Insurance Coverage and Care of Patients with Non–ST-Segment Elevation Acute Coronary Syndromes

TO THE EDITOR: Calvin and colleagues (1) report that patients insured by Medicaid (but not Medicare) were less likely to receive evidence-based care for non–ST-segment elevation acute coronary syndromes than were patients insured by health maintenance organizations or other private payers. However, the authors did not distinguish whether patients received Medicaid coverage through a managed care program—an important limitation. In 2001, at the time of study enrollment, Medicaid provided health coverage to nearly 34 million Americans, 18.8 million (56%) of whom were enrolled in managed care programs (2). Moreover, 19 states had active Section 1115 waivers to implement statewide mandatory managed care enrollment for Medicaid beneficiaries and 14 states had enrolled 75% or more of their Medicaid beneficiaries in managed care programs (2). Health maintenance organizations have been shown to favorably select younger and healthier Medicaid beneficiaries for enrollment (3); thus, Calvin and colleagues’ study focuses on a selected subset of the Medicaid population. Rather than comparing the average Medicaid beneficiary with the average health maintenance organization enrollee, their analysis compared Medicaid beneficiaries who have fee-for-service coverage, who are likely to be older and less healthy, with all individuals with private insurance, whether it was employer-based, purchased individually, or provided by Medicaid. Also, until November 2003, Calvin and colleagues categorized all patients enrolled in either Medicaid or Medicare dichotomously (“yes” if the patient was enrolled in either) and therefore could not distinguish patients enrolled in Medicaid or Medicare before this time. Patients younger than age 65 years enrolled in either Medicaid or Medicare were categorized as having Medicaid, whereas those age 65 years or older were categorized as having Medicare. However, from 2000 to 2004, the proportion of nonelderly Medicare beneficiaries has grown steadily to 15% of all Medicare beneficiaries (4). What proportion of the 6999 patients categorized as Medicaid beneficiaries was, in fact, Medicare beneficiaries who were totally or permanently disabled or had end-stage renal disease is not clear.

Calvin and colleagues should be commended for their examination of an important and understudied topic: quality of care for Medicaid beneficiaries. However, because of the limitations of their principal independent variable, their results cannot inform policymakers and health care professionals in the growing number of states who have enrolled most of their Medicaid beneficiaries in managed care programs.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: Dr. Ross points out that our recent study defined insurance status on the basis of the patient’s primary insurance provider. Data on the provision of secondary insurance coverage were not collected before 2003. As a result, we cannot distinguish Medicaid patients who were also enrolled in managed care programs or who had dual Medicaid and Medicare coverage. After November 2003, we collected data on multiple insurers but grouped patients in a hierarchy based on 1) managed care, 2) Medicare, and 3) Medicaid. Thus, Dr. Ross is correct in stating that this strategy may have excluded Medicaid patients who had additional managed care insurance. Our Medicaid study population may be slightly sicker or may have poorer socioeconomic status than Medicaid patients covered by managed care. Despite this, our analysis did adjust extensively for baseline demographic characteristics, disease severity, and comorbid illnesses. Even after this adjustment, we found statistically significant differences in both the use of evidence-based care medications and in-hospital outcomes among Medicaid patients versus patients with managed care insurance. While these results may or may not be generalizable to Medicaid or managed care, they are certainly reflective of the large proportion of Medicaid patients who are not covered by managed care. In our opinion, these findings highlight a sizable underserved patient population and a highly important concern to health care providers and policymakers.

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Potential Financial Conflicts of Interest: None disclosed.

Complications of Colonoscopy

TO THE EDITOR: Levin and colleagues (1) report a major complication in about 1 in 200 colonoscopies and a perforation rate approaching 1 in 1000. They point out that their results are consistent with other reports on complications (Table 2–14). However, if we (or any large private practice gastroenterology group) had such a complication rate, it would be cause for concern and in need of review.

The authors and editors state that a limitation of the study is that less than 1% of the procedures were screening colonoscopies and, thus, the complication rate may be higher than that of a screening group. In fact, the study specifically excluded all diagnostic complications.
coloscopies and looked at only what we would consider screening or surveillance colonoscopy. These are low-risk cases.

We suspect that the issue here is experience: A teaching institution where most of the procedures are done by residents and fellows would have the highest complication rates, and high-volume private practice ambulatory centers would have the lowest rates. In the past 6 years, we have had 3 perforations in 25,254 cases—a perforation rate 7.5 times less than that in the Kaiser Permanente group. (If we did not include our 2006 data, our perforation rate would be one tenth of the Kaiser Permanente group.) As seen in the Table, most data on perforation come from teaching centers. Two large studies are from high-volume private practice groups. The rate of perforation in these studies is less than one third of the rates in most of the other studies that had 10,000 procedures or more. (Studies with a low number of procedures are unreliable in determining the rate of an event that is uncommon.)

Assuming that Kaiser Permanente did not have residents or fellows doing procedures (there is no mention of this in Levin and colleagues’ study), then one needs to ask why the group has such a high rate of perforation. In a study of 16,000 colonoscopies, 39 physicians performed an average of 79 colonoscopies, but we do not know how many endoscopists were involved in the study. One endoscopist did 808 cases, with 6 complications (the study duration is 6 years, so this may be only 100 cases per year). We do not know how many endoscopists were involved in the study. One en-

<table>
<thead>
<tr>
<th>Author, Year (Reference)</th>
<th>Colonoscopies, n</th>
<th>Perforations, n (%)</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lo and Beaton, 1994 (3)</td>
<td>26,708</td>
<td>12 (0.045)</td>
<td>University, teaching</td>
</tr>
<tr>
<td>Farley et al., 1997 (4)</td>
<td>57,028</td>
<td>43 (0.075)</td>
<td>Mayo Clinic, teaching</td>
</tr>
<tr>
<td>Zubarki et al., 1999 (5)</td>
<td>1196</td>
<td>0 (0)</td>
<td>University, teaching</td>
</tr>
<tr>
<td>Anderson et al., 2000 (6)</td>
<td>10,486</td>
<td>20 (0.19)</td>
<td>Mayo Clinic, teaching</td>
</tr>
<tr>
<td>Imperiale et al., 2000 (7)</td>
<td>1994</td>
<td>1 (0.05)</td>
<td>University, teaching</td>
</tr>
<tr>
<td>Araghi-Zadeh et al., 2001 (8)</td>
<td>34,620</td>
<td>31 (0.09)</td>
<td>University, teaching</td>
</tr>
<tr>
<td>Nelson et al., 2002 (9)</td>
<td>3,196</td>
<td>0 (0)</td>
<td>VA, teaching</td>
</tr>
<tr>
<td>Misra et al., 2004 (10)</td>
<td>7,425</td>
<td>10 (0.13)</td>
<td>University, teaching</td>
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<td>Korman et al., 2003 (11)</td>
<td>116,000</td>
<td>37 (0.03)</td>
<td>ASC, private practice</td>
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<tr>
<td>Cobb et al., 2004 (12)</td>
<td>43,609</td>
<td>14 (0.032)</td>
<td>Teaching</td>
</tr>
<tr>
<td>Iqbal et al., 2005 (13)</td>
<td>78,702</td>
<td>66 (0.084)</td>
<td>Mayo Clinic, teaching</td>
</tr>
<tr>
<td>Rathgeber and Wick, 2006 (14)</td>
<td>12,407</td>
<td>2 (0.016)</td>
<td>Private practice</td>
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<tr>
<td>Levin et al., 2006 (1)</td>
<td>16,318</td>
<td>15 (0.09)</td>
<td>Kaiser Permanente</td>
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<tr>
<td>McDonnell, unpublished</td>
<td>29,254</td>
<td>3 (0.012)</td>
<td>ASC, private practice</td>
</tr>
</tbody>
</table>

* ASC = ambulatory surgical center; VA = Veterans Affairs.

References

* Potential Financial Conflicts of Interest: None disclosed.

IN RESPONSE: I thank Drs. McDonnell and Loura for their interest in our paper. Their comments reflect what may be a misunderstanding-
Letters

ing about how our study was conducted, which procedures and patients were included, and the status and training of the endoscopists in our study.

First, all the endoscopists included in our study were staff physicians, and no trainees were involved. Second, more than half of the identified colonoscopies in the various databases used to build the study data set were not included in the analysis. Of the 35,945 colonoscopies identified, only 16,318 were eventually included in the study data set. For 1994 to 1996, the Colon Cancer Prevention Program database included only colonoscopies done within 6 months of a flexible sigmoidoscopy. Therefore, the numbers of colonoscopies per endoscopist described in our paper represent only a fraction of the endoscopic activity of these endoscopists. Each endoscopist performed more procedures than were included in the final study data set.

We had a substantially higher rate of polyp detection and removal in our sample than one would have expected in a purely screening or surveillance population, primarily because most of our patients had a previous positive result on a test, such as a flexible sigmoidoscopy, barium enema, or fecal occult blood test, or had a positive family history and had a higher rate of polyp detection and removal. Our perforation rate was clearly related to the removal tissue at colonoscopy, primarily through the use of snare resection with electrocautery. When no tissue was removed, only 3 perforations occurred in 5235 procedures, 2 of which were in patients with abnormal colons and were due to either unsuspected colitis or a tortuous, narrowed sigmoid colon.

Our study had systematic follow-up for all hospitalizations using automated, electronic data to track hospitalizations. I would presume the University of Washington experience reported by Drs. McDonnell and Loura, although not specified, relied on self-reported or opportunistic follow-up of postcolonoscopy complications. I would question whether they have complete information on delayed perforations that may have occurred in patients who were not hospitalized at their medical center. As described by Zubark and colleagues (1), physician self-report of complications tends to underreport complications compared with systematic follow-up.

The 1 physician reported to have 6 complications over 808 cases performed many more colonoscopies than were reported in the study. He tended to be referred the more difficult polyp removal cases and therefore had a higher rate of complications than did some of his colleagues.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

BiDil for Heart Failure in Black Patients

TO THE EDITOR: We are surprised that the U.S. Food and Drug Administration’s (FDA) defense of their position to approve BiDil for black patients with heart failure (1) extended beyond the evidence that this combination pill works in black patients to the assertion that this therapy does not work in white patients. While the efficacy of hydralazine hydrochloride–isosorbide dinitrate in black patients is clearly established given the results of A-HeFT (African-American Heart Failure Trial), the lack of efficacy in white patients is not. The FDA’s contention is based on post hoc subgroup analyses of 2 older, smaller trials that studied this combination as primary treatment for heart failure only and did not address the contemporary question of whether the combination is effective as an adjunct to standard therapy in patients with refractory disease. In general, post hoc subgroup analyses should be interpreted with caution and should be used primarily for generating hypotheses (2)—not for determining policy, which appears to be the case here. The FDA position is not consistent with guidelines of the American Heart Association, American College of Cardiology, and Heart Failure Society of America for use of these medications, which note the particular benefit of this combination for black patients but have continued to list these medications as adjunctive therapies for all patients with refractory heart failure (3, 4), or even with statements by NitroMed and A-HeFT researchers that BiDil is likely to be effective in white patients and other groups (5, 6).

Had the FDA felt that approval of these 2 generic medications in a single combination pill was warranted, the approval should have been granted for the general indication of treating patients with severe heart failure. Choosing instead to restrict use to black patients does not make this medication more accessible to this target population (an apparent goal outlined in the FDA analysis [1]), as the cost implications that we describe in our critique suggest that this therapy may now be less accessible to many black patients with refractory heart failure. In addition, the FDA decision certainly makes this therapy less available to other racial groups and creates confusion for physicians treating a diverse population of patients. Imagine the physician faced with a hypertensive Asian patient with heart failure and refractory symptoms despite standard therapy. As a result of the FDA decision, use of the fixed hydralazine hydrochloride–isosorbide dinitrate combination in this patient is now “off-label” (and may pose issues for insurance reimbursement). Some might argue that this is appropriate, because the fixed combination has not been studied in Asian patients. However, it is difficult to accept that we know less about the efficacy of hydralazine hydrochloride–isosorbide dinitrate in this Asian patient (because its approval was based on a study with black participants only) than we do about the efficacy of almost every other medication that this patient might also be taking (which were approved on the basis of studies performed mostly with white participants).

Had the FDA approved BiDil for general use, the valuable phase IV observations that the FDA highlights in their discussion (1) would continue to inform the medical community about the appropriate use of these medications among the diverse patients we treat. With the restricted indication, these observations will no longer be forthcoming, and (for some) the question of efficacy of hydralazine hydrochloride–isosorbide dinitrate in nonblack patients will need to wait for future clinical trials.

We respect the FDA’s interest in approving any drug (including BiDil) that may benefit the 5 million Americans with heart failure, including black patients who develop this devastating illness at disproportionately high rates. However, we find the assertion that the urgency to approve a combination formulation of 2 already widely

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available generic medications justifies a departure from the FDA’s history of approving treatments of disease entities, not specific demographic groups, far less compelling. By restricting the indication for this therapy to a single race, the FDA decision distorts the clinical discussion on how we manage patients with refractory heart failure, the scientific discourse on how to appropriately study therapeutic efficacy in subgroups, and the larger political and societal debate on race and medicine.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: At first glance, Temple and Stockbridge (1) present an apparently reasonable rationale for the FDA’s approval of the heart failure drug BiDil (NitroMed, Lexington, Massachusetts) with a race-specific label for use only in “self-identified black patients.” Upon closer examination, however, their arguments fail to convince. Bibbins-Domingo and Fernandez (2) clearly show the limits of the post hoc subgroup analysis that the FDA used to justify the race-specific approval.

Beyond this, it is worth noting that since BiDil’s approval, NitroMed—BiDil’s corporate marketer—has made much of a recent FDA announcement that the coadministration of the much cheaper generic components of BiDil are not bioequivalent to the patented BiDil single-pill formulation (3). If bioequivalence is such an important issue as to warrant a separate FDA announcement, one wonders what Temple and Stockbridge make of the FDA’s previous findings that the doses of hydralazine hydrochloride–isosorbide dinitrate administered in V-HeFT I (Vasodilator-Heart Failure Trial I) were not bioequivalent to those administered in V-HeFT II and that neither dose was bioequivalent to that administered in A-HeFT (4). Again, the “very strong evidence” from “3 well-controlled studies” seems here to weaken somewhat.

NitroMed has 2 patents on BiDil. The first covers use in the general population without regard to race and expires in 2007. The second is race-specific to black patients and does not expire until 2020. NitroMed, therefore, had a powerful financial incentive to obtain race-specific approval. The FDA’s consent to a race-specific trial facilitated this goal (5).

Temple and Stockbridge also assert the difficulty in constructing a “reasonably powered” study in white patients, which they estimate would “require about 16 000 patients.” But this simply carries forward the fallacy of the relevance of race to assessing BiDil’s efficacy. Far more relevant would be to calculate the numbers needed for a reasonably powered study in patients with heart failure who have relevant biological characteristics—such as nonischemic versus ischemic heart failure; diabetes; or even, as a physician on the FDA Advisory Panel noted, a history of alcohol abuse (6).

Finally, Temple and Stockbridge mischaracterize my arguments about when it is appropriate to use racial categories in biomedical research for regulatory approval. It is precisely because I found insufficient evidence of BiDil’s race-specific efficacy that I, like representatives from the Association of Black Cardiologists and the International Society on Hypertension in Blacks, urged approval of BiDil without a race-specific indication.

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Potential Conflicts of Interest: Dr. Kahn testified at the FDA Advisory Committee hearing on BiDil and urged that it be approved without a race-specific label.

References

IN RESPONSE: Critics of the FDA’s approval of BiDil for treating heart failure in self-identified black persons have taken 2 positions: 1) Approval for blacks was premature because further testing should have been performed before approval to discover what characteristics in black and white patients might predict responses (1, 2), and 2) the FDA should have approved BiDil, but for the broader population...
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We note that Dr. Kahn, in his letter, states the latter is what he meant—not that there should have been no approval.

Our paper focused on why delaying approval would have been intolerable, given the dramatic effect shown in the black population and the extreme difficulty of assessing effects further in white patients or discovering clinical predictors of response. But approval for the black population alone was not based, as Bibbins-Domingo and Fernandez assert (2), on the argument that BiDil’s approval was urgently needed to address racial disparities in health. Approval for all patients would have accomplished that equally well. We approved the drug for the black population because the evidence did not support broader approval, a conclusion also reached by 7 of 9 Cardiovascular and Renal Drugs Advisory Committee members.

We are entirely aware of the risks of subset analysis and have regularly endorsed Yusuf and colleagues’ warnings about such analyses (4). But a replicated subset finding is not the same as a single subset finding, and the findings in V-HeFT I and II powerfully indicate a differential effect in black and white patients. We clearly did not assert that the absence of an effect in white patients has been proved, only that there is good evidence of a differential effect and that the effect in white patients, if any, is far smaller. Bibbins-Domingo and Fernandez argue that the findings in V-HeFT II, essentially identical outcomes with enalapril and hydralazine hydrochloride–isosorbide dinitrate in black patients, could have reflected a poor response to enalapril (another racial difference in response?), but that hypothesis doesn’t support their view. What was striking in V-HeFT II was the evidence of no effect of hydralazine hydrochloride–isosorbide dinitrate in white patients, in whom enalapril was known to work. Moreover, the possibility that the equal effect of the treatments in black patients represented no effect of either drug is thoroughly rebutted by A-HeFT. The placebo-controlled V-HeFT I also showed a strong difference in effect, with a nominally significant effect versus placebo in the black population, an effect similar in size to that seen in black patients in A-HeFT.

The postulated adverse consequences of our approval alleged by Bibbins-Domingo and Fernandez are hard to follow. Whether physicians should try the combination in white patients is not for us to say. Certainly there is no legal bar to such off-label use, and labeling does not contraindicate that use. Although some subset of the white population may prove to respond, without any evidence of this in studies that detected drug effects in a responsive population, we don’t believe labeling should recommend it.

Our threshold for making subset distinctions is high because of the potential for error, despite the current great interest in meaningful individualization of therapy. But errors can have 2 directions. When evidence of a difference is strong, it seems irresponsible to dodge its implications. The LIFE study (Losartan Intervention For Endpoint reduction in hypertension) (5) illustrates this. On the basis of that study, losartan (which was superior overall to atenolol in reducing stroke) was given a specific labeling claim for reduction of stroke. Because the finding was reversed in black patients, with atenolol nominally significantly superior to losartan, labeling notes that the LIFE study provides no evidence that the benefits of losartan apply to black patients.

Dr. Kahn focuses mainly on commercial matters that are not pertinent to regulatory approval, but he touches on 2 scientific issues.

The bioequivalence concerns he notes are pertinent to approval of generic drugs but do not weaken the inferences that can be drawn from differential effects in white and black patients seen in V-HeFT I and II. Dr. Kahn also proposes a “reasonably powered” study in patients with “relevant” biological characteristics, such as nonischemic versus ischemic heart failure, diabetes, or alcohol abuse. It is hard to know what he has in mind, but any study that sought to examine effects in many subgroups of this heart failure population, in whom we have no idea about which biological characteristics are relevant (and Kahn left out hypertension and cardiomyopathy as causes), would be vast and, without some plausible hypothesis, utterly unappealing to a sponsor. Indeed, what he is proposing poses the very problem that Bibbins-Domingo and Fernandez are concerned about.

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Potential Financial Conflicts of Interest: None disclosed.

References

CORRECTIONS

Correction: A Sustained Mortality Benefit from Screening for Abdominal Aortic Aneurysm

We would like to clarify a sentence in a recent article on the mortality benefits of screening for abdominal aortic aneurysm (AAA) (1). The first sentence of the Contribution part of the Editors’ Notes should have read: “This 7-year follow-up report of a large randomized trial in the United Kingdom found that men age 65 to 74 years who were invited to have ultrasonography and surveillance for AAA had lower AAA-related mortality rates than did those who were not invited (hazard ratio, 0.53 [CI, 0.42 to 0.68]).”

Reference

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