Therapy for Stable Angina in Women

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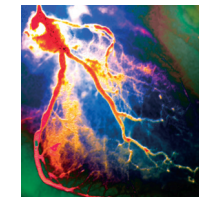

INTRODUCTION

Studies of conventional therapy for stable angina have focused primarily on men, with fewer women enrolled in prospective clinical trials. Despite this, cardiovascular disease (CVD) remains the leading killer in women, with death rates from CVD higher in women than in men.[1] Studies have shown that compared with men, women with stable typical angina exhibit more symptoms and functional impairment.[2,3] Stable angina is defined as retrosternal chest pain associated with exertion or stress and relieved by nitroglycerin or rest.

Most clinicians rely on an abnormal stress test result and atherosclerotic plaque (usually greater than 70% occlusion) in the coronary arteries to diagnose stable angina.[2] However, the data suggest that up to 30% of women with signs and symptoms of ischemia can be found to have nonobstructive disease on coronary angiography.[2] Further evaluation with invasive coronary reactivity testing reveals that many of these women have microvascular coronary disease (MCD), which is not associated with a benign outcome. Probably a dominant subset of cardiac syndrome X, MCD is characterized by obstructive coronary artery disease, recurrent chest pain, and evidence of ischemia, as detected by stress testing. The risks associated with MCD range from death secondary to cardiovascular collapse, nonfatal myocardial infarction (MI), nonfatal stroke, and congestive heart failure.[3] Mechanistic pathways for MCD include both endothelial and nonendothelial dysfunction.[4] A small percentage of women also have vasospastic (i.e., Prinz- metal's) angina, resulting from epicardial coronary spasm.

Understanding how the pathophysiology of stable angina differs in men and women helps clinicians identify appropriate treatment options. This article reviews pharmacological and nonpharmacological therapies for women with stable angina.

TREATMENT

Pharmacological Therapies

Aspirin

Multiple studies have demonstrated the beneficial effects of aspirin in both men and women with ischemic heart disease and stable angina. The Swedish Angina Pectoris Study (SAPAT) showed that patients receiving aspirin, as well as sotalol (e.g., Betapace, Berlex/Bayer; Sotalex, Bristol-Myers Squibb), experienced a 34% reduction in the risk of MI and an absolute reduction of 12 sudden deaths for every 1,000 patients treated.[2,5]

In a meta-analysis that compared chronic low-dose aspirin therapy with placebo in 17,000 patients, among 16 secondary prevention trials, there was no significant sex difference in the effect of aspirin on reducing major coronary events (relative risk [RR], 0.81 in men; 0.73 in women) or ischemic stroke (RR, 0.73 in men; 0.91 in women) ($P = 0.88$ for heterogeneity).[6] Although the results from this analysis were not stratified by the presence or absence of angina, they support the guideline recommendations that aspirin should be used for secondary prevention by all women.

In 2006, a sex-specific meta-analysis found that aspirin was not beneficial in the primary prevention of MI in women, although it did reduce the risk of a first stroke.[7] The U.S. Preventive Services Task Force did not recommend aspirin for the primary prevention of MI in women but did recommend aspirin for the primary prevention of stroke in women 55 years of age and older.[8]

Nitrates

Nitrates provide temporary, rapid relief from angina, resulting in a vasodilatory effect on the epicardial coronary arteries.[1] Nitrates also cause venodilation, thereby reducing preload and myocardial wall stress and oxygen demand.[9] Although no clinical trials have evaluated the use of nitrates in patients with MCD, an observational study of 99 patients with cardiac syndrome X showed that nitrates provided effective antianginal therapy in 40% to 50% of these patients.[10]

So far, the data do not definitively indicate whether one form of nitrate is better than another. The effects of nitrates on the duration and frequency of angina are not always predictable in patients with MCD; however, nitrates provide relief for many patients. A common side effect of nitrate use is tolerance; therefore, it is important to advise patients to observe nitrate-free intervals.[1]

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Beta-Adrenergic Receptor Blockers

Beta-adrenergic receptor blockers (beta blockers) provide multiple benefits in both men and women with stable angina. They lower the heart rate, decrease myocardial contractility, and ultimately decrease the oxygen requirements of the myocardium.[9] Beta blockers are particularly useful for reducing the number of daily ischemic episodes of angina that are precipitated by increased sympathetic activity.[1]

The Angina Prognosis Study in Stockholm (APSIS) investigated the use of beta blockers in men and women. The study reported similar event rates (cardiovascular-related death or nonfatal MI) for metoprolol (e.g., Lopressor, Novartis) and the calcium-channel blocker (CCB) verapamil (e.g., Covera-HS, Pfizer).[11] In an extension study of women with stable angina, the addition of beta blockers or verapamil to conventional therapy improved the prognosis in these patients without diabetes. The addition of beta blockers or verapamil resulted in a total mortality rate of 1.7% per year and a CVD mortality rate of 1.0% per year during the 9-year follow-up period.[11]

A meta-analysis comparing beta blockers, CCBs, and nitrates for stable angina found that beta blockers caused fewer adverse events compared with CCBs, whereas there was no difference between these drugs in terms of angina relief, as measured by the use of sublingual nitroglycerin.[12]

In a study by Kanza et al., the beta blocker atenolol (Tenormin, AstraZeneca) significantly decreased the rate of chest pain episodes per week compared with the CCB amlodipine (Norvasc, Pfizer) and the nitrate isosorbide mononitrate (e.g., Monoket, UCB) in women with MCD (15 ± 13; baseline, 24 ± 18; median, 15; $P < 0.05$).[13] Further, the newer generation of beta blockers with alpha-blocking properties, such as carvedilol (Coreg, GlaxoSmithKline), or those with antioxidant properties, such as nebivolol (Bystolic, Forest), may offer additional benefits for stable angina in women.[1] Carvedilol, with its additional vasodilatory properties, may be useful in women with MCD who have altered microvascular tone caused by an imbalance in the cardiac autonomic nervous system.[3]

One study indicated that 4 weeks of treatment with nebivolol had favorable effects on endothelial function in patients with cardiac syndrome X; both baseline and hyperemic brachial lumen diameters increased after therapy ($P < 0.001$ and $P = 0.002$, respectively).[14] The effect of nebivolol on endothelial function was assessed by a determination of inflammatory markers (i.e., Von Willebrand factor, C-reactive protein, and fibrinogen). A decrease in inflammatory markers was noted after 4 weeks of nebivolol use.[14]

In keeping with the American College of Cardiology (ACC) guidelines for the management of stable angina, both men and women with signs and symptoms of ischemia should receive first-line treatment with beta blockers.[15]

Angiotensin-Converting Enzyme (ACE) Inhibitors

The Women and Ischemic Syndrome Evaluation (WISE) study compared quinapril (Accupril, Pfizer) 80 mg daily with placebo in patients with MCD.[16] After 16 weeks, coronary flow reserve, determined by invasive coronary reactivity testing, improved more in women taking quinapril than in women taking placebo ($P < 0.019$). Women with the lowest baseline coronary flow reserve (less than 2.5) benefited the most from ACE inhibitor therapy. Patients also experienced fewer angina episodes with quinapril than with placebo ($P = 0.037$). Therefore, as stated in the ACC guidelines for the treatment of stable angina, ACE inhibitors are recommended for both men and women with ischemic heart disease and stable angina, particularly for patients with a reduced ejection fraction or with uncontrolled risk factors.[15]

Calcium-Channel Blockers

CCBs are prescribed for both men and women with stable angina. These drugs have a wide range of antianginal effects, including direct vasodilation, reduced afterload, increased coronary perfusion, and a lower heart rate.[9] In the meta-analysis by Heidenreich et al., similar rates of cardiac death and MI were noted in patients taking beta blockers compared with patients taking CCBs, for an odds ratio (OR) of 0.97 and a confidence interval (CI) of 0.67–1.38 ($P = 0.79$). However, significantly more patients taking CCBs discontinued taking the medication because of adverse effects ($P < 0.001$).[12]

CCBs are the preferred therapy in women with vasospastic angina because of the direct coronary vasodilatory effects of these drugs.[1] Although all CCBs are equally effective, nifedipine may provide the most rapid relief of anginal symptoms for patients with vasospastic angina.[17]

Statins

HMG–CoA reductase inhibitors (statins) are not typically used for antianginal therapy, but data from the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombosis in Myocardial Infarction (PROVE IT–TIMI 22) trial showed that high doses of statins further reduced cardiovascular endpoints over standard-dose therapy. The reduction was enhanced more in women, compared with men, with established CVD.[18] Women receiving intensive statin therapy had a 25% relative risk reduction compared with those receiving standard-dose therapy (hazard ratio [HR], 0.75; 95% CI, 0.57–0.99; $P = 0.04$) for the primary composite endpoint (death, MI, documented unstable angina requiring hospitalization, and revascularization within 30 days after randomization or stroke). By contrast, men showed a 14% relative risk reduction (HR, 0.86; 95% CI, 0.75–0.99; $P = 0.04$; P for interaction, 0.38).[18]

The updated Guidelines for the Prevention of Cardiovascular Disease in Women recommend low-density lipoprotein (LDL) levels of below 100 mg/dL and, preferably, below 70 mg/dL in high-risk women with established CVD.[19]

In a study by Treasure et al. that enrolled men and women, the use of lovastatin for at least 6 months improved the endothelium-mediated response in atherosclerotic coronary arteries, leading to diminished vasoconstriction and improved vasodilation.[20] The study showed that statins improved symptomatic coronary atherosclerosis in minimally obstructed vessels by normalizing the production of oxygen-derived free radicals. Oxidation has been shown to increase the rate of atherosclerosis.[20]

Ranolazine

Ranolazine (Ranexa, Gilead/CV Therapeutics) is a novel antianginal agent indicated for men and women with chronic stable angina. As an active piperazine derivative,[21] ranolazine

works by inhibiting the late sodium channels in the cell membrane.[22] Ranolazine has been shown to decrease the number of angina attacks, increase exercise duration, and increase the time to 1-mm ST-segment depression on treadmill testing in patients with severe chronic stable angina. It has no significant effect on heart rate or blood pressure.[23]

The Combination Assessment of Ranolazine in Stable Angina (CARISA) trial demonstrated that ranolazine decreased the need for sublingual nitroglycerin and reduced the number of anginal attacks equally in men and women; however, there was less overall improvement in exercise-induced chest pain in women.[23,24]

In a small double-blind, crossover trial—Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes (MERLIN TIMI-36)—women with MCD experienced a 29% reduction in recurrent ischemia compared with men during treatment with ranolazine. [24] Ranolazine therapy also led to improved Seattle Angina Questionnaire scores, physical functioning, stabilized angina symptoms, and overall quality of life in women with MCD.[24]

Therefore, ranolazine may be considered as an adjunct to first-line beta blockers, CCBs, or both, for the control of symptoms in women with chronic stable angina associated with obstructive coronary artery disease or MCD.[24]

Antiangina Drugs Currently Unavailable in the U.S.

Ivabradine

Ivabradine (Procoralan, Coralan, Servier; Ivabid, Abbott) inhibits the so-called "funny" channel (*If*), which is highly expressed in the sinoatrial node. Ivabradine lowers the heart rate and is approved in Europe for patients with chronic stable angina in normal sinus rhythm.

A European study compared the effects of ivabradine and the beta blocker atenolol on the time to ST depression during standard exercise stress testing in patients with stable angina.[25] The total exercise duration after 4 weeks of therapy improved by 64.2 ± 104.0 seconds with 5 mg of ivabradine and by 60.0 ± 114.4 seconds with 50 mg of atenolol ($P < 0.001$ for non-inferiority of ivabradine). This study, however, included only men; a study of ivabradine in women has not been performed. A prospective randomized trial of ivabradine in women is needed before a definitive conclusion can be drawn regarding the drug's efficacy in this population.

Perhexiline

Perxhexilline (Pexsig, Sigma) reduces fatty-acid metabolism through inhibition of carnitine palmitoyltransferase, thereby improving oxygenation. Perhexilline has vasodilatory properties, which translate into antianginal activity. Animal models have shown that the drug decreases heart rate, increases stroke volume, and reduces angina attacks.[26] Side effects, such as debilitating neuropathy, fatal hepatotoxicity, renal impairment, hypoglycemia, and dizziness, are rare and tend to occur with rapid oral loading of the drug.[26]

Perhexiline is used in Australia and New Zealand, usually as a last resort (because of its toxicity) when other therapies have been tried. Perhexiline has not been studied extensively in women; therefore, a prospective trial is warranted to assess its efficacy in women with stable angina.

Bepridil

Bepridil (Vascor, Johnson & Johnson) was first approved by the FDA in 1990. It is a CCB, but it is often placed in a category of its own. Bepridil acts as a direct negative chronotrope, ionotrope, and vasodilator and is thus able to provide angina relief. Another difference from commonly used CCBs is that bepridil inhibits receptor-operated, voltage-gated calcium channels as well as potassium currents and intracellular calcium/ calmodulin complexes. This action results in decreased myocardial oxygen consumption, coronary vasodilation, and increased coronary blood flow. Bepridil helps to decrease the frequency of angina attacks, as measured by the use of nitrates. However, concerns regarding prolongation of the corrected QT interval and torsade de pointes has limited its use in North America. Bepridil is sold in Europe, but it is no longer sold in the U.S.[27]

Nicorandil

Nicorandil (e.g., Ikorel, Zydus) has two mechanisms of action: venous dilation and arterial dilation. As a result of this dual mode of action, nicorandil improves myocardial oxygen demand, increases coronary blood supply, and decreases afterload. Unlike nitrates, the drug has not been associated with tolerance.[28] It is also classified as a vasodilator.

Nicorandil relieves angina symptoms, providing an increase in exercise capacity (12%–36%), time to onset of angina (20%–78%), and time to ST-segment changes (25%–94%).[28] Although nicorandil is used in patients with stable angina, no studies have evaluated this drug in women. Nicorandil is available in Europe. Common side effects are headache, dizziness, palpitations, nausea, and vomiting.[28]

Nonpharmacological Therapies

Lifestyle Modifications

Although most lifestyle changes provide equal benefits in men and women with ischemic heart disease, observational data suggest some sex differences for certain non-drug therapies. The INTERHEART study, a global case–control trial conducted in 52 countries, demonstrated that physical activity and moderate alcohol use were more protective against a future acute MI for women than for men.[29] By contrast, no difference between men and women was observed for current smoking status, abdominal obesity, high-risk diets (i.e., consisting of saturated fats, processed foods, low fiber intake, and high sugar intake and lacking fruits and vegetables), or psychosocial stress in terms of an association with future cardiac events.[29]

Data from the Nurses' Health Study (NHS) showed that women who adhered to a healthy diet, were nonsmokers, performed moderate to vigorous exercise for more than 30 minutes per day, had a body mass index (BMI) of less than 25, and were moderate consumers of alcohol had a relative risk of 0.17 (95% CI, 0.07–0.41) for future CVD events compared with women without these characteristsics.[30]

These lifestyle differences suggest that maintaining a healthy diet, participating in regular exercise, and limiting the amount of alcohol intake greatly benefits women with respect to cardiovascular health.

Menopausal Hormone Therapy

While not specifically meant to treat angina, menopausal

hormone therapy (HT) consistently provided reductions of up to 50% in CVD events in animal models and observational studies.[31] In 1998, however, the Heart and Estrogen/Progestin Replacement Study (HERS), a randomized, controlled secondary prevention trial, found no CVD benefit with the use of HT in menopausal women with established coronary arterial disease (RR, 0.99; 95% CI 0.8–1.22).[32] Further, in a *post hoc* analysis of the HERS trial, women receiving HT showed a significant (P = 0.009) increase in CVD events during the first year of treatment compared with women receiving placebo.[31]

Given these results, the North American Menopause Society,[33] the American Heart Association,[34] the Endocrine Society,[35] and the American College of Obstetricians and Gynecologists[36] have stated that HT is not recommended for coronary heart disease prevention or protection in menopausal women.

Cognitive Behavioral Therapy

Stress can provoke anginal attacks in both women and men. Cognitive behavioral therapy may be used as an adjunctive method of stress reduction. In one study, an 8-week program of cognitive behavioral therapy, consisting of autogenic training (stress reduction by mental exercises to produce relaxation), decreased the frequency and severity of symptoms in women with ischemia and unobstructed coronary arteries.[37]

Neurostimulation

Neurostimulation is used in patients with angina when other therapies have failed. Patients with refractory angina as a result of abnormal cardiac nociception may benefit from this therapy. Neurostimulation has been shown to increase coronary blood flow, to reduce the duration and frequency of anginal attacks, and to reverse ST-segment depression during stress testing.[1]

Enhanced External Counterpulsation

Patients with MCD and persistent angina have benefited from enhanced external counterpulsation (ECP) therapy. This noninvasive, outpatient modality has been shown to reduce angina and to improve regional ischemia.[1] In a study published in 2009, 26 of 30 patients (87%) with MCD benefited from this technique for almost 12 months.[38] Patients undergo 35 hours of therapy for 1 to 2 hours per day, 5 days per week, for 7 weeks.[39] The procedure may encourage blood vessels to open small channels (collateral vessels) that become extra branches. These channels may eventually become natural bypass vessels, thereby contributing to the relief of angina symptoms.

CONCLUSION

Women with stable angina often have normal coronary arteries on coronary angiography, but further testing may indicate that they have microvascular coronary disease (MCD). Current recommendations for women with stable angina include a combination therapeutic approach that includes aspirin, nitrates, beta blockers, statins, ACE inhibitors, and/or CCBs for long-term symptom control and cardiovascular risk reduction. Ranolazine appears to benefit women with both obstructive coronary artery disease and MCD and may be considered as add-on therapy.

Other potentially useful drugs (ivabradine, perhexiline, bepridil, nicorandil) are not available in the U.S. Lifestyle modifications and bio-behavioral strategies may also be used, but hormonal therapy is not indicated. Further studies are needed to improve our understanding of the effects of pharmacological and nonpharmacological therapies in women with stable angina.

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