

described in the published reports,<sup>1,2</sup> this calculation was erroneously made on the basis of the right eye only, resulting in fewer events as well as fewer people in whom a change in visual acuity could be ascertained. The published and revised numbers are presented in Table 1; the article is correct at NEJM.org. These changes do not materially change the conclusions of the study.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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## A Controlled Trial of a Prostacyclin and rt-PA in the Treatment of Severe Frostbite

**TO THE EDITOR:** Many alternatives have been proposed for the treatment of frostbite: hemodilution, platelet-aggregation inhibitors, low-molecular-weight heparin, alpha-adrenergic vasodilators, calcium-channel inhibitors, nonsteroidal anti-inflammatory agents, prostacyclin analogues, fibrinolytic agents, and hyperbaric oxygen. None have been assessed in prospective randomized trials. Small retrospective studies<sup>1-3</sup> suggest the efficacy of thrombolysis or prostacyclin analogues against spasm and thrombosis.

Between 1996 and 2008, we randomly assigned 47 patients (44 men and 3 women) with severe frostbite to one of three treatment regimens in an open-label study. Severe frostbite was defined as having at least one digit (finger or toe) with frostbite stage 3 (lesion extending just past the proximal phalanx) or stage 4 (lesion extending proximal to the metacarpal or metatarsal joint).<sup>4</sup> The study was approved by the ethics committee at the University of Grenoble.

Directly after their mountain rescue, patients meeting the study criteria (having no contraindications to use of the study drug, no severe trauma, and no hypothermia) received care that involved rapid rewarming of the areas with frostbite plus 250 mg of aspirin and intravenous administration of 400 mg of buflomedil. They then underwent randomization to receive one of three regimens for 8 days. One group received 250 mg of aspirin and buflomedil (400 mg for 1 hour per day), the second received 250 mg of aspirin plus a prostacyclin (0.5 to 2 ng of iloprost per kilogram of body weight per minute for 6 hours per day), and the third received 250 mg of aspirin,

iloprost (2 ng per kilogram per minute for 6 hours per day), and fibrinolysis (100 mg of recombinant tissue plasminogen activator [rt-PA] for the first day only). Treatment efficacy was evaluated after 8 days in all 47 study patients by means of bone scans obtained with the use of technetium scintigraphy, the results of which showed an excellent correlation with the level of final amputation required (predictive value of positive findings, 0.996).<sup>5</sup> (For additional details, see the table in the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

In most of the patients, whose mean age was 33.1 years and who had no notable medical or surgical history, frostbite occurred at high altitude (>2000 m). Frostbite occurred in the feet in 33 patients in the hands in 29 patients, and in both hands and feet in 15 patients. The baseline characteristics of the patients and the localization of the frostbite were similar across treatment groups, except that stage 4 lesions were more common in the group receiving prostacyclin plus rt-PA.

The risk of amputation in the buflomedil group was 60% (9 of 15 patients). As compared with this group, the risk of amputation was significantly lower in the other two groups — 0% (0 of 16 patients) in the group receiving prostacyclin alone and 19% (3 of 16 patients) in the group receiving prostacyclin plus rt-PA ( $P < 0.001$  and  $P < 0.03$ , respectively, by Fisher's exact test).

The efficacy of treatment with prostacyclin was confirmed when the number of digits amputated and the severity of the frostbite were considered (Table 1). However, our results do not rule out a

**Table 1. Number of Amputated Digits (Fingers or Toes) According to Treatment, Severity of Frostbite, and Time to Treatment.\***

Treatment Group	No. of Patients	All Stages of Frostbite		All Stages, ≤12 Hr to Treatment		All Stages, >12 Hr to Treatment		Stage 2		Stage 3		Stage 4 or Higher	
		Digits with Frostbite Amputated	no. (%)	Digits with Frostbite Amputated	no. (%)	Digits with Frostbite Amputated	no. (%)	Digits with Frostbite Amputated	no. (%)	Digits with Frostbite Amputated	no. (%)	Digits with Frostbite Amputated	no. (%)
All groups	47	407	47 (11.5)	271	13 (4.8)	136	34 (25.0)	155	4 (2.6)	215	31 (14.4)	37	12 (32.4)
Buflomedil	15	106	42 (39.6)	48	11 (22.9)	58	31 (53.4)	31	2 (6.5)	66	31 (47.0)	9	9 (100.0)
Iloprost	16	142	0	79	0	63	0	64	0	75	0	3	0
Iloprost plus rt-PA	16	159	5 (3.1)	144	2 (1.4)	15	3 (20.0)	60	2 (3.3)	74	0	25	3 (12.0)

\* Stage 2 frostbite was defined as having at least one digit (finger or toe) with frostbite, with the lesion confined to the distal phalanx; stage 3 as having at least one digit with frostbite, with the lesion extending just past the proximal phalanx; and stage 4 as having at least one digit with frostbite, with the lesion extending proximal to the metacarpal or metatarsal joint.

possible additive effect of rt-PA in selected patients. In addition, there were no significant differences according to frostbite localization, with 183 frozen fingers leading to 22 amputations (buflomedil, 49%; prostacyclin, 0%; prostacyclin plus rt-PA, 2%) and 224 frozen toes leading to 25 amputations (buflomedil, 34%; buflomedil, 0%; prostacyclin plus rt-PA, 4%). The only adverse reactions were minor (hot flushes in 55% of the patients, nausea in 25%, palpitation in 15%, and vomiting in 5%). None of these reactions led to discontinuation of the study medication.

On the basis of these results, we recommend that in the treatment of severe frostbite (stage 3 or above), after rapid rewarming, a combination of aspirin and prostacyclin should be used. The addition of rt-PA should be considered on a case-by-case basis, depending on the severity of injury (at least stage 4 frostbite), the presence of trauma (especially head trauma), any medical contraindications, and the amount of time passed since rewarming.

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## CORRECTION

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes (July 15, 2010;363:233-44). A correction is described in the Correspondence section of this issue of the *Journal* (Update of the ACCORD Eye Study [January 13, 2011;364:188-9]).