cussed with patients. These findings are consistent with a recent systematic review.[1]

This study does not address the applicability to women in perimenopause; the acceptability of raloxifene to women over a long period of time, particularly those with worse symptoms of estrogen deficiency; and the prevention of clinically important fractures and cardiovascular morbidity. Clinicians should not recommend raloxifene routinely until good quality information about these issues becomes available.[1]

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Medical Therapy for Stable Angina

Heidenrich PA, McDonald KM, Hastie T, et al. Meta-analysis of trials comparing β-blockers, calcium antagonists, and nitrates for stable angina. JAMA 1999; 281:1927-36.

Clinical question **Should we use β-blockers (BBs), calcium channel blockers (CCBs), or long-acting nitrates (LANs) as first-line therapy for patients with stable angina?**

Background The choice of preferred agent for stable angina remains controversial. BBs have been shown to reduce mortality following myocardial infarction and are recommended by some experts. However, others believe CCBs are equally efficacious and are better tolerated than BBs. Others recommend LANs. No agent has been proved superior for treating stable angina. The authors performed a meta-analysis to assess the relative efficacy and tolerability of these agents.

Population studied All patients in studies in this meta-analysis had stable angina. Many studies comparing BBs with CCBs excluded patients with recent myocardial infarction, heart failure, bradyarrhythmias and heart block, diabetes mellitus, and chronic obstructive pulmonary disease.

Study design and validity This meta-analysis was methodologically sound. The authors searched MEDLINE (1966-1997) and EMBASE (1974-1997) using explicit criteria and reviewed bibliographies from identified trials. Studies were eligible for inclusion if they were randomized controlled trials or crossover trials comparing agents from different classes and were written in English. The authors did not attempt to locate unpublished articles; however, publication bias against negative results is unlikely, since 75% of the studies showed no difference between agents. The authors reviewed the abstracts of 48% of the non-English articles: No data were found that contradicted this study's findings.

Data extraction was performed independently. Statistical analyses were appropriate. The lack of a systematic review of quality of the included studies is a minor concern with this study.

Outcomes measured The effectiveness of the different therapies was evaluated by measuring the number of angina episodes per week, the number of nitroglycerin tablets taken per week, total exercise time, and time to 1-mm ST segment depression during exercise. Tolerability was assessed using the combined rate of subject withdrawal because of adverse events, defined as death or cardiac or noncardiac symptoms. All-cause mortality was not assessed; most trials were too small or too short to address this important outcome.

Results Of the 90 studies included in the analysis, 72 compared BBs with CCBs. The mean duration of these studies was 8 weeks; only 2 were longer than 6 months. There were no significant differences reported between BBs and CCBs for cardiac death or myocardial infarction, nitroglycerin use per week, or time to 1-mm ST segment depression with exercise. Patients taking CCBs had slightly longer exercise times (effect size = 0.1; P = .05). Patients taking BBs had 0.31 fewer episodes of angina per week (P = .05) and were less likely to withdraw because of adverse effects (odds ratio = 0.72; 95% confidence interval, 0.6 - 0.86). The absolute difference in withdrawal rates was 2; that is, for every 100 patients treated with BBs, 2 fewer patients suffered an adverse event leading to study withdrawal than with patients taking CCBs.

Subgroup comparisons showed fewer episodes of angina among patients taking BBs than with patients taking nifedipine or short-acting CCBs. The odds of withdrawal because of adverse events were lower for BBs than with nifedipine, short-acting CCBs, and long-acting CCBs. In comparison with BBs, nifedipine was the most poorly tolerated CCB.

There were no differences noted between agents in the 12 studies comparing LANs with CCBs. In the 6 studies comparing BBs with LANs, there was a trend toward increased nitroglycerin use among patients taking LANs (2 tablets per week, P = .08), though there were significant differences in the 3 trials evaluating this outcome.

Recommendations for clinical practice **BBs are better tolerated than CCBs and are associated with fewer episodes of angina per week. They**

should be the first-line agents for treating stable angina. The authors note that these results may not be generalizable to patients with recent myocardial infarction, congestive heart failure, and diabetes mellitus, as subjects with those comorbidities were excluded from these trials. However, BBs have been shown to improve outcomes for patients in each of these groups[1-3] and should be the first-line agents for these patients as well. Nifedipine is poorly tolerated and should be avoided. LANs may be associated with an increase in as-needed nitroglycerin use and should be second-line agents.

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Low-Molecular-Weight Heparin for Deep Venous Thrombosis

Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. Ann Intern Med 1999; 130:800-9.

Clinical question **Is therapy with low-molecular-weight heparin (LMWH) as safe and effective as conventional unfractionated heparin (UFH) for the treatment of deep venous thrombosis (DVT)?**

Background Conventional treatment of acute DVT requires hospitalization and use of UFH. Treatment with LMWH is simpler and more convenient. This medication may be self-administered either once or twice daily and does not require close monitoring with laboratory tests or dosage adjustment. A key clinical issue is whether this form of therapy is as safe and effective as treatment with standard UFH. This study used the most recent data available to estimate the likelihood of clinically important patient-oriented outcomes.

Population studied The authors performed a meta-analysis of 11 studies with a total of 3674 patients with acute lower extremity DVT, with or without coexisting pulmonary embolism. The population included patients with distal DVT, previous venous thromboembolism, cancer, heart failure, prolonged bed rest, and recent surgery or trauma. All were followed up for at least 3 months.

Study design and validity The authors attempted to identify all studies published between 1985 and 1997 using the MEDLINE database. They also reviewed the reference lists of identified studies and contacted the investigators and pharmaceutical companies to locate unpublished studies. The authors used previously published study quality criteria,[1] including assessment of proper randomization, proper concealment of randomization, double-blinding, and the number of patients lost to follow-up. Included were only studies that enrolled patients with an acute lower extremity DVT, randomly assigned treatment groups, compared a fixed dose of LMWH with an adjusted dose of UFH, used objective methods to confirm DVT, and used objective methods to assess the clinical outcomes. One limitation of this study is that the authors pooled the results for different agents. The 2 agents available in the United States, enoxaparin (Lovenox) and dalteparin (Fragmin), were studied in 634 and 705 patients, respectively.

Outcomes measured Three patient-oriented outcomes were measured: major bleeding complications during the initial treatment period, recurrent thromboembolic events during 3 to 6 months, and mortality rates during 3 to 6 months after initiation of therapy. Data were also extracted for minor bleeding episodes, thrombocytopenia, the death rate from recurrent thromboembolism, and the death rate among participants with cancer.

Results Of 966 potentially relevant studies, only 11 met the inclusion criteria. The risk of a major bleeding episode favored LMWH (odds ratio [OR] = 0.57; 95% confidence interval [CI], 0.33 - 0.99), but the absolute risk reduction (ARR) was small and not statistically significant (ARR = 0.61%; 95% CI, 0.04% - 1.26%). Recurrent thromboembolic events were slightly less common in patients treated with LMWH, but again the difference was not statistically significant (OR = 0.85; 95% CI, 0.63 - 1.14). LMWH did significantly reduce the mortality rate over 3 to 6 months (OR = 0.71; 95% CI, 0.53 - 0.94; ARR = 1.65%; number needed to treat = 61). It has been observed that LMWH reduces mortality rates in patients with cancer, but this benefit alone could not explain the statistically significant reduction in mortality for all patients. The authors did not find statistically significant benefits of LMWH for minor bleeding episodes or for thrombocytopenia. A detailed sensitivity analysis generally confirmed the robustness of the results. More than 5 trials with negative results would have to be published in the future and included in a future meta-analysis to overcome the mortality advan-