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Modifying Prescribing Guidelines by Petitioning the FDA: The Metformin Experience

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The First Amendment to the U.S. Constitution guarantees "the right of the people...to petition the Government for a redress of grievances." When it comes to regulation of drugs and protection of public health, individuals have the right to address their concerns by directly petitioning the U.S. Food and Drug Administration (FDA). Any person (including a non-U.S. 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. It effectively lowers hemoglobin A1c levels by 1–2%, is weight neutral, safe, and inexpensive. Moreover, one trial demonstrated that it reduces cardiovascular disease complications in patients with newly diagnosed type 2 diabetes. 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 over 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 two 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 were examined and found to be largely unfounded unless kidney disease was advanced. Based on the available data, metformin can

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be safely used 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, since metformin is a generic drug, it lacked a pharmaceutical industry sponsor to take up its cause. Hence, in 2012 and 2013, we filed two separate citizen petitions to the FDA - one from collaborators at Cornell and the University of Pennsylvania, and one from Yale (co-signed by 111 diabetes experts) - asking the FDA to change the label and relax the renal contraindications.

In April 2016, the FDA issued a safety communication that partially granted our requests by requiring metformin's manufacturers to change the labeling of metformin in several ways (Table 1). Metformin is still contraindicated in patients with severe kidney dysfunction, defined as an estimated glomerular filtration rate (eGFR) below 30 mL/min/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/1.73 m^2. These changes could increase the estimated number of U.S. patients with type 2 diabetes eligible to take metformin by approximately 900,000 to 2.5 million individuals.[3]

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 prior to *any* radiological procedure using 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 varying 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 below 60 mL/min/1.73 m^2, or in patients with a history of liver disease, alcoholism, or heart failure. Estimated GFR should be then 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 versus intra-arterial contrast administration, recommending that metformin be held, irrespective of eGFR, when intra-arterial contrast is given, such as occurs during cardiac catheterization. There are few data to back this specific recommendation and the agency does not elaborate regarding distinct vascular territories and their proximity to the renal arterial supply, nor the volume of 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 prior to 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 due to atheroembolic sequelae, as well as, perhaps, a more abrupt and concentrated dose of contrast delivered to the kidneys.

Since data concerning the benefits and harms of medications evolve over time, 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's 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 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. Out of 1,915 citizen petitions that were 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 in order 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 (REMS). 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 partly based on the 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 metformin's long-standing safety record, 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 three other diabetes drug classes (SGLT-2 inhibitors, GLP-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 upon other considerations, including distance from HbA1c 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 CKD, and its use in patients undergoing contrast procedures has become much simpler.

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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, as well as in the final FDA decision.

CKD Stage	eGFR (mL/min per 1.73 m^2)	Cornell-Penn Citizen Petition	Yale Citizen Petition	FDA Decision
1	≥ 90	No restriction	No restriction	• Stop prior to or at time of intraarterial iodinated contrast procedures
2	60 to <90	No restriction	No restriction	• Stop prior to or at time of intraarterial iodinated contrast procedures
3a	45 to <60	• Avoid if kidney function expected to become unstable • More cautious follow up of kidney function • Do not titrate to full dose • Stop prior to or at time of intravascular iodinated contrast procedures; repeat eGFR in 48 hours before resuming metformin	• Avoid if kidney function expected to become unstable • More cautious follow up of kidney function	• More cautious follow up of kidney function • Stop prior to or at time of intravenous iodinated contrast procedures; repeat eGFR in 48 hours before resuming metformin • Stop prior to or at time of intraarterial iodinated contrast procedures
3b	30 to <45	• Avoid if kidney function expected to become unstable • More cautious follow up of kidney function • Do not titrate to full dose • Stop prior to or at time of intravascular	• Do not initiate at this stage, but drug can be continued • Avoid if kidney function expected to become unstable • More cautious follow up	• Do not initiate at this stage, but drug can be continued • More cautious follow up of kidney function • Stop prior to or at time of intravascular iodinated contrast procedures; repeat eGFR

CKD Stage	eGFR (mL/min per 1.73 m^2)	Cornell-Penn Citizen Petition	Yale Citizen Petition	FDA Decision
		iodinated contrast procedures; repeat eGFR in 48 hours before resuming metformin	of kidney function • Use half dose	in 48 hours before resuming metformin • Stop prior to or at time of intraarterial iodinated contrast procedures
4	15–<30	Do not use	Do not use	Do not use
5	<15	Do not use	Do not use	Do not use