Evidence-Based Clinical Vignettes
from the Care Management Institute:

Coronary Artery Disease

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Introduction

Coronary artery disease (CAD) is the leading cause of death and of premature, permanent disability in Americans 65 years and older.[1] According to the March 2002 Kaiser Permanente Care Management Institute (CMI) Cardiovascular Outcomes Report, more than 150,000 Kaiser Permanente (KP) members, representing 2.8% of all KP members 18 years and older, have CAD.[2] Of these patients, more than half have had previous myocardial infarction or have had coronary artery procedures such as bypass graft surgery, angioplasty or stenting.[2] In the year 2000 alone, nearly one in ten KP patients with CAD who were 45 years and older had percutaneous coronary intervention (PCI), or coronary artery bypass grafting.[2] The report also showed that nearly one in four patients who had a myocardial infarction (MI) experienced a recurrent MI or other major coronary event during the next two years.[2] Great opportunity exists to reduce the high rate of CAD-related morbidity and mortality, and a rich body of evidence supports various interventions that can significantly reduce adverse outcomes for our patients with CAD.

Beginning in mid-2001, CMI sponsored development of "Evidence–Based Guidelines for the Secondary Prevention of Coronary Artery Disease" (CAD Guidelines),[3] which was published in July 2002. Members of the guideline committee are listed in Table 1. The following clinical vignette highlights some of the key clinical guidelines.

Case Example

Mary was a 58-year-old woman who had been in good health generally. She did not exercise regularly and was about 20 pounds (9 kg) over her ideal weight, but her diet was relatively low in fat, she did not smoke, and she had no history of diabetes. She had been taking estrogen and progesterone hormone replacement therapy (HRT) for six years. Her recent blood lipid panel results were as follows: total cholesterol, 240 mg/dL (6.20 mmol/L); high-density lipoprotein cholesterol (HDL-C), 40 mg/dL (1.03 mmol/L); and low-density lipoprotein cholesterol (LDL-C), 150 mg/dL (3.88 mmol/L). She was taking hydrochlorothiazide (HCTZ) to treat hypertension, and her mother had experienced an MI at 60 years of age. Mary was seen at the emergency department for a prolonged episode of left shoulder and upper back pain which had begun after dinner that evening. The emergency department physician knew that women may have atypical symptoms during an acute coronary syndrome; Mary's heart was therefore evaluated as a possible source of her pain. Her electrocardiogram showed changes which indicated an acute, inferior wall MI. A subsequent angiogram showed a moderately narrowed right coronary arterial lumen, which was successfully treated with angioplasty and stent placement.

Table 1. Coronary Artery Disease Guidelines Workgroup, KP Care Management Institute

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Because she now had a diagnosis of CAD, Mary was a candidate for interventions that are effective for secondary prevention of CAD.

In the Summer 2002 issue of *The Permanente Journal,*[4] Jill Bowman and Dr Jim Dudl provided an excellent overview of evidence-based interventions that significantly reduce cardiovascular risk in patients who have diabetes mellitus. Although Mary did not have diabetes, most of those interventions are equally applicable to her. We review some of those interventions and explore some issues that are particularly germane to patients with CAD.

Two meta-analyses showed the protective effect of long-term beta blockade after MI.

Antiplatelet Therapy

Mary had a stent placed in her right coronary artery. The CAD Guidelines state that clopidogrel and aspirin should be taken daily for one month on the basis of the findings of Leon et al.[5] If a rash develops from clopidogrel, ticlopidine should be substituted. After one month, Mary should continue indefinitely to take daily aspirin alone. Recent data (reported after the CAD Guidelines were published) suggest that Mary may benefit from continuing to take clopidogrel and aspirin for at least one year. The CREDO trial[6] demonstrated that patients who had PCI and who continued to take clopidogrel for one year significantly reduced their risk of death, MI, or stroke compared with patients who continued to take clopidogrel for just one month after interventions (absolute risk reduction [ARR], 3%; number needed to treat [NNT] to prevent an event in one year, 33).

What is the preferred aspirin dosage? The recent Antithrombotic Trialists' Collaboration meta-analysis[7] indicates that dosages ranging from 75 mg to 325 mg daily are effective and that lower dosages (75 to 150 mg daily) are as effective as higher dosages (the lowest commercially available dose in the US is 81 mg). The use of daily aspirin after acute MI reduces the relative risk of a serious vascular event (MI, stroke, or death from a vascular event) within the first month by 30% (NNT to prevent one event in the first month, 26). Long-term aspirin therapy for patients who have had an MI reduces relative risk of a serious vascular event by 25% (NNT to prevent an event in two years, 28).

What if Mary is intolerant of aspirin or has an aspirin allergy? If Mary is unable to take aspirin, the CAD Guidelines recommend substituting 75 mg of clopidogrel daily. Clopidogrel is not otherwise favored over aspirin. Although clopidogrel is as effective as daily aspirin,[7] the CAD Guidelines committee believed that the risk of adverse effects (including rash, diarrhea, and a slight risk of thrombotic thrombocytopenic purpura) as well as the higher cost (compared with aspirin) should relegate clopidogrel to second-line therapy.

Table 2. Beta-blockers with and without intrinsic sympathomimetic activity (ISA)

No, or mild ISA	With ISA
acebutolol	alprenolol
atenolol	oxprenolol
betaxolol	pindolol
bisoprolol	practolol
carvedilol	xamoterol
labetalol	
metoprolol	
nadolol	
propranolol	
sotalol	
timolol	

Beta-Blockers

Mary should take a beta-adrenergic blocking agent (beta-blocker). Two meta-analyses[8,9] showed the protective effect of long-term beta blockade after MI. Although studies vary regarding duration of beta-blocker therapy, long-term use (up to 48 months in some studies) has reduced total incidence of mortality or reinfarction by approximately 25% (NNT to prevent one death per year, 84; NNT to prevent one reinfarction per year, 107). The CAD Guidelines recommend initiating beta-blocker therapy within hours of acute MI because the studies[9] that showed long-term benefit initiated beta-blocker therapy in the immediate postinfarction period.

What beta-blocker should Mary take? Beta-blockers without intrinsic sympathomimetic activity (ISA) (such as atenolol, metoprolol, or bisoprolol) should be used, because evidence suggests[8] that beta-blockers with ISA do not significantly reduce mortality after MI. Table 2 lists beta-blockers with and without ISA.

What if Mary has a comorbid condition, such as asthma, congestive heart failure, or diabetes? In their Cochrane review,[10] Salpeter et al found minimal decrease in forced expiratory volume in one second after a single dose of a cardioselective, non-ISA beta-blocker in patients with mild to moderate asthma. This decrease attenuated during a few weeks of continued therapy; the authors therefore concluded that beta-blockers could safely be prescribed to patients with controlled mild to moderate asthma. Because it is not cardioselective and was not examined in the meta-analysis, propranolol should not be prescribed for asthmatic patients. Beta-blockers should not be prescribed for patients with severe or poorly controlled asthma.

The CMI Heart Failure Guidelines group recently reviewed use of beta-blockers in patients with heart failure.[11] The CMI Guide to Heart Failure Management was published in the Winter 2003 issue of *The Permanente Journal* along with clinical vignettes by Dr Anthony Steimle.[12] Patients with CAD and heart failure due to left ventricular systolic dysfunction should receive a beta-blocker (metoprolol, bisoprolol, or carvedilol)

unless otherwise contraindicated, because these agents reduced risk of mortality (NNT, 23 per year) or hospitalization (NNT, 25 per year).[11]

Beta-blockers should be considered for secondary prevention of cardiovascular disease in patients with diabetes. Evidence suggests that beta-blockers may significantly reduce cardiac mortality (NNT, 29 in three years) in diabetic patients.[13]

If, in the future, Mary needs a major surgical procedure, should she continue to take beta-blockers? Yes. Even if Mary stopped taking beta-blockers at some point after her first coronary event, she should take them during the perioperative period. Mangano et al[14] showed that administration of atenolol perioperatively (during the hospital stay or for up to seven days) significantly reduced risk of subsequent vascular events in a broad population of patients with, or at risk for, CAD who had inpatient procedures that required general anesthesia. Vascular-event-free survival at one year was significantly greater in the group receiving atenolol (92%) compared with the untreated group (78%) (NNT, 7). Table 3 lists indications for perioperative beta-blocker therapy.

Lipid Management

The CAD Guidelines did not address the topic of lipid management. KP Southern California's dyslipidemia guidelines are completed and published in their guidelines handbook, also available on their Web site, linked to from the Permanente Knowledge Connection (PKC) Web site.[15] The guidelines recommend that all persons with CAD receive statin therapy, regardless of their baseline LDL-C and that patients with a ten-year risk of a cardiovascular event ≥ 25% be treated to a target LDL-C level of less than 100 mg/dL (2.59 mmol/L).[15]

The recently published Heart Protection Study (HPS)[16] makes a strong case for prescribing statins for all patients with CAD, including patients with a relatively low baseline LDL-C level. In the trial, 33% of treated patients had a baseline LDL-C level of less than 116 mg/dL (3.0 mmol/L) and were treated to an average LDL-C level of 69 mg/dL (1.8 mmol/L). This group had a significantly reduced risk of subsequent vascular events compared with the placebo group; the magnitude of risk reduction was similar to that of patients who began the study with a higher baseline LDL-C value, and a minimum baseline LDL-C level (below which no significant benefit existed) was not found.[16] The trial demonstrated overall 24% reduction in occurrence of a major vascular event for five years in patients treated with simvastatin compared with placebo[16] (NNT, 18). After adjusting for patient compliance in the treatment group and for other statin use in the placebo group, the NNT for patients with prior MI was about ten, regardless of baseline lipid level.

Mary should receive statin therapy, preferably lovastatin, at a dosage of 40 mg per day. A lipid panel should be repeated with alanine aminotransferase (ALT) levels checked in about two months, and the dosage of lovastatin should be increased to 80 mg per day if the LDL-C level remains higher than 100 mg/dL (2.59 mmol/L). If the LDL-C level remains higher than 100 mg/dL after two more months, a prescription of simvastatin at 80 mg per day should be considered.

Table 3. Indications for perioperative beta-blocker therapy in patients receiving inpatient procedures that require general anesthesia[13]

• Patients taking long-term beta-blocker therapy
• Patients with a diagnosis of CAD or peripheral vascular disease (PVD)
• Patients who have two or more of the following CAD risk factors: Age >65 years Hypertension (treated or untreated) Diabetes mellitus Hypercholesterolemia (total cholesterol >240 mg/dL [6.20 mmol/L], or any patient being treated for hypercholesterolemia) Current smoker or quit smoking within last six months

Angiotensin-Converting Enzyme (ACE) Inhibitors

The committees that developed the CMI Guidelines for CAD, diabetes, and heart failure have reviewed use of ACE inhibitors in patients with different levels of risk for a cardiovascular event. In patients who have CAD with preserved left ventricular function (such as our patient, Mary), ACE inhibitors should be prescribed long term, unless they are contraindicated.

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The landmark HOPE trial[17] showed that in patients 55 years and older who have or are at high risk for having CAD but who have normal left ventricular dysfunction or heart failure, the ACE inhibitor ramipril reduced the risk of MI, stroke, or cardiovascular death by 22% (absolute risk reduction (ARR), 3.7%; NNT to prevent an event for 4.5 years, 27). Patients who have acute MI benefit from receiving ACE inhibitors promptly. Ambrosioni[18] showed that administering zofenopril (a short-acting ACE inhibitor similar to captopril) within 24 hours of acute MI and continuing zofenopril therapy for six weeks significantly reduced first-year post-MI mortality rate (ARR, 4.2%; NNT, 24). Additionally, van den Heuvel[19] showed that administering captopril (25 mg, 3 times daily) within 24 to 48 hours after acute MI and

continuing captopril therapy for one year significantly reduced subsequent ischemia-related events (PCI, coronary artery bypass grafting, MI, angina, and death) within the first year (ARR, 15.7; NNT, 6.4).

Mary should begin taking an ACE inhibitor (eg, lisinopril with a target dosage of 20 mg per day) within 24 to 48 hours. An ACE inhibitor would also be recommended if Mary later developed left ventricular systolic dysfunction. The CMI Heart Failure Management Guidelines[11] recommend a target maximum daily dosage of lisinopril of 40 mg for patients with left ventricular systolic dysfunction.

What if Mary has renal dysfunction? At what serum creatinine level should ACE inhibitors be avoided? The recommendation of the Heart Failure Guidelines group is to use ACE inhibitors for patients who have a creatinine level of 3.0 mg/dL or less; the CAD Guidelines group did not address this issue. ACE inhibitor use in patients with creatinine levels higher than 3.0 mg/dL should be considered on a case-by-case basis.

What if Mary doesn't tolerate ACE inhibitors? Should an angiotensin receptor blocker (ARB) be used? Cough develops in about 10% of patients who take ACE inhibitors. Many such patients are unable to continue taking ACE inhibitors because of this adverse effect.[17] The CAD Guidelines group did not find sufficient evidence to support the use of an ARB in patients who have CAD with normal left ventricular function who cannot take ACE inhibitors. For patients who have left ventricular systolic dysfunction in addition to a history of MI, the Heart Failure Guidelines state that, on the basis of evidence, an ARB appears to be as effective as ACE inhibitors for reducing morbidity and mortality.[11] If Mary has diabetes, hypertension, and microalbuminuria, the consensus of the Diabetes Guidelines group is that an ARB should be used if she were unable to take an ACE inhibitor.[13]

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Calcium Channel Blockers

Calcium channel blockers have not shown reduced mortality for patients who have had an MI or for patients with stable or unstable angina and thus are not recommended as first-line therapy or monotherapy. If Mary could not take beta-blockers (eg, if she had severe asthma) data[20,21] suggest that a nondihydropyridine calcium channel blocker (verapamil or diltiazem) may be more effective than placebo in reducing incidence of nonfatal MI (but not mortality) in patients with CAD. However, in patients who have left ventricular systolic dysfunction, nondihydropyridine calcium channel blockers should not be used, because the risk of death or a cardiac event increases.[22] Immediate-release formulation of nifedipine should not be used in any patient with CAD, because the risk of cardiovascular mortality increases.[22] For patients who have CAD and hypertension, the consensus of the Guidelines group was that use of sustained-release formulations of nifedipine may be considered but only if use of an ACE inhibitor, beta-blocker, and diuretic, in any combination, fails to control blood pressure.

Oral Anticoagulant Therapy

Mary had an uncomplicated MI and is tolerating daily aspirin well. The CAD Guidelines recommend, on the basis of a meta-analysis by Anand and Yusuf,[23] that Mary continue to take aspirin rather than change to oral anticoagulant therapy. In some situations, however, oral anticoagulant therapy (warfarin) is appropriate instead of aspirin.

Atrial fibrillation: Warfarin should be used indefinitely at a target INR (international normalized ratio) between 2.0 and 3.0. Evidence supports use of warfarin to prevent stroke in patients with CAD: warfarin is significantly more effective than aspirin for reducing risk of stroke[24] (NNT per year to prevent stroke using warfarin compared with aspirin, 77).

Left ventricular thrombus or anterior infarction: The CAD Guidelines group found insufficient *randomized-trial* evidence to recommend use of warfarin to prevent stroke in post-MI patients who have left ventricular thrombus or anterior myocardial infarction. However, because a number of small *observational* studies suggest increased risk of embolic stroke in such patients,[25] consensus of the group was that warfarin should be prescribed for post-MI patients who have left ventricular thrombus and that after consultation with a cardiologist, use of warfarin should be considered in patients who have a large anterior MI.

Potential benefit of warfarin must be balanced against increased risk of bleeding. In the Anand and Yusuf meta-analysis,[23] risk of major bleeding in patients taking oral anticoagulants was six to eight times that of patients taking placebo (absolute risk increase [ARI], 4%) and two to three times that of patients taking aspirin (ARI, 1.5%). In patients when considered necessary, low-dose aspirin therapy (80-100 mg per day) combined with warfarin therapy may not increase risk of bleeding compared with warfarin therapy alone.[26,27] However, a cardiologist should be consulted before

using combined aspirin and warfarin therapy, because the CAD Guidelines group did not find evidence or formulate guidelines for combination therapy.

Hormone Replacement Therapy

Mary completed menopause about six years earlier. She had been taking estrogen and progesterone HRT, partly for symptoms of menopause but primarily because at the time, HRT was believed to decrease risk of CAD. The CAD Guidelines group found good evidence that HRT does not reduce the rate of coronary heart disease (CHD) and may increase the risk slightly, especially in the first year of treatment. The HERS[28] and HERS II[29] trials studied over 2000 postmenopausal women who had CAD and compared placebo with treatment using combined conjugated equine estrogen and medroxyprogesterone during four years (continuing an additional 2.7 years in HERS II). The treatment group experienced more vascular events than did the placebo group in the first year but fewer events than the placebo group in the fourth and fifth years.[28] Long-term use of HRT did not reduce overall risk of fatal or nonfatal coronary disease events.[29] In additional, the Women's Health Initiative (WHI) study of more than 16,000 women,[30] although not specifically studying women with CAD, found that the group taking HRT experienced, for each 10,000 person-years, seven CHD events and eight strokes more than the group taking placebo.

Mary should be advised to stop taking HRT, because her primary reason for continuing this treatment was to prevent cardiovascular events. The CAD Guidelines group could find no evidence to support tapering the dose compared with stopping immediately. If Mary had never taken HRT and was considering doing so for symptoms of menopause, she should be counseled about the small increase in absolute risk for CHD events and stroke, especially during the first year or two of treatment.

Antioxidant Supplements

During a follow-up visit with her primary clinician, Mary noted that a friend of hers had told her to take supplements of Vitamins E, C, and beta-carotene to reduce her risk of another heart attack. Is this advisable? The CAD Guidelines group made the following evidence-based recommendations:

Vitamin E: Vitamin E is not recommended because it does not reduce incidence of major cardiovascular events in CAD patients. The three largest randomized controlled trials to date,[17,31,32] which include over 41,000 patients, found no significant reduction in fatal or nonfatal cardiovascular events.

Beta-carotene: For patients with CAD, beta-carotene supplementation should not be recommended, because it has not been found beneficial and may increase risk of fatal CHD. Beta-carotene was part of the antioxidant treatment arm in the Heart Protection Study,[31] which showed no benefit for reducing cardiovascular events. In addition, a study by Rapola et al[33] showed that use of beta-carotene supplements by smokers who had previous MI significantly increased their risk of death from coronary disease (relative risk, 1.75) compared with risk in similar patients who took placebo.

Vitamin C: The CAD Guidelines group did not find any relevant randomized controlled trial that studied use of vitamin C in patients with CAD.

On the basis of CAD Guidelines, Mary was advised not to take antioxidant vitamins for the sole purpose of reducing her risk of a cardiovascular event.

Table 4. Consensus-based risk factor reduction and lifestyle modification recommendations for patients with coronary artery disease (CAD)

• Screening for depression should be strongly considered in first three months after acute MI.
• Clinicians should provide tools for self-management of CAD (available at http://pkc.kp.org).
• Patients with CAD should be given instructions for daily exercise.
• CAD patients should be encouraged to increase intake of omega-3 polyunsaturated fatty acids (1 g daily), either by taking supplements or eating fatty fish.
• Lifestyle modification and self-management skills should be reassessed annually.

Risk Factor Reduction and Lifestyle Modification

The CAD Guidelines group reviewed a number of studies[32,34-40] about cardiovascular disease risk factor reduction and lifestyle modification. Although evidence supports lifestyle modification such as smoking cessation, diet, weight reduction, prescribed exercise, and psychosocial counseling (in addition to lipid and blood pressure management), trials that evaluate specific exercise or weight reduction programs or diets vary in design. This variability makes development of specific, *evidence-based* recommendations difficult. Specific *consensus-based* risk factor reduction and lifestyle modification recommendations by the CAD Guidelines group are presented in Table 4.

According to a growing body of evidence, use of omega-3 fatty acids (n-3 polyunsaturated fatty acids) lowers the risk of recurrent vascular events in patients with CAD. The Lyon Diet Heart Study[41] evaluated long-

Table 5. Interventions for secondary prevention of coronary artery disease

Lifestyle modification: • Smoking cessation • Exercise • Weight management
Antiplatelet therapy: • Aspirin • Clopidogrel for 1 to 12 months after percutaneous intervention
Angiotensin-converting enzyme (ACE) inhibitors
Beta-blockers without intrinsic sympathomimetic activity: • Use for at least 48 months after acute MI • Use perioperatively in patients with, or at risk for, cardiovascular disease
Lipid management: • Use statins for all patients with CAD regardless of baseline lipid levels • Target LDL-C <100 mg/dL (<2.59 mmol/L)
Oral anticoagulant therapy for patients with atrial fibrillation
Diet containing at least 1 gm per day of omega-3 fatty acids

term outcomes of post-MI patients who ate a "prudent" Western diet compared with patients who ate the Mediterranean diet (more fruits, breads, vegetables, fish, and low-saturated-fat oils, a combination resulting in increased intake of plant-based omega-3 fatty acids). Using a Mediterranean diet, the NNT (to prevent a subsequent MI or death) for four years was nine.

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Bucher et al, in their meta-analysis of randomized controlled trials of increased intake of omega-3 fatty acids in patients with CAD,[42] found decreased mortality from MI (NNT, 96 for 20 months) and decreased overall mortality (NNT, 73 for 20 months) for patients with omega-3 fatty-acid-enriched diets. Clinical trials[30,32] have used various methods to enrich diets with omega-3 fatty acids, ranging from plant-based or fish-oil supplements to increased intake of fatty fish; no clearly optimal form of dietary enrichment could be found.

The CAD Guidelines group would reasonably recommend to Mary that she increase her intake of omega-3 fatty acids to about 1 gram daily, either by eating fatty fish (2-3 oz of salmon contains about 1 gram of omega-3 fatty acids), by taking fish oil capsules or by following the Mediterranean diet.

Summary

Mary has recovered well from her acute coronary event. Because her diagnosis was made quickly, she received appropriate intervention rapidly, consequently preventing future clinically significant myocardial damage. Many evidence-based interventions are available to Mary that will greatly reduce her risk of another cardiac event (Table 5). For example, Mary's medication regimen now optimally includes aspirin, clopidogrel (for at least the next month to one year), a beta-blocker, an ACE inhibitor, and a statin. She will need to stop HRT, even though she may experience symptoms associated with withdrawal of estrogen. She probably needs to consider and to make various lifestyle changes, many of which will require ongoing support from her health care providers, supplemented by self-management tools. A list of available self-management resources will be available on the Permanente Knowledge Connection Web site (http://pkc.kp.org). In the long term on the basis of interventions that we know are effective, Mary's chance for a good outcome is excellent. ❖

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To Choose One's Own Way

We who lived in concentration camps can remember the men who walked through the huts comforting others, giving away their last piece of bread. They may have been few in number, but they offer sufficient proof that everything can be taken from a man but one thing: the last of the human freedoms – to choose one's attitude in any given set of circumstances, to choose one's own way.

— Viktor Frankl, 1905-1997, author, neurologist and psychiatrist, Holocaust survivor