]; mean [SD] age, 62.1 [13.1] years) were enrolled in the study, and after exclusion of those who withdrew consent (n = 4), did not attend DOT (n = 4), or missed subsequent ABPM (n = 4), 48 participants completed this study for the primary outcome and 46 for the secondary outcome. Baseline characteristics are reported in Table 1. After DOT, daytime systolic BP remained 135 mm Hg or greater in 34 of 48 patients (71%) who experienced a mean (SD) decrease in systolic BP of 3 (10) mm Hg. In contrast, in 14 participants (29%), treatment-resistant hypertension resolved and systolic BP decreased by 26 (20) mm Hg (Table 2). This proportion was similar at 1 month in 14 of 46 patients (30%) who no longer had treatment-resistant hypertension.

Discussion | The results suggest that nonadherence to BP-lowering drug regimens is high among referred patients with apparent treatment-resistant hypertension, even among those who said they were adherent on questioning before DOT, had pristine pharmacy filling records, and had accurate pill counts. Moreover, this apparent nonadherence occurred despite more than 50% of these patients already having had an adverse vascular event related to uncontrolled hypertension. However, we cannot exclude the possibility that the process of being in the study or receiving treatment from a nurse in a clinic was associated with lower BP for some patients. Of interest, most of those with markedly improved BP after DOT had a sustained improvement in BP control seen at 1 month. Limitations of the study include that the patients were highly selected and likely do not represent most patients with hypertension in the community. The use of DOT as described here was strictly dichotomous (adherence vs nonadherence) and thus does not allow for precise assessment of the degree of nonadherence (eg, partial vs complete), as may be the case with therapeutic drug monitoring.5,6 Overall, the findings suggest that rigorous methods of adherence assessment and intervention such as DOT should be considered for patients with apparent treatment-resistant hypertension.

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Author Contributions: Drs Ruzicka and Hiremath had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ruzicka, Ramsay, McCormick, Hiremath.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Ruzicka, Leenen, Ramsay, Hiremath.

Critical revision of the manuscript for important intellectual content: Ruzicka, Ramsay, Bugeja, Edwards, McCormick, Hiremath.

Statistical analysis: Ruzicka, Ramsay, Hiremath.

Obtained funding: Ruzicka, Ramsay, Hiremath.

Administrative, technical, or material support: Ruzicka, Leenen, Ramsay, McCormick, Hiremath.

Supervision: Ruzicka, Ramsay, Bugeja, Edwards, McCormick, Hiremath.

Conflict of Interest Disclosures: Dr Ruzicka reported receiving grants from Physicians Services Incorporated and The Ottawa Hospital Academic Medical Organization—Innovation Fund Provincial Oversight Committee during the conduct of the study. Dr Hiremath reported receiving grants from the Canadian Institutes of Health Research, Physicians Services Incorporated, and The Ottawa Hospital Academic Medical Organization outside the submitted work. No other disclosures were reported.

Funding/Support: This study was funded by a peer-reviewed grant (Dr Ruzicka) provided by The Ottawa Hospital Academic Medical Organization and the Innovation Fund Provincial Oversight Committee (Ontario, Canada).

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Peter Magnier, MD, FRCPC, provided critical review of the concept and results of this study (not compensated); Valerie Cronin, RN, was the research coordinator for the study (compensated); and the Hypertension Clinic study staff conducted the direct observed therapy procedures (compensated).


Prevalence of Inappropriateness of Parenteral Vitamin B12 Administration in Ontario, Canada
Randomized clinical trials demonstrate that treating vitamin B12 (cobalamin, or hereinafter B12) deficiency with oral supple-
mentation substantially increases serum B₁₂ levels compared with intramuscular injections, with no difference in hematologic or neuropsychiatric outcomes.⁴ Despite this, some primary care physicians still inappropriately administer B₁₂ injections to elderly patients.⁵ To our knowledge, there is no published literature characterizing prescribing patterns of intramuscular B₁₂ using laboratory data to document patient serum levels. In this study, we assessed the prevalence of inappropriate B₁₂ supplementation using population-based databases and estimated the associated cost.

Methods | We performed a population-based, retrospective cohort study using health system administrative databases within ICES, formerly the Institute for Clinical Evaluative Sciences, in Ontario, Canada. Data sets were linked using unique, encoded identifiers and analyzed at ICES. All persons 65 years or older who received at least 1 intramuscular B₁₂ prescription from January 1, 2011, to September 30, 2015 (data on B₁₂ levels were not available until January 1, 2010), were included. Data were analyzed from July 26, 2018, to November 22, 2018. The primary outcome was the proportion of inappropriate B₁₂ supplementation, defined as persons with either a normal serum B₁₂ level (≥ 221 pmol/L), or without a documented B₁₂ level in the 12 months prior to their first intramuscular B₁₂ prescription. Vitamin B₁₂ supplementation was considered appropriate when persons had at least 1 documented level of marginal B₁₂ deficiency (≤ 221 pmol/L) in the year prior to receiving their first B₁₂ injection. Annual cost of inappropriate, once-monthly injections was estimated in Canadian dollars using the amount paid for a physician visit ($33.70), intramuscular injection ($3.89), and prescription cost ($6.74). Sunnybrook Health Sciences Centre’s research ethics board approved this study and waived patient written informed consent for deidentified data.

Results | A total of 405,469 intramuscular B₁₂ prescriptions were dispensed to 146,850 persons (Table); the majority (63.7%; n = 93,615) of these were inappropriate (Figure).

### Table. Characteristics of Patients Who Received an Intramuscular Vitamin B₁₂ Prescription⁶

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients, No. (%) (n = 146,850)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean (SD) 76.5 (8.1)</td>
</tr>
<tr>
<td>Median (IQR) [range]</td>
<td>76 (14.0) [65-110]</td>
</tr>
<tr>
<td>Age categorized, y</td>
<td>65-69 36,866 (25.1)</td>
</tr>
<tr>
<td></td>
<td>70-74 28,196 (19.2)</td>
</tr>
<tr>
<td></td>
<td>75-79 28,014 (19.1)</td>
</tr>
<tr>
<td></td>
<td>80-84 26,055 (17.7)</td>
</tr>
<tr>
<td>≥ 90 18,384 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male 60,037 (40.9)</td>
</tr>
<tr>
<td></td>
<td>Female 86,813 (59.1)</td>
</tr>
<tr>
<td>Location of residence</td>
<td>Rural 12,692 (8.6)</td>
</tr>
<tr>
<td></td>
<td>Urban 124,359 (84.7)</td>
</tr>
<tr>
<td>Neighborhood income quintile</td>
<td>Q1 (lowest) 32,905 (22.4)</td>
</tr>
<tr>
<td></td>
<td>Q2 32,230 (22.0)</td>
</tr>
<tr>
<td></td>
<td>Q3 29,828 (20.3)</td>
</tr>
<tr>
<td></td>
<td>Q4 27,679 (18.9)</td>
</tr>
<tr>
<td></td>
<td>Q5 (highest) 23,573 (16.1)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Crohn disease, ulcerative colitis, and malabsorption 9309 (6.3)</td>
</tr>
<tr>
<td></td>
<td>Pernicious anemia 40,908 (27.9)</td>
</tr>
<tr>
<td>ADG comorbidity classification scheme</td>
<td>Low scores (0–5) 24,135 (16.4)</td>
</tr>
<tr>
<td></td>
<td>Moderate scores (6–9) 51,920 (35.4)</td>
</tr>
<tr>
<td></td>
<td>High scores (≥10) 70,795 (48.2)</td>
</tr>
<tr>
<td></td>
<td>Dementia 14,844 (10.1)</td>
</tr>
<tr>
<td></td>
<td>Neuropathy 2471 (1.7)</td>
</tr>
</tbody>
</table>

Abbreviations: ADG, Aggregated Diagnosis Group; IQR, interquartile range.

* Some totals may not add up owing to missing data.

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preceding persons’ first intramuscular $B_{12}$ injection, 25.5% ($n = 37487$) had a normal $B_{12}$ level, whereas 38.2% ($n = 56128$) did not have a $B_{12}$ level documented. Findings were similar over a 24-month look-back period (data not shown). Only 43.1% ($n = 24175$) of the 56128 people without a $B_{12}$ level documented in the year preceding their first $B_{12}$ prescription had ever had one measured. This was performed a mean (SD) 1033.5 (488.1) days prior to their first prescription (range, 366-2801 days). Only 35.3% ($n = 8539$) of these 24175 persons had marginally deficient $B_{12}$ levels. The estimated annual cost of inappropriate $B_{12}$ prescribing was $45.6 million, assuming a 64% inappropriate prescription rate. Finally, only 1.7% ($n = 2498$) of persons prescribed intramuscular $B_{12}$ demonstrated any deficiency with a malabsorptive indication.

**Discussion**  Most parenteral $B_{12}$ in Ontario was prescribed to persons without evidence of deficiency in the year preceding their first $B_{12}$ prescription. Potential drivers of this include patient demands and poor physician awareness of the evidence informing $B_{12}$ supplementation. It is also questionable whether parenteral supplementation is required over oral supplementation because oral $B_{12}$ raises $B_{12}$ serum levels and improves sequelae of deficiency as well as, if not better than, intramuscular $B_{12}$, even for pernicious anemia. Plausible reasons why physicians prefer parenteral $B_{12}$ include low quality of evidence supporting oral $B_{12}$, society guidelines recommending intramuscular $B_{12}$ for all patients, poor physician understanding of how to prescribe oral $B_{12}$, and physician misperception that patients prefer parenteral over oral $B_{12}$.

Our study’s limitations include only looking 2 years before a person’s first documented prescription; using this abridged period might have misclassified persons undergoing treatment for chronic $B_{12}$ deficiency, and so with normal $B_{12}$ levels, as receiving inappropriate supplementation. We were also unable to access information on oral $B_{12}$, and could not understand why $B_{12}$ was prescribed without laboratory evidence of deficiency. Further studies should examine this issue, to inform quality improvement initiatives aimed at reducing this unnecessary care.

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**Correction:** This correction was accepted on August 26, 2019, to fix errors in the dates of data analysis in the Methods section.

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**Author Contributions:** Drs Cheung, Croxford, and Dharma had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Lin and Cheung contributed equally as co–senior authors to this study.

**Study concept and design:** Silverstein, Lin, Dharma, Cheung.

**Acquisition, analysis, or interpretation of data:** Lin, Dharma, Croxford, Earle, Cheung.

**Drafting of the manuscript:** Silverstein, Cheung.

**Critical revision of the manuscript for important intellectual content:** Lin, Dharma, Croxford, Earle, Cheung.

**Statistical analysis:** Dharma, Croxford, Cheung.

Obtained funding: Cheung.

Administrative, technical, or material support: Silverstein, Dharma, Cheung.

**Study supervision:** Lin, Cheung.

**Conflict of Interest Disclosures:** Dr Lin reported that she was a consultant for Pfizer and that she was on the advisory board of Amgen. No other disclosures were reported.

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**Role of the Funder/Sponsor:** The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Disclaimer:** No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). The opinions, results and, conclusions reported in this article are those of the authors and are independent from the funding sources and CIHI.

**Additional Contributions:** We thank IMS Brogan Inc for use of their Drug Information Database. No contributors received compensation for their assistance.


**Association of Mirabegron With the Risk of Arrhythmia in Adult Patients 66 Years or Older—A Population-Based Cohort Study**

Recently, mirabegron, the first $β_{3}$-adrenoceptor agonist, has been prescribed to treat overactive bladder (OAB) more frequently than antimuscarinic agents. The $β_{3}$-agonist medications have limited adverse effects compared with antimuscarinic agents, but $β_{3}$-adrenoceptors are associated with increases in contractile force and reductions in inotropic effects, actions which raise concerns of cardio-

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vascular (CV) adverse effects. These adverse effects have been reinforced by trials, finding a small increase in heart rate, blood pressure, and QTc intervals.\(^2\)\(^4\) Real-world data among older patients with CV comorbidities are lacking.\(^5\) We conducted a population-based cohort study to evaluate the risk of cardiac arrhythmias and other CV events in a population of patients 66 years and older receiving mirabegron.

### Methods

We used health care administrative data from 38,818 patients 66 years or older who initiated treatment between June 1, 2015, and March 31, 2017 (eTable 1 in the Supplement). Data were analyzed from June 1, 2015, to March 31, 2017. In Ontario, all health care services and medications are publicly funded for individuals 65 years and older. Information is recorded by the Ministry of Health and Long-term Care and data

Table 1. Baseline Characteristics of Users by Overactive Bladder-Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>Other OAB Drugs</th>
<th>Standardized Difference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>New users, No.</td>
<td>16,948</td>
<td>21,870</td>
<td>NA</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>76 (71-82)</td>
<td>76 (71-82)</td>
<td>NA</td>
</tr>
<tr>
<td>Male</td>
<td>6,342 (37.4)</td>
<td>7,287 (33.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Neighborhood income quintile(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2,907 (17.2)</td>
<td>4,100 (18.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>3,241 (19.1)</td>
<td>4,417 (20.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>3</td>
<td>3,353 (19.8)</td>
<td>4,338 (19.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>4</td>
<td>3,629 (21.4)</td>
<td>4,543 (20.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>5</td>
<td>3,745 (22.1)</td>
<td>4,363 (19.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Living in urban community</td>
<td>14,867 (87.7)</td>
<td>18,911 (86.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Living in long-term care</td>
<td>351 (2.1)</td>
<td>511 (2.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Charlson comorbidity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hospitalization</td>
<td>11,213 (66.2)</td>
<td>14,759 (67.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>0</td>
<td>2,565 (15.1)</td>
<td>3,113 (14.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>1</td>
<td>1,196 (7.1)</td>
<td>1,549 (7.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2+</td>
<td>1,974 (11.6)</td>
<td>2,449 (11.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>2,910 (17.2)</td>
<td>3,398 (15.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>4,560 (26.9)</td>
<td>5,819 (26.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5,951 (35.1)</td>
<td>7,806 (35.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13,190 (77.8)</td>
<td>17,203 (78.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV events in the past 5 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>425 (2.5)</td>
<td>531 (2.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1,015 (6.0)</td>
<td>1,215 (5.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>195 (1.2)</td>
<td>244 (1.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1,098 (6.5)</td>
<td>1,469 (6.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Angina</td>
<td>484 (2.9)</td>
<td>675 (3.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>35 (0.2)</td>
<td>36 (0.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1,766 (10.4)</td>
<td>2,347 (10.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Health care use in past year, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Physician</td>
<td>8 (4-15)</td>
<td>8 (4-14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiologist</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urologist</td>
<td>0 (0-1)</td>
<td>0 (0-0)</td>
<td>0.10</td>
</tr>
<tr>
<td>Different medications, No., median (IQR), No.</td>
<td>8 (5-11)</td>
<td>8 (5-11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Concurrent recent CV medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme</td>
<td>4,033 (23.8)</td>
<td>5,160 (23.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>3,667 (21.6)</td>
<td>4,611 (21.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Statin</td>
<td>7,729 (45.6)</td>
<td>9,641 (44.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Other lipid lowering agents</td>
<td>950 (5.6)</td>
<td>1,148 (5.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>3,606 (21.3)</td>
<td>4,684 (21.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>4,360 (25.7)</td>
<td>5,580 (25.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4,380 (25.8)</td>
<td>5,839 (26.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Platelet inhibitor</td>
<td>1,066 (6.3)</td>
<td>1,287 (5.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia treatments</td>
<td>3,197 (18.9)</td>
<td>3,217 (14.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Switched therapy within 1 y</td>
<td>960 (5.7)</td>
<td>1,306 (6.0)</td>
<td>0.023</td>
</tr>
<tr>
<td>Days on therapy, median (IQR)</td>
<td>104 (30-249)</td>
<td>81 (30-199)</td>
<td>0.194</td>
</tr>
</tbody>
</table>

Abbreviations: CV, cardiovascular; IQR, interquartile range; NA, not applicable; OAB, overactive bladder.

* Standardized difference of >0.1 used to signify a meaningful difference.

\(^b\)Neighborhood income quintile is based on each participant’s postal code.

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Table 2. Results of Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Events, No. (%)</th>
<th>Incidence Rate per 100 Person-Years</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mirabegron (n = 16,948)</td>
<td>Other OAB Drugs (n = 21,870)</td>
<td>Mirabegron</td>
</tr>
<tr>
<td>Primary outcome (hospitalization for arrhythmia or tachycardia)</td>
<td>284 (1.7)</td>
<td>340 (1.6)</td>
<td>3.6</td>
</tr>
<tr>
<td>Secondary outcome (hospitalization for myocardial infarction or stroke)</td>
<td>233 (1.4)</td>
<td>247 (1.1)</td>
<td>3.0</td>
</tr>
<tr>
<td>Subgroup analysis (primary outcome: no previous atrial fibrillation or ventricular arrhythmias at baseline)</td>
<td>177 (1.1)</td>
<td>190 (0.9)</td>
<td>2.4</td>
</tr>
<tr>
<td>Aged 75 or older</td>
<td>221 (2.5)</td>
<td>255 (2.2)</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Abbreviation: OAB, overactive bladder.

Discussion

A lack of evidence exists for assessing the safety of mirabegron in older patients with CV risk factors, and our work highlights the CV safety of mirabegron in a cohort of patients with higher prevalence of comorbidities than in previous clinical trials. In previous studies, the prevalence of diabetes ranged between 6% and 9% and that of hypertension ranged between 10% and 29%. In contrast, a 79% prevalence of hypertension and 36% prevalence of diabetes were found in the present study. Moreover, the mean age of patients in this cohort, 77 years, was higher than that of previous trials, where mean ages ranged from 58 to 60.

Our study was limited by our inability to ascertain lifestyle factors and over-the-counter medication use, and the potential for confounding by indication owing to prescriber perceptions of mirabegron risk. However, we anticipate these factors have minimal consequences given the use of stringent matching criteria and the HDPS.

The findings of this study suggest that mirabegron was not associated with a higher risk of CV events compared with other treatments. Our findings are not meant to endorse preferential use of mirabegron but to support a growing body of evidence that mirabegron is not associated with an excess risk of CV events compared with other treatments in older patients. These results appear to support current prescribing patterns and give a balanced view of real-world safety.

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COMMENT & RESPONSE

5α-Reductase Inhibitor Use in Patients With Prostate Cancer

To the Editor The article by Sarkar and colleagues recently published in JAMA Internal Medicine contributes to deeper knowledge of prostate cancer diagnosis in patients who are using 5α-reductase inhibitors (5-ARIs). As noted, the prediagnostic use of 5-ARIs is associated with delayed prostate cancer diagnosis, more advanced disease, and worse prostate cancer-specific and all-cause mortality compared with nonusers who underwent prostate-specific antigen (PSA) screening.

Although the recommendation of how to make the adjustment of PSA suppression by 5-ARIs is not completely clear, the association of correctly PSAd to prostate volume (PSAd density) is a tool that has been recognized as having greater specificity compared with using total PSA and has shown to be a significant predictor of different indices of cancer aggressiveness.

Moreover, several studies have shown prostate volume to have a significant role predicting prostate cancer with PSA values in the gray zone and thus propose it as a tool that must be taken into consideration in the diagnostic approach. It is presumed that users of 5-ARIs are patients with larger prostates, and a fundamental tool to avoid misinterpretation could be PSAd.

Although Sarkar and colleagues described multiple variables listed in Table 1 of their article, no mention is made of these fundamental clinical parameters at the time of diagnosis. This information could help elucidate differences between groups by (1) assessing the degree of PSA misinterpretation in real-life clinical practice, (2) knowing if for the same comparative PSAd there are still worse prostate cancer characteristics in 5-ARI users, or (3) identifying a subgroup for which there is not an increased risk of delayed or worst prostate cancer with the use of this medication.

In summary, we believe PSAd is a determining factor to be considered and it should be used to correlate to other clinical and laboratory factors to accurately describe differences between groups in the study by Sarkar and colleagues.

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5. Erdogan A, Polat S, Keskin E, Turan A. Is prostate volume better than PSA density and free/total PSA ratio in predicting prostate cancer in patients with PSA 2.5-10 ng/mL and 10.1-30 ng/mL? [published online March 12, 2019] Aging Male. doi:10.1080/13688553.2019.1578741
To the Editor Interpretation of observational studies is challenging when results are different from randomized trials. The recently published report by Sarkar and colleagues illustrates this challenge. A retrospective cohort of patients diagnosed with prostate cancer between 2001 and 2005 was described, and it was found that the use of 5-α reductase inhibitors (5-ARIs) was associated with a delayed diagnosis and a 39% increase in prostate cancer mortality. Initially, this conclusion seems at variance with the follow-up report of the randomized Prostate Cancer Prevention Trial, which showed no increase in prostate cancer mortality in men receiving finasteride compared with placebo.

Observational studies are prone to major biases. In the study by Sarkar and colleagues, the 39% improvement in prostate cancer mortality in men with a 2-year earlier diagnosis of prostate cancer and median 5.9 years of follow-up is implausible. Two large randomized trials of prostate-specific antigen (PSA) screening found only a 20% reduction and no reduction in prostate cancer mortality, respectively. As accurate assessment of 5-ARI medication adherence was not possible, the study by Sarkar and colleagues was subject to misadjustment of the PSA.

Men being treated with 5-ARIs are inherently different, which is illustrated by important differences in baseline characteristics in the study by Sarkar and colleagues, for which adequate adjustment is difficult. Also, men diagnosed with prostate cancer who received a 5-ARI will have fewer low-grade prostate cancers, enriching for high-grade tumors. National guidelines for treatment of benign prostatic hyperplasia recommend use of 5-ARIs for men with prostate enlargement. Because prostate size is directly related to PSA, aggressive prostate cancers are often missed on initial biopsy in large prostates, it is possible that men treated with 5-ARIs had a first biopsy that was benign but a biopsy years later showing cancer. Without knowing the biopsy and PSA history, these confounding factors cannot be adjusted. Finally, the seismic changes in PSA screening guidelines in the United States between 2001 and 2015 likely influenced screening and biopsy patterns, and are not included in the analysis.

The authors’ analysis did not adjust for survival bias: as the prostate cancer survival clock started earlier in men not receiving a 5-ARI, there is an associated longer survival in them, exacerbated by the significant baseline age differences (65 years vs 70 years).

Adjustment for these powerful study biases is beyond the reach of the most sophisticated statistical approaches. Because a key study hypothesis was that lack of PSA adjustment for 5-ARIs led to delayed diagnosis, a superior approach would have been to examine the time between first PSA screening results greater than 4.0 and biopsy in men receiving or not receiving a 5-ARI.

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In Reply We would like to thank Medina and colleagues and Thompson Jr and colleagues for their interest and thoughtful comments on our article. We completely agree that the goal of observational studies is not to refute clinical trials, but rather to complement them through assessment of real-world practice. In the Prostate Cancer Prevention Trial, prostate-specific antigen (PSA) values for men being treated with finasteride (a 5-α reductase inhibitor [5-ARI]) were automatically adjusted for the effect of the medication by a relatively complicated formula where the PSA was doubled for the first couple of years, then multiplied by 2.3 for subsequent years.

Our study was motivated by the question of what happens in real-world practice if PSA values are not automatically adjusted. The data in our study suggest that PSA adjustment is not routinely performed, which may lead to substantial delays in diagnosis, more advanced disease, and a small increase in the risk of prostate cancer mortality.

Our colleagues bring up important considerations. First, they mention that the magnitude of effect seems implausible given the small benefit from PSA screening trials. However, one trial had very high rates of PSA screening in the control arm, which substantially dilutes the expected effect. We believe the best estimate comes from a modeling study using data from the randomized screening trials that showed a reduction in prostate cancer mortality of 7% to 9% for every year of earlier diagnosis. Our study suggested a potential delay in diagnosis of 2 to 3 years, which would be expected to increase the risk of death by 14% to 27%, similar to the observed effect size. Also, the absolute increase risk in prostate cancer mortality (5%) is very similar to the increase in stage IV cancers in the 5-ARI group (5%), which supports the plausibility of our findings.

It is true that use of 5-ARIs have consistently been shown to reduce the incidence of Gleason grade 6 cancers but not Gleason grade 7 and higher cancers. To avoid the problem of enriching for high-grade prostate cancer in the 5-ARI group, we did an analysis where Gleason grade 6 cancers were excluded from both groups. The results were largely unchanged.

The survival clock started at the time of diagnosis of prostate cancer in both groups. The potential for differences in lead
time would only exist if use of 5-ARIs was associated with significant delays in diagnosis, which the trials suggest may lead to poorer outcomes, providing external support for our findings. We agree that the PSA density can be a helpful parameter. Unfortunately, the prostate volume was not consistently known for patients in the study and therefore could not be included in the analysis. Similarly, prostate volume is not typically known by primary care physicians when they would need to interpret the PSA values. However, PSA density could be used by urologists at the time of transrectal ultrasound before deciding to proceed with biopsy. This may lead to fewer unnecessary biopsies and perhaps less overdiagnosis of clinically insignificant prostate cancers.

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Conflict of Interest Disclosures: None reported.


Benefits of Targeted Use of 5α-Reductase Inhibitors in Patients With Prostate Cancer

To the Editor I would like to offer 2 points to expand on the important analysis by Sarkar and colleagues. First, use of a single prostate-specific antigen (PSA) multiplier for all men using 5α-reductase inhibitors (5-ARIs) is probably not optimal. The goal is to estimate what each man’s PSA would have been in the absence of drug treatment. However, because 5-ARIs inhibit the common age-associated increase in gland volume and PSA, the PSA trajectory for a man being treated with a drug vs his counterfactual trajectory with no drug diverge over time. Furthermore, the benign prostatic hyperplasia component of total PSA would be higher in an older man vs a younger one. Therefore, a larger multiplier may be optimal in older men with longer-term 5-ARI exposure to further avoid delayed diagnosis. Alternatively, men taking 5-ARIs could benefit from monitoring with newer biomarkers that are less sensitive to alterations in androgen levels, such as urinary PCA3 or ERG fusion assays.

Second, the article that was cited to represent the US Food and Drug Administration’s argument that 5-ARIs may cause high-grade prostate cancer is a frequently cited Perspectives publication that was not subjected to full peer review, despite its inclusion of reanalyzed data. The US Food and Drug Administration analysts reproduced results we obtained in the Prostate Cancer Prevention Trial from a binary logistic model adjusting for gland volume and number of biopsy cores (sampling density), in which risk of high-grade cancer (Gleason score, 7-10) is compared with a reference group with low-grade and no cancer combined. A more important probabilistic model in that trial estimated separate relative risks for high-grade cancer and low-grade cancer vs no cancer while adjusting for sampling density. This model yielded odds ratios for finasteride vs placebo of 0.47 (95% CI, 0.41-0.54) for low-grade cancer and 0.88 (95% CI, 0.72-1.09) for high-grade cancer. Other authors found similar results using alternate methods for sampling density adjustment.

There is now ample evidence that 5-ARIs, under reasonable PSA interpretation guidelines, make biopsies more efficient and therefore reduce risk of low-grade cancers while accelerating detection of cancers that are more likely to require treatment. Several recent long-term follow-up studies of high-quality cohorts, including the Prostate Cancer Prevention Trial, reported not increases but nonsignificant decreases in lethal prostate cancer associated with 5-ARI use, despite the likely effect of diagnostic delay when care is received outside of a trial protocol. This is not a blanket endorsement of 5-ARIs for chemoprevention; however, targeted use of these agents in carefully selected men at high risk is reasonable after weighing the established risks and benefits, and will become increasingly reasonable as risk-assessment tools continue to improve.

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Conflict of Interest Disclosures: None reported.
In Reply We would like to thank Gann for his important perspective on this topic and for his interest in our study.1 In his letter, Gann notes an important modeling article that takes the size of the prostate into account when determining the effect of use of a 5-α reductase inhibitor (5-ARI) on the development of low-grade and high-grade prostate cancers.2 There is extensive debate in the literature on whether 5-ARIs directly increase the risk of high-grade cancers through some biologic mechanism. Although this is still an open question, the majority of the data seems to suggest that use of 5-ARIs does not directly increase this risk. Owing to the inherent limitations in observational data, we do not feel that our study meaningfully contributes to this question.

Our study focused specifically on whether the prostate-specific antigen (PSA) suppression from use of 5-ARIs was associated with later diagnoses, more advanced disease, and worse overall outcomes. It appears that in routine practice, 5-ARI-induced PSA suppression does affect early prostate cancer diagnosis. Gann nicely explains some of the factors that can affect the degree of PSA suppression from 5-ARI use. He notes that age, prostate volume, and duration of 5-ARI use could be included in the interpretation of the PSA. Unfortunately, incorporating all of these factors into a decision-making process is difficult within the constraints of a busy clinic. Primary care physicians will usually not know how large a man's prostate is or how much to increase the multiplier for a given age and duration of treatment. Compliance with the medication would also need to be considered.

Because this is effectively the status quo that led to the findings of our study, we would propose 2 possible solutions. First, one could build a decision aid into the electronic medical record that provides an automatic correction for age and duration of 5-ARI usage. Second, one could default to the conventional doubling rule in which the PSA is multiplied by 2 to get the corrected value. The doubling rule may oversimplify the decision, but it is probably the most feasible recommendation for routine practice. There are certainly other possible solutions. The main goal of our study was to raise awareness of the issue and to stimulate discussion among the community on the best way to deal with 5-ARI–associated PSA suppression. Hopefully, new screening tests will allow us to move away from PSA in the future; however, their utility will need to be demonstrated before they are broadly accepted.

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State-Level Approaches to Expanding Pharmacists’ Authority to Dispense Naloxone May Affect Accessibility

To the Editor We read with great interest the recently published study by Abouk and colleagues1 that identified reduced opioid-related mortality in states granting pharmacists direct authority to dispense naloxone. We agree that empowering pharmacists to dispense naloxone can profoundly influence overdose risk and concur that the method of implementing such policies can greatly influence their effectiveness. However, categorizing naloxone access laws (NALs) as either providing pharmacists direct or indirect authority to dispense naloxone is an oversimplification. Based on this methodology, most states were grouped in the indirect category despite noteworthy state-to-state heterogeneity in implementation. Two recent studies, similarly designed and concurrently published in JAMA,2,3 assessed the influence of Texas’ and California’s NALs on naloxone accessibility from community pharmacies. The surprisingly divergent results highlight the importance of how NALs are implemented.

The Texas NAL provides only indirect authority to pharmacists, and the Texas Health and Human Services Commission has not issued a statewide standing order to facilitate access.4 Thus, pharmacists in Texas are unable to autonomously dispense naloxone unless they or their pharmacies develop a unique standing order with a prescriber. While this extra step of developing unique standing orders represents a potential barrier to pharmacy-based naloxone access, robust chain-level implementation, accompanied by internal pharmacist education, appears to have increased readiness to dispense naloxone. In the Texas study,2 naloxone was accessible via standing order from 83.7% of pharmacies audited.

In contrast, the California NAL provides pharmacists direct authority to dispense naloxone. However, the protocol requires pharmacists to complete several time-consuming tasks, which constitute substantial barriers to participation.5 Pharmacists must complete 1 hour of naloxone-centered education, and with each dispensing, they must administer a screening questionnaire, provide patient education with 19 legally mandated components, and notify the patient’s physician. Without encouragement from management for implementation of a chain-specific standing order, California pharmacists may be less motivated to begin dispensing naloxone under the statewide protocol. Thus, despite providing direct authority to dispense naloxone, this method of implementation appears to limit the influence of California’s NAL because naloxone was accessible in only 23.5% of pharmacies audited in the California study.3

In conclusion, we agree with Abouk and colleagues’ assertion1 that how NALs are implemented can substantially influence their real-world effectiveness, but we assert that classifying these state-level policies as granting pharmacists direct or indirect authority is an oversimplification. Further research is needed to identify the optimal approach for
empowering pharmacists to reduce opioid-related mortality by distributing naloxone.

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Conflict of Interest Disclosures: None reported.

4. S 1462, 84th Leg, 1st Sess (Tx 2015).
5. Cal Reg Code §1746.

In Reply We appreciate the comments by Hill and colleagues concerning the way we categorized naloxone access laws (NALs) in our article.1 We acknowledge the oversimplification of our investigation in our assessment of the effect of NALs on opioid overdose deaths. The fact is that all NALs are different in some manner, whether it is by statute or by implementation. It would be paralyzing to study every dimension of every state policy independently because it would be difficult to determine what common features appear to be most effective. Some type of aggregation is necessary if we are trying to learn about these laws, what they do in practice, and what works. This trade-off likely resonates with many researchers. Studying too many dimensions at once reduces power and makes it difficult to learn about the effects of potential common features across policies. On the other hand, aggregating too much masks the effects of dimensions that matter and dimensions that do not. Our article was motivated by concerns that the literature has not adequately mentioned the elderly in the Discussion section. In addition, several studies involving elderly people were cited without being mentioned, which may mislead the readers about the generalizability of the results. For example, Choosing Wisely Canada2 recommended against the use of sedative-hypnotic medications as a first-line therapy for elderly patients. This biased content naturally leads to a question of whether the suggested evidence can be generalized to all adults. Unfortunately, the limitations resulting from these unbalanced citations were not mentioned in the Discussion section. In addition, several studies involving elderly people were cited without being mentioned, which may mislead the readers about the generalizability of the results. For example, Choosing Wisely Canada2 recommended against the use of sedative-hypnotic medications as a first-line therapy for elderly patients. This overgeneralization to interpret such recommendations as indications to avoid the use of sedative-hypnotic drugs and to consider them unnecessary in all adults.

Second, the adverse reactions associated with zolpidem were not sufficiently mentioned. It has been widely accepted that zolpidem contributes to visual hallucinations, sleepwalking, night eating, and sleep driving.3 Whereas falls and fractures are the main concerns in the elderly,4 adverse reactions to zolpidem can occur in any age group. This may be associated with the distorted prescription patterns of zolpidem. Zolpidem is generally prescribed at a higher dosage and for longer periods than recommended.5 Hence, relevant references in the article1 predominantly focused on the elderly. Regarding the nonpharmacological interventions, which are used to reduce sedative-hypnotic use among inpatients, 10 of 13 (77%) studies were based on elderly patients. This biased content naturally leads to a question of whether the suggested evidence can be generalized to all adults. Unfortunately, the limitations resulting from these unbalanced citations were not mentioned in the Discussion section. In addition, several studies involving elderly people were cited without being mentioned, which may mislead the readers about the generalizability of the results. For example, Choosing Wisely Canada2 recommended against the use of sedative-hypnotic medications as a first-line therapy for elderly patients. This overgeneralization to interpret such recommendations as indications to avoid the use of sedative-hypnotic drugs and to consider them unnecessary in all adults.

An Elderly Bias, Nocturia, and Adverse Effects of Sedative-Hypnotic Medication

To the Editor We read with great interest the recently published Special Communication by Soong and colleagues.1 They persuasively showed why the initiation of sedative-hypnotic medications should be minimized along with the strategies that can be exploited. However, we raise 2 concerns, which were not adequately mentioned in the article.

First, the evidence regarding the harmful effects of sedative-hypnotic drug use and the effectiveness of nonpharmacological strategies relied too much on results from studies on the elderly population. By sheer numbers alone, 27 of 45 (60%) references in the article1 predominantly focused on the elderly. Regarding the nonpharmacological interventions, which are used to reduce sedative-hypnotic use among inpatients, 10 of 13 (77%) studies were based on elderly patients. This biased content naturally leads to a question of whether the suggested evidence can be generalized to all adults. Unfortunately, the limitations resulting from these unbalanced citations were not mentioned in the Discussion section. In addition, several studies involving elderly people were cited without being mentioned, which may mislead the readers about the generalizability of the results. For example, Choosing Wisely Canada2 recommended against the use of sedative-hypnotic medications as a first-line therapy for elderly patients. This overgeneralization to interpret such recommendations as indications to avoid the use of sedative-hypnotic drugs and to consider them unnecessary in all adults.
comments on zolpidem-related adverse reactions and unsafe use may motivate health care providers to avoid prescribing the so-called sleep pills.

In summary, clarifications about the target population and emphasis on the known adverse reactions associated with zolpidem will improve this short communication.

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In Reply We thank Bliwise for his comments on our article and for highlighting the role of nocturia in disordered sleep. Routinely in hospital settings, diuretics such as furosemide may be unnecessarily dosed in the late evening (known as q 12 hours, or 9 AM and 9 PM), contributing to nocturia, interrupted sleep, and increasing the risk of falls. Unnecessary continuous intravenous maintenance fluids that are not reassessed may also contribute and are important to address.

Additionally, according to Pressman and colleagues,2 awakenings perceived to be stimulated by a need to void are actually caused by undiagnosed obstructive sleep apnea, which suggests that frequent nocturia should prompt solicitation of other symptoms of sleep apnea and subsequent study. Nocturia has been found to be comparable with snoring as a screening tool for sleep apnea.3 Treatment of underlying sleep apnea can reduce the frequency of awakening to void by 50%.4

We also thank Cho and colleagues for raising the important issues on the limitations of available evidence around the adverse effects of sedative-hypnotic medications and interventions to reduce their use. We agree that the majority of cited literature in our article directly involved the elderly population. However, we directed our literature search to any adult population and did not limit to any particular age group. The findings of our study reflect the available published literature, some of which was not limited to age. For example, Kolla and colleagues5 included the entire hospitalized population and perhaps more attention ought to be focused on causes of the latter. I agree with Soong and colleagues4 that focusing more precisely on why awakenings occur and what happens after they do may broaden the perspective on nocturnal treatments to promote sleep. A complementary perspective is that the target organ for such interventions may not always be brain, but rather bladder and/or kidney.

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To the Editor In their extraordinarily important article, Soong and colleagues emphasize the significance of reducing sedative-hypnotic medication usage in noncritically ill inpatients. Falls and fractures represent major morbidities associated with the usage of such medications, and there can be little doubt that numerous nonpharmacologic approaches for poor sleep remain vastly underutilized in the inpatient setting. As the authors note, however, addressing the underlying cause of such sleep disturbance is a necessary first step for interventions that promote better sleep.

Patients arise from bed for many reasons, but voiding urgency (nocturia), either as a cause or an effect of awakening at night, has been recognized widely as a condition strongly associated with disordered sleep and occurs perhaps with higher prevalence in this regard than either pain or even psychiatric conditions. Urinary urgency at any time, but particularly at night, has been associated with both falls and fractures, and even mortality, and observational evidence suggests that some of these effects may be mediated by poor sleep quality.

Nocturia is so mundane and ubiquitous in middle-aged and elderly populations so as to defy its recognition as a clinically significant issue. Yet every bed-rise episode represents an incremental exposure for a fall. Some sedative-hypnotic medications may well contribute to this added risk, but if the ultimate reason for leaving the bed is to use the bathroom,
showed the increased risks of falls related to zolpidem remained present even after adjusting for age. Similarly, we cited several other studies that included adult inpatients of all age groups. It may be reasonable to state that the adverse events associated with sedative-hypnotic medications, or the interventions suggested in these studies, lack ample evidence to extend to younger populations. However, as a corollary, there is also no physiological reason that risks or benefits would reverse in a younger population. Because we are recommending minimizing use of a medication that might increase risks (and is prescribed without appropriate indications in the first place), it is unlikely that deprescribing sedative-hypnotic medications will result in greater harm in younger populations. In fact, given that sedative-hypnotic coingestion is associated with increased lethality of opioid overdoses, it would be reasonable to anticipate harm reduction in any efforts and curb inappropriate sedative-hypnotic prescribing. We would welcome more evidence and study regarding the younger population.

Regarding the association of zolpidem with complex and sometimes amnestic behaviors, there is sufficient validation of those adverse effects that a new black-box warning has been issued.6 However, the cited article focuses on hypnotics in hospitalized patients, and our broad search strategy did not identify publications specifically addressing these complex behaviors in hospitalized patients. Nonetheless, we agree that caution is needed, carefully weighing risks and benefits prior to initiation is needed, carefully weighing risks and benefits prior to curb inappropriate sedative-hypnotic prescribing. We would welcome more evidence and study regarding the younger population.

What If Miró’s Dots and Lines Are Not Simply Dots and Lines?

To the Editor We read with interest the recently published Perspective by Taran and Detsky1 that explored how diagnosing disease may be thought of in similar terms as interpreting modern art. The authors compared diagnosing with the experience of finding paintings’ meaning through the impressions that Catalan painter Joan Miró’s paintings Bleu I, Bleu II, and Bleu III transmit to the viewer. After different interpretations, they suggest the following question: What if the paintings were simply dots and lines?

According to Taran and Detsky,1 these paintings were composed with a technique called automatic drawing (psychic automatism), in which Miró allowed his hand to roam freely on the canvas without knowing how the piece would unfold. In the 1920s, Miró was among the first artists to develop automatic drawing: it represented the beginning of Surrealism as an art movement.2 However, Miró always balanced the type of spontaneity and automatism encouraged by the surrealists with meticulous planning and execution to achieve finished works that, owing to their precision, seemed representative despite their considerable level of abstraction.

In February 1960, Miró began to think of a series of blue paintings. He drew tiny sketches in ink, colored pencil, or ballpoint pen—lines, spots, and traces. Then he meditated. Finally, after a long preparation, he attacked the first painting: “The most recent works are the three large blue canvases, and it took me a long time to do them, not to paint them, but to meditate on them. It took a tremendous effort, a great deal of inner tension…. The preliminary stage was intellectual… I began by drawing in charcoal, with a lot of precision (I always get to work very early in the morning). In the afternoon, I only looked at what I had drawn. All the rest of the day, I was preparing myself. Finally, I began to paint: first the bottom, all blue; but it was not simply a matter of posing in color, like a house painter: all the movements of the brush, those of the wrist, the breathing of a hand also intervened. ‘Perfect’ the bottom put me in condition to continue the rest. This fight exhausted me; I have not painted anything since.”3(p3) Miró completed the triptych on March 4, 1961.

After reading this small part of the longest of Miró’s explanations, it is difficult to think that the paintings were simply dots and lines.

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Conflict of Interest Disclosures: None reported.

References

Conflict of Interest Disclosures: None reported.
In Reply We thank Guardiola and Baños for their comments on our article and for showing us the quote attributed to Joan Miró. It helps explain the process he used to create the triptych. But it still does not explain what the paintings mean, at least not to the artist. As we say in our essay, that’s part of the beauty of art: interpretation is subjective and cannot be imposed on others.

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Conflict of Interest Disclosures: None reported.

Studies Making Use of the Same Randomized Clinical Trial Cohorts

To the Editor We read the article by Smyth et al with interest. The authors performed a large meta-analysis to determine whether participants in large, multicenter dialysis trials were similar to the general population undergoing dialysis in terms of age, comorbidities, and mortality rate. They concluded that participants in large, multicenter randomized clinical trials of patients with end-stage kidney disease undergoing dialysis are younger, have a different pattern of comorbidities, and have a lower mortality rate than the general population of patients undergoing dialysis. This finding has implications for the generalization of trial results to the broader patient population and for future trial design. However, after carefully reading the article, we are concerned that studies making use of the same cohort of patients were included multiple times in the analysis. There were several studies described in eTable 1 in the Supplement that look quite likely to be making use of the same cohort of patients.

For instance, the 2 studies numbered 120 and 121 in eTable 1 of the Supplement were conducted by the same group of authors, and both of these studies had the same number of participants from the same hospitals, with similar baseline characteristics. Hence, we suspect that these studies made use of the same cohorts, and thus one of these studies should have been removed as a duplicate of the other. Other pairs of studies in eTable 1 of the Supplement that deserve further scrutiny include the pairs numbered 27 and 28, the pairs numbered 78 and 80, the pairs numbered 111 and 112, and the pairs numbered 130 and 131, and the pairs numbered 150 and 151.

The authors should look more closely at these pairs of studies to determine whether they used the same study population and then select the ones with the best quality or the largest sample size for analysis to ensure the accuracy of their analysis.

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In Reply On behalf of my coauthors, I write to report errors in our article, “Representativeness of Randomized Clinical Trial Cohorts in End-stage Kidney Disease: A Meta-analysis,” that was published online in July 8, 2019, in JAMA Internal Medicine. In that article, we reported on a meta-analysis of 189 randomized clinical trials (RCTs) comprising 80,104 participants to determine whether participants in large, multicenter dialysis trials were similar to the general population undergoing dialysis in terms of age, comorbidities, and mortality rate. We found that “participants in large, multicenter RCTs of patients with end-stage kidney disease undergoing dialysis are younger, have a different pattern of comorbidities, and have a lower mortality rate than the general population of patients undergoing dialysis.”

I thank Jiang et al.2 for bringing to our attention their concerns about the inclusion of some of the trial cohorts in our meta-analysis and the possibility that some of these are duplicates.3–6 I have reviewed all of the articles in question. Of the 6 identified pairs, 4 are clearly distinct cohorts.7–9 However, 2 pairs represent duplicated cohorts, of which 1 cohort was published 3 times.3–7

The cohorts reported in the 3 articles by Kauric-Klein et al.7–9 that were published in 20124–5 and 20177 appear to be the same. The later article9 does not reference the former articles4,5 and makes no mention of the cohort being published previously. The cohorts in the 2 articles published by Martin et al.6,7 also appear to be the same. One assesses treatment for 24 weeks,6 and the other reports on an additional 28 weeks of data (including the participants in the first trial),7 but neither article references or mentions the publication of the same data elsewhere.

In our systematic review, we identified 5229 records; after removal of duplicates by screening titles and abstracts, we reviewed 545 full-text articles. Of these articles, 356 were excluded, leaving 189 trials for our meta-analysis. Following our protocol, I reviewed all of the trials with 2 of my coauthors (A.H. and K.T.) to identify and exclude reports of trials that were secondary or accessory publications from the same cohort. While we were effective in excluding articles that acknowledged the publication of data from the same cohort elsewhere, among the many articles reviewed, we failed to note the similarities between these articles.

Thus, I have reanalyzed all the data based on 186 trials and 79,104 participants—without the duplicated data4–6—and found that the overall age and mortality rate remain the same; there was a difference of 0.1 years in mean age when analysis was restricted to US-only studies. The findings of the new analysis without these studies do not affect the overall results, conclusions, or interpretations of our meta-analysis. I confirm that there are no other errors that need attention and apologize to the readers and editors of JAMA Internal Medicine for any confusion. I have requested that the article be corrected online. The corrected analysis affects information in the original abstract, the Results and Discussion sections, Tables 1, 2, 3, and 4, the Figure, and the Supplement.

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CORRECTION

Pervasive Errors Due to Duplicate Trial Cohorts: With regard to the Original Investigation “Representativeness of Randomized Clinical Trial Cohorts in End-stage Kidney Disease: A Meta-analysis,” by Smyth et al,1 published online July 8, 2019, Jiang et al2 raised concerns about the inclusion of some of the trial cohorts in the meta-analysis and the possibility that some of these cohorts might be duplicates. Of the 6 pairs of cohorts identified by Jiang et al,2 4 are clearly distinct cohorts. However, 2 pairs represent duplicated cohorts, of which 1 cohort was published 3 times. The authors of the meta-analysis realigned all the data based on 186 trials and 79,104 participants (ie, without the duplicated data) and found that the overall age, mortality rate, and study conclusions remain the same.3 The corrected analysis affects information in the original abstract, the Results and Discussion sections, Tables 1, 2, 3, and 4, the Figure, and the Supplement. This article was corrected online.


Error in Dates of Data Analysis in the Methods: The Research Letter titled, “Prevalence of Inappropriateness of Parenteral Vitamin B\textsubscript{12} Administration in Ontario, Canada,”1 published online July 15, 2019, contained an error in the Methods section regarding the dates of data analysis. The dates of data analysis were written to be from July 26, 2019, to November 22, 2019. The dates should be from July 26, 2018, to November 22, 2018. The dates have been corrected.


Incomplete Title: The Original Investigation by Budathoki et al1 published online August 26, 2019, had an incomplete title. The correct full title is “Association of Animal and Plant Protein Intake With All-Cause and Cause-Specific Mortality in a Japanese Cohort.” This article was corrected online.