Bisphosphonates are an important option for the prevention of fractures in postmenopausal women. However, the complex instructions for the administration of oral bisphosphonates are inconvenient or unsuitable for many patients, and adherence to long-term therapy is poor. The introduction of oral regimens for administration once weekly and, recently, once monthly has been associated with improved tolerability for patients, although adherence remains suboptimal. The demonstration that once-yearly intravenous infusions of zoledronic acid produced a sustained reduction in bone turnover and increased bone mineral density raised the prospect that even less frequent administration and the hope of better adherence might be realized. Now, the potential strengths of this treatment regimen are further supported by evidence that once-yearly infusions of zoledronic acid are associated with a reduction in fractures in postmenopausal women with osteoporosis, as reported by Black et al. in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) (NCT00049829) study in this issue of the Journal. The efficacy data from the HORIZON study are impressive. At 3 years, vertebral fractures were reduced by 70%, hip fractures by 41%, and nonvertebral fractures by 25%. Although a direct comparison with other treatments cannot be made in the absence of head-to-head studies of fracture outcome, the magnitude of effect appears to be at least similar to and possibly better than (in the case of vertebral fractures) that reported for other interventions. More important, the data indicate a broad spectrum of antifracture efficacy extending across nonvertebral fractures and including those at the hip. The study was adequately powered to demonstrate these reductions in fractures. Of the 7765 women who underwent randomization, 84% remained in active follow-up throughout the 3-year trial period. In particular, the mean age of women in this study (73 years) and the inclusion of women until the age of 89 years ensured that the number of hip fractures (88 in the placebo group vs. 52 in the zoledronic acid group) was sufficient to allow for a demonstration of efficacy at this key site.

No excess of deaths was seen in the treatment group. The increased frequency of symptoms reflecting an acute-phase reaction after infusion of zoledronic acid is to be expected (the reported events occurred mainly after the first infusion), and the absence of long-term adverse effects on renal function is reassuring. However, the significant increase in atrial fibrillation as a serious adverse event associated with zoledronic acid treatment was unexpected, particularly since the majority of these events occurred more than 30 days after infusion and therefore could not be attributed to early, transient hypocalcemia. The increased frequency of atrial fibrillation was not observed in a small electrocardiographic substudy, nor did it translate into an excess rate of death from cardiovascular causes. A letter in this issue of the Journal indicates a trend toward serious adverse events involving atrial fibrillation after alendronate treatment, an observation that also bears further study. Thus, it is a potential concern, and a causal relationship must be given serious consideration. For this reason, safety data from ongoing studies must be monitored closely.
clinical trials of zoledronic acid are awaited with interest.

Although the association of osteonecrosis of the jaw with bisphosphonate therapy has been reported mainly in patients with cancer who were receiving high total doses, the possible occurrence of this adverse event during therapy for osteoporosis has created sufficient anxiety to change clinical practice in some parts of the world. Because the association has been recognized only recently, its frequency has not been evaluated in prospective clinical trials. Thus, it is reassuring that despite adjudication and expert review of possible symptoms or signs of osteonecrosis of the jaw in the HORIZON study, only two potential cases were identified, and both subsequently resolved with appropriate therapy. Since one of the affected women was in the placebo group, these results provide no evidence for a specific association between osteonecrosis of the jaw and zoledronic acid in the doses used for treatment of osteoporosis in postmenopausal women. The findings also emphasize that the condition may develop in the absence of current bisphosphonate therapy. Of possible relevance to this issue, the degree of suppression of bone turnover that is induced by zoledronic acid, as assessed with the use of biochemical markers, was similar in the study by Black et al. to that reported with other bisphosphonates.

Of the currently available options for the treatment of osteoporosis, only alendronate, risedronate, and strontium ranelate have a spectrum of antifracture efficacy similar to that shown for zoledronic acid. Therefore, these drugs can be regarded as front-line options for the majority of postmenopausal women at high risk for fracture. In clinical practice, the choice of treatment will depend on a number of factors, including the preference of patients. Whereas the once-yearly regimen of zoledronic acid is likely to be attractive to some women, the need for intravenous infusion may deter others, particularly in regions where such administration would have to be provided in secondary care settings rather than in primary care offices. Intravenous zoledronic acid may be particularly appropriate for women who are admitted to the hospital with a fracture (especially a hip fracture), for whom the first infusion could be given during their hospital stay. In addition, among the growing population of very elderly women with osteoporosis, oral bisphosphonates are unsuitable for a substantial minority, and zoledronic acid may provide a potential alternative for these women. The only intravenous bisphosphonate approved for osteoporosis is ibandronate, which is administered every 3 months as a single intravenous (“push”) injection during a period of 15 to 30 seconds, but robust evidence for a reduction in nonvertebral fractures after the administration of ibandronate is lacking.

Despite the availability of effective treatments for osteoporosis, poor adherence to drug regimens reduces the benefit and presents a major challenge for health professionals. Intravenous administration ensures that treatment is correctly delivered and avoids the stringent administration instructions required for oral bisphosphonates. In the case of zoledronic acid, even a single infusion appears to ensure efficacy for at least 1 year and probably longer. The practicality and acceptability of annual intravenous therapy in large numbers of women remain to be tested. Nevertheless, increased treatment choices for patients are to be welcomed and may provide one means of improving adherence and treatment outcomes in osteoporosis.

Dr. Compston reports serving on advisory boards for Procter & Gamble, Servier, Nycomed, Shire, and Crescent Diagnostics; receiving speaking fees from Procter & Gamble, Nycomed, Servier, Shire, and Eli Lilly; serving on data and safety monitoring boards for Novartis and Amgen; receiving research grants from Procter & Gamble and Servier; and having served as an expert witness in medicolegal and patent disputes related to alendronate. No other potential conflict of interest relevant to this article was reported.

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Beyond Epicardial Reperfusion

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The pathogenesis of an acute myocardial infarction consists of the rupture of atherosclerotic plaque, followed by a sudden thrombotic coronary occlusion. Pioneering studies performed more than 40 years ago, even before there was full recognition of the underlying pathobiology, showed that nonselective intracoronary fibrinolysis can restore perfusion to the jeopardized vascular territory. Primary percutaneous coronary intervention (PCI) has now emerged as the optimal mode of reperfusion therapy, if performed by an experienced team within 90 minutes after the first medical contact. Primary PCI results in patency of the occluded artery in almost all patients and in normalization of epicardial perfusion, according to Thrombolysis in Myocardial Infarction (TIMI) grading, in more than 90% of patients.2

Despite the general success of primary PCI, approximately 15% of patients have inadequate myocardial perfusion in the absence of angiographic evidence of mechanical vessel obstruction. This “no-reflow” phenomenon may be due to microvascular damage after myocardial ischemia, to cell necrosis and regional inflammatory responses induced by reperfusion, or to both. In addition, microvascular obstruction may be caused by the embolization of atheromatous and thrombotic debris, either spontaneously or after mechanical dilation of the culprit lesion (Fig. 1). This inadequate myocardial perfusion is clinically relevant, since it is associated with larger myocardial infarcts, greater impairment of left ventricular function, and a worse clinical outcome than those in patients with adequate perfusion.3

These clinical observations have led to intensive research on the salvage of viable myocardium with the use of adjuvant pharmacologic therapy in the setting of primary PCI. The Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL) trial4 showed a favorable clinical outcome when platelet aggregation was inhibited with the use of a glycoprotein IIb/IIIa inhibitor, if administered before primary stent implantation in the coronary artery. In daily clinical practice, an antiplatelet and anticoagulation regimen consisting of aspirin, clopidogrel, and heparin serves as standard adjuvant pharmacotherapy in patients undergoing primary PCI, whereas the administration of a glycoprotein IIb/IIIa inhibitor is recommended in patients showing poor ST-segment resolution or evidence of a no-reflow phenomenon.

Mechanical thrombectomy and embolic protective devices are logical therapeutic approaches to treat or prevent microembolization. However, randomized trials have failed to show a beneficial effect of these devices on myocardial reperfusion, infarct size, or clinical outcome.5,6 The Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) (NCT00168792) trial7 tested the use of adjuvant fibrinolytic therapy with tenecteplase before primary PCI. This trial was stopped prematurely owing to a higher incidence of cardiac complications and stroke in the tenecteplase group than in the group that did not receive tenecteplase. Consequently, the optimal aggressive pharmacologic strategy to be used as an adjunct to primary PCI remains undefined.

In this context, the study by Sezer et al.8 in this issue of the Journal is of particular interest. The investigators evaluated the effect of intracoronary streptokinase immediately after successful PCI on myocardial perfusion in patients who also received a standard medical regimen including aspirin, heparin, clopidogrel, and a glycoprotein IIb/IIIa inhibitor. The local administration of streptokinase has the advantage over systemic fibrinolytic...