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Medical Management of the Post-MI Patient

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LEARNING OBJECTIVES

1. Given a specific patient, identify the risk factors associated with coronary artery disease.
2. Outline secondary prevention goals in accordance with the American College of Cardiology/American Heart Association Guidelines for patients who have experienced a myocardial infarction.
3. Describe the potential benefits of using drugs that inhibit the renin-angiotensin- aldosterone system.
4. Devise a specific therapeutic strategy for a patient who has experienced a myocardial infarction based upon his or her individual needs.

ABSTRACT: The prevalence of coronary disease in the United States U.S. continues to increase as the population ages. There are approximately 7.8 million patients in the U.S. who have suffered an acute myocardial infarction (AMI), with almost one-half million new infarcts occurring each year. The 2004 update of the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Patients with ST segment Elevation Myocardial Infarction (STEMI) delineates treatment for the acute phase of an MI—AMI—and also addresses the post-discharge care of the patient. Recommendations are weighted according to the body of evidence supporting their use. Aggressive management of risk factors such as smoking, hypertension, hyperlipidemia, diabetes, and obesity are now emphasized. Drug therapy, including aspirin, β-blockers, and statins have been recognized as being able to reduce mortality. Data from several trials evaluating the role of inhibition of the renin-angiotensin-aldosterone system (RAAS) are presented. Pharmacists can play a critical role in the treatment and prevention of AMI. Identification of patients at high risk for cardiovascular events will allow the pharmacist to intervene and provide information to the patient regarding the importance of adherence to the prescribed medical regimen and healthy lifestyle changes. The pharmacist should also monitor the patient for potential adverse reactions, as well as achievement of the goals outlined in the ACC/AHA Guidelines.

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Introduction

It is estimated that greater than 70 million people in the U.S. have 1 or more types of cardiovascular disease (CVD), with a large proportion of these patients being 65 years of age or older. The AHA 2005 Update of Heart Disease and Stroke Statistics states that the prevalence of coronary artery disease (CAD) in patients in the U.S. is greater than 13 million, with over 7 million Americans having had an AMI, almost 5 million having had congestive heart failure (CHF), and 5.4 million having had a history of stroke.[1] In addition, the AHA has stated that 1 in 4 males and females have some form of CVD, with women having comparable rates of first major cardiovascular events 10 years later in life than men. Based on these numbers, it is not surprising that according to the AHA, heart disease is currently the number one cause of death, disability, and heath care expenditures in the U.S. CVD has held the title of the number 1 killer of Americans every year since 1918. In 2002, CVD was the cause of 38% of all deaths, which accounts for 1 of every 2.6 deaths, or approximately 1.7 million deaths yearly. Percentage breakdown of deaths from CVD includes the following: coronary heart disease, 53%; stroke, 18%; CHF, 6%; hypertension, 5%; diseases of the arteries, 4%; and other cardiac diseases, 13%. As the population continues to age, the incidence of chronic CVD such as CAD and CHF will also continue to rise. The incidence of cancer death has surpassed heart disease death in patients under age 85. However, when one considers the entire population regardless of age and stroke as a cause of death, then CVD remains the number one killer. Moreover, the total direct and indirect costs for CVD in America are estimated at $365 billion, resulting in an ever-increasing burden on our economy.

Risk Factors

Risk factors for the development of CVD are commonly encountered. The major modifiable risk factors for CVD are diabetes mellitus, hypertension, hyperlipidemia, obesity, presence of the metabolic syndrome, physical inactivity, and cigarette smoking. What is troubling is that these are not just problems that affect the older population, since teenage obesity, type 2 diabetes mellitus (DM), and smoking are also becoming growing problems. For example, it is estimated that approximately 30% of high school students smoke, with nearly 5000 teenagers having their first cigarette every day.[1] Furthermore, as the incidence of obesity and type 2 DM increases, so do the complications that ensue. This includes various manifestations of atherosclerotic vascular disease.[1] It has become apparent, however, that CVD is a complex disorder involving abnormal neurohormonal, metabolic, inflammatory, and immunologic findings. Additional risk factors or risk markers such as elevated concentrations of C-reactive protein and hyperhomocysteinemia are also being examined.

It has been estimated that hypertension affects approximately 50 million individuals in the U.S. and approximately one billion worldwide. The presence of hypertension dramatically increases the risk of both AMI and stroke.[1] Much of the earlier research on hypertension was focused on diastolic blood pressure; however, more recently, the importance of systolic blood pressure has been appreciated. In persons older than 50 years of age, systolic blood pressure greater than 140 mm Hg is a much more important risk factor for CVD than diastolic blood pressure. The relationship between blood pressure and adverse outcomes is continuous and consistent. The most recent Joint National Committee report has established

the category of prehypertension, which includes systolic blood pressure between 120 and 139 mm Hg and diastolic blood pressure between 80 and 89 mm Hg. Patients with prehypertension should be encouraged to engage in lifestyle modification (exercise, sodium restriction, and weight reduction).

Hyperlipidemia is also a risk factor for CVD, with men and women with low HDL cholesterol and high total cholesterol levels having the highest risk of heart attack.[1] There have been numerous trials demonstrating the benefit of statin therapy as effective preventive therapy. The ideal goal for LDL cholesterol continues to be refined. The most recent Guidelines suggest an optional LDL goal of 70 mg/dl for those patients at highest risk for cardiovascular events.

The prevalence of DM is increasing dramatically, with an 8.2% rise from 2000 to 2001 alone. There are many suspected causes for this dramatic increase, including poorer dietary habits and lack of physical activity, which can lead to an increase in obesity. Currently, diabetes is the 6th leading cause of death, with the majority of diabetics dying from some type of heart or blood vessel disease.[3-5] Patients with diabetes have an increased risk of cardiovascular death and stroke that is 2 to 4 times higher than those without diabetes. In fact, the presence of diabetes is now considered a "CHD risk equivalent," meaning that patients with diabetes are as likely to have a MI or die from CVD as patients who have known coronary disease.

The prevalence of overweight Americans has increased by almost 10% over the past 10 years.[1] This is a concern for several reasons. To begin, abdominal obesity is considered an independent risk factor for ischemic stroke.[1] Furthermore, both overweight and obese patients have significant decreases in life expectancy.

Another related risk factor that is growing in importance is the metabolic syndrome. The metabolic syndrome is defined as the presence of 3 or more of the following conditions in any one patient: waist circumference greater than 40 inches in men or greater than 35 inches in women, triglycerides greater than 150 mg/dL, HDL or high-density lipoprotein levels less than 40 mg/dL in men or less than 50 mg/dL in women, blood pressure greater than 130/85 mm Hg, or fasting glucose higher than 110 mg/dL. Currently, there are over 47 million Americans that are at an increased risk of developing CVD and death from CVD causes attributable to the metabolic syndrome.[1] It is often decreased physical activity and poor nutritional habits that lead to obesity and the presence of the metabolic syndrome.

Finally, cigarette smokers have a 2- to 3-fold increased risk of dying from coronary disease.[1] Cigarette smoking is the single most preventable cause of premature death in the U.S. Smoking enhances thrombogenesis and platelet reactivity. Smoking 1 to 4 cigarettes per day can double or triple your risk for CHD. On average, smokers die almost 7 years earlier than nonsmokers.

Patient Presentation

Over 1.1 million Americans experience an AMI each year. Of those, almost one-third will have a STEMI.[1,5] One-third of patients who experience a STEMI will die within the first 24 hours of their heart attack, and those who survive have an increased risk of related illness that is 2 to 9 times higher than that of the general population.[5] In addition, less than 25% of patients having an AMI

have a history of angina, making it important for all health care professionals to review all of the signs and symptoms of AMI with their patients. Typical signs and symptoms of coronary ischemia include midline chest discomfort that may radiate to the jaw, left arm, or back, diaphoresis, nausea, and vomiting. However, up to 30% of patients may present with atypical chest pain that is either stabbing, epigastric, and/or pleuretic in nature. Women, diabetics, and the elderly are the patients who most commonly present with atypical symptoms. In addition, these patients may also be more likely to have a "silent MI," with no symptoms present at the time of the infarct. The diagnosis may be made with an abnormal electrocardiographic finding on a routine visit. CAD is the most significant underlying condition that leads to AMI. Plaque rupture or erosion within the cardiac vessels can cause thrombosis and reduced myocardial perfusion and oxygenation, thus causing myocardial ischemia and/or infarction.

Acute Management of the Patient

When patients present to the emergency department ED with chest pain, an ischemic cause needs to be considered. A patient may have similar symptoms with unstable angina or an acute MI. An electrocardiogram (EKG) should be performed immediately to determine if either ST segment elevation or ST segment depression may be present. It is essential to perform an EKG within 10 minutes after the patient arrives, as therapy for STEMI would need to be initiated as soon as possible. If, however, ST segment depression is present on the EKG, cardiac biomarkers such as troponin and creatine kinase myocardial-brand (CKMB) should be taken to determine if the patient has had a nonSTEMI, or NSTEMI. Both of these biomarkers are sensitive and specific for MI, and they usually appear in the blood approximately 6 hours after necrosis onset. Troponin and CKMB peak within the first 24-36 hours after the MI; CKMB, however, will usually return to normal ranges within 2 days, while troponin will often stay elevated for up to 5 days. Initial management of coronary ischemia includes administration of an aspirin, β-blocker, nitroglycerin, morphine, and heparin.[1]

The 2004 update of the ACC/AHA Guidelines for the Management of Patients with STEMI addresses care of the AMI patient during the initial phase and it also discusses post-MI management. These Guidelines describe 3 different classes of recommendations—I, II, and III:

- Class I recommendations are conditions for which there is evidence and/or general agreement that a procedure or treatment is beneficial, useful, and effective.[5]
- Class II recommendations are based upon evidence for which there is conflicting data or differences of opinion but are generally considered useful.
- Class III recommendations describe conditions for which the treatment is not useful and, in some cases, may actually be harmful.

The following are Class I recommendations per these Guidelines. To begin, when a patient presents with symptoms of acute coronary syndromes (ACS), aspirin at a dose of 162-325 mg should be chewed to produce a rapid anti-thrombotic effect. If a patient has a true aspirin allergy, then clopidogrel, which works by blocking ADP receptors causing decreased platelet adhesion and aggregation, should be given as a 300-mg loading dose. Heparin (either unfractionated or low-molecular-weight heparin) should initiated in patients at high risk for systemic emboli and in patients not undergoing

reperfusion therapy, assuming there are no contraindications present to anticoagulation. Nitroglycerin is another agent that should be immediately given, as it relieves myocardial ischemia by decreasing both preload and afterload via coronary vasodilation. When patients with sublingual nitroglycerin at home experience chest pain, they should take one dose, and if chest pain is still present after 5 minutes, then they should call EMS. The ACC/AHA recommends the use of intravenous nitrates for several reasons, even though their use does not reduce mortality.[5] These reasons include relief of ischemic discomfort, management of hypertension, and decreasing pulmonary congestion. In addition, a β-blocker should be administered within 24 hours of AMI to all patients without a contraindication, as initial therapy with these agents is thought to decrease the magnitude of the infarction, rate of reinfarction, and associated complications such as tachyarrhythmias. It has been shown that early administration of a β-blocker reduces short-term mortality in this patient population.[5] Morphine is the agent of choice for relief of pain and anxiety, as it causes peripheral vasodilation, decreasing myocardial oxygen demand.[5]

Once it has been determined that there is ST segment elevation on the EKG, treatment with either thrombolytic therapy or primary percutaneous coronary intervention (PCI) should be initiated immediately.[5] Evidence shows that quick restoration of flow to the blocked artery is essential in determining both short- and long-term outcomes.[5] Initiation of thrombolytic therapy should occur within 30 minutes of presentation to the ED, and PCI should be performed within 90 minutes if a patient is not given a thrombolytic. If a patient does not meet the electrocardiographic criteria (ST segment elevation) for thrombolytic therapy, it should be withheld.

Administration of medications that inhibit the RAAS, such as angiotension converting enzyme inhibitors (ACE-I), angiotension receptor blockers (ARB), and aldosterone antagonists, play an important role in the management of the post MI patient. It is currently a Class I recommendation to administer an ACE-I orally to patients who can tolerate it during the first 24 hours after an AMI, and it should be a part of daily post-MI management.[5] It is also a Class I recommendation to give an ARB to patients intolerant of ACE-I, a Class II recommendation to give an ARB to patients with an ejection fraction $\leq 40\%$ or who have signs of heart failure and can tolerate an ACE-I.[5]

Beginning in January 2005, Centers for Medicare and Medicaid Services (CMS) and Joint Commission on Accreditation of Healthcare Organizations (JCAHO) revised the AMI and CHF measures and indicated that the use of ACE-Is or ARBs would be considered appropriate treatment for heart failure and AMI patients with left ventricular dysfunction. Finally, post-MI patients with systolic heart failure that are on therapeutic doses of an ACE-I or an ARB already should also start on an aldosterone antagonist, as long as they meet the following criteria: creatinine less than 2.5 mg/dL in men, creatinine less than 2.0 mg/dL in women; and have a potassium less than 5.0 mg/dL.[5]

Post-Infarction Management

Secondary prevention in post-MI patients is of utmost importance, as 18% of men and 35% of women will experience another AMI within 6 years of their first one. This prevention includes daily aspirin; a β-blocker; ACE-I; initiation of therapies to manage hypertension, hyperlipidemia, and diabetes; and smoking cessation counseling. All patients should be counseled prior to

discharge on lifestyle modifications and drug therapies for secondary prevention. They should also be given instructions on recognition of cardiac symptoms and what action to take if any symptoms occur. Ideally, family members should learn about cardiopulmonary resuscitation. In addition, health care professionals should be educated on all secondary prevention goals.

The blood pressure goal is less than 140/90 mm Hg or lower and less than 130/80 mm Hg in patients with diabetes or chronic kidney disease.[5,6] Lipid management goals call for a LDL cholesterol substantially less than 100 mg/dL, triglycerides less than 150 mg/dL, and non-HDL cholesterol substantially less than 130 mg/dL.[5] Statin therapy with lifestyle modifications are usually needed to reach these goals. In diabetic patients, the goal HBA_{1C} should be less than 7%.[5] It is also reasonable for the goal LDL to be less than 70 mg/dL in diabetic patients with CVD.[7] Smoking cessation, weight management, and physical activity are also essential in management of these patients. Finally, antiplatelet agents, β-blockers, and ACE-I should be continued daily in all post- STEMI patients without contraindications.[5]

Anti-Thrombotic Agents

Aspirin at a dose of 75 to 162 mg should be given daily to achieve an anti-thrombotic effect causing near total inhibition of thromboxane A_2. The Antiplatelet Trialists' Collaboration found up to a 25% decrease in recurrent cardiovascular events such as MI, stroke, and vascular death in patients who were receiving extended-duration antiplatelet therapy.[8] Clopidogrel at a daily dose of 75 mg can be substituted for those patients with an aspirin contraindication.[5] If the patient has a stent implanted, then combination therapy with aspirin and clopidogrel is indicated. The duration of the combination therapy will vary depending on the type of stent implanted and the risk of bleeding for an individual patient.

β-Blockers

β-blockers are also considered an important class of medications for post-MI care. They should be initiated within the acute phase of the event and then continued indefinitely in all patients without a contraindication.[5] Patients with moderate-to-severe left ventricular dysfunction, however, should have their doses titrated much more slowly. The positive effects of β-blockers have been seen in many different populations, including those with or without reperfusion therapy, and for patients in all age groups.[5] In addition, those patients with the highest baseline risk, which are patients with decreased ventricular dysfunction or ventricular arrhythmias, are those who will receive the greatest benefit with β-blockers.[5]

Blockade of the Renin-Angiotensin-Aldosterone System

The RAAS plays a significant role in the pathogenesis of cardiovascular disease, with the peptide angiotension II being one of major factors. Initiation of the RAAS system increases cardiac workload through 2 main mechanisms—vasoconstriction and intravascular volume expansion. Renin is released into the body's circulation as a result of decreased glomerular filtration by the kidney. It is then converted to angtiotension I, which becomes angiotension II (a potent vasoconstrictor), after it is cleaved by angiotension-converting enzyme (ACE). This enzyme is also responsible for the degradation of bradykinin, a potent vasodilator. In addition to the RAAS pathway, there are alternative pathways that create angiotension II. These include both the chymase and the chymotrypsin pathways.[9,10] The RAAS also affects the cardiovascular system at the

cellular level. Angiotension II promotes atherosclerosis via several mechanisms, including increasing inflammation, endothelial dysfunction, and the proliferation of fibrosis.[10]

There are 2 types of receptors through which angiotension II work: type 1 (ATI) and type 2 (ATII). ATI receptor stimulation is associated with vasoconstriction, cell growth (hypertrophy), sodium and water retention, as well as sympathetic activation. ATI receptors are abundantly distributed throughout the body and reside in blood vessels, heart, kidney, adrenal glands, brain, and lungs. On the other hand, stimulation of the AII receptor results in vasodilation and antiproliferation. The ATII receptors are located primarily in the heart, vascular epithelium, uterus, ovary, pancreas and adrenal gland.[10] The balance of ATI:ATII receptor activity mediates the overall effects of angiotensin II. Currently available ARBs inhibit the action of angiotensin II on the ATI receptor and allow angiotensin II to stimulate the unblocked ATII receptor.[11]

Evidence for Angiotension-Converting Enzyme Inhibition

ACE inhibitors have become the standard of care for many different medical conditions over the past 20 years. In numerous studies, they have been shown to decrease blood pressure, left ventricular remodeling, and proteinuria. In post-MI patients, including those with or without systolic dysfunction, ACE-I has been shown to decrease morbidity and mortality. In addition to this reduction in cardiovascular mortality, blockade of the RAAS system has also lead to decreased progression of renal insufficiency in patients with both type 1 and 2 DM, and increased survival in patients with congestive heart failure and left ventricular systolic dysfunction.

The ACE Inhibitor Myocardial Infarction Collaborative Group performed a systematic overview of data from more than 100,000 patients post MI.[12] This review found that early post-MI therapy with ACE-I had 4 primary conclusions. All trials found a similar 30-day mortality rate, with a rate of 5 lives saved per 1,000 patients that were treated with an ACE-, duration of roughly 1 month. In addition, during the first few days after MI, the benefit of ACE inhibition is the greatest. As well, the patients with the highest baseline risk received the most benefit from these agents. Finally, these agents were not found to be hazardous in any of the patient subgroups. However, it is important to keep in mind that hypotension, renal failure, cough, hyperkalemia, and angioedema are adverse effects that can result after administration of these agents.

In late 1992, the "Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction," or SAVE trial, was published. This trial was the first of its kind to show a reduction in mortality and decreased morbidity secondary to cardiovascular events in this population of patients.[13] Patients were randomized to either captopril or placebo 3 to 16 days after MI, and patients were then followed for an average of 42 months. The target dose of captopril in the treatment arm was 50 mg 3 times daily and patient compliance of the study medication was followed by pill counts. Follow-up visits were scheduled at 2 weeks after randomization, then every 3 months for the first year, and then every 4 months, thereafter. Endpoints included mortality from all causes, mortality from cardiovascular causes, and mortality combined with a decreasing ejection fraction. When looking at the results, mortality from all causes was significantly higher in patients in the placebo arm (P =

0.019). In addition, events secondary to cardiovascular causes were also significantly higher in the placebo-treated patients (P = 0.014). The number of patients still receiving study medication was similar between both groups at the completion of the study. In addition, the following adverse events occurred significantly more often in the captopril-treated patients: dizziness, taste disturbance, cough, and diarrhea. The authors of this study concluded that captopril started early after MI and continued long term resulted in increased survival and less morbidity from cardiovascular events.

"The effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure," otherwise known as the AIRE study, was published the year following the SAVE trial.[14] In this study, 2006 patients were randomized 3 to 10 days after AMI to receive either placebo or ramipril. In addition, the patients had to have clinical evidence of heart failure. The primary endpoint was mortality from all causes, and secondary endpoint was time to first validated secondary event, which included death, progression of severe resistant heart failure, reinfarction, or stroke. Ramipril was initiated at 2.5 mg twice daily and titrated to a goal dose of 5 mg twice daily. Patients were followed for an average of 15 months, with patients being seen in clinic at weeks 4 and 12 after randomization, then every 12 weeks thereafter. At the end of the study, patients in the ramipril arm had a relative risk reduction of death of 27% over placebo, which was statistically significant (P = 0.002). There were more study medication withdrawals in the ramipril group compared with the placebo group. The main reason for study medication withdrawal in the ramipril group was intolerance, while the primary reason in the control arm was progression to severe heart failure. The authors of this study concluded that treatment with ramipril in post-MI patients with signs of heart failure reduced both mortality and secondary events, including death, reinfarction, or progression to severe heart failure.

In 1995, another trial was published to answer the question of whether patients with systolic dysfunction post MI would benefit from long-term ACE inhibition. This trial was "A clinical trial of the angiotension-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction," also know as the TRACE study.[15] If patients had echocardiographic evidence of left ventricular systolic dysfunction post MI, then they were randomized to either trandolapril or placebo on days 3 to 7 post MI. Follow-up occurred for 24 to 50 months once randomized. Patients in the active arm were initiated on trandolapril 1 mg daily and titrated to a goal dose of 4 mg daily. The primary endpoint investigated in this study was mortality from any cause. Secondary endpoints included death from cardiovascular causes, sudden death, progression to severe heart failure, reinfarction, and change in wall motion index. At the end of follow-up, 35% of patients in the trandolapril arm had died compared with 42% in the placebo arm, which was found to be a statistically significant difference (P = 0.001). When looking at the Kaplan-Meier estimate of mortality, the lines begin to diverge at 1 month and continued to separate for the remainder of the study in favor of trandolapril. There were also significantly fewer deaths from cardiovascular causes in the treatment arm when compared with the control group (P = 0.001). In addition, progression to severe heart failure occurred much more frequently in the placebo group.

There were no significant differences between groups for the endpoint of recurrent fatal or non-fatal MI; however, there was a trend toward a greater reduction with ramipril. As expected, hyperkalemia, hypotension, and cough were reported more frequently in patients receiving the active treatment.

In conclusion, these 3 studies confirm the benefit of ACE inhibition in patients post MI with clinical signs of heart failure. Although patient characteristics differed in all 3 of the trials, reductions in mortality were seen in all of the studies, ranging from 19% and 27%. As a result of these trials, ACE-I has been considered the "gold standard" for blocking the RAAS in post-MI patients for years.

Evidence for Angiotensin Receptor Blockade

Despite the benefit of ACE inhibition, it is well known that many patients cannot tolerate the drugs because of cough or angioedema. Two trials were recently published that establish the role of ARBs in patients with either heart failure postMI or established heart failure already on optimal therapy.

In late 2003, the VALIANT trial was published. This trial compared valsartan, captopril, or both in MI complicated by heart failure, left ventricular dysfunction, or both.[16] Patients receiving standard of care were randomized 0.5 to 10 days after MI to therapy with valsartan (n = 4909), captopril (n = 4909), or the combination of valsartan plus captopril (n = 4885). These agents were titrated in 4 steps to the following target doses: valsartan 160 mg twice daily, captopril 50 mg 3 times daily, or valsartan 80 mg twice daily plus captopril 50 mg 2 times daily in the combination group. Investigators could increase or decrease doses at their discretion during the 24.7-month average follow-up period. The primary endpoint in this study was all-cause mortality. There were 2 treatment comparison groups: valsartan versus captopril and valsartan plus captopril versus captopril alone. In addition, this study was designed to assess the noninferiority of valsartan if it was not shown to be undoubtedly superior or inferior to captopril. The secondary endpoint that was looked at was cardiovascular morbidity and mortality that included recurrent MI and hospitalizations for heart failure.

At the conclusion of VALIANT, mortality was found to be similar in all 3 treatment groups.[16] A total of 19.5% died in the captopril group, as did 19.3% in the combination group, and 19.9% in the valsartan group ($P = 0.98$). The secondary endpoint of cardiovascular causes, recurrent MI, or hospitalizations was also comparable in all 3 groups. In a prior heart failure study (VAL-HeFT), the combination treatment with an ACE-I, ARB, and a β-blocker was associated with an increased patient mortality. As a result of VAL-HeFT, the combination therapy with these 3 types of agents was not recommended. However, a subgroup analysis found that there was no increased in mortality in patients taking all 3 of these agents in VALIANT. The safety of the combination of an ACE-I, ARB and β-blocker was also supported in the CHARM-added trial.[17]

Since valsartan was not clearly found to be either superior or inferior to captopril in this patient population, the pre-specified analysis to test for noninferiority was carried out.[16] Valsartan was found to be noninferior to captopril in both the intention-to-treat and per-protocol analyses that were performed, thus demonstrating that this ARB is no less effective that the ACE-I captopril. Tolerability and safety differed among the 3

treatment groups, although the groups were similar in the number of patients that were no longer taking study medication by the conclusion of the trial. The combination group had the most frequent number of adverse effects, while the valsartan-treated patients had the least number of adverse effects. Hypotension occurred more frequently in the valsartan plus captopril group, while it was lowest in the captopril monotherapy group. Discontinuation secondary to renal causes was more common in the valsartan-treated patients, while taste disturbances, rash, and angioedema were more prevalent in the captopril-treated patients.

Prior to VALIANT, there were several studies that showed ARBs were not superior—and possibly—inferior to the ACE-I captopril. The ELITE II trial compared losartan with captopril.[18] In this study, there were no significant differences between the 2 groups in all-cause mortality and sudden death. However, some have questioned whether or not the dose of losartan was comparable to that of captopril. The OPTIMAAL trial was similar to the ELITE II trial in that it compared the ARB losartan with the ACE-I captopril.[18] This trial was in post-MI patients who had high-risk features. As in ELITE II, the results were somewhat disappointing, as losartan did not show a survival benefit and possibly showed a decline in survival when compared with the proven ACE-I captopril.

Another ARB that has showed promise in patients with heart failure is candesartan. Although it is beyond the scope of this article to discuss candesartan in detail, it did show promise in treating patients with heart failure in the CHARM trial.[17]

As a result of both the VALIANT and CHARM studies, several organizations have now revised their guidelines to address the use of an ARB in post-MI patients. For example, the ACC/AHA Guidelines for the management of patients with STEMI have addressed treatment with an ARB, specifically valsartan or candesartan, to their list of recommendations. In the post-MI patient population, it is now a Class I recommendation to start a patient on an ARB if he is intolerant to an ACE-I and has either signs of heart failure or an ejection fraction less than 40%.[5] Moreover, it is a Class IIa recommendation to start an ARB as an alternative to an ACE-I.[5] In addition, in November 2004, the Centers for Medicare and Medicaid Services along with the Joint Commission incorporated ARBs into their treatment recommendations for patients postMI or those with heart failure.[20] At this time, there are still many questions that go unanswered. For most clinicians, an ACE-I has remained the standard of care in post-MI patients, since there is such a large amount of evidence supporting their use. There is, however, a growing amount of evidence supporting the use of an ARB. Whether an ARB or an aldosterone antagonist should be added to an ACE-I in a post-MI patient with left ventricular dysfunction remains controversial.

Evidence for Aldosterone Blockade

Aldosterone excess has several harmful effects on the cardiovascular system, including increasing ventricular hypertrophy and increased endothelial cell dysfunction. Although we know that ACE-I and ARBs decrease aldosterone levels in patients post MI with left ventricular dysfunction, "aldosterone escape" still occurs. Therefore, agents that target the aldosterone receptor are also beneficial in this patient population. Currently there are 2 aldosterone antagonists on the market, sprironolactone and eplerenone. Spironolactone was found to decrease mortality in patients with class III

or IV heart failure in the RALES trial.[21] However, eplerenone, a selective aldosterone blocker at the mineralocorticoid receptor, was approved by the FDA for treatment of patients postMI with left ventricular systolic dysfunction and clinical signs of heart failure.[22]

The EPHESUS trial, also known as "Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction trial" was composed of over 6,500 patients with an average of 16 months of follow-up.[23] Patients were randomly assigned to receive either eplerenone 25 mg/day (titrated to 50 mg/day) or placebo. The 2 primary endpoints of EPHESUS were death from any cause and death from cardiovascular causes or first hospitalization for heart failure, acute MI, stroke, or ventricular arrhythmia. The major secondary endpoints were death from cardiovascular causes and death from any cause or hospitalization. Patients were enrolled in the study if they were 3-14 days postMI with left ventricular dysfunction and symptoms of heart failure or diabetes. In addition, exclusion criteria included the following: use of potassium-sparing diuretics, serum creatinine greater than 2.5 mg/dL, and serum potassium greater than 5 mmol/liter. Careful monitoring of the serum potassium occurred throughout the study.

At the conclusion of the trial, 14.4% of the patients in the treatment arm had died compared with 16.7% in the placebo arm (P= 0.008).[23] In addition, the endpoint of death from cardiovascular causes or hospitalization for cardiovascular events was also significantly reduced in the eplerenone arm. Death from secondary causes was also decreased in the treatment (P= 0.005). Adverse effects that were more common in the treatment arm included serious hyperkalemia and gastrointestinal disturbances, thus suggesting the importance of checking the potassium frequently in patients on aldosterone antagonists. Furthermore, it is also essential to monitor renal function in patients on these agents. As a result of both RALES and EPHESUS, it is now an ACC/AHA class I recommendation to treat post-MI patients with signs and symptoms of heart failure with an aldosterone antagonist. Although eplerenone was studied specifically in patients post MI, most would still recommend choosing spironolactone first, as it is much less expensive and has shown benefit in patients with heart failure. However, if patients experience adverse effects such as gynecomastia or impotence, eplerenone is a suitable option, as it only affects the mineralcorticoid receptor and is not associated with an increase in these side effects when compared with placebo.

Conflicting Data

It should be noted that not all trials have shown positive effects from RAAS inhibition. The recently published PEACE (Prevention of events with ACE inhibition) Trial showed no significant benefit from the addition of the ACE-I trandolapril in over 8200 patients with stable CAD but without a history of heart failure.[24] This trial cannot be directly compared with the other preventive ACE-I trials (HOPE and EUROPA).[25,26] Each trial had slightly different patient populations, had different endpoints, and used a different ACE-I. Another hypothesis is that the difference in clinical outcomes in the PEACE trial was owing to the higher use of other beneficial concomitant medications and better control of blood pressure and dyslipidemia.

What to Avoid

There are several therapies that have recently proved to be either useless or

harmful, which were considered potentially useful in the past decade. Antioxidant vitamins such as vitamin E and Vitamin C should not be used to prevent CVD. Although earlier epidemiologic trials suggested a potential use for these agents, more recent randomized controlled trials have shown no benefit.

In the case of hormone replacement therapy, there is actually demonstrated harm. The Women's Health Initiative enrolled women who did not have documented CAD.[27] The trial was terminated early because of the increase of breast cancer and CVD events in the hormone treated group.

Conclusion

The care of the patient with acute ischemia and chronic CAD continues to evolve. The most recent ACC/AHA Guidelines for the treatment of STEMI address both the acute and chronic issues facing these patients. All patients who have suffered an acute MI should be treated aggressively to prevent a recurrence. Drug regimens should include antithrombotics, ACE-Is, β-blockers, and statins. An ARB may be substituted for an ACE-I in patients intolerant to ACE-Is. For patients with the additional comorbidity of diabetes, the addition of an ACE-I and/or an ARB will also provide renal protection. If an ACE-I is used for the symptoms of heart failure, there is controversy whether an ARB should added before an aldosterone antagonist.

The pharmacist in the institutional setting and the community pharmacy must take an active role in enhancing patient adherence to their drug regimen. He also needs to emphasize the importance of implementing a healthy lifestyle and aggressively controlling the risk factors associated with cardiovascular events.

Table 1. Trials with ACE Inhibitors

Study	Patient Population	Drug
SAVE	HF-Post AMI	captopril
AIRE	HF-Post AMI	ramipril
TRACE	HF-Post AMI	trandolapril
HOPE	High risk	ramipril
EUROPA	CAD	perindopril
PEACE	Stable CAD	trandolapril

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