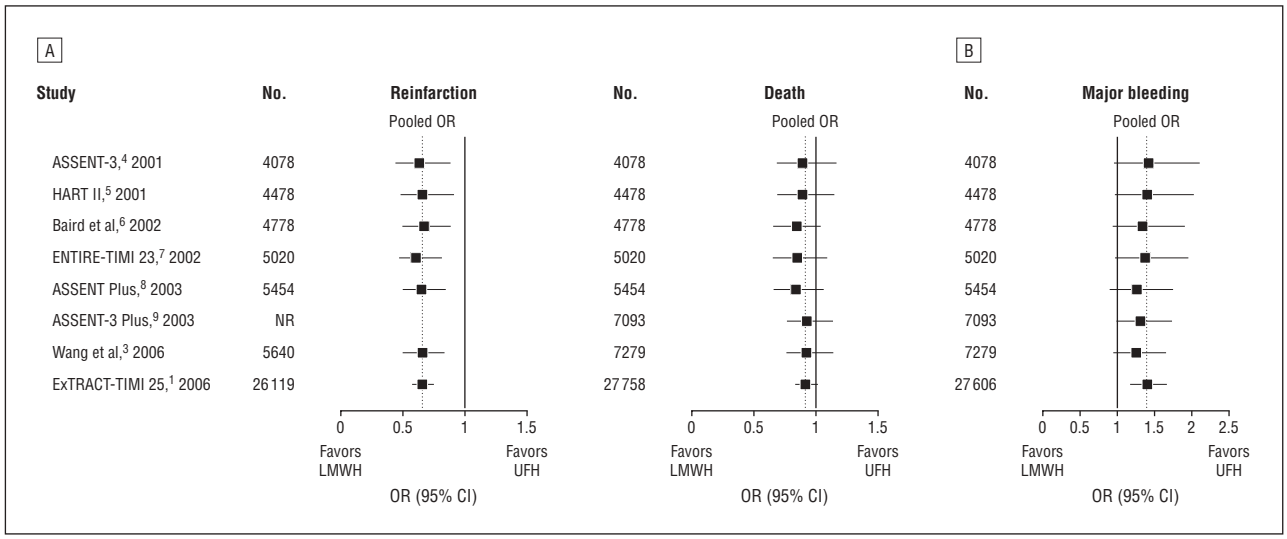

Figure. Cumulative meta-analysis of randomized trials comparing LMWH with UFH showing reinfarction and death at 30 days (A) and major bleeding during hospitalization or at 7 days (B). ASSENT indicates Assessment of the Safety and Efficacy of a New Thrombolytic Regimen; CI, confidence interval; ENTIRE-TIMI 23, Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy–Thrombolysis in Myocardial Infarction 23; ExTRACT-TIMI 25, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction; HART II, Second Trial of Heparin and Aspirin Reperfusion Therapy; LMWH, low-molecular-weight heparin; OR, odds ratio; and UFH, unfractionated heparin.

mates of the efficacy and safety of LMWH compared with UFH in patients with STEMI treated with thrombolysis.

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Patient- and Physician-Oriented Web Sites and Drug Surveillance: Bisphosphonates and Severe Bone, Joint, and Muscle Pain

Postmarketing surveillance and the determination of the real-world safety profile of prescription drugs is arguably flawed. Recent identification of significant adverse effects associated with newly approved prescription drugs support the sometimes-held view that a new system needs to be introduced. The present voluntary system has not provided a sufficient early warning system, and some have called for active systems that probe for potential adverse effects of approved prescription drugs.[1] Patient-oriented Web sites may provide an opportunity to identify potential adverse effects early in a drug's postmarket history.

In 2005, Wysowski and Chang[2] published a letter regarding a series of case reports submitted to the Food and Drug Administration (FDA) on severe bone, joint, and muscle pain associated with the use of alendronate so-

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Table. Patient Response Summary

Question	Response, %	Response Count, No. (N = 367)
Why were you prescribed a bisphosphonate drug?		(n = 366)
Osteoporosis	51.9	190
Osteopenia	46.7	171
Do not know	1.4	5
Did you experience adverse effects that you attributed to the use of the bisphosphonate?		(n = 362)
Yes	83.1	301
No	5.8	21
Perhaps	11.0	40
Which of the bisphosphonate drugs do you think caused the adverse effect?[a]		(n = 352)
Actonel	23.6	83
Aredia	0.3	1
Boniva	44.6	157
Fosamax	31.5	111
Zometa	0	0
How old were you when you experienced the adverse effect? Age, y		(n = 350)
≤50	13.9	49
51-60	54.3	190
61-70	20.9	73
≥71	10.9	38
Of the following, which best describes the adverse effect you experienced?		(n = 317)
Fatigue only	2.5	8
Muscle pain only	4.7	15
Joint pain only	10.4	33
Muscle and joint pain	24.9	79
Muscle and joint pain along with fatigue	56.9	180
Muscle fatigue	0.6	2

(continued)

dium and risedronate sodium for 1995 to 2002. In all, 116 case reports of serious adverse events were voluntarily submitted. A subsequent FDA Alert was issued on January 2008 concerning serious and sometimes incapacitating bone, joint, and muscle pain associated with bisphosphonate use.[3] One such case was seen at Massachusetts General Hospital, prompting an investigation into the literature on the topic. The patient pointed us to a patient-oriented Web site called "Askapatient" (http://www.askapatient.com) that noted multiple case reports of the development of an influenzalike syndrome early in the treatment with bisphosphonate drugs and subsequent severe and sometimes incapacitating joint, bone, and muscle pain. The site posts comments from patients on their experiences with prescription drugs and asks them to rate the drug using a scale of 1 (poor) to 5 (excellent). Several patient reports indicated a persistence of symptoms for months.

We approached the site administrator and obtained permission to post a survey (using SurveyMonkey.com) on the site that was specific to the question of joint, bone, and muscle pain with bisphosphonate use. The survey went live in late October 2008 and was taken down in late January 2009. The results of the survey are provided in the **Table**.

A physician community–based Web site (http://www.sermo.com) was also reviewed simultaneous to the posting of the survey at Askapatient. One case of an influenzalike syndrome with joint, bone, and muscle pain was posted by a physician. Importantly, when asked if this adverse event had been seen by other clinicians, 63% of the respondents indicated it had not. This number is in keeping with the patient experience noted by Askapatient respondents when queried concerning their prescriber's impression that bisphosphonate use was not a possible cause of the symptoms. Golomb and colleagues[4] previously noted this lack of appropriate attribution on the part of clinicians to muscle pain and the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.

User-submitted reviews are commonplace in most commercial domains. Health care has been a notable exception. Web sites such as Askapatient provide a window into the patient experience and a potential resource for developing a better understanding of the true adverse effect profile of prescription drugs. Probing sites such as Askapatient or Sermo does not equate to true pharmacovigilance. These sites and others may provide a unique window into the drug therapy experience from both the prescriber and patient/consumer perspective. Causality, incidence, and confounders cannot be identified with such probing. The value of such sites has yet to be explored in health care. Given the poor showing of the existing voluntary reporting system, probing user and provider community Web sites may provide a valuable tool.

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Table. Patient Response Summary (continued)

Question	Response, %	Response Count, No. (N = 367)
How long after you started taking the drug did you experience the adverse effect?		(n = 342)
<24 h	25.1	86
<2 wk	18.4	63
<30 d	7.6	26
In the first 6 mo of treatment	28.7	98
Other	20.2	69
On a scale of 1-10 (with 10 being the most severe), how severe were your symptoms?		(n = 336)
1-5	15.2	51
6-8	38.7	130
9-10	46.1	155
How long did the symptoms last?		(n = 302)
<1 wk	14.6	44
<1 mo	13.6	41
<3 mo	11.3	34
<6 mo	11.9	36
<1 y	14.2	43
>1 y	34.4	104
Did you discuss your symptoms with your prescriber?		(n = 335)
Yes	73.4	246
No	26.6	89
Did your prescriber attribute your symptoms to the drug?		(n = 288)
Yes	38.2	110
No	61.8	178

[a] Actonel (risedronate sodium; Procter & Gamble Pharmaceuticals, Cincinnati, Ohio); Aredia (pamidronate disodium; Novartis Pharmaceuticals, East Hanover, New Jersey); Boniva (ibandronate sodium; Roche Therapeutics Inc, Nutley, New Jersey); Fosamax (alendronate sodium; Merck, Whitehouse Station, New Jersey); Zometa (zoledronic acid; Novartis Pharmaceuticals).

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COMMENTS AND OPINIONS

Cold-Induced Dehydration Decreases Tissue Perfusion and Increases Blood Pressure

It was with great interest that I read the recent article by Alpérovitch and colleagues[1] titled "Relationship Between Blood Pressure and Outdoor Temperature in a Large Sample of Elderly Individuals: The Three-City Study." As much as I agree that the subject itself is interesting, there is a very important aspect left out of this article, and that is tissue perfusion. One of the principal problems of tissue perfusion is having enough blood volume to do this. If there is insufficient volume, then constant redistribution will have to take place, and an insufficient tissue perfusion is associated with hypertension.[2]

Two indicators of insufficient blood volume are plasma levels of the peptide hormones antidiuretic hormone (ADH) and angiotensin (AngII). In the cold, however, the secretion of ADH is attenuated, and this could lead to an exaggerated decrease in blood volume unless there was a compensatory increase in fluid intake. In some humans, this physiological regulatory process apparently breaks down because AngII levels are chronically elevated, probably due to insufficient fluid intake. The presence of AngII is associated with hypertension, and hence it is a potential risk factor in perfusion. In reality, however, it signals an already decreased volume. Furthermore, one of the principal actions of both ADH and AngII is vasoconstriction, which would normally work to reduce adequate perfusion throughout the vascular system.[2]

Studies in rats and mice have shown recently that inhibition of the AT1 receptor[3] or absence of converting enzyme[4] increased daily water intake up to twice the normal volume. This would have the direct effect of increasing volume and thus flow and tissue perfusion. Brattleboro rats that have a genetic defect preventing them from synthesizing ADH must drink and excrete over 200 mL/d and remain lean. In several experimental hypertensive models, they did not develop an elevated blood pressure,[5] suggesting that tissue perfusion is essential for the prevention of hypertension.

In conclusion, these results would suggest that cold-induced dehydration would lead to decreased tissue perfusion and thus to an increase in blood pressure. A possible solution to this would be an increased water intake. However, in an elderly patient already with arterial stiffness and hypertension, it is not clear that increased drink-

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