RELATIONSHIP BETWEEN DEPRESSION AND CORONARY ARTERY DISEASE IN POSTMENOPAUSAL WOMEN

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STATEMENT BY THE AUTHOR

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Abstract

Coronary artery disease (CAD) and depression are both highly prevalent diseases. They both significantly affect an individual’s quality of life and impose an economic burden on society. There are several physiological and psychological factors that seem to link depression with the development of CAD. At the same time, no clinical guidelines have been established to assist health care providers in disease prevention and risk reduction in this possibly fatal relationship. Overwhelming evidence suggests that depression is often underdiagnosed and undertreated in patients with CAD (Nemeroff et al., 1998). The universal observation, independent of country and culture also shows a twofold prevalence of depressive disorder among women (Sadock & Sadock, 2003). This information becomes especially significant for postmenopausal women when they lose the protective hormonal effect and suddenly become more vulnerable to the destructive effects of CAD. This paper was designed to provide a thorough literature review and to analyze the current body of knowledge about the relationship of depression and CAD in postmenopausal women. For the purpose of this paper, the terms CAD, cardiovascular disease (CVD), and coronary heart disease (CHD) will be used interchangeably.
Introduction

Significance of the Problem

According to the World Health Organization and the World Bank, depression is currently the fourth leading cause of disability worldwide, and its incidence is increasing rapidly. In Western countries, up to one third of the population has had an episode of depression at some point in their lives and fifteen to twenty percent can be diagnosed with chronic depression. In the United states, this potentially life-threatening mood disorder affects up to ten percent of the population, or approximately 17.6 million Americans each year (Andrew, 2002). It is projected that depression will be the second leading cause of death and/or morbidity by the year 2020. “The economic cost of depressive illness is estimated at $30-44 billion a year in the United States alone” (Andrew, 2002).

Cardiovascular disease, which is currently the leading cause of death and morbidity in the industrialized world, is projected to become the number one single cause of mortality by 2020. Thus, if only because both conditions are so common, there will be many patients with both diseases. However, there appears to be an interaction between the two diseases that augments their respective importance when they are combined. Another source of data reports that the cardiovascular disease mortality rate has decreased in men during the past twenty years, but steadily increased in women. In the United States, more than 500,000 women die of cardiovascular disease (CVD) each year and half of the deaths could be attributed to the destructive effect of CAD (Welty, 2001). Although many factors can influence an individual’s risk for CAD, some factors are
unique to women, including their reproductive status. Menopause is associated with a significant elevation in serum cholesterol levels and a three-fold increase in the risk of CAD. It has been suggested that these changes result from a reduction in the level of estrogen. By the age of 65, women are nearly as likely to suffer a myocardial infarction and are much more likely to die from it (Kosak, 1997). Based on the above information, women appear to be at an increased risk for the development of this comorbidity of CAD and depression. Even though depression can affect anyone, research over the past two decades demonstrated that people with heart disease are more likely to suffer from depression than otherwise healthy people (National Institute of Mental Health, 2002).

Purpose

The purpose of this paper is to analyze physiological and psychological links between depression and CAD in postmenopausal women. The extensive body of research that has been conducted in the past decade will be presented to provide a comprehensive overview and assist in research dissemination and utilization in clinical settings.

Overview

This paper is designed to address the following topics: CAD, depression, and its effect on postmenopausal women. A thorough review of literature relevant to this topic will be provided, along with recommendations for clinical practice and future research.

Review of literature

Depression

Depression is divided into different types depending on the severity and length of time the symptoms have been present. Appendix A provides specific diagnostic criteria
for Major Depressive Disorder as listed in the latest version of Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000).

Major depression is the most common clinical psychiatric problem seen in primary care settings with increasing numbers of patients receiving their treatment from their primary care provider. A study that reviewed prescription of psychotropic medications between 1984 and 1994 revealed that patient visits to primary care providers for treatment of depression doubled (Lustman et al., 1997). At the same time, many years of research document a failure to detect major depression and a sub-optimal use of antidepressants in primary care settings with results in underdiagnosis and undertreatment. For example, in a 1994 study that examined patients who received care at a variety of primary and specialist care offices, only 29% of those with depression of high severity received an antidepressant. In another study that examined distressed individuals who were high users of primary care services, 45% were diagnosed with depression and in need of treatment and only one in nine received the adequate dose for the proper duration of antidepressant therapy (Levenson, 2000; Katon & Schulberg, 1992). Refer to Appendix B for the primary reasons of under-diagnosis and under-treatment of depression in medically ill patients in primary care settings.

The presence of long-term depression results in a wide range of unfavorable consequences for patient, family, healthcare provider, and even society. With the most severe outcome being suicide, other long-term effects decrease the quality of life and cause impaired daily functioning.
Rates for depression in males and females are the same until girls reach puberty, at which time their risk for depression doubles compared to males of the same age. So what can account for such a wide gap in the incidences of depression between the two sexes? Experts believe that women may be more prone to develop depression secondary to hormonal changes that take place throughout their lifetime: puberty, pregnancy, and menopause; as well as monthly variations of the menstrual cycle. Besides hormonal fluctuations, other factors, such as reproductive, genetic, interpersonal skills, and certain psychological and personality characteristics increase women's vulnerability to the depressive disorder. Appendix C lists specific factors that place women at higher risk of depression compared to males. Depression in women may also occur earlier, last longer, be more recurrent in nature, and are more likely to be associated with stressful life events. Their symptoms often appear to be less typical of depression, such as sleeping and eating excessively. Depression in women is also more likely to coincide with anxiety disorders, especially panic and phobic symptoms, and eating disorders (The Cleveland Clinic Department of Psychiatry and Psychology, 2004).

Depression in Postmenopausal Women.

In United States the average age of menopause is 51 years of age (Buttarø et al., 2003). Postmenopause is defined as amenorrhea over a period of twelve months, throughout the life span (Buttarø et al., 2003). During this time, ovarian function and ovarian follicle production diminishes resulting in reduction of circulating estradiol, the principal endogenous form of estrogen in premenopausal women. Ovarian production of progesterone is reduced as well (Buttarø et al., 2003).
Although research regarding the connection between depression and menopause has been quite involved for the past fifty years, an extensive literature review still presents a wide variety of opinions and positions about the significance of menopause in the development of depressive disorder in postmenopausal women. For instance, McKinley and colleagues (1992) concluded that the depression rate of postmenopausal women is equivalent to perimenopausal women. However, Maarten and colleagues (2002) showed that the transition from perimenopause to postmenopause seems to be independently related to a high increase of depressive symptomatology, suggesting that decrease of ovarian estrogen production is a risk factor for depressive symptomatology. This result is also consistent with the Schmidt and colleagues (1997) findings, but contradicts the (1990) Ballinger study that found “hardly no connection at all between the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels and the development of major depression”. The heterogeneous picture thus shows that the methods for investigation vary significantly and thus are difficult to compare, and lead to selective biases. A wide variety of diagnostic tools also confirm this. Some investigations are based exclusively on questionnaires, while others rely on expert opinion, still some employ extensive psychiatric interviews with limited gynecological evaluation. Very different methods are also used for follow-up evaluations.

A review of neurobiologic mechanisms shows that there are many plausible mechanisms by which estrogen and progesterone may affect the central nervous system, mood, and mental performance. Control of mood and behavior involves many different neurotransmitter systems, including glutamate, gamma aminobutyric acid (GABA),
acetylcholine (Ach), serotonin (5-HT), noradrenaline (NA) and neuropeptides. Given that
the observation and prevalence and symptomatology of mood disorders are often
different between males and females, it is presumed that the gonadal steroid hormones
are somehow involved (Steiner et al., 2003). According to Steiner and colleagues (2003)
“interaction between neurotransmitters and steroid hormones is extremely complex and
delicately balanced, where each system appears to have a modulatory function on another
and changes in one system may have a dramatic effect on other systems”. Glucocorticoid
and gonadal steroid receptors are abundant in different areas of the brain. Gonadal steroid
receptors are found in the amygdala, hippocampus, basal forebrain, cortex, cerebellum,
locus coeruleus, midbrain raphe nuclei, pituitary gland and hypothalamus. Estrogen
receptors are located in the preoptic area, amygdala and hypothalamus (McEwen, 1988;
Stomati et al., 1998).

Studies have shown that steroid hormones can modulate neuronal transmission by
a wide variety of mechanisms. “They may affect the synthesis and release of
neurotransmitters, as well as the expression of receptors, membrane plasticity and
permeability. It has been suggested that steroid hormone receptors function as general
transcription factors to achieve an integration of neural information in the central nerves
system” (Steiner et al., 2003). Steroids are believed to act primarily by classical genomic
mechanism through intracellular receptors to modulate transcription and protein
synthesis. Recently, it has been shown that steroids can also produce a rapid effect on
electrical excitability and synaptic function through direct membrane mechanisms, such
as ligand-gated ion channels, G-proteins and neurotransmitter transporters, thus directly
activating secondary messenger system, cytokines and dopamine release (Steiner et al., 2003). For instance, topical application of estrogen or progesterone to the nervous tissue has been shown to result in a rapid change in membrane potential, and sex steroids can affect membrane fluidity, thereby modifying ion transport or receptor function (Maggi & Perez, 1985).

Several current research studies are attempting to establish the role and potential relevance of estrogen and other sex steroids to depression and other psychiatric disorders. So far, estrogen has been described as 5-HT, NA, Ach agonist, as well as modulator for dopamine receptors (Steiner et al., 2003). By understanding physiologic effects of all the above neurotransmitters, one can see how specific symptoms of depression could emerge. For instance, a deficiency of 5-HT will have a direct effect on mood, anxiety level, appetite, and sleep; decrease in dopamine could have a negative effect on memory, cognition, and motivation; and deficiency in NA will have a direct effect on energy level, concentration, attention, arousal, learning ability and sleep (Personal communication, Martha Fankhauser, September 1, 2004). For this reason, sudden loss of an estrogen modulating effect may underlie the development of postmenopausal depression in vulnerable populations.

*Articles Related to Depression in Postmenopausal Women*

*Article #1*

The purpose of this study was to determine whether depressive symptomatology in healthy women is independently related to menopausal transition (Maartens et al., 2002). The population sample consisted of exclusively Caucasian women born between
1941 and 1947, living in the city of Eindhoven, the Netherlands, that were invited to take part in a screening program. From a total of 8098 women involved in the program, 78% or 6648 participated. About 92% of them returned questionnaires of which 81% were completed, bringing the total number to 4975. All women that were using estrogen and/or have undergone hysterectomy and/or ovariectomy were excluded. The final population sample included 2820 women. After three and a half years, 2748 of them returned another postal questionnaire, of which 76% were fully completed (n=2103) (Maartens et al., 2002).

Depressive symptomatology was assessed using the Edinburgh Depression Scale (EDS). Scores vary from 0 to 30. Specificity and sensitivity of the instrument in assessing depression have been well established and validated for women of non-childbearing age. Multiple logistic regressions were also used to analyze the independent relationship between an intra-individual change in the EDS score during a follow-up period and menopausal transition. Depression and menopause were clearly defined. The results of the study show that, besides the classic determinant for depression, transition from pre to perimenopause and peri to postmenopause was significantly related to a high increase (>5.4) of the EDS score), thus suggesting that a decrease of ovarian estrogen production is a risk factor for depressive symptomatology in menopausal women (Maartens et al., 2002).

Article #2

In this study, Amore and colleagues (2004) concentrated their effort on the assessment of changes in depressive and anxiety symptoms in pre- and postmenopausal
periods. The study design was a cross-sectional postal survey of a sample of menopausal women living in the territory of “Azienda Sanita Locale” of Ferrara and recruited through the local General Registry Office. Questionnaires were designed on the basis of the Women Health Questionnaire (WHQ) and mailed to 4073 women. Besides the WHQ, women were also asked to fill out a personal file to define social status, cultural level, family characteristics, recent menstrual cycles, gynecological surgical histories, drug consumption, life events in the last year and lifetime (Amore et al., 2004).

From 4073 mailed questionnaires, 1434 were completed and returned. The analysis was carried out with the statistical package SAS, version 8.1. The symptom severity ratings from the WHQ were entered in a principal-component factor analysis using Varimax rotation. To consider missing answers, a mean substitution was performed. Factor analysis resulted in eight clusters of symptoms. Among psychiatric symptoms, three different clusters were identified: depressive symptoms, depressed mood with anxiety symptoms, and anxiety. The results revealed that cluster “depressive symptoms” were significantly different in the premenopausal group when compared to the postmenopausal group, with greater levels of symptomatology in the postmenopausal group. Prior depression was the most predictive variable of subsequent depression in postmenopausal women. Other factors related to more pronounced depressive symptoms, were the number of life events, the postmenopausal status, the place of residence and a lower socio-economic level (Amore et al., 2004).
Article #3

The main purpose of the research conducted by Zarate and colleagues (2002) was to assess the effect of low-dose conjugated equine estrogen (E) on circulating neurotransmitters and the efficacy for the treatment of psychological symptoms.

This study took place in the Endocrine Research Unit, Instituto Maxicano del Seguro Social, Mexico. Study participants included 40 postmenopausal women ages 45-56 years with general complaints of hot flashes, mild depression, anxiety, irritability, and mood instability. Women with a history of breast cancer, abnormal uterine bleeding, coronary heart disease, peripheral vascular illness, gallbladder disease, hypertension and diabetes mellitus were excluded. Of the above participant population, thirty women received conjugated equine E and ten acted as a comparison group. All women in the control group received conjugated equine E, 0.312 mg/day for 21 days per cycle during six cycles and added chlormadinone acetate, 2 mg/day for the last 5 days of each cycle. Symptoms of depression and psychological well-being were evaluated by the use of the Green Scale for Climateric Women and the Blatt-Kupperman Menopausal Index at base line at the end of the study. Serum levels of dopamine (DA), noradrenaline (NA), serotonin (5HT), and B-endorphin were quantified by specific assays at baseline and at the end of the treatment (Zarate et al., 2002).

The findings of this study demonstrated that low baseline levels of DA, 5HT, and B-endorphin increased significantly (p<0.001) from 181.9 +/- 47.8 pg/ml to 202.9 +/- 32.8 pg/ml; from 206.4 +/- 94.2 ng/ml to 279.2 +/- 67.9 ng/ml; from 11.2 +/- 1.8 pmol/L to 13.8 +/- 2.4 pmol/L, respectively, after conjugated equine E. In parallel, augmented
baseline noradrenaline levels diminished significantly (p<0.05) from 30.2 +/- 4.7 ng/ml to 24.0 +/- 4.7 ng/ml. These results corresponded with alleviation of psychological symptoms in all but eight treated women (Zarate et al., 2002). Based on the above findings, the authors of the study concluded that gonadal steroid hormones might have a role in the treatment of psychological symptoms associated with menopause, as well as depression associated with menopause (Zarate et al., 2002).

The above studies conclude that women appear to be more vulnerable to the depressive symptomatology during the postmenopausal period, thus reinforcing the hypothesis of hypothalamic-pituitary-gonadal axis malfunctioning associated with menopause. For this reason regular screening for depression should be offered to this age group by the primary health care providers.

*Article #4*

This study intended to further validate results of previous research in regards to modification in depressive mood in postmenopausal clinically depressed women using estrogen replacement therapy (Carranza-Lira & Valentino-Figueroa, 1999).

In this study, participants included twelve post-hysterectomy women, 40 years of age and older, who were not receiving nor had ever received HRT. All had serum levels of follicle stimulating hormone (FSH) and estradiol (E2) measured. One group of six received conjugated equine estrogen (CEE) 0.625 mg/day; the control group did not receive any treatment. Mood was assessed with the Hamilton Depression Rating Scale (HAM-D) at baseline and after a 6-month follow up period. Depressed mood was defined as a score higher than 15 points. Differences between both groups were assessed with the
Mann-Whitney U-test, taking into consideration factors such as age, body mass index, waist-hip ration, number of pregnancies, abortions, and cesarean sections (Carranza-Lira & Valentino-Figueroa, 1999).

Results revealed that the estrogen replacement therapy (ERT) group had a statistically significant decrease in depressive symptomatology 21 vs. 13 points, $P<0.03$), while the control group had no significant changes (22 vs. 22). Final HAM-D scores were significantly lower ($P<0.05$) in those under ERT, when compared with those in the control group. Based on the results, authors of the study concluded that depressive mood decreased after six months with CEE, so prescription of ERT can be useful in postmenopausal women with depressed mood (Carranza-Lira & Valentino-Figueroa, 1999). One has also to take into consideration the small size of this study, as well as the short period of follow up. Thus, long-term studies are needed to verify this response will be maintained and also to look for any other possible factors that are independent of the hormonal status.

*Article #5*

In this research, Antonjevic and colleagues (2003) attempted to evaluate the impact of menopause on sleep-endocrine alterations that are often associated with menopause. Authors based their research on the fact that aging and menopause are associated with alterations of sleep electro-encephalogram (EEG). Major depression also has been linked with typical sleep-endocrine changes, including enhanced activity of the hypothalamic-pituitary (HPA) axis. Based on the above knowledge, the following
hypothesis was proposed-- after menopause, sleep-endocrine alterations associated with major depression are accelerated (Antonijevic et al., 2003).

The methods involved 16 depressed patients, seven of whom were premenopausal and nine of whom were postmenopausal as well as 19 controls who were matched for reproductive status and age, with ten of them being premenopausal and nine postmenopausal. All patients scored above 16 points on the Hamilton Depression Scale in pre-study period, which is consistent with clinical diagnosis of major depressive disorder. All the subjects were of normal height and weight and underwent a rigid medical and psychiatric examination (Antonijevic et al., 2003).

Nocturnal EEG recording and hormone secretion of ACTH, cortisol, GH, estradiol, LH, FSH, and leptin were obtained from all subjects on two successive nights, with the first night serving as an adaptation to the laboratory settings. Statistical analysis was performed using MANOVA for diagnosis and reproductive factor and between-subject factors. The findings of this study demonstrated that nocturnal cortisol secretion was increased in postmenopausal patients with depression, while a decrease was noted in postmenopausal controls. Sleep alterations typically associated with depression, namely a reduction in sleep continuity and slow wave sleep (SWS) and an increased REM density, were prominent in post, but not in premenopausal women. An inverse correlation was also noted between decline in SWS and sleep continuity and FSH secretion in patients with depression, suggesting a role of menopause for these sleep-endocrine alterations typically associated with major depression. In contrast, in premenopausal women primary
shift from SWS and delta-EEG activity from the first to the second non-REM period was noted, which was not related to age or hormone secretion (Antonijevic et al., 2003).

Although the authors agree that a relatively small population sample precludes a definite conclusion, the data opens up the possibility that the sleep-endocrine changes typically associated with major depression are most prominent in postmenopausal women. Whether the predromal alteration of the distribution of SWS and delta EEG activity in younger patients with a first episode of major depression has a predictive value for the future course of the disease remains to be investigated (Antonijevic et al., 2003).

_Coronal Artery Disease (CAD)_

As was discussed earlier, CAD remains the primary cause of death in United States. Each year 1.1 million Americans suffer a myocardial infarction, mostly as a result of CAD leading to coronary thrombosis. Half of these heart attacks are fatal with the majority of deaths attributable to left ventricular failure and cardiogenic shock within ninety-six hours after infarction. (Buttaro et al., 2003).

CAD is the end result of a complex process called atherosclerosis. This process eventually causes blockage of coronary arteries and prevents oxygenation of the cardiac muscle. There are many steps in the process leading to atherosclerosis and some are not fully understood. A recent research focus has been directed toward the interaction between cholesterol and the process known as oxidation and inflammatory response. In general, in patients with CAD, the presence of one of the three following syndromes represents a different degree of severity: stable angina, acute coronary syndromes, and myocardial infarction. The CAD risk factors divided into two categories: modifiable and
nonmodifiable. Nonmodifiable risk factors include: gender, age, and family history.

Modifiable risk factors consist of smoking cessation, cholesterol levels, diabetes mellitus, and hypertension management (Buttaro et al., 2003). In addition, Pasternak and others have developed an evidence-based system where CAD risk factors have been arranged into a hierarchy based on four factors:

1. Risk factors for which there is a strong relationship to CAD and for which interventions have been proven to reduce the incidence of CAD events, such as cigarette smoking, low-density lipoprotein cholesterol, dietary factors, hypertension, thrombogenic factors.

2. Risk factors that strongly suggest a causal relationship to CAD and for which interventions are likely, based on current pathophysiologic understanding and epidemiologic and clinical trial evidence, to reduce the incidence of CAD events, such as diabetes, physical inactivity, high-density lipoprotein cholesterol, obesity, postmenopausal status.

3. Risk factors that are clearly associated with an increased CAD risk and for which modification might lower the incidence of CAD events, such as psychosocial factors including stress and depression, triglycerides, Lp(a) lipoprotein, homocysteine, and oxidative stress.

4. Risk factors associated with increased risk but that cannot be modified or whose modification would be unlikely to change incidence of CAD events, such as age, gender, and family history (Buttaro et al., 2003).

Refer to appendix D for secondary prevention guidelines for patients with CAD.
**Coronary Artery Disease in Postmenopausal Women**

Heart disease incidence in women increases dramatically after menopause and causes more deaths than breast, uterine, and ovarian cancers combined (Buttarro et al., 2003). For a postmenopausal woman, the lifetime risk of dying from CAD is 31%. In recent years, CAD related mortality has decreased less pronounced in women compared to men (Wegner, 2002). Hospital mortality related to CAD is greater for women than for men, 16% versus 11%. Also, both one-year mortality and reinfarction are greater among women who suffered infarct than among their male peers. Cardiovascular surgery database shows that operative mortality for women is 4.5% compared to 2.6% for men (Wegner, 2002).

The link between the presence of estrogen and a low incidence of atherosclerosis in premenopausal women is not completely understood. At the same time, research suggests that estrogen provides protection from elevation of low-density lipoproteins (LDL) cholesterol, as well as maintenance of higher levels of high-density lipoprotein (HDL) cholesterol (Gorodeski, 1994). In the presence of estrogen, low-density lipoprotein (LDL) cholesterol decreases on average 10 to 15% and high-density lipoprotein (HDL) cholesterol comparably increases (Wegner, 2002). Other protective mechanisms of estrogen consist of the ability to prevent CAD by reducing plaque deposition in blood vessel linings and possibly by promoting dilatation of the coronary arteries and thus improving coronary blood flow, as well as lessening inflammatory response to atherosclerosis, and decreasing vascular smooth muscle proliferation (Wegner, 2002). During postmenopause, endogenous estrogen sources diminish, and a
rise in LDL, with a drop in HDL are commonly observed (Gorodeski, 1994). At the same time, with oral replacement of estrogen, triglyceride levels increase and the risk of deep vein thrombosis increases as well. Both are risk factors for a coronary event.

Based on the above information, risks and benefits of estrogen and progesterone replacement therapy in healthy postmenopausal women have been a subject of considerable debate over the past three decades. In general, the majority of studies conducted in the 1970 to 1990’s agree that most women would benefit from taking hormone replacement therapy (HRT). As reported by Gorodeski (1994), many studies of hormone replacement therapy suffer from methodological problems, such as bias, improper selection of controls, or bias of environmental controls. Of the thirty-four studies reviewed by the above author, only one had an experimental design, but it was of small magnitude. Some of the other factors not taken into account included tobacco use; using mostly upper-middle class patient populations for interventional groups who are better educated than control groups; as well as physician bias that drew mostly low risk patients into the control group (Grodeski, 1994). The culmination of this debate took place with the results of the Women’s Health Initiative (WHI) randomized controlled trial (2002) and Heart and Estrogen/Progestin Replacement Study (HERS). Although the anticipated changes in lipoproteins were present in the group receiving a combination of estrogen progesterone, such as decrease in LDL cholesterol, elevation of HDL cholesterol and triglycerides, after 4.1 years of follow up there was absolutely no difference between the HRT group and placebo group in total coronary events (Wegner, 2002). Moreover, WHI researchers discovered a small, but statistically significant increase in risk of CHD in
women on HRT compared to placebo. Most of the heightened risk was present in the first year and most of the events were non-fatal acute coronary events (Warren & Halpert, 2004).

At the same time, the critics of the WHI study cite several inconsistencies that might have had a great influence on research results and applicability for the intended population. First of all, only two forms of HRT, Premarine that is derived from urine of pregnant horses and Prempro, synthetic progestine, have been investigated. Study results therefore are limited to only these types of HRT and exclude other forms of hormone replacement. Also, selection of the older, first time users of HRT with the average age of study participant 63.3 years of age does not correspond with the intended age of first time HRT users that usually consists of women between 45 and 55 years of age. From the entire population sample, 66% of women were over 60 years of age and 21% were between 70-79 years old. Additionally, 36% of these women were already being treated for hypertension, 35% were overweight, and 34% were obese; 12.5% were receiving cholesterol lowering agents, 4% had diabetes and 16% had a family history of breast cancer, which does not correspond well with the study’s presentation of healthy menopausal women (Elizabeth Lee Vliet, personal communication, November 22, 2004). According to Genazzani, President of the National Society of Gynecological Endocrinology, “we would never choose that kind of HRT combination for elderly patients with those clinical characteristics” (Vliet, 2004). Additionally, the International Menopause Society’s revised position paper from August 2004 states, “the different types and regimens of hormone therapy do not have the same tissue and metabolic effects and
should not be grouped together as having a class effect... judging from the accelerated rate of cardiovascular events after premature menopause, and the loss of cardio protection after stopping hormone therapy, sudden cessation of HRT may even be harmful". This shows that results of the WHI study should be viewed in relation to the population sample.

The most recent controversy on HRT has focused on oestrogen plus progestin (OPT) arm of the study that was primarily focused on evaluating the effect of estrogen on colon cancer and hip fractures. In this part of the study, women were randomly assigned to receive placebo or 0.625 mg of conjugated equine estrogens (CEE) with 2.5 mg of medroxy-progesterone acetate (MPA). The arm was prematurely terminated after 5.2 years of follow up secondary to significant increase in risk of breast cancer and cardiovascular disease (Warren & Halpert, 2004). These safety concerns were not found in women in the estrogen only therapy group, thus this arm of the study is expected to continue until its scheduled completion in 2005 (Warren & Halpert, 2004).

Another change that takes place in postmenopausal women is the distribution of body fat. Obesity is the oldest identified risk factor for CAD. It is not an independent risk factor for CAD but over the years has proven to have a tight association with hypertension, dyslipedimia, hyperinsulinemia, insulin resistance and diabetes. It was also discovered that body fat distribution is a better prognostic factor than weight, with androgenic or centralized body obesity tightly associated with CAD (Gorodeski, 1994). As we know, following menopause, a woman’s fat distribution changes from mostly gluteal-type obesity to centralized obesity. This increase in waist-hip ratio has been
shown to have a positive correlation with CAD, even after controlling for hypertension, glucose intolerance, blood lipids, smoking, and body mass index (Gorodeski, 1994).

While reviewing the following articles related to CAD in postmenopausal women, one should keep in mind the historical development that took place in the research world, related to inconsistent findings, to further understand the relationship between CAD and depression in this specific patient population.

*Articles Related to Coronary Artery Disease in Postmenopausal Women*

*Article #1*

In their research study, Dallongeville and colleagues (1995) examined the relationship between menopause and cardiovascular risk factors, and the effect on these risk factors of progestin alone or in combination with estrogen.

The methods involved 3440 women between ages 45 and 65 who received a systematic check up between January 1991 and April 1993 (Dallongeville et al., 1995). To insure consistency, all biological measures were performed at a central laboratory. For this study, women were divided into three categories: premenopausal (n=1233), postmenopausal (n=1774), and perimenopausal (n=433). Operational definitions were clearly provided. None of the study participants were previously exposed to HRT. The effect of menopause on cardiovascular risk factors was evaluated in the perimenopausal group and postmenopausal group. In addition, the effect of progestin was assessed in a group of 397 perimenopausal women, and the effect of combined estrogen and progesterone therapy was studied in another group of 1746 postmenopausal women (Dallongeville et al., 1995).
In general, menopause was associated with a higher level of serum cholesterol (6.4 vs. 5.9 mmol/l), triglycerides (1.2 vs. 1.0 mmol/l), apolipoprotein (apo) B (1.3 vs. 1.1 g/l), apo A-I (1.9 vs. 1.8 g/l), as well as with elevated diastolic blood pressure (79.7 vs. 77.0 mmHg). Multivariance analysis indicated that these effects were independent of age, body mass index (BMI), glycemia, smoking, alcohol intake, exercise and parity. Researchers compared perimenopausal women treated with progestin alone (n=95) to perimenopausal women not using HRT (n=302). Results reveal no statistical significance in the level of cholesterol, triglycerides, apo B, apo A-I, glycemia and blood pressure between two groups. At the same time, postmenopausal women using a combination of estrogen and progestin (n=369) had significantly lower level of serum cholesterol (6.1 vs. 6.4 mmol/l), triglycerides (1.0 vs 1.2 mmol/l), apo B (1.2 vs. 1.3 g/l), systolic (131.9 vs. 137.9 mmHg) and diastolic (76.9 vs. 79.7 mmHg) blood pressure than postmenopausal women without hormonal therapy (n=1377), taking into account confounding variables. In contrast, serum apo A-I levels were not altered by the combined hormonal therapy (Dallongeville et al., 1995). Based on the findings, Dallongeville and colleagues concluded that menopause is associated with the aggravation of multiple cardiovascular risk factors, as well as the possible benefit of HRT on these factors.

Article #2

Wildman and colleagues (1995) examined the effects of diet and exercise on the progression of menopause-associated changes in blood vessel composition. The research was based on knowledge from cross-sectional studies that subclinical atherosclerosis has
been linked to higher CAD and stroke rates and is greatest among postmenopausal women (Wildman et al., 2004).

In this research, 535 women ages 44 to 50 years old were randomly assigned to a lifestyle-intervention group (n=260) or to an assessment only control group (n=257). Eligible women were required to be premenopausal and to have normal to high-normal ranges of diastolic blood pressure, body mass index (BMI), fasting glucose, and cholesterol levels. Exclusion criteria included hormone therapy and the current use of anti-hypertensive, lipid-lowering, insulin, thyroid, or psychotropic medications. The aim of the intervention was to reduce total dietary and saturated fat and cholesterol, prevent weight gain, and increase physical activity level. Specific goals of the lifestyle intervention were to reduce dietary fat to 25% and saturated fat to less than 7% of total calories. Reduce cholesterol intake to no more than 100mg per day and total caloric intake to 1300kcal/day. Leisure-time physical activity was to be increased to 1000 to 1500 kcal/week of energy expenditure. Regular meetings with a trained nutritionist and a behavioral interventionist were scheduled for the intervention group. Carotid scans were used to assess intima-media thickness of the carotid artery, internal carotid artery, and bulb segment of the carotid artery twice in 353 women during the course of four years. A third scan was obtained 2.5 years later for 113 women (Wildman et al., 2004).

The progression of intima-media thickness was observed for the average of all segments. Among controls, menopause was associated with accelerated intima-media thickness progression (0.003mm/year for premenopausal women vs. 0.008mm/year for perimenopausal and postmenopausal women. Additionally, among the 160
perimenopausal and postmenopausal women, the interventions slowed intima-media thickness progression (0.008 mm/year for the control group vs. 0.004 mm/year for the intervention group). As we can see, this data demonstrates that menopausal transition is associated with accelerated subclinical atherosclerosis progression, and that diet and exercise intervention slows menopause-related atherosclerosis progression (Wildman et al., 2004).

Article #3

Research by Svendsen and colleagues (1994) intended to assist in establishing a vital relationship between menopause related body composition changes that have a potential link to CAD. To assess the variation with age and menopause, 407 healthy, normal women aged 18 to 75 years had body composition and fat distribution measured by dual-energy x-ray absorptiometry (DEXA). Cross-sectional research design was utilized (Svendsen et al., 1994).

The abdominal to total-body tissue ration was calculated as an indicator of fat distribution. Comparison between groups was made with the Student’s unpaired t-test. Product-moment correlation coefficients were calculated. Significance and independence of predictive variables, such as age, menopausal status, and years since menopause were assessed by multiple linear regression analyses. The statistical analysis system was used for all analyses (Svendsen et al., 1994).

The results revealed the following findings: postmenopausal women had significantly more fat, a more central fat distribution, and less lean tissue mass (LTM) than premenopausal women. In premenopausal and postmenopausal women, age only
correlated with abdominal to total-body fat tissue ration, where as years since menopause correlated with fat tissue mass (FTM), fat %, abdominal fat %, and the abdominal to total-body fat tissue ration. Additionally, abdominal to total-body fat tissue ration was statistically significant related to age, but tended also to be independently related to years since menopause. LTM was statistically significant related to menopausal status independent of age and years since menopause (Svendsen et al., 1994). Over all, results suggest, that menopause has a dramatic effect on the body’s composition and on fat distribution that could have a potentially negative effect on the cardiovascular status.

Article #4

Grady and colleague (2002) evaluated the effects of cardiovascular disease outcomes during 6.8 years of hormone replacement therapy. This study was based on the context of The Heart and Estrogen/progestine Replacement Study (HERS) that found no overall reduction in the risk of coronary heart disease (CHD) events among postmenopausal women with CHD. Moreover, in the hormone group, findings did suggest a higher risk of CHD during the first year, and a decreased risk during years three through five. The main objective of this study was to determine if the risk reduction observed in the later years of HERS persisted and resulted in an overall reduced risk of CHD with additional years of follow-up (Grady et al., 2002).

In this study, design and settings consisted of a randomized, blinded, placebo-controlled trial over 4.1 years of duration (HERS) and subsequent, unblended follow-up for 2.7 years (HERS II) conducted at outpatient and community settings at 20 US clinical centers. The population sample consisted of 2763 postmenopausal women with CHD, the
average age was 67 that were enrolled in HERS; 2321 women (93% of those surviving) consented to follow-up in HERS II (Grady et al., 2002).

Participants were randomly assigned to receive 0.625mg/d of conjugated estrogens and 2.5 mg of medroxyprogesterone acetate (n=1380), or placebo (n=1383) during HERS. During HERS II, open-label hormone therapy was prescribed at the personal physicians’ discretion. Measured primary outcomes consisted of nonfatal infarction and CHD death. Secondary cardiovascular events were coronary revascularization, hospitalization for unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease (Grady et al., 2002).

Results revealed that there were no significant decreases in rates of primary CHD events or secondary cardiovascular events among women assigned to the hormone group, compared with the placebo group in HERS, HERS II, or overall. Based on the above results researchers concluded that lower rates of CHD events among women in the hormone group in the final years of HERS did not persist during additional years of follow up. For this reason, postmenopausal hormone therapy should not be used to reduce the risk for CHD events in women (Grady et al., 2002).

Relationship Between Depression and Coronary Artery Disease

Folk tales have long linked negative emotions and death, however only recently have scientific studies examined the connection between them. The very first related scientific effort to establish this relationship was a study by Malzberg (1937). He compared the mortality rate of patients with involutional depression in the New York
State civil hospital system and the rate in the general population of the state. As hypothesized, the mortality rate for the depressed patients was elevated, as it was for patients with both cardiovascular and infectious diseases. However, the study conspicuously confounded the influence of involutional depression with that of chronic institutionalization. Although results were dramatic, they were not convincing, and the issues involved were not further tested for almost forty years (Glassman & Shapiro, 1998). Beginning in the 1970s, investigators compared mortality among patients treated for major depression and the general population. Nine of ten studies found an increased mortality from cardiovascular disease among depressed patients even after adjustment for traditional cardiovascular risk factors (Glassman & Shapiro, 1998). Depression has been cited as a significant risk factor for recurrent cardiac events in patients with established CVD. Depending on the study, 20-50% of patients who die from myocardial infarction are thought to be significantly depressed prior to infarction (Glassman & Shapiro, 1998). Major depression also doubles the risk that patients with newly diagnosed CAD will experience an adverse cardiovascular event within the following twelve months (Carney et al., 1988). Compared to nondepressed patients, ones with depression are at much greater risk of death due to a cardiac-related event for up to ten years following establishment of the CAD diagnosis (Bauer et al., 1995).

Recent advances in neurobiology, endocrinology and neuropsychiatry have demonstrated that there are numerous neurochemical, neuroendocrine, and neuroanatomic alterations in depression. Some of these alterations may also reflect important physiological changes that may contribute to the increased vulnerability of
depressed patients to the development of CAD. The following section will explore potential behavioral and physiologic relationships that may contribute to such a relationship.

_Sympathoadrenal Hyperactivity_

Two main components of “fight or flight” stress response are the hypothalamic-pituitary adrenocortical (HPA) axis and sympathetic nervous system. In response to stress, hypothalamic neurons increase synthesis and release of corticotropin-releasing hormone (CRH) to the hypothalamo-hypophyseal portal system that promotes secretion of the adenocorticotropic hormone (ACTH). ACTH, with the assistance of the sympathetic nervous system, then triggers the release of cortisol and catecholamines from adrenal glands. Adrenal glucocorticoids normally modulate activity of the HPA system by providing feedback to the pituitary, hippocampus and hypothalamus. Endocrine and autonomic alterations in depressed patients include excess cortisol secretion and impaired feedback regulation of plasma cortisol, altered CRH and ACTH concentration, and abnormal regulation of catecholamines. Some of these changes may directly or indirectly affect the cardiovascular system (Grippo & Johnson, 2002).

The above findings have been documented in hundreds of studies presenting evidence of HPA axis hyperactivity in patients with major depression. One of them being the dexamethasone suppression test. Dexamethasone is a synthetic glucocorticoid that by mimicking cortisol induces a negative feedback to the pituitary, hypothalamus and hippocampus. In a healthy individual the administration of dexamethasone will result in the reduction of circulating cortisol due to its negative feedback on the HPA pathway.
Studies have shown that cortisol is not suppressed following the administration of dexamethasone in 50% of clinically depressed adults, indicating its hypersecretion during depression (Grippo & Johnson, 2002; Nemeroff et al., 1998). Individuals with a high concentration of cortisol also demonstrated to have an increased plasma concentration of norepinephrine that has its affect on vascular and extravascular compartments.

Interaction between the HPA axis and the sympathetic nervous system may be involved in the risk of adverse cardiovascular events in depression. The CRH pathway has been demonstrated to have extra hypothalamic connections to central components of the autonomic nervous system that leads to stimulation of sympathetic outflow. Thus, increasing circulating catecholamines, such as epinephrine, and norepinephrine that contribute to an increase in heart rate and contractility in depressed patients by stimulating B-adrenergic receptors. These endogenous neurotransmitters can be a trigger for malignant cardiac arrhythmias, especially in patients with reduced left ventricular function (Grippo & Johnson, 2002). Elevated heart rate has been not only associated with sudden death, myocardial ischemia, arrhythmias and cardiac failure, but also an increase in other cardiovascular risk factors such as hypertension, increased body mass index and increased blood glucose (Carney et al., 1993). Carney and colleagues (1987) found that depressed patients with CAD at cardiac catheterization had a significantly higher prevalence of ventricular tachycardia and longer duration of each episode compared with a group of non-depressed controls with CAD. Based on the above information it appears plausible that the HPA axis and the sympathetic nervous system may mediate the connection between depression and CAD through several mechanisms.
Stress

Grippo and Johnson (2002) hypothesized that it is possible that depression is associated with altered HPA axis function and elevated sympathetic activity, which in turn may lead to cardiovascular dysregulation, however, often times a common variable – the presence of exogenous stress – may influence both mood and cardiovascular regulation. The stress response usually evokes alpha-adrenergic simulation, which results in vasoconstriction, thus raising blood pressure. Under normal circumstances, the coronary arteries then dilate in response to the increase in blood pressure. Research has demonstrated that stressful life events influence the pathogenesis of depressive disorder, resulting in altered neurochemical function, such as changes in the utilization of norepinephrine, dopamine, and serotonin. Activation of the sympathetic nervous system takes place as well. If this alteration persists for a prolonged period of time, one can hypothesize that compensatory function of cardiovascular system will take its toll resulting in coronary vasoconstriction and increased heart rate and contractility. The effects of these alterations on the development of CAD have been discussed in a previous section.

Research also demonstrates that psychosocial variables such as education level, social class, bereavement, major life events, retirement, nervous tension, anxiety, and anger have all been linked to sudden cardiac death (Silva, 1986). Stress influences blood pressure in both humans and animals. Many animal models of stress-induced hypertension have been developed and used to demonstrate that environmental stressors are involved in the pathogenesis of hypertension. Stress may promote hypertension
through repeated blood pressure elevation, stimulation of the nervous system to produce vasoconstrictive hormones, changes in vascular resistance or CNS alterations. In a series from Duke University, positive mental stress test results were more predictive than exercise test for provoking cardiac distress, and it may well be that patients with depression have an exaggerated response to stressful situations (Grippo & Johnson, 2002). In general it appears that individuals who experience life stress may be at risk for adverse cardiovascular outcomes, as well as having an increased risk for depression, thus creating a possibility that CAD and depression might be two outcomes of the same causative agent.

*Heart Rate Variability*

Heart rate variability (HRV) reflects the capacity of the autonomic nervous system to vary the intervals between consecutive heart beats according to hemodynamic fluctuations and other physiologic perturbations (Grippo & Johnson, 2002). It is defined specifically as the standard deviation of successive R-to-R intervals in sinus rhythm and is thought to reflect the balance between sympathetic and parasympathetic nervous systems on the cardiac pacemaker (Nemoroff et al., 1998). Both peripheral and central nervous system factors can influence heart rate and its variability. Several neurotransmitters acting both centrally and peripherally, including norepinephrine, dopamine, acetylcholine and serotonin, may be involved in the modulation of heart rate variability, although the central role has been given to the cholinergic vagus nerve, a component of the parasympathetic nervous system (Nemoroff et al., 2002; Rechlin et al, 1994).
A high degree of HRV is observed in normal individuals with good cardiac function, whereas HRV may be decreased in patients with severe CAD or heart failure. Several investigators identified reduced overall heart rate variability or beat-to-beat variability in depressed patients both with and without CVD, compared to non-depressed individuals (Pitzalis et al., 2001; Rechlin et al, 1994). Diminished HRV is believed to represent decreased parasympathetic activity, possibly predisposing to both ventricular arrhythmias and the excessive cardiovascular mortality found in MDD (Nemeroff et al., 2002).

Another mechanism of action that could be responsible for reduced HRV in depressed individuals may be related to abnormal catecholamine regulation. Peripheral norepinephrine hyperactivity in depressed patients may lead to increased sympathetic cardiac tone and in turn, reduced HRV. Peripheral or central dopamine may also modulate HRV via its influence on sympathetic activity. Activation of inhibitory dopamine receptors present on noradrenergic nerve terminals in both central and peripheral nervous system leads to a decrease in norepinephrine release (Grippo & Johnson, 2002). These findings suggest that decreased dopamine activity in either the central or peripheral nervous system may lead to norepinephrine alterations and influencing HRV. This hypothesis is also consistent with evidence regarding hypoactivity of dopaminergic activity in depression.

Another major influence on HRV comes from parasympathetic innervations of the heart. Together with increased sympathetic tone, reduced vagal stimulation has been suggested to have a dominant influence on HRV in humans. However, even though one
might hypothesis that cholinergic activity in the central nervous system might be increased in depression, this mechanism of action has not received much experimental attention.

Further recent pharmacological data suggests that central serotonergic mechanisms may also affect HRV in depressed patients. Treatment with fluoxetine, a serotonin reuptake inhibitor, was shown to increase 24 hour HRV in depressed subjects (Khaykin et al., 1998). However, several other studies have reported no significant changes in HRV in depressed patients treated with serotonin reuptake inhibitors (Grippo & Johnson, 2002). Theoretically it still remains possible that central serotonin may mediate sympathetic outflow to affect HRV through its ultimate effect on the discharge of peripheral noradrenergic neurons or by its interaction with other central neurotransmitters such as dopamine or norepinephrine (Grippo & Johnson, 2002).

Platelets Reactivity

Platelets play a key role in the pathogenesis of acute coronary syndrome by exerting their effect on hemostasis, thrombosis and atherosclerosis through interaction with subendothelial tissues, as well as plasma coagulatory factors (Nemoeroff et al., 1998). In 1991 Markovitz and Matthews proposed that enhanced platelet responses to psychological stress might contribute to the development of CAD. Serotonin, secreted by platelets, acting on HT2 receptors, induces both platelets aggregation and coronary vasoconstriction. This vasoconstriction appears to occur when normal endothelial cell counterregulatory mechanisms of vascular relaxation are impaired, as observed in CAD (Nemeroff et al., 1998).
Further, patients suffering from both depression and CAD were reported to exhibit evidence of platelet activation. Musselman and colleagues used a flow cytometry to identify specific epitopes on the prothrobinaese complex to demonstrate that patients with depression had increased activation of their glycoprotein IIb/IIIa receptors (1996). This finding is especially remarkable because daily treatment of the CAD patients with aspirin does not alleviate their depression-associated platelet aggregation. At the same time, preliminary data suggests that treatment with selective serotonin reuptake inhibitors (SSRIs) reduces the level of platelet activation similar to non-depressed controls (Nemeroff et al., 1998).

Although more research is needed to evaluate the relationship between platelet activation and clinical outcomes, increased platelet reactivity may play an important role in creating a link between depression and CAD.

**Immune System Dysfunction**

Recent developments in psycho-neuro-immunology suggest that depression can modify the immune system, while at the same time, immune system abnormalities may play a role in the development of depression. The function of the immune system in depressed individuals is complex, involving hyperactivity of some factors with depression of others. Further more, the influence of the immune system in the link between depression and cardiovascular disease may involve both peripheral and central nervous system mechanisms (Grippo & Johnson, 2002).

Proinflammatory cytokines have been implicated in the pathogenesis of atherosclerosis, a process that leads to the development of CAD. Damage to the
endothelium of coronary vessels, imposed by atherosclerotic changes, leads to the release of proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and necrosis factor alpha (TNF-L). Release of the above listed cytokines induces leukocyte chemoattraction with exaggerated adhesion to endothelium. Macrophages and T-cells act as inflammatory mediators by invading into vascular tissue and further activating cytokine cascade as well as growth release factor. A continuous degradation of the plaque matrix by macrophages leads to plaque instability, thrombus formation resulting in vascular occlusion (Joynt et al., 2003). The magnitude of the proinflammatory response to the endothelial damage thus may predict progression and prognosis of coronary disease.

We also know that depression is associated with an excessive secretion of IL-1, TNF-L and interferon. Literatures reports that when TNF-L is administered to humans, it results in depressive symptoms such as fatigue, malaise, lethargy and anorexia, similarly to IL- that has been shown to induce psychomotor and appetite disturbance, sleep alterations and lethargy (Grippo & Johnson, 2002). According to Maes and colleagues (1996), depressed patients with and without cardiovascular disease have been shown to have elevated levels of plasma inflammatory markers, such as C-reactive protein (CRP), fibrinogen, IL-1, IL-6. They further suggested that increased levels of inflammatory molecules seen in depressed patients may represent a response to chronic psychosocial distress. So, it appears that augmented inflammatory response to endothelial damage and consequent accelerated progression of atherosclerosis and plaque rapture might explain the link between depression and CAD (Joynt et al., 2003).
In contrast to the activation of some immunological components involved in nonspecific immune response, research data shows that depressed individuals present with a blunted cell-mediated immune response, indicating immunosuppression (Maes, 1995). Several immunological factors specific to cell mediated immunity have shown decreased activity in depressed individuals, such as Natural Killers (NK), T-helper cells and T-suppressors-cytotoxic cells, as well B-cells responsible for humoral-mediated immunity (Grippo & Johnson, 2002).

At the same time, the nature of the relationship between the inflammatory process and depressive disorder is not well defined. It is unclear whether immune abnormalities play an etiological role in depression or conversely, whether depression leads to an altered immunological response. Inflammatory hyper-responsiveness has been postulated to play a role in endothelial damage to the cerebral vasculature and thus contribute to the development of a specific subtype of depression known as vascular depression that is characterized by apathy, psychomotor changes, and cognitive impairment. This type of depression is more common in elderly and less often associated with a family history of depression. The vascular changes seen there correlate with degree of atherosclerosis present, which further supports the likelihood of a common underlying process between depression and CAD (Joynt et al., 2003). Currently there is no evidence to suggest that vascular dementia is more common in individuals with CAD than without.

Joynt and colleagues (2003) also suggest that it is possible that interleukins and other cytokines might affect the onset and progression of depression via systemic rather than via local endothelial damage. This argument is supported by the findings that
patients treated with IL-1 and interferon for cancer or chronic viral infection tend to develop a syndrome of depressive symptoms such as anorexia and decreased social interaction (Maes et al., 1996).

At the present time it seems likely that inflammation impacts the progression of cardiovascular disease, but it remains unclear whether the inflammation seen in depressed patients is a result of the stress response or whether inflammation contributes to the pathogenesis of depression.

*Fatigue and Decreased Physical Activity.*

By definition depressed patients often suffer from fatigue, low energy level, psychomotor retardation and amotivation (American Psychiatric Association, 2000). Excess fatigue, especially in elderly individuals that are already at risk for developing CAD, may play a contributing role in development of cardiovascular abnormalities.

Excess fatigue has been shown to be a precursor to myocardial infarction and death by several research studies (Appels & Mulder, 2002; Rissanen et al., 2002). Exhaustion that is commonly described by depressed individuals is considered to be a short term-term risk factor for acute coronary syndrome, and is predictive of future myocardial infarctions independent of blood pressure, smoking, cholesterol, age, and the use of anti-hypertensive agents (Appels & Mulder, 2002). While it is possible for cardiac decompensation to be manifested by excessive tiredness, data indicates that exhaustion is unlikely to be solely a consequence of an underlying cardiovascular disease (Grippo & Johnson, 2002).
Grippo and Johnson (2002) also believe that it is important to recognize that excess fatigue may not be a cause of cardiovascular disease, but rather interact with other risk factors, such as a low level of physical activity, which is in itself a risk factor for adverse cardiac event. The above authors also point out that the possibility that fatigue and physical inactivity influence the relationship between depression and CAD is supported by the fact that physical exercise is often used as a preventative measure and part of a treatment component for both of the pathological processes. Beniamini and colleagues (1997) have demonstrated that strength training has been shown to improve mood and self-esteem in cardiac rehabilitation patients. As we already know physical activity promotes release of neurotransmitters, such as serotonin, dopamine, norepinephrine, and endorphins that are vital in mood regulation (Martha Fankhauser, personal communication, September 11, 2004). In a sample of patients with heart failure, those assigned to one year of supervised exercise training showed a 63% reduction in mortality, relative to the control group that continued their normal activities. Additionally, regular exercise has also demonstrated to have a positive effect on heart rate variability that is implicated for both CAD and depression (Kristal-Boneh et al., 1995).

**Noncompliance**

As we know, noncompliance with preventative measures and medical regimen has been shown to worsen the prognosis of CAD. Joynt and colleagues (2003) bring an example of two large studies that took place in the early 1990s and suggested a twofold to threefold increase of mortality for noncompliant patients in the year following
myocardial infarction. At the same time, the nature of depression itself increases the individual’s risk for not following primary and secondary prevention guidelines secondary to a decrease in energy, motivation, and a desire for change. Depressed patients may be more likely than nondepressed individuals to have their cardiovascular risk factors in check, such as smoking, hypertension, diabetes, hypercholesterolemia, and obesity (Joynt et al., 2003). Studies done to evaluate compliance in patients with CVD found that depressed patients were less likely to comply with the recommendation for daily aspirin therapy, as well as to adhere to a cardiac rehabilitation program after MI compared to the nondepressed population (Ades et al., 1992; Wang et al., 2002).

Some authors speculate that it may be noncompliance itself, rather than noncompliance with a specific medical regimen that is so detrimental to a prognosis. Alternatively, noncompliance may be a marker for depression, which we know to be associated with poor prognosis.

The following section will provide research evidence to further assist in establishing the relationship between CAD and depression.

*Articles Related to Relationship Between Depression and Coronary Artery Disease*

*Article #1*

A study conducted by Barefoot and colleagues (1996) was based on previous findings which established that patients with CAD have an increased risk of death if they were depressed at the time of hospitalization, however follow up periods were limited in these studies. Therefore, current investigation is focused to investigate this phenomenon over an extended period of time (Barefoot et al., 1996).
Patients with established CAD (> 75% narrowing in diameter of at least one coronary artery, n=1250) were assessed for depression with Zung’s Self-Rating Depression Scale (SDS) and were followed for subsequent mortality. Patients were recruited over a six-year period and follow-ups ranged up to 19.4 years. Patients’ SDS scores were divided into groups using standard criteria for purposes of effect-size calculation and data representation. Those with score less than 50 (n=789) were classified as nondepressed, those with scores between 50-59 (n=321) were considered to have mild depression, and those with scores of more than 60 (n=140) were classified as having moderate to severe depression. All data was summarized in a chart. Patients were contacted six and twelve months after hospitalization and annually thereafter. Data analysis was performed using Cox proportional-hazard model (Barefoot et al., 1996).

As expected, hazard scores were strong predictors of cardiac mortality. More than half of patients (51.4%) in the moderate to severely depressed group died of cardiovascular causes, compared with 42.4% of the mildly depressed patients and 35.5% of the nondepressed patients. After an adjustment for hazard scores, the odds of a cardiac death were 69% greater in the moderate/severe group and 38% greater in the mildly depressed group than in the nondepressed group. Increased risk was not confined to the initial months after hospitalization. Patients with high SDS scores at baseline still had a higher risk of cardiac death more than five years later. Compared with nondepressed, patients with moderate to severe depression who had an 84% greater risk five to ten years later and a 72% greater risk after more than ten years. The heightened long-term risk of depressed patients suggests that depression may be persistent or frequently recurrent and
is associated with CAD progression, triggering of acute events, or both (Barefoot et al., 1996).

Article #2

The focus of Carney and colleagues’ (1988) study was to evaluate heart rate variability between depressed and non-depressed patients with CAD. The authors based their research on existing evidence that depression is a common psychiatric complaint in patients with CAD, and it has been associated with increased mortality and medical morbidity in this type of patient population (Carney et al., 1988).

Seventy-seven patients, undergoing elective cardiac catheterization for evaluation of suspected CAD were administered a diagnostic psychiatric interview one day before catheterization by Master’s level psychologists with experience and training in psychiatric diagnosis and their mean heart rates and heart rate variability were determined from the results of a 24 hours ambulatory ECG (Carney et al., 1988).

The mean heart rate for depressed patients with CAD was significantly higher than for nondepressed CAD patients, independent of the patient’s age, smoking status, beta-blocker therapy. Heart rate variability was lower in depressed patients but did not achieve significance. Based on the findings, it was concluded that an elevated heart rate may represent an increased sympathetic tone in depressed CAD patients, and may help to explain the increased morbidity and mortality reported in these patient populations (Carney et al., 1988). The findings are consistent with previous research that points out that an increased heart rate is a significant predictor of mortality in patients at risk for myocardial infarction or sudden death. As well as the present current gold standard of
treatment following myocardial infarction with beta-blockade that reduces heart rate and thus decreases morbidity and mortality (Carney et al., 1988).

Article #3

In their research, Wang and colleagues (2002) evaluated the impact of depressive symptoms and psychosocial factors on compliance with antihypertensive medications. The objective goal of this research was to address the epidemic of poor compliance with antihypertensive medication by identifying factors that are associated with poor adherence, such as modifiable psychosocial and behavioral characteristics of the patients (Wang et al., 2002).

Four hundred ninety six treated hypertensive patients were drawn from a large HMO and a VA medical center to conduct a cross-sectional study. Data collection consisted of an especially developed survey instrument that aimed to assess patients’ psychosocial and behavioral characteristics, including health beliefs, knowledge, and social support regarding blood pressure medications. Satisfaction with health care, depressive symptoms and its severity, alcohol consumption, tobacco use, and internal versus external locus of control were also included in the survey. Patient demographics, clinical characteristics and features of antihypertensive medication regimen were recorded. To calculate actual adherence to prescribed regimen, all prescriptions filled for antihypertensive medication were recorded for a 365-day study period. Adjusted odds ratios (ORs) of antihypertensive compliance were based on original logistic regression model (Wang et al., 2002).
After adjusting for the potential confounding effects of demographics, clinical, and other psychosocial variables, researchers found that depression was significantly associated with noncompliance. There was also a trend toward an improved compliance for patients perceiving that their health is controlled by external factors. There was no association between knowledge of hypertension, health beliefs and behaviors, social support, or satisfaction with health care (Wang et al., 2002).

Based on the findings, Wang and colleagues concluded that depressive symptomatology may be under-recognized but is a modifiable risk factor for poor compliance with antihypertensive medications.

Article #4

The purpose of the Carney and colleagues (1993) research was to examine the relationship between ventricular tachycardia and psychiatric depression in patients with diagnosed CAD. Authors hypothesized that depressed patients with CAD would have a higher prevalence of ventricular tachycardia (VT) than nondepressed patients with CAD (Carney et al., 1993).

Methods included one hundred and three patients that were found to have significant CAD by elective diagnostic cardiac catheterization. All patients were administered a standardized psychiatric interview and underwent 24-hour Holter monitoring (Carney et al., 1993).

Out of the above listed patient population, twenty one (20%) met the criteria for either a major or minor depressive disorder. There were no significant differences between depressed and nondepressed patients in respect to CAD severity or ventricular
function. Results revealed that five (23.8%) of the depressed patients and three (3.7%) of the nondepressed patients exhibited episodes of VT during the 24 hours of Holter monitoring (p<0.008). Even after controlling for relevant covariates this difference still remained significant (Carney et al., 1993).

Based on the findings, Carney and colleagues concluded that there is a higher prevalence of VT among patients with CAD and depression than among those with CAD patients without depression, thus furthering our understanding about the high mortality rate in depressed patients with CAD (Carney et al., 1993).

Article #5

Shimbo and colleagues (2002) evaluated an exaggeration of serotonin-mediated platelet reactivity in relationship to depression and acute coronary syndromes. The study was based on previous findings that depression is a valuable prognostic factor for Acute Coronary Syndrome (ACS) survivors (Shimbo et al., 2002).

Methods involved a total of thirty patients: fifteen clinically depressed and fifteen matched non-depressed. There were no statistical differences in demographic characteristics, clinical and laboratory parameters, or medication use between the depression and non-depressed group (Shimbo et al., 2002).

Platelet reactivity was measured by whole blood impedance aggregometry. Whole blood platelet aggregation has been suggested to be superior to platelet-rich plasma in assessing platelet reactivity because platelet-rich plasma and optical aggregometry require manipulation of whole blood and removal of intrinsic components, which make studies of platelet function less physiologic (Shimbo et al., 2002).
Results were expressed as mean +/- SEM. The 2-tailed independent sample t test was used to test for statistical difference between depressed and non-depressed groups. A p value <0.05 was considered statistically significant. The data demonstrated that 5-HT-mediated platelet reactivity is significantly increased in depressed patients relative non-depressed matched controls. This data suggests that the higher ACS risk associated with depression may be caused in part by exaggerated platelet activity (Shimbo et al., 2002).

To support the findings, researchers offered an explanation that an increase in 5HT-mediated platelet activity may be a consequence of 5-HT2A receptors upregulation that takes place during depression, and thus increases the response of the platelet signaling system (Shimbo et al., 2002). Shimbo and colleagues also noticed that whether antidepressant therapy decreases ACS risk in depressed patients remains unexplored, but could potentially play a role in decreasing the risk for ACS events.

Article #6

The main purpose of the Song and colleagues’ (1999) research was to examine the effects of psychological stress on selected immune-inflammatory variables in relation to plasma cortisol level.

In this study, researchers evaluated the effect of academic examination stress on the serum concentration of IL-1 receptor (R) antagonist (A), soluble (s) IL-2R, soluble glycoprotein 130 (sgp130), clara cell protein (CC16), sCD8 and sCD14 in thirty eight university students. The relationships among changes in the above immune-inflammatory variables, level of serum cortisol, and sores on the Perceived Stress Scale (PSS) or the State-Trait Anxiety Inventory (STAI) were examined (Song et al., 1999). Subjects
consisted of twelve male students, thirteen female students, who were not using oral contraceptives, and thirteen female students who had used contraceptive drugs for at least three consecutive months. Exclusion criteria for subjects were the following: subjects with a past or present history of psychiatric disorder; subjects who had ever taken major psychotropic medications, or subjects who were drug abusers or heavy smokers (i.e. >15 cigarettes daily); subjects with any endocrine, immune or metabolic disorders; subjects who currently suffered from infectious, allergic or inflammatory diseases; subjects with abnormal routine blood tests; subjects who took any medical drugs or suffered from any disease during the study span; and subjects who fainted during blood drawing (Song et al., 1999).

Song and colleagues based their study on the previous knowledge that increase in plasma IL-1, IL-2, IL-6 and IL-1RA, sIL-2R, sIL-6R and sCD8 and a decrease in CC16 concentration have been reported in both unmediated depressed and schizophrenic patients (1999).

The results revealed that academic examination stress was associated with a significant increase in PSS and STAI scores, and in serum sgp130 and sCD14 concentrations in students with high, but not with low, stress perception. There were also stress induced differences in serum IL-1RA, sIL-6R and CC16 concentration between students with high vs. low stress-induced anxiety. Importantly, the stress-induced increase in serum CD8 was significantly more pronounced in male students, whereas the increase in serum sgp130 was significantly more pronounced in female students taking contraceptive drugs (Song et al., 1999).
Based on the above findings, Song and colleagues concluded that psychological stress induced immune-inflammatory changes pointing toward complex regulatory responses in IL-6 signaling, a decrease anti-inflammatory capacity of the serum, and interactions with T cell and monocytic activation. They also believe that sex hormones may modify stress-induced immune-inflammatory responses (Song et al., 1999).

Article #7

McGowan and colleagues (2004) research study evaluated the relationship between vital exhaustion, depression and co-morbid illnesses in patients following first myocardial infarction. It was based on the current body of knowledge that vital exhaustion and depression appear to be independent risk factors for cardiovascular disease, yet the direction of the relationship was never established. The purpose of this research was to examine the association between depression and vital exhaustion and to investigate the extent to which any association is the result of comorbid illness (McGowan et al., 2004).

The methods of this study consisted of three hundred and five consecutive patients that were examined on average 3.6 days following hospital admission with first myocardial infarction (MI). Subjects were considered for inclusion if they were less than eighty years of age, they had no prior history of MI, their MI was not related to the performance of an invasive medical procedure, and they met World Health Organization (WHO) criteria for MI. These criteria required that two of the following features were present: history of typical chest pain, characteristic EKG changes, and a rise of creatining phosphokinase (CPK) up to twice the normal limits (McGowan et al., 2004).
Vital exhaustion was characterized by the feeling of excess fatigue, lack of energy, irritability, and demoralization. The Maastricht Questionnaire (MQ; vital exhaustion) was administered together with the Hospital Anxiety and Depression Scale (HADS) as soon as subjects were sufficiently well to complete them. Details of comorbid physical illness were recorded as well. The factors structure of the MQ was explored using factor analysis. Analysis was performed using SPSS Version 10.1 for Windows (McGowan et al., 2004).

The results revealed the following findings. Depression and vital exhaustion were highly correlated ($r = 0.61, P<0.01$). This correlation did not diminish when controlling for age, sex, and comorbidity ($r = 0.69, P<0.01$). Factor analysis of MQ score gave a four-factor solution: fatigue (18.2% of variance, depression 17.9%, lack of concentration 9.5%, and sleep difficulties 8.1%). Importantly, the fatigue dimensions of the MQ remained highly associated with HADS depression score ($r = 0.50, P<0.01$), controlling for age, sex, and comorbidity (McGowan et al., 2004).

Based on these findings, McGowan and colleagues (2004) concluded that depression and fatigue are highly correlated and their association is not attributed to comorbid physical illnesses or the tendency of the MQ to measure depression. Authors also recommend that future studies should investigate fatigue instead of vital exhaustion as a potential factor for poor cardiac prognosis independent of the influence of depression (McGowan et al., 2004).
Significance of the Relationship Between Depression and Coronary Artery Disease for Postmenopausal Women.

The previous sections have demonstrated that postmenopausal women are at increased risk for developing both depression and CAD. Furthermore, hormonal postmenopausal changes are demonstrated to have a significant influence on both pathophysiological mechanisms making this relationship even more important for this age group. At the same time, HRT benefits that demonstrated a 35-50% reduction in risk of coronary events in more than thirty estrogen studies over the past thirty years, have been recently refuted with the completion of HERS, a 6.8 years long randomized, blinded, placebo-controlled trial that found no overall reduction in risk of CHD (Grady et al., 2002). As was reported previously, there are several different areas of criticism about the methodology of the study that may have an effect on the interpretation of the findings.

*Depression and cardiovascular sequela in postmenopausal women* was the first part of HERS of the Women's Health Initiative Observations Study were 91,676 women were followed for an average of 4.1 years. The purpose of this research was to investigate prevalence, cardiovascular correlates, and the relationship to subsequent cardiovascular events of depressive symptoms among generally healthy postmenopausal women (Wasswetheil-Smoller et al., 2004).

Depression was measured at a baseline with a short form of the Center for Epidemiological Studies Depression Scale. The risk of cardiovascular disease (CVD) events were estimated from COX proportional hazards models adjusting for multiple demographic, clinical, and risk factor covariates (Wasswetheil-Smoller et al., 2004).
Depressive symptoms were reported by 15.8% of all women. Depression was significantly related to CVD risk and comorbidity such as hypertension and a history of stroke or angina. Among women with no history of CVD, depression was found to be an independent predictor of CVD death and all-cause mortality. Adjustments were made for age, education, income, diabetes, hypertension, smoking, high cholesterol level, body mass index, and physical activity (Wasswetheil-Smoller et al., 2004). The results of this study conclude, that a large proportion of postmenopausal women report depressive symptoms that are significantly related to an increased risk of CVD (Wasswetheil-Smoller et al., 2004). Authors suggested a need for a further clinical trial to assess the efficacy of early recognition and treatment of depression and its role of lowering CVD risk.

Recommendations for Clinical Practice and Future Research.

This paper provided an overview of the literature on the physiological and psychological links between depression and CAD in postmenopausal women. Understanding this relationship by health care providers, such as advanced practice and registered nurses and physicians will result in improved diagnosing and more effective interventions, as well as a better utilization of primary and secondary preventative measures. Specifically, an in depth literature review revealed that regular screening of postmenopausal women for signs and symptoms of depression by primary health care providers could be vital in the primary and secondary prevention of CAD and the preservation of an individual’s well-being. Health care providers should be conscious of the fact that regular physical exercise has been demonstrated to have a positive effect on
heart rate variability that is implicated for both CAD and depression and has been a significant predictor of morbidity and mortality. Research data further suggests that treatment of depression with SSRIs may also reduce the level of platelet activation and thus minimize the risk of developing CAD. Furthermore, prophylactics with aspirin 75-325 mg per day, the gold standard of prevention and treatment of an acute coronary event, has not proven to be effective against platelet aggregation that is associated and possibly caused by depression. Recent advances in clinical research have also demonstrated that regular physical exercise and a healthy diet has a positive effect on menopause-related atherosclerotic changes as well as menopause-related changes in body fat distribution, and thus should be utilized as primary preventative measures.

The importance of collaboration among specialty providers, such as psychiatric mental health, obstetrics and gynecology, cardiology, and primary health care providers, will be essential in the provision of a holistic approach to care. The potential cause and effect relationship between depression and CAD in menopausal women should potentate further screening in women exhibiting either depression or CAD. As we have learned from the research findings, depressed individuals are more likely to have an increase in cardiovascular risk factors, such as smoking, hypertension, diabetes, hypercholesterolemia, and obesity compared to non-depressed individuals. For this reason, regular physical examination and screening procedures should be utilized for this population group. Consultations and expert opinion should become vital in providing an optimal treatment regimen and to ensure a continuity of care. Also, as was demonstrated
in the case of HRT, the ability to actively evaluate research becomes especially important in our ever-changing guidelines of clinical practice.

In order to reduce cardiovascular morbidity and mortality in depressed, postmenopausal women, it may be insufficient just to treat depression with conventional therapies, but rather take a holistic approach that encompasses a deeper understanding of the body, mind, and spirit at the time of physiological changes in a woman’s life. More importantly, widely used pharmacological antidepressants, such as MAOIs, TCAs, and some antipsychotic agents are potentially cardiotoxic. With the recent advances of the SSRI group of antidepressants, more medically ill patients can be treated without complicating cardiovascular side effects. A new case of depressive disorder that presents at the time of menopause should be alarming in term of hormonal inbalances, where laboratory evaluation will provide necessary guidance of hormone replacement therapy. Co-morbidity of depression and anxiety will have a definite effect on treatment choices for both the disease processes based on a side effect profile, and on the desired outcomes. One should also remember that depressive episodes may have residual physiological effects that do not normalize even with the successful treatment of depression.

Further research in this area will help us to gain a better understanding of the central and peripheral nervous system mechanisms that underlie depression and influence pathogenesis of CAD, helping us to achieve optimal clinical practice. We have yet to determine whether early recognition and treatment of depressed individuals may decrease their risk of developing CAD. Further research in this area would allow us to advance the current knowledge regarding the role of antidepressant therapy in the prevention and
treatment of these highly co-morbid disease processes. Contradictory results regarding cardiovascular risks and benefits of HRT is another area of research that would offer a potential benefit for the consumer by further exploring the effects of various types of HRT, where many questions remain unanswered. Understanding the cause and effect relationship of depression and CAD and their connection to hormonal changes in postmenopausal women will result in the development of more comprehensive treatment programs targeted for this specific population group.
Appendix A

Diagnostic Criteria for Major Depressive Disorder

To make a diagnosis of Major Depressive episode five or more of the following symptoms must be present during the same two weeks period and present a change from a previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. As in any DSM-IV diagnostic criteria, unless specified, symptoms related to general medical condition should be excluded, along with mood-incongruent delusions or hallucinations.

1) depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others.

2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

3) significant weight loss when not dieting or weight gain (change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

4) insomnia or hypersomnia nearly every day

5) psychomotor agitation or retardation nearly every day (observed by others, not merely subjective feelings of restlessness or being slowed down)

6) fatigue or loss of energy nearly every day

7) feeling of worthless or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8) diminished ability to think or concentrate, or indecisiveness, nearly every day
(either by subjective account or as observed by others)

9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation
without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet a criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social,
occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiologic effect of substance or a general
medical condition

E. The symptoms are not better accounted for by Bereavement, after loss of a loved one,
the symptoms persist for longer than two month or are characterized by marked
functional impairment, morbid preoccupation with worthlessness, suicidal ideation,
psychotic symptoms, or psychomotor retardation.

Additionally, severity of the depressive episode should also be assessed as follows:
Mild: Few, if any of the above listed symptoms in excess of those required to make a
diagnosis and symptoms result in only minor impairment in occupational functioning or
in usual social activities.

Moderate: Symptoms of functional impairment between “mild” and “severe”.

Severe Without Psychotic Features: Several symptoms in excess of those required to
make a diagnosis, and symptoms markedly interfere with occupational functioning or
with usual social activities or relationship with others.
Severe With Psychotic Features: Delusions and hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent (American Psychiatric Association, DSM-IV-TR, 2000).
Appendix B

Causes of Under-diagnosis and Under-treatment of Depression in Medically Ill Patients

- Emphasis on somatic symptoms rather than cognitive and mood complaints
- Reluctance to stigmatize patients with psychiatric diagnosis
- Mild or nonspecific symptoms of depression
- Fear of antidepressant side effects
- Mistaken notion that reactive depressions are not pathological (exp. "Should be depressed, she has cancer")
- Time limitations in primary care
- Inadequate training of primary care physicians in psychiatry.

(Katon & Schulberg, 1992).
Appendix C

Factors that Place Women at Higher Risk for Depression Compared to Males

- Loss of parent before age 10
- Physical or sexual abuse as a child
- History of mood disorders in early reproductive years
- Family history of mood disorders
- Use of certain contraceptives
- Use of certain infertility treatments
- Ongoing psychological and social stress
- Loss of social support system or the threat to such a loss

(The Cleveland Clinic Department of Psychiatry and Psychology, 2004).
Appendix D

Coronary Artery Disease: Secondary Prevention

- Smoking: complete cessation
- Blood pressure control: <140/90 mm Hg, <135/85 mm Hg if heart failure or renal insufficiency, <130/80 if diabetes
- Lipids: LDL<100 as goal, <7% saturated fat diet, <20 mg/day cholesterol, triglycerides <200 as goal
- Physical activity: 30 minutes 3-4 days/week minimum, 30 minutes/day optimal
- Weight management: Body mass index (BMI) of 18.5-24.9 kg/m²
- Diabetes Mellitus: Hemoglobin A1c <7% is advised
- Medications: ASA 75-325 mg PO daily, if ASA is contraindicated use clopidogrel or warfarin; Beta blockers implemented with first 24 hours, ACE inhibitors within first 24 hours following acute coronary syndrome.

(American Heart Association, 2004)
References


