Citizen Petition to the US Food and Drug Administration to Change Prescribing Guidelines

The Metformin Experience

The First Amendment to the US Constitution guarantees “the right of the people...to petition the Government for a redress of grievances.” When it comes to the regulation of drugs and protection of public health, individuals have the right to address their concerns by directly petitioning the US Food and Drug Administration (FDA). Any person (including a non-US citizen) can request that the FDA “issue, amend, or revoke a regulation or order or take or refrain from taking any other form of administrative action.” Although healthcare professionals rarely submit such petitions, they can exert a powerful impact on the labeling requirements for drugs.

Metformin is one such example. Metformin is widely accepted as the first-line drug for the treatment of type 2 diabetes mellitus. It effectively lowers hemoglobin A1c levels by 1% to 2% and is weight neutral, safe, and inexpensive. Moreover, one trial demonstrated that it reduces cardiovascular disease complications in patients with newly diagnosed type 2 diabetes mellitus. When metformin was first approved in 1994, it was contraindicated in patients with heart failure and in those with elevated creatinine levels because of concerns about lactic acidosis. This restriction on drug use usually necessitated a switch from metformin to a glucose-lowering agent in a different category, one that frequently carried other risks (such as hypoglycemia), appreciably increased cost, or both. In 2006, the FDA eliminated the heart failure contraindication in response to 2 observational studies.1 These studies suggested that metformin is safe and may actually confer mortality benefits in patients with heart failure.1 However, the contraindication in patients with elevated creatinine levels remained unchanged. Since then, concerns over lactic acidosis have been examined and found to be largely unfounded unless kidney disease is advanced. On the basis of the available data, metformin can be used safely in patients with mild to moderate renal dysfunction, as long as patients are monitored appropriately.2

A change in the metformin label was once more clearly needed. However, because metformin is a generic drug, it lacked a pharmaceutical industry sponsor to take up its cause. Hence, in 2012 and 2013, we filed 2 separate citizen petitions to the FDA, one from collaborators at Cornell and the University of Pennsylvania and one from Yale (cosigned by 111 diabetes experts), asking the FDA to change the label and to relax the renal contraindications.

In April of 2016, the FDA issued a safety communication that partially granted our requests by requiring the manufacturers of metformin to change the labeling of metformin in several ways (Table). Metformin is still contraindicated in patients with severe kidney dysfunction, defined as an estimated glomerular filtration rate (eGFR) <30 mL-min⁻¹·1.73 m⁻². However, its use is now allowed in patients with mild to moderate kidney dysfunction, defined as an eGFR between 30 and 60 mL-min⁻¹·1.73 m⁻². These changes could increase the estimated number of US patients with type 2 diabetes mellitus who are eligible to take metformin by ≈900,000 to 2.5 million.3

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In addition, the FDA changed the requirements for discontinuation of metformin around administration of iodinated contrast media. Previously, the metformin label recommended that the drug be temporarily discontinued at the time of or before any radiological procedure with intravascular contrast, withheld for 48 hours after the procedure, and restarted only after renal function was found to be normal. This warning, however, did not make a distinction between patients with various degrees of kidney dysfunction. The new label recommends stopping metformin at the time of or before administration of iodinated intravenous contrast only in patients with an eGFR <60 mL·min\(^{-1}\)·1.73 m\(^{-2}\) or in patients with a history of liver disease, alcoholism, or heart failure. eGFR should then be re-evaluated after 48 hours, with metformin restarted if kidney function is stable. These recommendations are based on the minimal risk of metformin-associated lactic acidosis in patients without chronic kidney disease undergoing intravenous iodinated contrast media administration.

Of note, the FDA now makes a distinction between intravenous and intra-arterial contrast administration, recommending that metformin be held, regardless of eGFR, when intra-arterial contrast is given such as during cardiac catheterization. There are few data to back this specific recommendation, and the agency does not elaborate on distinct vascular territories and their proximity to the renal arterial supply or the volume of con-

**Table.** Specific Recommendations for the Use of Metformin in Patients With Chronic Kidney Disease Outlined in the Cornell-Penn and Yale Citizen Petitions to the FDA and in the Final FDA Decision

<table>
<thead>
<tr>
<th>Chronic Kidney Disease Stage</th>
<th>eGFR, mL·min(^{-1})·1.73 m(^{-2})</th>
<th>Cornell-Penn Citizen Petition</th>
<th>Yale Citizen Petition</th>
<th>FDA Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>No restriction</td>
<td>No restriction</td>
<td>Stop before or at the time of intra-arterial iodinated contrast procedures</td>
</tr>
<tr>
<td>2</td>
<td>60–&lt;90</td>
<td>No restriction</td>
<td>No restriction</td>
<td>Stop before or at the time of intra-arterial iodinated contrast procedures</td>
</tr>
<tr>
<td>3a</td>
<td>45–&lt;60</td>
<td>Avoid if kidney function is expected to become unstable</td>
<td>Monitor kidney function more frequently</td>
<td>Stop before or at the time of intravenous iodinated contrast procedures; repeat eGFR in 48 h before resuming metformin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor kidney function more frequently</td>
<td></td>
<td>Stop before or at the time of intra-arterial iodinated contrast procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not titrate to full dose</td>
<td></td>
<td>Stop before or at the time of intravenous iodinated contrast procedures; repeat eGFR in 48 h before resuming metformin</td>
</tr>
<tr>
<td>3b</td>
<td>30–&lt;45</td>
<td>Avoid if kidney function is expected to become unstable</td>
<td>Do not initiate at this stage, but drug can be continued</td>
<td>Stop before or at the time of intravenous iodinated contrast procedures; repeat eGFR in 48 h before resuming metformin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor kidney function more frequently</td>
<td></td>
<td>Stop before or at the time of intra-arterial iodinated contrast procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not titrate to full dose</td>
<td></td>
<td>Use half-dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor kidney function more frequently</td>
<td></td>
<td>Stop before or at the time of intra-arterial iodinated contrast procedures</td>
</tr>
<tr>
<td>4</td>
<td>15–&lt;30</td>
<td>Do not use</td>
<td>Do not use</td>
<td>Do not use</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Do not use</td>
<td>Do not use</td>
<td>Do not use</td>
</tr>
</tbody>
</table>

eGFR indicates estimated glomerular filtration rate; and FDA, Food and Drug Administration.
Citizen Petition: The Metformin Experience

Contrast used. The American College of Radiology agrees that in patients undergoing “arterial catheter studies that might result in emboli (atheromatous or other) to the renal arteries,” metformin should be temporarily discontinued at the time of or before the procedure and restarted 48 hours after the procedure only after kidney function is found to be normal.4 The rationale appears to be that certain intra-arterial procedures confer a higher risk for contrast-induced nephropathy resulting from atheroembolic sequelae, as well as, perhaps, a more abrupt and concentrated dose of contrast delivered to the kidneys.

Because data on the benefits and harms of medications evolve over time, the FDA must continually revisit the questions of effectiveness and safety for existing drugs as new evidence emerges. Clinicians and researchers can influence this process by formally petitioning the agency. The case of metformin suggests that this mechanism can be effective.

What is involved in filing a citizen petition? A petition must include a description of actions being requested, and these actions must fall under the jurisdiction of the FDA commissioner. Moreover, the petition must include a persuasive statement of grounds such as data from randomized, controlled trials. Finally, it must include a statement on environmental and economic impacts (if any), as well as certification that the evidence included is well balanced and unbiased. The citizen petition needs to be submitted electronically.

Despite the availability of this mechanism to affect drug policy, citizen petitions are infrequently filed by clinicians. Of 1915 citizen petitions filed between 2001 and 2013, 82% were filed by individuals working for industry.5 Most of these petitions were focused primarily on blocking or delaying FDA approval of generic products to extend brand market profitability. When citizen petitions are filed by individuals or organizations not working on behalf of industry, they most often request labeling changes, addition or removal of boxed warnings, risk communications, or placement of drugs into a Risk Evaluation and Mitigation Strategy. On average, it takes the FDA 3 years to reach a final decision, and it denies the petitioners’ request in the vast majority of cases (87%).5

Why were the metformin petitions successful? The initial decision to restrict the use of metformin in patients with kidney dysfunction was based partly on experience with an earlier drug in the same biguanide class, phenformin. However, phenformin was associated with a much higher risk of lactic acidosis compared with metformin. Multiple studies have since evaluated the risk of lactic acidosis in metformin-treated patients and found it to be exceedingly low.2 In addition, the initial label for metformin was based on serum creatinine cut points before the ubiquitous use of eGFR in clinical practice. Given these considerations and the long-standing safety record of metformin, we were able to make a strong case that the benefits of metformin outweigh the potential risk in patients with mild to moderate kidney disease.

What are the implications for cardiologists? Until recently, metformin was the only glucose-lowering agent shown to improve cardiovascular outcomes. Emerging evidence now suggests that members of 3 other diabetes drug classes (sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide-1 agonists, and thiazolidinediones) reduce cardiovascular events in those with established macrovascular disease. The decision to use one class of agents over another will depend on other considerations, including distance from the hemoglobin A1c target, side effects and safety considerations, patient preferences, and, importantly, cost. With the new label changes, metformin remains an excellent option in stable patients with mild to moderate chronic kidney disease, and its use in patients undergoing contrast procedures has become much simpler.

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Footnotes
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REFERENCES


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