

**Use of Bisphosphonates in Multiple Myeloma:
IMWG Response to Mayo Clinic Consensus Statement**

To the Editor: The International Myeloma Working Group (IMWG), which comprises 85 investigators specializing in the area of multiple myeloma, has reviewed and considered the recent Mayo Clinic consensus statement for the use of bisphosphonates (BPs) in multiple myeloma.¹ Although the IMWG is in general agreement with the Mayo consensus statement, several important issues have been raised and are discussed subsequently. These comments are in response to the recommendations of the Mayo group, which is normally part of the IMWG.

Recommendations for Using BP in Myeloma.

Starting BP Therapy. It is agreed that pretreatment dental evaluation is important in patients who will be treated with intravenous BP.²

Bisphosphonate therapy is appropriate for patients with overt lytic bone disease on radiographs.

Most investigators favor the use of other imaging studies in addition to radiographs to clarify the exact status of myeloma-related bone disease as a basis for the decision to initiate BP therapy and to monitor bone disease serially. Magnetic resonance imaging with gadolinium enhancement (confirmable with computed tomography if necessary) and/or whole-body computed tomography/positron emission tomography (if available) can be used to identify focal bone destruction.³ Emphasis is placed on direct documentation of myeloma-related bone destruction or loss.

The role of bone density testing is complex. Currently, it is not widely used in patients with myeloma. Nonetheless, those who do not use it concede and those who do use it emphasize its potential importance and utility both at baseline and for monitoring. Bone loss, increasing age, female sex, and planned high-dose corticosteroid use predict increased fracture risk and the potential need for oral or intravenous BP therapy. Other monitoring tools include N-telopeptide and/or deoxypyridinoline measurements, which can indicate enhanced bone turnover.

Even when all bone test results are inconclusive, some investigators still recommend intravenous BP therapy for this small subset of patients without definite bone disease but with documented active myeloma. However, BP use is not recommended in patients with smoldering myeloma.

Duration of BP Therapy. We concur that BP use should no longer be indefinite or open ended.

We agree that the duration of BP therapy should be modified on the basis of evidence of ongoing active bone disease.

In patients who have achieved a complete response or a very good partial response with transplantation and/or a novel therapy combination and have no active bone disease, BP therapy is not recommended beyond the first year. This recommendation is based on results from the Inter-Groupe Francophone du Myelome trial, which showed no delay in time to onset of bone events with ongoing BP use.⁴

For patients achieving less than a very good partial response and/or those with ongoing active bone disease, further BP use is recommended. After 2 years, patients without active bone disease can discontinue BP use. Because no data indicating the value of a reduced-frequency (and/or reduced-dose) schedule are available, stopping BP treatment at 2 years is recommended, rather than the Mayo recommendation to decrease BP use to a schedule of periodic treatment such as every 3 months.

For patients with continued active bone disease after 2 years of BP therapy, further BP use is recommended at the discretion of the primary physician. Pamidronate or clodronate is preferred for longer-term use (>2 years).

In patients who experience relapse with new bone disease, BP therapy, using pamidronate or clodronate if available, should be reinstated.

Careful monitoring of renal function, including serum creatinine and periodic urinary protein measurements, is required with long-term BP use.

As noted by the Mayo Clinic team, osteonecrosis of the jaw (ONJ) is the major new concern with long-term BP use.⁵⁻⁸ Use of pamidronate or clodronate has the lowest risk, especially with treatment duration of 1 or 2 years and the recommended dental precautions. The risk of ONJ with pamidronate is 1% to 2% within the first 2 years of treatment, and the risk associated with clodronate is 0% to 0.5% (only rare cases have been reported). The risk with zoledronic acid is approximately 2-fold higher than that with pamidronate.⁵⁻⁸ Oral nitrogen-containing BPs have been associated with ONJ⁵⁻⁸ and thus are not currently recommended as an alternative to clodronate.

Patients who develop ONJ should discontinue BP therapy.

Choice of BP Therapy. There is nearly unanimous consensus that pamidronate has equivalent efficacy compared to other BPs plus a favorable toxicity profile. Thus, in general, investigators favor pamidronate over zoledronic acid, as did the Mayo team.¹

Outside the United States, clodronate is a widely available oral alternative that is considered an equally safe option.⁹⁻¹¹

Zoledronic acid is the primary choice of a few experts (13%), based on the convenience of the shorter infusion time but also because of the possible added clinical benefits of reduction in bone events and/or improved survival compared with other BPs. Ongoing further studies of zoledronic acid are needed to assess schedules and infusion times, which may reduce the risk of complications and/or enhance outcomes.

Dental Evaluation. Consensus exists concerning the need for dental evaluation. The scope of baseline and serial evaluation depends on local details within the health care system as well as personal resources. Physicians should emphasize to their patients the need to avoid dental procedures such as extractions while they are receiving BP therapy.

Conclusion. As noted recently,¹² the preparation of good guidelines is a complex process. We hope that the added details provided herein will enhance the Mayo consensus statement.

Brian G. M. Durie, MD, for the IMWG¹³
Cedars-Sinai Outpatient Cancer Center
Los Angeles, Calif

Members of the International Myeloma Working Group.

Brian G. M. Durie, MD; Michel Attal, MD; Meral Beksac, MD; Andrew Belch, MD; William Bensinger, MD; Joan Bladé, MD; Mario Boccadoro, MD; Michele Cavo, MD; Raymond L. Comenzo, MD; Meletios A. Dimopoulos, MD; Hermann Einsele, MD; Dorotea Fantl, MD; Gostä Gahrton, MD; Hartmut Goldschmidt, MD; Jean-Luc Harousseau, MD; Hiroyuki Hata, MD; Joy Ho, MD; Vania Hungria, MD; Douglas Joshua, MD; Heinz Ludwig, MD; Giampaolo Merlini, MD; Angelina Rodriguez-Morales, MD; Antonio Palumbo, MD; Ray Powles, MD; Donna E. Reece, MD; Anthony Reiman, MD; Jesús San Miguel, MD; Paul Richardson, MD; Orhan Sezer, MD; Kazayuki Shimizu, MD; Seema Singhal, MD; Pieter Sonneveld, MD; David Vesole, MD; Jan Westin, MD; Patrizia Tosi, MD; Guido Tricot, MD; Ingemar Turesson, MD; Jeffrey Zonder, MD.

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In reply: The Mayo Clinic Myeloma Group is pleased that the IMWG agrees in principle with most of our BP recommendations. We believe that our groups concur on the most important aspects of our proposed guidelines. We agree that the duration of BP therapy should no longer be indefinite, that pamidronate is the preferred drug, and that patients should have baseline and regular dental evaluations. We cannot dispute the IMWG recommendations to include more forms of imaging studies to assist in the decision to initiate BP therapy. We have summarized in Table 1 the main aspects of the Mayo Clinic recommendations and the response from the IMWG.

Since our guidelines were published, new information has become available that supports the conclusions made by us and the IMWG. Zervas et al¹ reviewed their experience with 303 patients with multiple myeloma and found that zoledronic acid produced a 9.5-fold greater risk for developing ONJ than pamidronate alone ($P=.042$) and a 4.5-fold greater risk than subsequent use of pamidronate plus zoledronic acid ($P=-.018$). In the absence of randomized trials, their findings provide strong support for the preference of pamidronate over zoledronic acid.

TABLE 1. Comparison of Mayo Clinic Consensus Statement and IMWG Recommendations*

Clinical scenario	Mayo Clinic consensus statement	Response from the IMWG
Indication for initiating BP therapy in patients with myeloma	All myeloma patients with lytic bone disease on plain radiographs; patients with osteopenia or osteoporosis on bone mineral density studies	In addition to radiographs, the IMWG recommends other imaging studies including MRI with gadolinium enhancement, CT, and/or whole-body CT/PET to determine the presence or absence of bone lesions that may benefit from BP prophylaxis
Smoldering myeloma	BPs are not recommended except in the setting of a clinical trial	BPs are not recommended
Duration of BP therapy	Monthly for 2 y After 2 y: Discontinue if myeloma is in complete response or stable plateau phase Decrease to every 3 mo if disease is active	1 y After 1 y: Discontinue if complete response or VGPR occurs and no active bone disease is evident Continue BP therapy if less than a VGPR occurs and/or ongoing active bone disease is evident After 2 y: Discontinue BPs if no active bone disease is evident If active bone disease is present, further BP use is recommended at the discretion of the primary physician
Choice of BP	Pamidronate	Pamidronate or clodronate

*BP = bisphosphonate; CT = computed tomography; IMWG = International Myeloma Working Group; MRI = magnetic resonance imaging; PET = positron emission tomography; VGPR = very good partial response.

Attal et al² conducted a randomized trial evaluating the utility of thalidomide and pamidronate in patients with multiple myeloma who had completed tandem autologous stem cell transplantation. Seven hundred eighty patients were enrolled and randomly assigned to no therapy (arm A), pamidronate alone (arm B), or pamidronate plus thalidomide (arm C). The 3-year postrandomization probability of event-free survival was 36% in arm A, 37% in arm B, and 52% in arm C ($P<.009$). The 4-year postdiagnosis probability of survival was 77% in arm A, 74% in arm B, and 87% in arm C ($P<.04$). The proportion of patients who had skeletal events was 24% in arm A, 21% in arm B, and 18% in arm C ($P=.40$). On the basis of these findings, it appears that, as proposed by us and by the IMWG, prolonged treatment with BPs does not decrease the incidence of bone events or improve survival.

Martha Q. Lacy, MD, and
S. Vincent Rajkumar, MD, for the
Mayo Clinic Myeloma Group
College of Medicine, Mayo Clinic
Rochester, Minn

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Impact of the FDA Black Box Warning on Physician Antidepressant Prescribing and Practice Patterns: Opening Pandora's Suicide Box

To the Editor: After a decade-long decline, annual suicide rates in American children and adolescents increased in 2004. A report released in February 2007 described an 18% increase in the suicide rate in persons aged 1 through 19 years between 2003 and 2004.¹ The incidence of suicide, the third-leading cause of death in 15- to 19-year-old Americans, increased from 7.3 to 8.2 per 100,000 persons in 2004.

This increase in suicides directly parallels the US Food and Drug Administration (FDA) recommendation for caution in prescribing antidepressants to children and adolescents. A March 2004 FDA advisory warned that antidepressants could cause worsening depression and increased suicidality. Within a month, the number of antidepressant prescriptions filled for children nationally declined 10%.² In October 2004, after public committee hearings held in September, the FDA issued a black box warning (BBW),³ its most serious warning, for children and adolescents (defined as ≤ 18 years, making no clear distinction between adolescents and children), on all antidepressants marketed in the United States. Although the FDA encouraged prescribers to "balance this risk with the clinical need,"⁴ prescriptions filled for children and adolescents had decreased an additional 10% by June 2005,² 2 months after the labeling appeared.

Testimony at FDA hearings raised concern that a BBW could create unintended barriers to care if generalist physicians became reluctant to prescribe antidepressants. This is especially critical because visits to nonpsychiatric generalist (primary care) physicians account nationally for more than 60% of physician visits for depression.⁵

The FDA panel's decision-making process has been hotly debated in the media and academic literature. Remarkably, not one child or adolescent among the 4400 cases the FDA reviewed completed suicide. Furthermore, the FDA inveighed against "suicidality"—a vague clinical concept encompassing everything from passive death wishes to near-lethal suicide attempts. Meanwhile, untreated depression is the single most widely recognized risk factor for suicide at all ages, even as depression in children is underrecognized and undertreated in a nation with woefully inadequate numbers of child and adolescent psychiatrists. Thus, family practitioners and pediatricians write most antidepressant prescriptions for young Americans. Large observational pharmacoepidemiological studies link increasing rates of selective serotonin reuptake inhibitor antidepressant prescriptions and decreased national suicide rates.^{6,7} In contrast, decreased antidepressant prescribing by primary care physicians could lead to increased suicide rates, an effect opposite the FDA's intent.

Mayo Clinic Survey. The reasons for the 20% decrease in prescriptions filled for children and adolescents by June 2005 remain unclear. Similarly unclear is whether a subsequent expansion of the upper age limit within the BBW will have additional impact on physicians' prescribing practices. Specifically, in December 2006, an FDA panel voted 6 to 2 to expand the warning to include adults through age 24,⁸ a group at high risk for both initial episodes of depression and suicide, particularly in men. To gain insight into antidepressant drug use across all ages, we conducted an anonymous Web survey of physicians at the Mayo Clinic in Rochester, Minn, between November 2005 and January 2006. About half of the sample that responded prescribe for both adults and children and the other half for adults only. Most questionnaire items could be answered only by those actually prescribing antidepressants at some point in their careers.

Of the 1433 doctoral-level health care professionals surveyed, 344 (24%) responded, including 44 (64%) of 69 psychiatry and psychology department members, 89 (32%) of 275 generalists, and 211 (19%) of 1089 specialists. Of the 344 respondents, 324 (94%) indicated that they were currently treating patients. Two of the survey respondents did not answer the question regarding age groups treated. Twenty-one (7%) of the remaining 322 respondents treated exclusively children and adolescents, 152 (47%) treated only adults, and 149 (46%) treated both groups. Of the 324 respondents who were currently treating patients, 247 (76%) indicated that they prescribed antidepressants, including 37 psychiatrists, 79 generalists, and 131 specialists.

Of the 247 respondents who prescribed antidepressants, 233 (94%) had heard about the BBW, including all 37 psychiatrists and 78 (99%) of the 79 generalists vs 118 (90%) of the 131 specialists. Overall, 176 (76%) of the 233 physicians

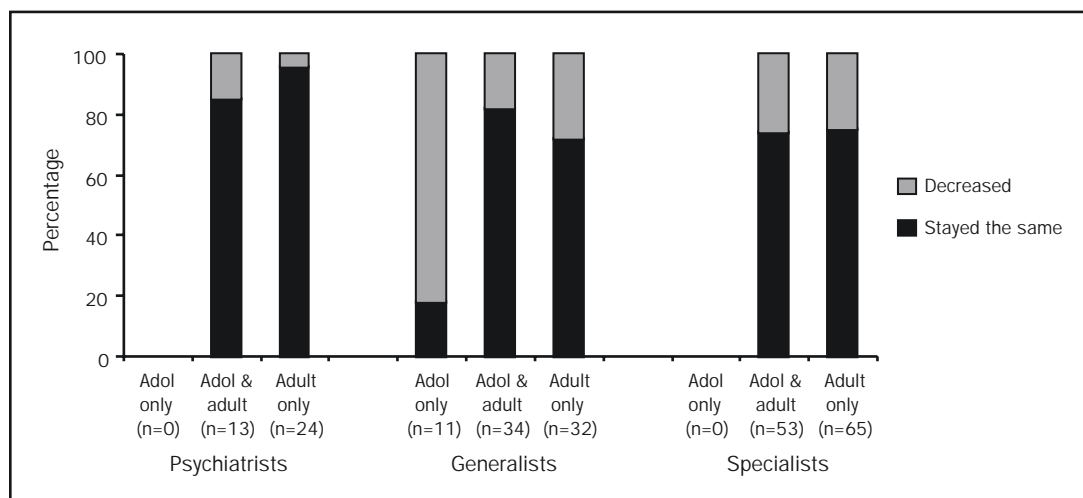


FIGURE 1. Impact of antidepressant prescribing behavior by patient age among physicians aware of the BBW (N=232). Adol = adolescents and children.

who were aware of the BBW reported continuing to prescribe at the same rate, whereas 57 (24%) had decreased or stopped prescribing antidepressants. (One generalist did not respond to the question specifically addressing age groups treated, which resulted in a sample size of 232). Figure 1 shows the changes in prescribing patterns by physician group.

Decreased prescribing in response to the BBW was particularly marked for generalists seeing children and adolescents only, with 82% (9/11) indicating that they had decreased or stopped antidepressant prescribing vs only 28% (9/32) of generalists treating exclusively adults and 18% (6/34) seeing both adults and children. Psychiatrists did not report notable decreases in prescribing—the 8% decline reported in psychiatrists treating both adults and children appears to be related to less willingness of patients or guardians to accept medication. Whether they treated adults only or adults and children, 25% of specialists decreased or stopped prescribing antidepressants

to patients in any age group. No physician group in our survey increased prescribing of antidepressants.

In addition to rates of antidepressant prescribing, the survey collected information on practice pattern response after the BBW across the 3 physician groups. The data included in Table 1 are from all respondents who prescribed antidepressants, whether or not they had heard of the BBW (n=247). All physician groups reported changes in practice patterns, with 35% of psychiatrists, 12% of generalists, and 9% of specialists spending more time reviewing the treatment plan at the initial meeting. In addition, 11% of psychiatrists, 15% of generalists, and 4% of specialists saw or contacted patients sooner after the first appointment, and 4% of specialists said they would try counseling patients first before prescribing antidepressants. In the largest practice pattern change, we found that a total of 43% (23% + 20%) of specialists and 26% (17% + 9%) of generalists reported increasing their referrals to a psychiatrist or other mental health specialist for consultation.

TABLE 1. Most Common Practice Pattern Responses* After FDA Black Box Warning, by Physician Group (N=247)†

Psychiatrists (n=37)	Generalists (n=79)	Other specialists (n=131)
No change in practice (41%)	No change in practice (30%)	No change in practice (32%)
Spend more time explaining treatment to patients and families (19%)	More likely to refer patients to a mental health specialist for consultation (17%)	More likely to refer patients to a mental health specialist for consultation (23%)
Spend more time explaining rationale for prescribing antidepressants (16%)	See patients sooner or contact them personally after initial appointment (15%)	Less likely to prescribe antidepressants and will refer patients to a psychiatrist for antidepressant prescriptions (20%)
See patients sooner or contact them personally after initial appointment (11%)	Spend more time explaining rationale for prescribing antidepressants (12%)	Spend more time explaining rationale for prescribing antidepressants (9%)
Patients/families less willing to agree with antidepressant prescription (8%)	Less likely to prescribe antidepressants themselves and will refer patients to a psychiatrist for antidepressant prescriptions (9%)	More likely to counsel patients themselves first before prescribing antidepressants (4%) and see patients sooner or contact them personally after initial appointment (4%)‡
Other (5%)	Other (17%)	Other (8%)

*Not all practice pattern changes are listed. The electronic survey allowed selection of only 1 practice pattern response, with all responses totaling 100%.

†FDA = Food and Drug Administration.

‡ An equal number of specialists chose these 2 responses.

Discussion. The FDA intended the BBW to improve physician-patient communication and encourage closer physician monitoring. Although our research suggests that this expectation was realistic, the FDA did not adequately take into account the implications of nonpsychiatric physicians ceasing to prescribe. We found that large numbers of both generalists and nonpsychiatric specialists who formerly would have written antidepressant prescriptions themselves are choosing instead to refer patients to psychiatrists or other mental health specialists.

The FDA panel should have known from existing research that FDA warnings are linked to decreased prescribing.⁹ Our findings underscore the impact of a BBW on physician prescribing and practice patterns across all age groups. Although the results of our survey showed that nonpsychiatrists were less likely to prescribe antidepressants to any age group, the decreased prescribing was particularly marked in children. Despite the limitations of our pilot research, including low response rates, a possibly nonrepresentative academic medical center setting, and an inability to correlate physician self-report with actual prescribing, our study results suggest that the FDA's BBW markedly altered physician prescribing and practice patterns.

In addition, the FDA BBW mandates closer follow-up of patients taking antidepressants without addressing the stark realities of the current mental health system,¹⁰ including (1) insurance plans with poor or absent mental health coverage, (2) increased copayments for individual mental health visits, (3) strict limits on outpatient mental health visits and inpatient psychiatric care, and (4) limited access to mental health providers. Current shortages—particularly of child and adolescent psychiatrists—are not expected to reverse in the near future. Despite FDA expectations of increased medication monitoring, patients cannot afford and physicians cannot provide the recommended contacts, let alone the gold standard of combined medication and counseling.¹¹

In terms of increasing physician-patient communication, our results indicate that the BBW may have selectively succeeded in obtaining one of the FDA's goals, providing earlier contact and more communication, which was noted in all physician groups and particularly in psychiatrists. As antidepressant experts with nowhere to refer patients, more than a third of our psychiatrists reported talking to patients more, as did smaller proportions of both generalists and specialists. Of concern in the current environment of limited psychiatric resources, many generalists and specialists are choosing to no longer prescribe antidepressants themselves and instead refer their patients to mental health specialists for care that may not be available in a timely fashion, if at all.

Given that reduced prescribing by generalists in our survey was most marked in children and adolescents, we fear that decreased antidepressant prescribing due to BBW concerns may underlie increasing youth suicide rates.¹ Disconcertingly, a warning of increased "suicidality"—in the absence of any actual suicides—could conceivably have driven increased suicide rates already observed in American youths in 2004, the year the BBW took effect. An argument can be made that the

BBW did not take effect until late 2004. However, as we described previously, antidepressant prescriptions filled for children and adolescents had decreased by 10%² in April 2004, 1 month after the initial FDA public advisory.

We fear that the correlation seen between declining youth antidepressant prescription rates and increasing suicide rates could soon be seen in older populations, particularly with the FDA currently considering its panel's recommendation to extend the BBW to young adults. Further research is needed to clarify why nonpsychiatrists have decreased antidepressant prescribing, opting instead for referrals to limited psychiatry resources already unable to handle the demand. If further research confirms the BBW's role in reduced antidepressant prescribing and increased suicide rates, revising the BBW and getting generalists and nonpsychiatric specialists to prescribe these drugs again should become public health priorities.

Timothy W. Lineberry, MD
J. Michael Bostwick, MD
Timothy J. Beebe, PhD
Paul A. Decker, MS
College of Medicine, Mayo Clinic
Rochester, Minn

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Sorafenib-Induced Pancreatitis

To the Editor: Sorafenib is a multikinase inhibitor recently approved by the US Food and Drug Administration for use in the treatment of metastatic renal cell carcinoma. The long-term and toxic effects of sorafenib are currently unknown. We describe a patient who experienced sorafenib-induced pancreatitis.

Report of a Case. A 53-year-old woman had renal cell carcinoma metastatic to the lungs and bones. Treatment with sorafenib, 400 mg twice a day, was initiated. Three weeks later, severe epigastric pain, nausea, and vomiting developed. Her serum amylase level was 1361 U/L (reference range, 26-102 U/L) with a lipase level of 99 U/L (10-73 U/L). Abdominal computed tomography showed normal findings. Sorafenib was discontinued, and the patient was hospitalized for treatment of acute pancreatitis. At discharge 2 weeks later, she continued to have moderate pain requiring narcotics. Pancreatitis was grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE).

Eight weeks after sorafenib discontinuation, the patient's pain had improved, and her amylase and lipase levels were 863 U/L and 44 U/L, respectively. She was subsequently referred to our medical center for further evaluation.

Repeated abdominal computed tomography at our institution revealed a normal pancreas, liver, gallbladder, and biliary ducts. Endoscopic ultrasonography showed a normal gallbladder, common bile duct, and main pancreatic duct. Abnormal hyperechogenic foci were noted in the pancreas, along with strands and lobulation consistent with chronic pancreatitis.

The patient did not drink alcohol and had no prior hepatobiliary disease, no family history of pancreatitis, no preceding viral illness, and normal serum triglyceride and calcium levels. Sorafenib was her only medication. The temporal association with initiation of sorafenib and lack of other causes support the diagnosis of sorafenib-induced pancreatitis.

Discussion. Sorafenib is an oral multikinase inhibitor with antiangiogenic and antiproliferative activity. It inhibits platelet-derived growth factor receptor, vascular endothelial growth factor (VEGF) receptor, and the Ras/Raf/MEK pathway.¹ Common adverse effects include diarrhea, rash, fatigue, and hypertension.² Postmarketing data³ have noted both lipase and amylase elevations.

In one study, clinical pancreatitis was reported in 3 of 451 sorafenib-treated patients (1 had CTCAE grade 2, and 2 had CTCAE grade 4).³ Two of these patients subsequently resumed sorafenib.³ A phase 1 study of 69 sorafenib-treated patients reported 3 cases of dose-independent grade 3 pancreatitis. All 3 patients recovered after withdrawal of sorafenib.⁴ In our patient, the severity of symptoms and their incomplete resolution precluded reinitiation of sorafenib.

Our hypothesis is that the anti-VEGF effects of sorafenib cause ischemia of pancreatic tissue, increasing the risk of pancreatitis. Also, its continued action impairs the protective effects of VEGF and platelet-derived growth factor,⁵ increasing the severity of the resulting pancreatitis. Pancreatitis

should be included in the differential diagnosis of patients with abdominal pain who are receiving sorafenib. Recognition of adverse effects from novel agents is essential to ensure appropriate diagnosis and treatment.

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Surabhi Amar, MD
Kevin J. Wu, MD
Winston W. Tan, MD
College of Medicine, Mayo Clinic
Jacksonville, Fla

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Did a Flawed Study Design Affect the Results of the VYTAL Study?

To the Editor: I am concerned that the design of the Vytorin vs Atorvastatin in Patients With Type 2 Diabetes Mellitus and Hypercholesterolemia (VYTAL) Study, as outlined by Goldberg et al,¹ affected the results they reported. The problem is the large number of "participating centers" and "study investigators" (147) and the small number of patients per center. Given the number of patients randomized, each site supplied a mean of only 8.4 patients or 1.66 patients per study arm.

Unclear in this report is why the participation of 147 centers was needed to enroll 1229 patients. The patients being studied, individuals with type 2 diabetes and hypercholesterolemia who were between 18 and 80 years of age and had hemoglobin A_{1c} levels of 8.5% or less, are, unfortunately, common. The reason for so many centers and so few patients per center was not specified. Center selection itself could introduce bias depending on the selection criteria, but I will confine my remarks primarily to the study design, which may have led to some unintended biases.

Because the study used random assignment, some centers would have no patients in some study arms, whereas others would have all their patients randomized to just 1 or 2 arms. This design could lead to bias because of individual practice variations, especially in reference to the intensity of treatment

of the comorbidity (diabetes). It is unlikely that nonpharmaceutical interventions such as dietary counseling, staff encouragement, and follow-up visit variations were controlled in all 147 centers. Whether the centers were all primary care facilities or included subspecialty care could have impacted these other interventions because of variations in treatment regimens and goals for patients with diabetes and lipid abnormalities.

Having few patients per center might also dilute patient anonymity, leading to unintended effects on compliance and other factors. Including a large number of sites can also lead to difficulty in controlling the introduction of investigator biases. For example, prerandomization bias may have occurred because it is unclear how patients were selected at each center. The authors state that they were “randomized...after washout and placebo run-in periods,” but how they were initially selected or if there were any selection criteria is unclear. Without a study-wide protocol to prevent enrollment bias toward failures of current lipid-lowering treatment, there could be a positive trend toward one study arm. Knowing the number of patients whose hypercholesterolemia was controlled or not controlled with what specific medications at selection is important if this study portends to evaluate first-line treatment options, as stated in the conclusion.

Thus, it is possible that, by designing a study with such a large number of centers and resultant small number of patients per center, the efforts for randomness, double blinding, and clinical usefulness may have been defeated.

David E. McMahon, MD
Mount Carmel Medical Center
Columbus, Ohio

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In reply: We appreciate Dr McMahon’s comments regarding the potential for study bias and error in the VYTAL Study. The study design and recruitment procedure in this trial were similar to those used in other relatively large shorter-term efficacy studies, including the Vytorin Versus Atorvastatin (VYVA) Study, which compared the safety and efficacy of ezetimibe/simvastatin vs atorvastatin in 1902 patients randomized to treatment at 216 sites,¹ and a recent study that compared ezetimibe/simvastatin vs rosuvastatin in 2959 patients with hypercholesterolemia who were randomized to treatment at 214 centers.² Although recruitment from fewer sites is possible, the potential for site-related bias would be greater. In the VYTAL Study, patients were randomized by allocation concealment using an interactive voice response system to ensure an even distribution of patients among treatment groups. This even distribution is confirmed by the fact that the baseline characteristics among the treatment groups were well balanced.

To avoid individual site variations, all the investigators followed a standard protocol that defined the procedure for

dietary considerations, screening and enrollment criteria, randomization, and follow-up visits. Furthermore, patients were enrolled after a 4-week placebo run-in period before the study treatment was initiated. Should there have been between-site(s) treatment differences as suggested by Dr McMahon, we would have expected greater variability in baseline characteristics and measurements to result during this run-in period, including baseline low-density lipoprotein cholesterol levels, which were found to be similar across treatment groups.

To be eligible for entry into the trial, patients were not allowed to receive lipid-lowering drug therapy for 6 to 8 weeks before enrollment. This requirement provided adequate time for wash-out of any lingering lipid-altering effects. Thus, the results of the study are representative of the expected response to the initiation of therapy with ezetimibe/simvastatin or atorvastatin in the study population. Moreover, the lipid-altering effects of ezetimibe/simvastatin and atorvastatin demonstrated in this trial are similar to the results shown in previous trials in different patient populations.^{1,3,4}

We agree that using a study design that minimizes bias is important, and we believe that the protocol used in the VYTAL trial fulfilled that goal.

Ronald B. Goldberg, MD
University of Miami
Miami, Fla

John R. Guyton, MD
Duke University
Durham, NC

Theodore Mazzone, MD
University of Illinois
Chicago

Ruth S. Weinstock, MD, PhD
SUNY Upstate Medical University
and Veterans Affairs Medical Center
Syracuse, NY

Adam Polis, MA
Patricia Edwards, RN, BSN
Joanne E. Tomassini, PhD
Andrew M. Tershakovec, MD
Merck & Co, Inc
West Point, Pa

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