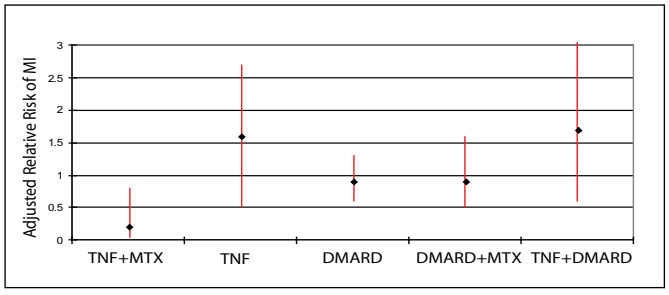
Cases of acute myocardial infarction (AMI) were risk-set matched with 4 controls for age, gender, and date of AMI. All analyses were adjusted for 38 confounding risk factors (including surrogate variables for smoking and dyslipidemias) as well as concomitant aspirin and NSAID treatment (prescription or over-the-counter use).

A total of 19,233 RA patients (mean age 54.7 years, 79.4% women) were identified. Of these, 13,383 patients took MTX, 14,958 took other DMARDs, and 4,943 took TNF inhibitors. Treatment groups included TNF inhibitors (monotherapy), TNF inhibitors plus MTX, TNF inhibitors plus non-MTX DMARDS, non-MTX DMARDs alone, and MTX plus non-TNF DMARDs.

During 74,006 person-years of follow-up, 441 cases of AMI were identified, of which 8% were fatal. Treatment with TNF inhibitors plus MTX significantly reduced the risk of AMI vs MTX monotherapy (multivariate-adjusted relative risk 0.20 (95% CI 0.05 – 0.88, p<0.03; Figure 1). No statistical difference was seen with TNF-inhibitor monotherapy (RR 1.17, 95% CI 0.50–2.75), TNF-inhibitor with other DMARDs (RR 1.78, 95% CI 0.60–5.27), other DMARD therapies without MTX (RR 0.88, 95% CI 0.60–1.31) or a combination of DMARDs and MTX (RR 0.93, 95% CI 0.54–1.62) vs MTX monotherapy. Systemic corticosteroid use was an independent risk factor which significantly increased the risk of AMI (adjusted RR 1.37, 95% CI 1.07–1.75, p<0.01).

Figure 1. Adjusted Relative Risk of AMI, Compared to MTX Monotherapy.



These results indicate that combination therapy using a TNF-inhibitor plus MTX is associated with a reduction in the risk of acute myocardial infarction by 80% vs MTX monotherapy in patients with RA. Such a dramatic effect enhances the therapeutic gains of TNF-inhibitor therapy in patients with RA and should be seriously considered, particularly in high-risk patients.

Non-Vertebral Fracture Reduction with High- vs Low-Dose Ibandronate

Results from the Oral IBandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) study showed a significant (p=0.0001) 62% reduction in the risk of vertebral fractures in women with postmenopausal osteoporosis treated with oral ibandronate, either as 2.5 mg daily or as 20 mg every other day for 12 doses every 3 months [Chesnut CH et al. *Bone Miner Res* 2004]. Although the study was not powered to evaluate the outcome in non-vertebral fractures, a significant (p=0.013) relative risk reduction for non-vertebral fractures of 69% was seen in a subgroup of high risk patients (mean femoral neck bone mineral density (BMD) T-score ≤3).

This meta-analysis was conducted to assess the efficacy of high vs low doses of ibandronate on non-vertebral factures. All randomized-controlled trials of ibandronate were reviewed and variable definitions of high vs low doses were explored. A time to event analysis was conducted comparing high annual cumulative exposure (ACE) with low ACE with 2-year data taken from two equivalent non-inferiority trials [Reginster JY et al. *Ann Rheum Dis* 2006; Emkey R et al. *Arthritis Rheum* 2005]. Hazard ratios, derived from a Cox model, were adjusted for clinical fracture, age, BMD, and study. ACE was based on an oral bioavailability of 0.6% and IV bioavailability of 100%.

A reduced non-vertebral fracture rate was seen when comparing combined high doses equivalent to an ACE of ≥10.8 mg with a low ACE of 5.5 mg (HR 0.620; relative risk reduction: 38%; 95% CI 0.40-0.97; p=0.04). Similar treatment effects were seen when high doses (ACE ≥10.8 mg) were compared with medium doses equivalent to an ACE of 5.5-7.2 mg. There was a dose-response effect with increasing ACE (7.2-12 mg) compared with ACE 5.5 mg. Adjustment for covariates in the analysis had a minimal effect.

A significant effect on non-vertebral fracture risk reduction was seen when combining trials using high ibandronate doses equivalent to an ACE of ≥10.8 mg versus a low ACE of 5.5 mg, and also with ACE ≥10.8 mg versus ACE ≤7.2 mg.

The treatment effect was dose-dependent. Higher doses of ibandronate significantly increase bone mineral density at the spine and hip, and reduce the risk of non-vertebral fractures more effectively than lower doses.