

**Table 1. Patient Population Stratified According to Time from Dispatch of Emergency Medical Services (EMS) Personnel to Placement of Impedance Threshold Device (ITD) and Time from Dispatch to Arrival of EMS Personnel.**

Subgroup	Sham ITD	Active ITD	Difference (%)*
	<i>no. of survivors to hospital discharge with modified Rankin score <math>\leq 3</math>/total no. (%)†</i>		
Time from EMS dispatch to ITD placement — min			
0 to 8	93/972 (9.6)	81/921 (8.8)	-0.8
>8 to 16	137/2315 (5.9)	128/2337 (5.5)	-0.4
>16	20/837 (2.4)	30/881 (3.4)	1.0
Not available	10/221 (4.5)	15/234 (6.4)	1.9
Time from EMS dispatch to EMS arrival — min			
0 to 5	134/1834 (7.3)	124/1789 (6.9)	-0.4
>5 to 10	120/2291 (5.2)	124/2348 (5.3)	0.04
>10	6/220 (2.7)	6/236 (2.5)	-0.2

\* The between-group differences were not significant.

† The modified Rankin scale is a validated scale that is commonly used to measure the performance of daily activities by people who have had a stroke. Scores range from 0 to 6, with higher numbers indicating greater disability.

CPR. The positive results of the ResQTrial, the most recently reported randomized trial comparing active compression–decompression CPR plus ITD with standard CPR, suggests there may be a synergistic effect between these two interventions that would explain the discordant findings noted in the two meta-analyses. Although useful, meta-analyses are limited by methodologic differences between trials. Since blinding of active compression–decompression CPR is not possible, the best scientific approach to answer the question regarding the relative contribution of each intervention toward improved survival with the device combination would be to conduct a large randomized study comparing active compression–decompression CPR with an active ITD and a sham ITD.

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Since publication of their article, the authors report no further potential conflict of interest.

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## Breast-Cancer Adjuvant Therapy with Zoledronic Acid

**TO THE EDITOR:** On the basis of data obtained in the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial (Current Controlled Trials number, ISRCTN79831382), Coleman et al. (Oct. 13 issue)<sup>1</sup> question the capacity of the amino-bisphosphonate zoledronic acid to reduce the re-

currence of breast cancer in the adjuvant setting. This reduction was previously reported in the Austrian Breast and Colorectal Cancer Study Group (ABCSG-12) trial (ClinicalTrials.gov number, NCT00295646).<sup>2</sup>

A notable difference in the initial treatment

schedule of zoledronic acid in the ABCSG-12 study (once every 6 months) and the AZURE study (once every 3 to 4 weeks) could account for this apparent discrepancy. It is known that the aminobisphosphonate-induced activation of  $V\gamma 9V\delta 2$  T cells, which have been proposed to be key mediators of the antitumor effects of aminobisphosphonates, is reduced with each subsequent administration of aminobisphosphonate. Therefore, the more frequent administration of zoledronic acid in the AZURE study might have induced a state of functional exhaustion in  $V\gamma 9V\delta 2$  T cells and impaired antitumor activity.<sup>3,4</sup>

Interestingly, in the AZURE study, patients were randomly assigned to treatment according to statin use or nonuse. Since statins inhibit  $V\gamma 9V\delta 2$  T-cell activation by preventing the aminobisphosphonate-induced accumulation of its activating ligand, isopentenyl pyrophosphate, it is unfortunate that the authors provide no information on differences in outcome according to statin use or nonuse, since this might have provided essential additional insight into the putative antitumor mechanism of aminobisphosphonate therapy.<sup>5</sup>

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**THE AUTHORS REPLY:** We think it is unlikely that the apparent differences in outcome between the AZURE and ABCSG-12 studies were related to functional exhaustion of  $V\gamma 9V\delta 2$  T cells induced by the intensive regimen of zoledronic acid used in our trial. Such an explanation would not be consistent with the significant heterogeneity of treatment effects according to menopausal status. In the AZURE trial, significant improvements in disease outcomes were seen in women more than 5 years after menopause, whereas in the ABCSG-12 trial, all women received ovarian-suppression therapy to induce menopause; thus, the results from the two trials could be considered consistent.

The use of statins in 6% of the AZURE trial population did not modify the treatment effects observed with zoledronic acid. The hazard ratios for disease recurrence or death were 0.81 (95% confidence interval [CI], 0.43 to 1.51) in 198 patients who received statins and 1.01 (95% CI, 0.87 to 1.17) in 3161 patients who did not receive statins. Similarly, in the patients who had undergone menopause more than 5 years earlier and who appeared to benefit from treatment with zoledronic acid, statin use did not influence the treatment effect (hazard ratio for disease recurrence or death with statin therapy, 0.65; 95% CI, 0.30 to 1.39; and hazard ratio for disease recurrence or death without statin therapy, 0.80; 95% CI, 0.61 to 1.05).

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