navigate with our patients the fragmented medical system we will inherit. Second, it will allow us to engage with the system as leaders in order to improve it.

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Drug Discontinuation and Follow-up Rates in Oral Antithrombotic Trials

Missing data are common, challenging the validity of trial results.1 However, it is unclear how to characterize the extent of missing data. The CONSORT statement2 specifies reporting number lost to follow-up but does not define it operationally. The US Food and Drug Administration (FDA) recently published a review3 providing the follow-up completeness by a specific methodology for major oral antithrombotic trials. In this report, we compare the FDA follow-up rates with the published rates. We also analyze drug discontinuation rates as a possible contributory cause of incomplete follow-up and compare them with the outcomes because excessive incomplete follow-up may cause the end point rate difference, rather than representing true drug effect.

Methods | One of us (T.A.M.), while working at the FDA, evaluated incomplete follow-up as follows: First, identify the earliest last follow-up date defined by the study documentation. Then, using all available information (eg, visits, telephone calls, hospitalizations), determine for each patient the last contact date at which end points (other than vital status alone) were ascertained. Count the patient as having incomplete follow-up if the latter date was prior to the earliest last follow-up date and the patient was not known to be dead. For the publication we used one of the terms “lost to follow-up,” “unable to contact,” “withdrew consent,” “unknown status,” or similar (as reported). For all denominators we used patients randomized. We also extracted drug discontinuation rates from the FDA review and calculated primary end point differences between arms and incomplete follow-up rates. Institutional review board approval was not required for this study.

Results | The FDA review calculated incomplete follow-up for 23 of the 25 trials discussed. We excluded 2 of the 23 trials because their publications did not report follow-up. The Table summarizes the remaining 21 trials having both publication and FDA-calculated rates. The trials randomized 270 089 patients observed for a median (range) duration of 20 (8-43) months with last enrollment dates spanning 1995 to 2011.

The mean published rate of loss to follow-up was 0.4% (median, 0.3%; range, 0.005%-2%). The published rates were consistently lower than the FDA-calculated incomplete follow-up rates: mean, 12% (median, 13%; range, 2%-23%). There was no correlation between the published and FDA-calculated rates, as shown by the scatterplot in the Figure and a linear regression analysis ($R, 0.07; P = .76$). With the inclusion of all missing follow-up categories, the published rates (mean, 2.7%; median, 0.9%) remained substantially lower than the FDA-calculated rates.

Whereas the published rate of loss to follow-up is usually less than the end point rate difference, the FDA-calculated rates of loss to follow-up were substantially greater than the latter differences. The mean end point rate difference was 1.3% (median, 1.0%; range, 0.2%-3.0%).

The mean drug discontinuation rate was 24.9% (median, 23.7%; range, 7.2%-39.4%). These rates were not correlated with either publication ($R, 0.28; P = .22$) or FDA-calculated follow-up rates ($R, 0.25; P = .27$).

Discussion | In this study, published rates of loss to follow-up were very low whereas the FDA-calculated incomplete follow-up rates are typically double-digit percentages uncorrelated with the published rates. The published rates consistently seem to be inadequate representations of the completeness and quality of follow-up. The extent to which the FDA-calculated rates exceed the end point rate differences implies that the end point differences may be due to differential follow-up rather than drug effect.

We recommend that incomplete follow-up rates, like $P$ values, should be considered critical estimates of the reliability of trial results. The FDA has done so in its approval deliberations, for example, for the ATLAS trial. While its publication reported a rate of loss to follow-up of 0.3%, the FDA-calculated incomplete follow-up rate was 20%. An FDA advisory committee recommended against approving rivaroxaban for acute coronary syndromes based on the latter rate,4 and the FDA did not approve rivaroxaban for that indication.

The high rates of therapy discontinuation offer one explanation for why incomplete follow-up is common because these patients no longer need to return to the study sites to pick up drug supplies.
Prior studies have reported similar controversy regarding published rates of loss to follow-up. Our unique contribution is the comparison with the FDA independent assessment of follow-up completeness. It is clear that capturing and reporting of follow-up must be improved for better confidence in the validity of trial results. We suggest the FDA-calculated follow-up assessment methodology as a start.

### Table. Drug Discontinuation, Follow-up Completeness, and End Point Differences in Oral Antithrombotic Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Patients, No.</th>
<th>Median Follow-up, mo</th>
<th>% Drug Discontinuation</th>
<th>Publication Loss to Follow-up</th>
<th>FDA-Calculated Incomplete Follow-up</th>
<th>Primary End Point Difference Between Arms</th>
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<tr>
<td>APPRAISE-2</td>
<td>Apixaban</td>
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<td>8</td>
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<td>2</td>
<td>0.4</td>
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<td>ARISTOTLE</td>
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<td>RELY</td>
<td>Dabigatran</td>
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<td>9</td>
<td>0.7</td>
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<tr>
<td>ENGAGE</td>
<td>Edoxaban</td>
<td>21 105</td>
<td>34</td>
<td>33.7</td>
<td>0.005</td>
<td>10</td>
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<tr>
<td>ATLAS</td>
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<td>28.2</td>
<td>0.3</td>
<td>20</td>
<td>1.2</td>
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<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban</td>
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<td>22</td>
<td>23.7</td>
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<td>0.7</td>
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<tr>
<td>SPORTIF-III</td>
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<td>43</td>
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<tr>
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<td>0.1</td>
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<tr>
<td>TRITON</td>
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<tr>
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<tr>
<td>TRA2P</td>
<td>Vorapaxar</td>
<td>26 449</td>
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<tr>
<td>TRACER</td>
<td>Vorapaxar</td>
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<td>16</td>
<td>28.2</td>
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<td>1.1</td>
</tr>
</tbody>
</table>

Abbreviation: FDA, Food and Drug Administration.

### Figure. Scatterplot of Rates of Incomplete Follow-up vs Loss to Follow-up in Oral Antithrombotic Trials

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**Disclaimer:** Whereas some of the work was performed while one of us was an FDA Team Leader, the opinions expressed are our own and should not be construed as official FDA policy.

**Additional Information:** Dr Marciniak is former Medical Team Leader, Cardio-renal Division, FDA.

Editor’s Note
Making Data Submitted to the Food and Drug Administration More Visible

The visibility of clinical research and its underlying data has grown through efforts such as the National Library of Medicine’s online trial registry, ClinicalTrials.gov, along with data-sharing initiatives, such as the Yale Open Data Access Project (in which I am involved). While the Food and Drug Administration (FDA) has similarly enhanced clinical research visibility by making FDA-prepared documents more widely available, much important material, including clinical trial data, is considered confidential information or trade secrets.¹ A Research Letter in this issue of JAMA Internal Medicine illustrates how this potentially limits our understanding of the research supporting therapies regulated by the FDA.² Marciniak and colleagues examined participant loss-to-follow-up rates for major trials of oral antithrombotic therapies, comparing the rates reported in medical journal publications with the rates independently estimated by Marciniak using data submitted by manufacturers to the FDA as part of an analysis investigating the cancer risk associated with these therapies that was performed when he was an FDA medical officer. Their analysis demonstrated substantial discrepancies between the published and the independently estimated loss-to-follow-up rates. While this research has implications for any interpretation of antithrombotics’ therapeutic efficacy and safety, it also demonstrates the need for greater data visibility and the importance of making all clinical trial data submitted to the FDA widely available, including to external researchers for independent scrutiny. As recently explained by the Institute of Medicine, “Patients and their physicians depend on clinical trials for reliable evidence on what therapies are effective and safe. Responsible sharing of the data gleaned from clinical trials will increase the validity and extent of this evidence.”³

Joseph S. Ross, MD, MHS
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Distribution of Opioids by Different Types of Medicare Prescribers

Researchers have suggested that the opioid overdose epidemic¹ is primarily driven by small groups of prolific prescribers and “corrupt pill mills.”²,³ For example, the California Workers’ Compensation Institute found that 1% of prescribers accounted for one-third of schedule II opioid prescriptions and 10% accounted for 80% of prescriptions.⁴ This propagates a message that opioid overprescribing is a problem of a small group of high-volume prescribers, while general use is likely safe and effective. Medicare data provide the opportunity to address the question of whether such prescribing patterns occur across a national population.

Methods | We examined data from individual prescribers (eg, physicians, nurse practitioners, physician assistants, and dentists) from the 2013 Medicare Part D (prescription drug coverage) claims data set created by the Centers for Medicare and Medicaid Services.⁵ Part D covers approximately 68% of the roughly 50 million people on Medicare, the federal insurance program for Americans who have certain disabilities or are 65 years or older.

For each prescriber National Provider Identifier (NPI) number (N = 808,020), the data identify each drug prescribed, total number of claims, and total costs. Each NPI includes location and specialty of practice. The data represent 1,188,393,892 claims for $80,941,763,731. We focused on schedule II opioid prescriptions containing hydrocodone, oxycodone, fentanyl, morphine, methadone, hydromorphone, oxymorphone, meperidine, codeine, opium, or levorphanol.

We calculated the cumulative claims for schedule II opioids from the top individual prescribers (sorted by number of claims) relative to the total claims for all prescribers. For comparisons, we repeated this for prescription costs, for all drugs, and for each state.

Results | Figure 1 reports which Medicare prescriber specialties account for the most opioid drug claims. Figure 2 reports the concentration of drug claims among the most prolific individual prescribers. Respective California Workers’ Compensation Institute data are included. Notably, the top 10% of Medicare prescribers account for a smaller proportion of opioid claims (56.7%) than for all Medicare prescribers and for the California Workers’ Compensation prescribers. Minimal regional variation is observed across provider states, with per-state values ranging from 56.6% to 57.7%. Excluding hydrocodone (schedule III prior to 2014) yields similar trends with the same top 3 prescribing specialties and 57.9% of claims from the top 10% of prescribers.

Discussion | The data studied represent a comprehensive national population of Medicare Part D prescribers but do not necessarily reflect clinicians’ complete practices, patient factors (eg, comorbidities and prescription indications), or medication dosing to inform morphine equivalents. With those cautions, 2 important findings are evident. Opioid prescriptions are concentrated in specialty services in pain, anesthesia, and physical medicine and rehabilit-