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HORMONE REPLACEMENT THERAPY AND CORONARY HEART DISEASE IN WOMEN: AN EPIDEMIOLOGIC REVIEW AND DESCRIPTIVE STUDY OF POST MYOCARDIAL INFARCTION WOMEN

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HORMONE REPLACEMENT THERAPY AND CORONARY HEART DISEASE IN WOMEN
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By

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ABSTRACT

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By

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Coronary heart disease (CHD) is the leading cause of death among women in the United States. A promising prevention for CHD in older women is hormone replacement therapy (HRT). Epidemiologic evidence suggests that HRT decreases the risk of myocardial infarction (MI) by up to 50%. Despite established benefits, HRT is under utilized among elderly women. Physician prescribing behavior may be low for a cardioprotective use of HRT. This study examined prevalence of HRT use among a series of women hospitalized for MI and the frequency of having discussed HRT with a physician. Women were either interviewed post discharge or in-hospital. A total of 156 women responded with 23% using HRT, while 54% reported never having discussed HRT with a physician. Only one women reported discussion of HRT with her cardiologist. The current study supports observations that HRT use among older women is low and cardiologist initiated discussion remains low.

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INTRODUCTION

Coronary heart disease (CHD) is a major public health concern in the United States. It is the leading cause of disability and death among women. A promising preventive intervention for CHD risk in older women is hormone replacement therapy (HRT). Epidemiologic evidence from research conducted over the last two decades suggests that HRT decreases the risk of myocardial infarction (MI), the major subgroup of CHD, by up to 50%. More recent studies also suggest that hormone use may be an effective secondary preventive measure which decreases the risk of recurring MI.

This thesis begins by examining the literature over the past 15 years that deals with the burden of CHD among women, patterns of HRT use, and the impact of HRT on MI risk. It then presents data from a recently assembled series of community-recruited MI patients, who reported on their frequency of HRT use and their history of HRT discussion with a health care professional. The thesis ends with a discussion on the strengths and weaknesses of utilizing an existing database to answer questions on HRT use among community women.

Questions specifically addressed by this thesis are:

- What does the current literature reveal about HRT utilization and its impact on CHD in older women?
- What is the prevalence of HRT use in a series of community recruited MI patients?
- What proportion of women have ever discussed HRT with a health care professional?
- What characteristics are associated with women who are on HRT at the time of their MI?
- What are the strengths and weaknesses of the existing MICH database to address these questions?
- What are the lessons learned from accessing the MICH database for research?

Answers to these questions will be useful for present and future assessments of trends in HRT use and for guiding physicians who provide information to older women on the use of hormone therapy.

Chapter 1

BACKGROUND

Incidence/Prevalence of CHD in Women

Coronary heart disease (CHD) continues to be the leading cause of death in the United States. The US mortality rate for heart disease in 1995 was 289.5 per 100,000.[1] The age-adjusted incidence rate of initial acute myocardial infarction (MI) in women was 137 per 100,000 in 1990.[2] Although the incidence of MI, as well as all CHD, is lower in women than in men until age 85, this disease has a major impact on the morbidity and mortality of postmenopausal women. The CHD mortality rate (per 100,000) in 1995 was 318.9 for women 55 to 59 years, 532.5 for 60 to 64 years, 820.4 for 65 to 69 years, and was 1,323.4 for 70 to 74 years (accounting for over 350,000 deaths per year). The prevalence of CHD during the postmenopausal years is high-- 13% among women 45-65 years, increasing to 33% among women over 65 years.[3] This contributes to a great deal of the nation's morbidity costs. In 1993, 875,000 females diagnosed with CHD were discharged from short-stay hospitals.[3]

The risk of CHD among women varies with ethnicity. African Americans have a higher MI mortality rate than Caucasians. In 1992, CHD age-adjusted death rates (per 100,000) were 64.1 for Caucasian women and 85.0 for African-American women (a 32.6% higher risk

for the African Americans).[3] Compared to Caucasian women, African-American women have a higher prevalence of CHD risk factors. Over 40% of African-American females are diagnosed with hypertension (HTN), 30% have high cholesterol, 45% are obese, and over 20% have diabetes.[4] The prevalence of these risk factors in Caucasian women is 20% for hypertension, 20% for high cholesterol, 20% for obesity, and 10% for diabetes. These statistics are troubling since many MI deaths (30% - 40%) are attributed to hypertension and high cholesterol (Table 1).

Table 1: CHD Deaths Attributable to Specific CHD Risk Factors*

Risk Factor	CHD # attributed deaths	% of deaths
Smoking, Currnt/Former	148,879	25.1
Chol ≥ 5.2 mmol/L	253,194	42.7
High BP SBP>140	171,121	28.9
Obesity >110%desirble	190,456	32.1
No exercise	205,254	34.6
Diabetes	77,709	13.1
Total	593,111	---

*Prevention of Myocardial Infarction. Manson JE, et al. Ed. NY, Oxford University Press 1996

Prognosis following an MI differs depending on gender and ethnicity. Forty-four percent of women who experience an MI die within the first year compared to 27% of men.[1]

Based on findings from the Framingham Heart Study and others since, within 6 years of an MI: 31% of women will experience a subsequent attack; 34% will develop angina; 18% will have a stroke; 20% will be disabled with heart failure; and 6% will experience a sudden death.[5] Partly because women tend to be older when the MI occurs, they are twice as likely as men to die within the first few weeks. It has been speculated that the decreased survival in women may be due to their increased mean age at the time of infarction, and there are studies which report similar survival rates for men and women after age adjustment.[6,2] However, in another study it was demonstrated that excess mortality in women was not a function of age at the time of infarction. After a women develops CHD, case fatality rates exceed those of men. [7] Prognosis following an MI is worse for African-American women compared with Caucasian women. The case-fatality rate (per 10,000) for African-American women has been reported at 47.5 versus 35.5 in Caucasian women.[8] The differential may in part be explained by the higher prevalence of multiple risk factors in African-American women. A postmenopausal woman currently has a 31% lifetime mortality risk from CHD, in contrast to a 2.8% mortality risk from hip fracture or breast cancer.[5]

Trends

Coronary heart disease mortality rates have been declining significantly over the past few decades. Data from the Framingham Heart Study have shown for women a 51% decline in mortality from CHD during the 1970's and a further 25% decline between 1985 and 1990.[4]

Despite the role risk factors play in the incidence of disease, the substantial decline in mortality has recently been attributed to advancements in medical management.[9] A 'period' effect, such as medical advances in heart surgery, impacts changes in the outcome, such as CHD mortality, across multiple age cohorts. Declining rates of CHD-specific mortality disappear for very elderly women and have slowed considerably for women in general. A period effect would explain the former lack of declining mortality, whereby costly medical advances are reserved for those less advanced in age but do impact more than one birth cohort. The declines in mortality observed over the last decade do appear for each postmenopausal birth cohort.[7] However, recent years have observed half the decline in CHD mortality rates of earlier years.

Given that CHD is a major contributor to morbidity and mortality in older women, primary and secondary prevention measures impacting incidence and prognosis are important. This is especially relevant as the population shifts to a larger proportion of older women. By the year 2015, the proportion of all women in the United States who will be greater than 45 years of age will increase to 45%.[10] Because life expectancy is greater for women today than for women 50 years ago, there is a substantial number of years that may be impacted by CHD preventive measures.

Hormone Replacement Therapy

Prevalence

One such preventive measure being examined for its impact on CHD in women is hormone replacement therapy (HRT). Hormone replacement has been a commonly prescribed therapy for postmenopausal women, extensively used for the relief of menopausal symptoms. During the mid-1980's hormone therapy became indicated for the prevention of osteoporosis and more recently considered as a therapy to impact coronary heart disease risk. Currently, HRT is prescribed for approximately 30% of women experiencing menopausal symptoms who range in age from 40 to 60 years.[11-13] Short-term utilization (less than 5 years) is most common in women seeking menopausal symptom relief which can quite often be obtained in a year or two. [14]

An older but smaller proportion of women are also prescribed HRT for decreasing or preventing osteoporosis. Currently, 15 to 20 million women are at risk of bone fracture and are candidates for preventing or slowing the disease with hormone therapy.[15] Such women are commonly older, aged 55 to 85 years. Hormone replacement has been shown to both prevent and partially reverse osteoporosis disease.[16-18]

Despite the established benefits to HRT use in the postmenopausal years, only half of the women prescribed therapy continue use beyond one year. A survey conducted at a Massachusetts Women's Health Center in 1987 demonstrated that 30% of HRT

prescriptions are never filled and 20% of women stopped treatment within 9 months. [19] Factors affecting the use of HRT included complications, fears, and mistrust of the medical profession. Breakthrough bleeding, cramping, and bloating occurs in about 10% of HRT users and is associated with high dropout rates.[20] For many, achieving a therapeutic dose that is consistent with benefits but associated with little or no complications requires additional return visits and often results in noncompliance.

Some women may decline HRT use because it has been linked to breast and endometrial cancers. The association between breast cancer risk and HRT has been investigated extensively. Meta-analyses including 39 observational studies and 1 clinical trial estimate no increased risk of breast cancer for those who are on HRT less than 5 years. [21] However, epidemiologic studies do suggest a 20% to 30% increase in risk of breast cancer for long-term current users of HRT compared to women who have never used HRT (RR=1.25).[22] The relationship of hormone use and endometrial cancer has long been established. Estrogen alone significantly increases severe uterine hyperplasia in about 1/3rd of women. The relative risk for endometrial cancer among estrogen users is reported to be 8.22.[21] These risks are based on estrogen use alone, whereas current hormone replacement for women with natural menopause consists of a combined estrogen and progesterone therapy which attenuates the risk of endometrial cancer (RR=1.3 and RR=0.9, CI not reported) but may also attenuate the benefit (RR=1.2 and RR=0.5).[20] Other studies suggest the degree of CHD protection may be as great as that of estrogen

(RR=0.53, CI:0.30-0.87).[23] When the side effects associated with use and the fear of cancer are included in reasons for noncompliance, from 20% up to 40% of women prescribed HRT either never begin or cease treatment an average of 8 months after initiation.[24] Physician knowledge and attitudes about HRT also play a role in women's use of HRT. It is estimated that only 30% of postmenopausal women in the US have ever been prescribed HRT and less than 40% of those with a prescription continue it after 1 year.[25]

Estrogen therapy accounts for a majority (over 80%) of hormone therapy use and is the most often measured formulation in the research on HRT. Estrogen combined with progestin has accounted for less than 20% of HRT use. Table 2 lists the studies which estimate prevalence of HRT among older, postmenopausal subjects. Estimates of HRT use, which may vary according to a study's time period, the sample age range, or study location, range from 6% up to 32% in studies from the previous decade.

Table 2: Studies on Prevalence of HRT Use Among Women 45 years and Older

Author	Sample	Size	μ Age (range)	Surgical menop. % of total	Natural menop. % of total	Prevalence % of total
Barrett 1989 Cal.	Affluent Retirees	1957	67.5 yrs	17 HRT: 48%	83 HRT: 28%	31 *ERT 23
Harris 1990 California	Affluent Community	954	-- (50 - 65)	un- reported	un- reported	32 ERT 26
Cauley 1990 4 US cities	Whites of osteo study	9704	72 yrs (65 - 85+)	11 HRT: 34%	84 HRT:11%	14 ERT 11
Manolio 1993 4 US co.	Elderly of CVD Study	2955	72.5 yrs (65 - 100)	37 HRT: 24%	63 HRT: 8%	12 ERT 09
Nabulsi 1993 South U.S.	4 popu samples	4958	no μ (45 - 64)	21 HRT: 40%	63 HRT: 9%	21 ERT 17
Folsom 1995	Women with driver's license	41,837	(55 - 79)	unreported	unreported	10
Hemminki 1993 Finland	Random smpl all	1680	no μ (50 - 64)	19 HRT: 38%	81 HRT:13%	22 ERT 07
von Muhlen 95	White retiree	589	(50 - 89)	-0-	100	27 (ERT 22)
Handa 1996 N.C.	Elderly	2602 of 28,000	73.5 yrs (64 - 101)	Un- reported	un- reported	6 ERT 05
Derby 1993 New Eng	Urban Community	2230	57 yrs (45 - 68)	43 HRT: 20%	57 HRT: 4%	11 ERT 09

The highest reported prevalence of HRT use has been observed among groups younger than 65 years and among women of higher socio-economic status (SES). Prevalence was measured in a 1992 random sample of 2000 Finnish women who returned a mailed survey (response rate: 84%). The majority (81%) reported natural menopause and prevalence of HRT use was 22%. [26] A similar finding was observed in a population sample of 4 southern U.S. communities during 1991. Personal interviews were conducted on 4958 postmenopausal women of whom 79% reported natural menopause. Prevalence of current HRT use was 21%. [27] Both of these studies measured HRT prevalence in postmenopausal women less than 65 years of age and therefore may be an overestimate of the true prevalence among older women in the general population.

Postmenopausal use of estrogen was assessed in 1057 older women aged 50 to 79 years in a 1984-1987 cross-sectional study.[28] Subjects were a community sample of upper-middle class, Caucasian women first recruited for a cohort study 10 years prior. Prevalence of estrogen use was 31% (n=328), and a small proportion of these (8%, n=86) were taking combination therapy. Prevalence of HRT use differed by age and was highest among women 65-69 years. Use among women in their 70th decade was 25%. The lowest frequency was for those on combination therapy. Only 3.7% of women in their 60's and 2% of women in their 70's reported current use of combined therapy.

In a study of 9704 older women, age 65 years and greater, from a multi-center

population-based study during 1986-1988, HRT prevalence was less than 15%.[29] The study targeted non African-American women for inclusion in research on risk factors for osteoporosis from population lists of four major U.S. cities (Baltimore, Minneapolis, Portland, and a Pittsburgh valley). This study included predominately women with naturally induced menopause (84%). Overall, 13.7% of women reported current use of oral estrogen (10.9% took estrogen alone, 2.8% took combined). Current use declined sharply with age from 17% for those age 65-69, to 10% for those 75-79, and to 4% for women 85+. Because women volunteered themselves for the study, they are likely to have been healthier than the general population. Consequently, these prevalence rates may be overestimates of use among women in the general population.

The above studies on HRT prevalence among older women were conducted on homogeneous populations who may or may not reflect the general population of older women. To address this issue, patterns of estrogen utilization were examined within the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE), an existing database which conducted baseline interviews in 1987.[30] The Duke EPESE population was a random sample of 28,000 persons over the age of 65 who lived in 5 adjacent counties in the Piedmont region of North Carolina. The study provided a racially-balanced, well-sampled community population of older women. The principle outcomes were self reported current and past use of estrogen at baseline interviewing. Sampling identified 5226 men and women for enrollment and interviews were completed by 4162 (80%) participants, of whom 2688 (65%) were women. Prevalence

of current use was 6.1% while 18.5% reported past use in the 2688 women responding. Estrogen use for more than 2 years was significantly more common among current users than among those reporting past use. The authors suggest that their findings do not reflect a regional phenomenon , as estrogen use in the southeast United States is comparable with use in other parts of the country. However, the studies cited, as well as their own, were conducted many years ago (1980's) when formulations and dosages were dramatically different than today and may not accurately reflect current use patterns.

User Characteristics

Hormone users have been distinguished from non-users by selected characteristics identified in many studies. These include differences in health and in lifestyle factors. There are a few factors which have consistently been observed across different samples studied and include socio-economic status and health behavior. Women who use hormones after menopause are more likely to be Caucasian, educated, upper middle class, and lean. These factors themselves place women at lower risk for heart disease.

The type of characteristics detected can differ depending on how the data was gathered. A major concern is that women who take hormones are by definition compliant, and compliance itself has been shown to decrease a subject's risk of CHD mortality.[31] The difficulty with identifying characteristics associated with HRT use in observational studies is that information on why women were prescribed hormones or why they may not have been offered hormones is nonexistent. We are therefore unable

to contrast these groups and obtain a true picture. Table 3 lists the characteristics most commonly distinguishing hormone users from an excellent review by Scalley and Benrich, 1993.

Table 3: Selected Characteristics Distinguishing HRT Users from Nonusers*

Characteristic (cross-sectional and case-control)	Users compared to nonusers
Demographics	Higher education Higher income Caucasian race
Clinical factors	Surgical menopause Lower weight Better cardiac risk profile Past oral contraceptive use
Health behavior	More active More likely under physician care
Knowledge	More knowledgeable about HRT benefits
Attitudes / Beliefs	Views menopause as medical condition Less concerned about medical risks, side effects, or stigma Views symptom relief as reason for HRT use

*Adapted from: Scalley EK and Benrich JB. An overview of estrogen replacement therapy in postmenopausal women. J Women's Health 1993; 2(3): 289-94.

Studies conducted on the characteristics of use representing a wide range of observational study designs are examined in greater detail below.

National Surveys

A national household survey on estrogen use with data obtained from 5 biennial cross-sectional surveys examined selection-to-use factors between 1981 and 1990. [32] Among the 13,186 persons surveyed, 3,279 were women 40-64 years of age and form the basis of this analysis. Regression analysis controlling for age was employed. Postmenopausal estrogen use was positively associated with income, with LDL cholesterol levels, with exercising weekly, and with yearly cholesterol checks($p=<0.005$). A positive trend with education was suggested but not significant ($p=0.25$). An inverse association with estrogen use was observed for smoking and body mass index ($p<0.005$). Only a small proportion of women used HRT and had experienced natural menopause (3.5%, CI 0.7-6.2). Although women reporting surgical menopause made up approximately 29% of the women each survey, the majority of HRT users were those with surgical menopause (80%). Thus the group status may have determined other factors associated with HRT use in this study. Women seeking or agreeing to have hysterectomies may have different characteristics, such as SES, educational level, or health care seeking behaviors when compared to those who do not have a hysterectomy. Cholesterol checks may be an indicator for recent healthcare encounters which are required for HRT initiation and surveillance.

Population Based Surveys

The characteristics of hormone use were examined in 1984 using sociodemographic and health-related information obtained in a telephone survey of 2137 women aged 40-52 years, randomly selected from a driver's license list of Pittsburgh-area women

(response rate of 89%).[12] Overall, 6% of those surveyed reported current hormone use. Hormone users tended to be older and thinner than nonusers. Only 813 women of the sample were postmenopausal (38%) with 27% of the total representing hysterectomized women and 11% of women with natural menopause. In separate analysis of women having natural menopause (n=231), HRT use (5%, n=11) was associated with higher education, lower BMI, and greater alcohol consumption. The post (natural) menopausal women of this sample were relatively young (68% < 50 years) and the numbers small. Yet the factors associated with use are consistent with characteristics associated with use from other studies.

Report of current use was examined during 1980 among 1057 women aged 38-82 years from a southern California community.[28] Current users were more likely to have had surgically-induced menopause, to have been past users of estrogen, and were significantly younger (66 years vs 69 years). Age-adjusted characteristics were analyzed. Estrogen users had statistically significantly lower weight, diastolic blood pressure, and fasting glucose levels in comparison with nonusers. However, mean differences between the groups were of minimal clinical difference; BMI difference of 0.85%, a blood pressure difference of 2.4 Hg/d, and a glucose difference of 0.06 mg. Other CHD risk factors (e.g. hypertension, previous MI, family history, cholesterol levels, and triglyceride levels) were equivalent regardless of HRT use or nonuse. This sample of women were all from a similar SES background and biologic variables did not differ in significantly important ways between HRT users and non-users, with the exception of hysterectomy status.

Medical Facility Surveys

A 1990 study on osteoporosis examined characteristics of HRT use in a homogeneous group of Caucasian women who attended multi-site health clinics (N=9704).[29] The sample consisted of women aged 65 years and older predominately with naturally-induced menopause (84%). Estrogen use was more common among women who had higher education ($p< 0.001$), who were thinner ($p< 0.001$), and who participated in sports or recreational exercise ($p< 0.001$). Estrogen use was associated with surgical menopause ($p< 0.001$), with a diagnosis of osteoporosis ($p< 0.001$), and with alcohol use ($p< 0.001$). A difference of 20% to 40% was observed for each of these factors between current users and non-users.

The above study stratified women according to surgical or natural menopause. When women were stratified by route to menopause, age (OR 0.68, CI .67-.69), educational level (OR 0.60, CI .49-.74), obesity (0.58, CI .49-.69), and alcohol use (OR 1.4, CI .1.1-1.6) were associated with current HRT use non-differentially in both strata. However, only among women experiencing natural menopause, were there positive association between HRT use and a diagnosis of osteoporosis (OR 2.58, CI 2.4-3.4)) and increased physical activity (OR 1.59, CI 1.3-1.8).

The previously mentioned study (EPESE) on estrogen utilization among a racially balanced random sample of 28,000 elderly persons also found differences between users and nonusers.[30] For demographic variables, estrogen use was negatively associated with age (OR: 0.88, CI: 0.85-0.92), with number of children (OR: 0.09,

CI:0.05-0.17), with rural residence (OR:0.3, CI: 0.2-0.6), and with Medicaid coverage (OR:0.02, CI:0.00-0.14). A positive association was observed for use with income (OR:6.3, CI: 2.2-19.9), being married (OR:2.8, CI:1.8-4.4), and private insurance coverage (OR:6.4, cCI: 3.3-12.1). For medical and behavioral variables, estrogen use was negatively associated with functional status (OR:0.7, CI: 0.6-0.9), and the presence of obesity (OR:0.2, CI:0.1-0.9). Estrogen use was positively associated with alcohol consumption (OR: 5.6, CI:3.6-8.8), cigarette smoking (OR:5.6, CI: 3.6-5.9) and calcium supplementation (OR: 3.7, CI: 3.3-5.9). Especially strong was the association between ethnicity and estrogen use. Caucasians were 10 times more likely than African Americans to be current users. Nine percent of Caucasians (n=90) reported current use and another 270 (24%) were past users. The corresponding percentages for African-American women were 1% (n=12) current use and 10% (n=122) for past use. Population-based studies on elderly minorities (EPESE study) confirmed low usage patterns showing minorities to be significantly less likely to report use of hormone therapy.[30]

Although several studies have reported that hormone users were healthier and had greater access to healthcare,[12,29,30] a few studies do not confirm these findings. Several studies have found that smoking, drinking alcohol, and consuming a high fat diet are more common among hormone users.[28,30,33] In the Nurses' Heath Study, HRT users tended to be slightly younger with lower body weight but also reported higher fat consumption and higher rates of abnormal cholesterol levels, two risk factors that play a major role in CHD.[33]

The majority of women on HRT (80% - 90%) are those taking estrogen alone which is common for women who have had a hysterectomy. A concern is that women with a hysterectomy differ from women who go through natural menopause. The major difference may be that women having the surgery are a subgroup who come under routine medical care. Studies have found that women under routine gynecologic care are more likely to be estrogen users.[34,35] However, an encounter with a health care provider does not ensure that hormone replacement will be addressed. Although a plausible explanation for ethnic differences in HRT use is physician access, there are studies which refute this explanation. A population-based study in Philadelphia of women 45- years and over observed that African-American women were more likely to be managed for diabetes and therefore more likely to have frequent physician visits, but were half as likely to have ever used hormone therapy.[22] Perhaps the very conditions that bring African-American women into clinics (e.g., diabetes) are also conditions in which clinicians are more reluctant to recommend HRT use. African Americans may be less likely to have access or to use HRT when no chronic illness is present. However, even minority women having contact with a health care provider on a regular basis have been shown to have significantly lower rates of HRT utilization.[12]

Attitudes and Behavior

Only a few studies have examined the receptiveness of women to HRT as a preventive or management therapy for heart disease. The importance placed on hormone therapy by women was examined during 1993 with a postal questionnaire to 1649 women aged 20-69 years.[36] The sample was random and taken from 8 general practice listings in northeast England. A 75% response rate was achieved. The majority of women listed

HRT promotion as 'not important'. However, few (9%) named heart disease as a threat to their health and fewer (7%) realized the role HRT may have in heart disease prevention. Even when stratified for age, no trend in the fear of heart disease appeared, although the level of knowledge about risk factors for CHD was very high (> 85% correctly identified CHD risk factors).

A survey of 600 Stanford women graduates, median age 50, confirmed these findings for United States women.[37] Although knowledge of potential long term benefits and risks of hormone therapy was high, only 27% rated the benefit on heart disease to be most important. However, these women under estimated their risk of heart disease. When asked what illness they feared most, 3 times as many feared breast cancer as feared heart disease (48% vs 16%). Although these women may or may not have underestimated their risk of CHD, their fears could explain the importance placed on the motivation for preventing disease.

Experiences with menopause, as well as attitudes, can impact the probability of hormone use. For those women who experience debilitating symptoms associated with menopause, the need to seek relief provides the opportunity for discussing HRT and heart disease prevention. Women not experiencing debilitating symptoms (as well as healthy elderly women in general) and women without a primary care physician may not have the opportunity provided to them to discuss the risks and benefits of HRT for MI risk reduction.

Trends

The few studies that have examined changes in HRT use over time have found that prevalence is increasing somewhat among post menopausal women. A study conducted during the 1980s examined estrogen use among 2215 post menopausal females aged 40-64 years sampled from 5 biennial cross-sectional household surveys and observed increasing prevalence over time.[32] Among all women surveyed, the prevalence of estrogen use had doubled from 5.3% (CI: 3.2-7.4) in 1981/82 to 10.9% (CI: 7.5-14.4) in 1989/90. The majority of estrogen use was among women with surgical menopause (80% of users each survey). Among women with natural menopause, estrogen use also increased from 1.5% (CI: 0.04-2.9) to 3.5% (CI: 0.7-6.2) resulting in a 57% increase over time.

The use of estrogen and its duration has increased significantly during the past decade worldwide. A series of cross-sectional studies (repeated at 2-year intervals) of women from Finland aged 45 to 65 years reported a fivefold increase in use from less than 5% in 1976 to nearly 20% by 1989.[14] Regional and characteristic differences were observed. The greatest trend in HRT prevalence was within the metropolitan area of Helsinki (from 6% in 1979 to 30% use in 1989). Different from the earlier surveys was the increased use of HRT in 1989 among postmenopausal women and those in rural areas. The first group to adopt HRT were highly educated women. Its use then spread to other educational groups with increases in prevalence seen among those of primary and secondary schooling with each succeeding survey (from 5% or less among all educational groups in 1979 to over 15% in 1989). For all surveyed periods, the highest

prevalence by age was among those 50 to 54 years.

In South Australia, there was a 40% increase between a 1991 survey and a 1993 survey in the number of women taking HRT.[38] Current HRT use significantly increased from 13.6% (CI: 11.3-15.9) in 1991 to 19% (CI: 16.2-21.8) in 1993. The highest rates were for those in the 50 to 54 years age group (46.2% current use and 57.8% ever use).

Studies have also observed an increased trend in the number of women remaining on HRT for long-term use. In the United States during the 1970's only 20% of HRT users continued use for 5 or more years. While in 1992, the proportion remaining on HRT for 5 years or more was 31%.[39] Other countries also report increases in duration of use. The Finland study observed that for HRT users in 1989, 32% had used it for up to 1 year, 43% between 1 and 5 years, and 25% more than 5 years.[14] These percentages were significantly greater than each previous cross-sectional survey. Of those 60 years and older, 37% had remained on HRT for more than 5 years. In the South Australian study, a significant increase ($p<0.01$) in the median duration of therapy was observed, from 38 months in 1991 to 54 months in 1993.[38]

Two developments directly impacting on HRT use in postmenopausal women of older age occurred during the mid to late 1980s and may have led to a resurgence of HRT use. These were the addition of progestin to attenuate the risk of endometrial cancer, and a 1984 National Institutes of Health Consensus Conference advocating routine

estrogen replacement to prevent bone loss.[28]

Although there has been an increased trend in HRT utilization, it is still under utilized among women who might benefit. There are more than 30 million postmenopausal women in the United States.[40] Life expectancy for women reaching menopause is 28 years or 1/3rd of a woman's life span. At present only 2 to 3 million women in the United States use HRT.[20]

The Effect of Hormone Replacement on Coronary Heart Disease

Substantial evidence from epidemiologic studies supports the cardio-protective effect of estrogen. Table 4 lists the studies conducted on HRT and MI or CHD. A 30-40% reduction in risk of MI has been observed among women remaining on HRT for 5 years (short-term users), the reduction appears even lower with long-term use(5-10 years).[33,10,41] It is clear that the majority of HRT research has been conducted with estrogen exposure rather than combined therapy. This may be mainly due to the high prevalence of hysterectomized women among hormone users who only need to be on estrogen. The table also highlights a benefit observed in several studies among past users of HRT, although the magnitude is less than that of current use. In addition, these studies suggest a protective effect in several different outcomes; CHD events, MI events, and total mortality.

Table 4: Overview of the Impact of Hormone Use on CHD

Study	Design	Sample	Outcome	Current Use (Past use)	Estimated Protective Effect (95% CI)
Henderson88	Inception Cohort FU 1-6y	8841 44-101	AMI	14% ERT 14% (43%)	OR=0.5 (p= .003) OR=0.6 (p= .002)
Stampfer 91	Inception Cohort	48,470 30-63y	CHD	ERT 22% (25%)	RR=0.56 (.4-.8)
Falkeborn 92	Cohort Prescrp list	23,174 ≥35y	Primary MI	21% ERT 17%	RR=0.80 (.71-.92) RR=0.50 (.30-.87)
Rosenberg 93	Case/control	1716 45-69 y	MI	22% ERT 19%	RR=0.90 (.70-1.2) RR=0.60 (p < .05)
Mann 94	Case/control	7605 45-64y	Primary MI	8% ERT % NA	OR=0.70 (.49-1.0)
Psaty 94	Case/control	1695 μ=68 y	AMI	23% ERT 18% (38%)	RR=0.68 (.38-1.2) RR=0.69 (.44-1.1)
Folsom 95	Cohort 3y FU	41,070 >45 y	Total death CHD	11% ERT % NA (28%)	RR=0.78 (.65-.94) RR=0.74 (.48-1.1)
Grodstein 96	Inception Cohort 16y FU	59,337 30-55y	AMI	24% ERT 13% (21%)	RR=0.39 (.19-.78) RR=0.69 (.48-1.0)
Schairer 97	Popu Cohort	23,346 45-79	All Mortality CHD death	33% ERT % NA	RR=0.77 (.73-.81) RR=0.60 (.53-.67)
Newton 97	Hx Cohort	726 μ=66 yr	Reinfarction	17% ERT 16% (22%)	RR=0.64 (.32-1.2) RR=0.90 (.62-1.3)

* ERT=estrogen replacement therapy with absolute values reported

Epidemiologic Studies

However, the evidence of a protective effect of HRT risk of MI in postmenopausal women is not conclusive, as there are currently no results from randomized clinical trials. Two large trials have been implemented (WHI and PEPI) with results still a few years off. The evidence that we do have on the relationship of HRT use and MI covers a wide spectrum of study designs--from cross sectional to cohort. Caution is advised in the interpretation of the findings on HRT and CHD because of biases inherent in the design and with the analysis of the data. Examples include selection biases from a 'healthy user' effect and from a 'physician referral' effect, confounding from HRT/CHD associated factors, and effect modification. Findings on HRT and CHD risk are examined in light of the various threats to validity for each type of study design. The following is a review of the strengths and weaknesses of each study type in HRT research and a summary of the evidence from these studies.

Cross-Sectional Studies

One of the earliest examinations of HRT and CHD in post menopausal women was conducted on the Framingham Offspring cohort during 1983 through 1987.[42] A cross-sectional design was employed measuring HRT use and lipid profiles in 938 postmenopausal women. Self-reported HRT use was obtained by a physician-administered questionnaire. The use of estrogen was significantly associated with increased levels of HDL-C ($p=.04$) but not with LDL-C levels. Combined therapy was also significantly associated with increased HDL-C ($p=.03$) , as well as, with decreased LDL-C levels ($p=.04$) and total cholesterol ($p=.02$). Other similar studies have

observed a significantly lower LDL level in HRT users.[27] In this cross-sectional comparison, as with studies of similar design, there is no means for determining whether exposed subjects (users) represent a more health-conscious and compliant group than non-users. It is well established that people who are health-conscious (e.g., physically active, good eating habits, non-smoking) are at decreased risk of CHD. In addition, people who are compliant, even with placebos, reduce their risk of CHD due to these and related behaviors.[CDP] In the case of health and compliant behavior leading women to request or be prescribed HRT, the positive effect on CHD would be spuriously attributed to the exposure (HRT) where measured cross-sectionally. For the above study, age of the postmenopausal women ranged from 31 years to 69 years. Given this wide range in ages, exposure status at the time of study measurement may have little to do with exposure at the time the disease process began.

Several cross-sectional designs have been conducted to examine HRT exposure and angiographically-documented CHD.[43] Exposure was determined by self-report at the time of radiologic exam. Although angiographically determined atherosclerosis is a more definitive means of identifying predisposition to CHD than a single lipid measurement, it is still a proxy measure of mediating pathology. Inherent in the design of all cross-sectional studies is the problem of 'temporality' or an inability to determine whether HRT use preceded atherosclerosis, particularly subclinical disease. In addition, the tendency for healthy women to self-select toward HRT use can not be determined from this design.

Case - Control Studies

Case-Control studies are those which identify existing cases of MI or CHD and retrospectively determine exposure to HRT. Ideally, these studies should focus on all newly diagnosed (incident) cases, include deceased cases as well as those alive, and include controls that have had the same opportunity to be exposed as the cases. Hospital-based studies, having clearly defined diagnostic criteria, provide a good means of identifying the incident cases of MI for a certain geographic area. In addition, medical information is readily available for each subject. However, these studies can provide inaccurate estimates due to the inability to identify and include fatal cases occurring from sudden MI's. For women, 39% of initial MIs are fatal without symptoms, and thus may not be included in hospital-based studies.[8] Another source of bias is the misclassification of cases as controls. There may be many patients in the hospital, or even in the population at large, who suffer silent MI's, and would therefore be identified as a control if included in the study. Both types of misclassification classification can lead to inaccurate estimates of the impact of HRT on risk of MI and may explain the various effect estimates (RRs from 0.6 to 0.9) found in the many case-control studies.[11,44,45]

Self-selection bias according to exposure factors (a problem for all observational designs) can also occur. Women who are healthier in general and more involved in their medical decisions may be more likely to seek out a physician to request the use of HRT for protective benefits. The bias may also occur regarding professional factors. Physicians may be more likely to suggest and prescribe HRT to women who are

generally in good health than to those who suffer from diabetes, hypertension, venous thrombosis, or obesity.[46] Self-selection biases are confounding and can spuriously produce a protective effect that is much larger than truly exists.

To test whether a reduction in MI in HRT users may have been overestimated because of a greater tendency for women at low risk to use estrogens, a case-control matched study was conducted in 1993.[11] The authors selected first MI cases among Massachusetts women aged 45-69 years in which each of 858 cases was age-matched with a control from the same geographic area. Important correlates of estrogen use (early menopause, smoking, parental MI hx, HT, diabetes, education, leanness, and exercise level) and MI were controlled by conditional logistic regression. The estimated relative risk for ever use of estrogen was 0.9 (CI: 0.7-1.2) and the estimate decreased with increasing duration of use (RR=0.6, CI: 0.4-1.1for 5 or more years). The association with long-term duration was stronger for recent use (RR=0.5, CI: 0.3-1.1)than for past users, but not significant. The results suggest that estrogen use may reduce the risk of first MI. However, this reduction is related to duration and recency of use, and estimates may be smaller than previously shown by similar studies. In addition, due to the retrospective design of the above study, selection bias from ill women tending to quit, or be removed from, therapy may spuriously produce a larger estimate of benefit for HRT users.

Unlike women with a hysterectomy, women experiencing natural menopause require estrogen therapy combined with progestin to attenuate the risk of uterine cancer. The

effect of combined therapy on risk of MI cannot be assumed from estrogen therapy. The addition of progestogens may reduce or eliminate the cardioprotective effect gained by elevations in HDL and lowering of LDL that is associated with estrogen use alone.[41,45] Therefore, studies have targeted the exposure of combined therapy and examined its impact on MI. If estrogen has a true beneficial affect on MI risk then it is expected that combined therapy may also impact on risk, since combination therapy does include estrogen.

A population based case-control study among those enrolled in a group health plan examined this relationship.[44] Cases were 502 postmenopausal women who had sustained an incident fatal or nonfatal MI between 1986 through 1990. Controls were a stratified random sample of 1193 non-MI females matched to the cases by age and interviewed in the same calendar year as the diagnosed case. Telephone interviews were conducted with survivors (and with proxies of mortality cases) and subjects were classified into 1 of 3 groups: nonusers (reference group), estrogen users, and combined-therapy users. The main purpose of the study was to address whether combined HRT increased the risk of MI which previous studies had suggested due to adverse lipid effects. Cases were similar to controls on mean age, length of membership in the HMO, height, weight, number of pregnancies, and proportion with hysterectomy. However, the controls were a significantly healthier group with lower cholesterol and blood pressure levels, fewer diabetics, fewer hypertensives, and fewer smokers. Both estrogen and combined hormone use were associated with a decreased risk of MI in unadjusted analyses (RR=0.63, CI 0.44-0.89 and RR= 0.47, CI 0.27-0.8

respectively). After adjustment for major coronary risk factors (age, diabetes, smoking, HTN), the relative risk for combined HRT moved closer to the null effect (0.69) and both CIs included 1.0. The strengths of this study include: 1) the use of population-based controls rather than hospital-based controls, which more accurately reflects the underlying exposure distribution in the source population; 2) complete case identification which accounted for fatal, as well as, non fatal MIs avoiding a differential due to missed cases; and 3) the use of incident cases only so that those with obvious underlying disease processes do not obscure the estimates. In addition, all subjects were members of the same HMO for a similar duration and so had equal access to medical care. Limitations of the design that deserve attention are that: 1) bias may still be introduced with physician and/or patient self-selection to the exposure--patients seeking hormones may also be more aggressive in their lifestyle behaviors and physicians choosing to prescribe hormones may be more aggressive in other prevention strategies; 2) duration for combined-therapy users was relatively short--averaging less than 2 years for all subjects, exposures of three years or more may be required before an impact is detected; and 3) women who were 'not' current users served as the reference group. If women who stop therapy are more likely to be ill, they may also be more likely to suffer an adverse event. The results observed may not be a true estimate of the risk due to exposure.

Cohort Studies

In prospective cohort studies, subjects free of CHD are classified according to hormone exposure status and followed several years for the occurrence of an MI.

Confidence in the effect estimate is higher with this type of design because exposure is ascertained before clinical disease develops. However, there are biases inherent in this design as well. The loss of patients from follow-up (attrition) due to lack of interest, migration, or death from other causes is particularly problematic. In addition, changes in exposure status can occur over time making it difficult to classify subjects correctly at the end of the study. In the case of hormone therapy it is necessary to provide thorough follow-up to establish exposure as to current use, past use, or nonuse and to achieve a situation where all exposure groups have an equal probability of disease detection. For HRT, it is suggested that the greatest benefit occurs with long-term use of 5-10 years [11] and follow-up may require 10 years to observe an effect.

There have been many cohort studies conducted to examine HRT and heart disease. In general, a 'cohort' describes any designated group of persons who are followed over time. This is distinguished from an 'inception' cohort which refers to a group identified at an early, uniform point prior to the development of symptoms. A concern for HRT studies is the ability, or inability, to determine disease status at the time of recruitment. There may be underlying heart disease present at menopause when women make the decision about HRT use. Unless a cohort is followed from menarche through menopause, it is difficult to determine whether the disease process at postmenopausal status has already begun or whether women with disease select to HRT use. Studies have addressed this concern by eliminating women from the analysis who have a history of CHD or poor lipid levels and recalculating risk estimates. The Lipids Research Clinics (LRC) Program identified cohort of 2270 women whose status of

CVD and level of cholesterol were determined at baseline. They followed subjects an average of 8.5 years.[47] The investigators then analyzed the risk of death according to exposure within the subgroups of women with existing CVD disease and with elevated lipid levels. The overall age-adjusted relative risk (RR) of CVD death in estrogen users compared with nonusers was 0.34 (CI: 0.12-0.81). After exclusion of women with prevalent CVD, the relative risk in estrogen users compared to nonusers was similar but of less magnitude -- 0.42 (CI: 0.0-1.0). Because this estimate is similar to the estimate prior to exclusion but has a confidence interval much wider and including 1, the difference may be due to decreased power from a reduced sample size. The number of deaths for the group after exclusion was very small, in users (n=1) and in nonusers (n=6). However, even with a larger sample size the bias due to underlying disease status is still a concern. Previous history of CVD was measured by self report and by baseline lipid level, which may not accurately identify those with or without disease. No current studies on HRT have examined the CHD association utilizing an inception cohort and bias due to the failure of determining underlying disease remains a concern in the interpretation of findings.

The above study also highlights the epidemiologic concerns of effect modification and confounding. Effect modification occurs when the magnitude of an association between a causal agent and a disease differs according to the level of a third variable. In the above example, estrogen use was more protective against CVD in hyperlipidemic women (RR: 0.21, CI:0.0-0.5) than in women from the target population (RR:0.34, CI: 0.12-0.81). Among women selected because of elevated

lipid levels, the negative association of subsequent CVD mortality and estrogen use was most pronounced. However, the women with estrogen-induced hypertriglyceridemia may not be at increased risk of CVD, as their high lipidemic counterparts would be. Initial analysis of women according to total cholesterol suggested a significant reduction in mortality for estrogen users. When HDL level was substituted for total cholesterol in the multi-variate model, the estrogen association was no longer significant ($p=0.29$) suggesting that the reduction in mortality may be mediated by the HDL-C fraction.

A Confounder is a variable that is causally related to the disease outcome and is associated with, but not a consequence of, the exposure. The LRC study allowed for the interpretation of confounding through statistical control of variables most commonly characterized for HRT users--education, exercise, and type of menopause. Education is associated with healthier lifestyles and lower risk of mortality and is associated with greater involvement with one's own medical care, including seeking and using hormone therapy. The CVD mortality rates of the LRC study were calculated separately for those with less than a high school education, those who were high school graduates, and those with some college education. If education was confounding the relationship with CVD we would expect the association between estrogen and CVD to disappear. In this case, at each education level, estrogen users had significantly lower (age adjusted) cardiovascular death rate than nonusers. The CVD death rates (per 10,000) for those with less than a high school education was 14 (users) vs 40 (nonusers); for high school graduates, 16.5 (users) vs 37 (nonusers); and

for those with some college, 9 (users) vs 23 (nonusers). Exercise and hysterectomy may also confound the association between estrogen and CVD risk and were included as covariates in the LRC multi-variate model. A negative association between estrogen use and CVD mortality remained regardless of exercise level or type of menopause.

Another example that has been suggested is that frequent contact with physicians increases the probability of disease detection and confounds the association between HRT and MI risk . In other words, those with an opportunity for exposure to HRT are more likely to be healthy because conditions such as high cholesterol are kept under control. If this were true and an over estimation of the relative risk was observed then controlling for the confounder would result in a higher (or null) estimate. To further assess whether frequent medical care might account for HRT's benefit in postmenopausal estrogen users, a multi-variate analysis was conducted on 48,470 participants of the Nurses' Health Study.[33] Researchers followed postmenopausal women who were free from heart disease at baseline for 10 years. In an analysis limited to women who reported having visited a physician in the previous year, results were similar to those for the sample as a whole. The age-adjusted relative risks for CHD remained low-- 0.45 (95% CI: 0.31-0.66) for current users and 0.79 (95% CI: 0.60-1.05) for past users.

That type of menopause, access to health care, smoking, and risk factors for CVD do not confound the association between estrogen use and CHD risk is supported by the Nurses Health Study.[33] This cohort consisted of 48,470 postmenopausal professional

nurses and followed them for over 20 years with less than 8% attrition. The study observed a reduced risk of MI among women reporting current estrogen use, as well as, women reporting past long-term use of 5 years or more. There were 405 cases of non-fatal MI and coronary deaths. After adjustment for age, HTN, diabetes, and smoking the relative risk of CHD associated with estrogen use was 0.56 (CI: 0.40-0.80). The CHD risk was significantly reduced among both those with hysterectomy (RR=0.4, CI:0.22-0.73) and those with natural menopause (RR=0.62, CI:0.39-0.97). The association was similar in analyses limited to women who had recently visited a physician (RR=0.45, CI: 0.31-0.66) and in those without a history of smoking, diabetes, HTN, and hypercholesteremia (RR=0.53, CI: 0.31-0.91). The Nurses' Health Study is the largest and most internally valid study conducted on the effect of estrogen and risk of CHD.

Though the majority of studies have evaluated CHD risk with estrogen use alone, studies, including the PEPI trial, have examined combination therapy with progestin. Preliminary results suggest that combined therapy provides equal reductions in CHD risk and, with some dosing plans, a more favorable effect on HDL. In a recent update to the Nurses' Health Study on 59,337 women with 16 years of follow up, women taking estrogen combined with progestin showed decreased risk of CHD compared with non users (RR= 0.39, CI: 0.19-0.78).[13] A prospective cohort study utilizing prescription record linkage followed the entire female population of HRT users in a Swedish region for 5 to 8 years to assess the effects of combined hormone therapy. For the 23,174 women age 35 years and older, combined therapy reduced the risk of

first MI (RR= 0.53, CI: 0.30-0.87). The MI risk was reduced only among women with at least one year of combined therapy.[23] The risk of MI in those filling prescriptions during a 3-year period was compared with the risk of MI estimated for the general population. Confidence in the estimates is reduced due to potential confounding. A small random postal survey of the general population observed a less healthy group than the HRT users regarding body weight, level of exercise, and lower education. The confounding from unmeasured lifestyle factors may also be great. In addition, misclassification may be substantial. Use was defined as anyone filling at least one prescription during a 3-year period. Noncompliers may have been included in the cohort and women from the general population with exposure before and after the 3-year period may have been included in the nonexposed comparison group. Such misclassification could spuriously decrease the protective effect.

More recent cohort studies have also examined the impact of HRT on recurrent MI risk in women with pre-existing CHD. In a retrospective cohort study of 726 women (mean age=66) who had survived a first MI between 1980 and 1991, a marked reduction in reinfarctions was observed for those on estrogen therapy.[48] Adjusting for age and time since first infarction, the relative risk was 0.64 (CI: 0.32-1.3) for current users and 0.9 (CI: 0.62-1.3) for past users. Other studies found that in women with established CHD the risk reduction of recurrent MI may be as great as 80%. [43] The benefit of HRT may be greatest in these populations who have experienced a cardiac event. In women who have previously experienced an MI, the relative risk may be as low as 0.2 for estrogen users.[49]

Caution is required in the interpretation of observational study results for many reasons, including those of selection bias, effect modification, and confounding. Cohort studies, as well as others, may suffer from self-selection which can bias the estimate in either direction-- where healthy persons who are at lower risk of CHD seek out HRT, where ill persons refuse or are not recommended HRT by a physician, or where those at increased risk of CHD death (i.e., smokers or those with family history of CHD) are recommended HRT. Given the magnitude of the difference in CHD mortality risk between estrogen user and nonuser, it seems less likely that an unidentified factor could completely confound and explain the association. However, self selection of HRT use remains a major concern in the interpretation of the HRT and CHD risk association from observational studies.

Mechanism of Action

The biological mechanism for HRT's hypothesized impact on MI is chiefly due to the hormone's effect on risk factors for CHD. In animal studies, estrogen prevents low density lipoprotein cholesterol (LDL-C) buildup in coronary arteries.[50,51] Excess LDL-C is a known risk factor for heart disease in humans. Although the effect of lipoprotein levels has a substantial impact on CHD risk, other factors also play a role. Additional studies in animals demonstrate that estrogen has a vasodilating effect that can improve cardio-performance in ischemic heart disease.[52-54] These animal studies are all well-controlled randomized designs which introduce little, if no internal biases when blinded. All but one of the above studies were blinded. However, it is unclear how generalizable animal models are to similar human designs.

In-vitro studies have examined human arterial responses to estrogen exposure. Atherosclerosis-free arteries were removed from patients undergoing heart transplantation, precontracted with a prostaglandin, and exposed to estradiol-17 β or control. The estradiol induced significant relaxation in coronary arteries pre-contracted with thromboxane compared to control solution (82% vs 12% $p< 0.01$).[55] Coronary artery rings obtained from explanted hearts during cardiac transplantation were precontracted with prostaglandin and exposed to either estradiol or control substance. Results showed that estradiol induced a significant relaxation of the smooth muscle cells (85% vs 10%, $p< 0.05$).[56] These studies support the biologic relationship but suffer from low external validity. Explanted tissues may not react similarly to those of endogenous organs. However, if the relationship is true, we would expect these results in explanted tissues.

In vivo studies of humans suggest that HRT modifies CHD risk through lipid profile changes, thrombolytic changes, and vasomotor effects. Half of the reduction in risk of MI has been shown to be due to 10% to 15% decreases in LDL-C and corresponding increases in HDL-C while using HRT.[57,58] Other studies have speculated that 25% to 50% of the risk reduction is due to the impact of HRT on vasomotor parameters such as vessel wall elasticity and cholesterol oxidation in the endothelium.[41,59]

Studies on estrogen use in menopausal women have consistently shown it to favorably effect the lipid profile. The LDL-C levels is decreased 10%-15% and HDL-C increased 10% with use. A cross-sectional examination of the association of HRT with plasma

lipid levels was conducted on 15,800 men and women 45 to 64 years of age of the Atherosclerosis Risk in Communities (ARC) study.[27] Current estrogen users had significantly higher HDL-C and lower levels of LDL-C than non users ($p< 0.001$). The PEPI trial (a large multi center randomized trial) was conducted in 1994 and examined effects of HRT on lipid profiles in women prospectively. Participants were blinded and randomized to estrogen, combination therapy with progestin, or placebo and followed for up to 10 years. Preliminary results have demonstrated significant increases in HDL and significant decreases in LDL, as well as, decreases in fibrinogen levels (a contributing factor in atherosclerosis which is associated with CHD). In addition, the combination therapy was found to elevate HDL-C levels without increasing the risk of endometrial hyperplasia.[41] The results of this study, a randomized controlled trial, suggest strong support for a protective effect of HRT on MI through its positive impact on CHD risk factors. It should be emphasized that this evidence from randomized trial results is on HRT and intermediaries of CHD disease. Clinical trials on disease outcomes have yet to be reported.

Strength of Evidence

The following paragraphs include six criteria commonly used to assess a causal relationship. The evidence for HRT as protective of CHD is considered in the context of each of these criteria.

1) Strength of the Association: The relative risks for MI among HRT users has been

as low as 0.30 and consistently less than 0.80 across the various designs of observational studies. The stronger study designs, cohort studies, have reported relative risks of CHD mortality in HRT users of 0.34 (CI: 0.12-0.81),[47] relative risks of MI in HRT users of 0.59 (CI: 0.42-0.82), [17] to 0.56 (CI: 0.40-0.80).[22]

2) Consistency of the Association: Protective effects of HRT use on the risk of CHD have been observed among different samples of women, from fairly healthy professionals (Nurses' Health Study) to retired community populations (Rancho Bernardo, CA Study). A protective effect due to HRT use has been observed when the analysis is confined to subgroups of women with differing underlying CHD risk factors. For women healthy at baseline, the relative risk of MI among HRT users is 0.40 (CI: 0.12-0.82).[22] For women who access a physician regularly, the relative risk of MI among HRT users is 0.45 (CI: 031-0.66), and even among women with pre-existing heart disease, an HRT protective effect is observed with a relative risk of 0.64 (CI: 0.32-1.3).[48]

3) Dose-Response Relationship: The HRT and MI relationship shows substantial evidence for a dose-response effect. The longer women remain on HRT the lower their risk of MI. For those on HRT at least 5 years a 30% to 40% reduction in MI risk has been observed compared to those on HRT for a year or two.[60], while a 50% to 80% reduction is observed for those with long-term HRT use of 5 to 10 years.[11] In addition, the association is significantly stronger for recent use (RR: 0.50) than for past use ($P < 0.05$).[11] The combination therapies also support the dose-response relationship as one

would expect if a causal link is present the combination therapies would also show a benefit, although not as strong due to the presence of progesterone. A protective effect has also been observed for combination therapies with a relative risk of 0.53 (CI: 0.30-0.87).[23]

4) Temporality: The direction of the association must be from cause to effect to argue for a causal relationship. The inability to detect subclinical CHD disease often makes this criteria difficult to meet. The HRT and MI question has been examined in prospective studies on cohorts who were premenopausal (women in their thirties) and followed them for over 20 years. The relative risks observed have been low (RR: 0.40 and 0.50) and it is unlikely that coronary heart disease existed in many women so young. Therefore, effect estimates most likely suggest that the protection of HRT did occur prior to the disease process. And in women with pre-existing disease the protection from subsequent reinfarction that was observed is also temporally correct.

5) Specificity of Association: This criterion refers to the situation that a factor in the causal pathway is a singular cause (or protection) of a single disease process. The requirement to meet this criterion is less strict than the other 5 criteria because in the real world a disease can be caused by multiple factors and a single factor can cause or lead to multiple diseases. An example of a true causal factor for disease which is not specific is smoking. That the HRT and MI link does not meet this criterion strictly is mainly due to the multi-faceted aspects of heart disease, which can be attributed to several causal pathways (i.e., smoking, diabetes, HTN, family history). In addition,

HRT can impact on other disease processes such as osteoporosis and menopausal illnesses. Because HRT is implicated in reducing risk through its effect on atherosclerosis and lipid profiles, it may be a sufficient but not necessary benefit in risk reduction. This does not by itself weaken the causal argument.

6) Biologic Plausibility/Coherence: Additional support for a causal link exists if biological plausibility is present in terms of the current knowledge about the exposure and the disease. This is certainly true with HRT and CHD. Use of HRT has been shown in clinical trials to positively impact the lipid profile, a major risk factor for CHD. Women on HRT significantly decrease their LDL-C and total cholesterol levels and increase their HDL-C levels.[41] Because high LDL-C levels lead to atherosclerotic plaque formation and atherosclerosis leads to the MI event, it is biologically plausible that HRT impacts positively on MI risk. Also, when a woman's estrogen levels are high (e.g., pre menopausal), there exists significant gender differences in the incidence of CHD. These gender differences lessen or disappear for women in the post menopausal years, suggesting a link between intrinsic estrogen and CHD risk. Therefore, it is plausible that extrinsic estrogen may play a similar protective role in CHD risk. The CHD link is further strengthened by animal models which show that estrogen treatment prevents LDL-C buildup in coronary arteries and has a positive vasodilating effect on arteries.

Coherence of the evidence is provided by the protective effect of HRT exposure observed in different groups. A protective effect is suggested for those reporting no

history of CHD and in those with a history of CHD,[47, 33] in younger postmenopausal women and in older women,[17] and in women of countries other than the United States.[23]

A preponderance of evidence on HRT and MI over the last ten years suggests a significant impact due to HRT exposure and the association meets 5 of the 6 criterion for a causal relationship. This strongly supports the view that HRT is protective against MI events. The consistency of findings is especially apparent in the cohort studies which have produced a summary relative risk of 0.50 (CI: 0.4-0.5) in a meta-analysis study.[44] The relative risk of CHD in estrogen users compared with never users in several recent meta-analyses was consistently below unity (0.55 to 0.65) in users regardless of the endpoints investigated--fatal or nonfatal MI, fatal or nonfatal CHD, coronary stenosis, or sudden death.[21, 44] However, it should be emphasized that an over-riding problem of the evidence for a protective effect of HRT on CHD is that of self-selection and its threat to the validity of reported findings. Selection bias is not addressed by the above criterion but could effect any study that is not a randomized design.

Even though a publication bias toward accepting studies which show an affect may exist for even peer-reviewed journals, the epidemiologic studies reported cover a wide range of designs which have consistently demonstrated reductions in risk of CHD among women using HRT. Table 4 (page 27) presented an overview of principal studies in the last ten years regarding estrogen's impact on CHD. A 30% - 50%

decreased risk of MI has been observed for current users of HRT and a smaller but still significant decreased risk of 15% to 35% for past users.[47,17,23,33] It is unlikely that the protective effect is entirely explained by design flaws, selection biases, or confounding. Evidence from multiple epidemiologic studies argues favorably for HRT as a preventative therapy in reducing the risk of MI in postmenopausal women.

Thesis Rationale

The relationship between HRT and CHD is a major public health issue. Prevention of later-life disability in the management of health for older women is important. Because the majority of HRT use has been recommended to women who have had hysterectomies and to women seeking relief of menopausal symptoms (60%-80%), older women in the general population who do not fall into these categories may be less aware of the benefits of HRT for CHD risk reduction. However, they may also be more likely to reject hormone therapy because of complications or fears of cancer. Previous studies report that, on average, 30%-40% of postmenopausal women are prescribed HRT and only half of those prescribed HRT remain on therapy beyond 1 year.[19, 26] Prevalence of HRT use among women $\geq$ 65 years in non-select populations is less than 14% and decreases with age. The prevalence of HRT use among a population of women who have experienced MI remains unclear.

Support by health professionals regarding the utilization of HRT in older women and especially in women who have coronary heart disease may be changing. Physicians are now being encouraged to consider HRT as a prophylaxis in the management of MI. The 1996 US Preventive Health Task Force recommends counseling all perimenopausal and postmenopausal women regarding the risks and benefits of HRT.[61] The American College of Physicians in 1992 made a general recommendation to consider preventive hormone therapy for women who have or are at risk of CHD.[62] Physicians from the Cardiovascular Division of Harvard Medical School advocate cardiologists take an active role in educating all postmenopausal women with CHD of

the benefits/risks of hormone replacement.[63] Interestingly, a survey by Ferguson, et al addressing women's decisions for using estrogen revealed that the most important reason for starting estrogen was a recommendation by a physician.[34] With recent support of professional medical groups advocating counseling women at risk of CHD about HRT, studies are needed to update estimates of HRT use and physician discussion of HRT use.

Thesis Objectives

This thesis describes HRT use and discussion of HRT use with a health care provider among women who presented to community hospitals for myocardial infarction. The initial objectives were to estimate the prevalence of HRT use (and HRT discussion with a physician) among a series of population-based MI patients, to contrast the obtained prevalence rates with those of previous studies, and to compare prevalence rates between ethnic groups. However, these objectives required modification following problems with data collection which resulted in a failure to reach the projected sample size, thus limiting study power and generalizability. In light of this, the objectives were modified to a descriptive analysis of the sample data for frequency of HRT use and of discussion with a physician.

Chapter 2

METHODS

The MICH Study

Purpose

The parent study for this thesis research is the Michigan Inter-Institutional Collaborative Heart Study (MICH) which recruited patients from five hospitals of the central Michigan area of Genesee and Saginaw Counties. The MICH study is implemented by a committee at Michigan State University, College of Human Medicine. The purpose of the MICH study was to collect key data on AMI patients during hospitalization and one year following the AMI event. Initial study aims were to assess quality of medical care for women and minorities, cost effectiveness of various treatments, and the impact of AMI on quality of life and return to work.

Geographic Setting

Genesee County has approximately 370,000 residents, 51% of who are female and 18% African American or other minority.[64] Saginaw County has approximately 250,000 residents and a similar demographic composition to that of Genesee County. The MICH study is a population-based case series of acute myocardial infarction (AMI) hospital patients recruited from these two counties.

Eligibility and case definition

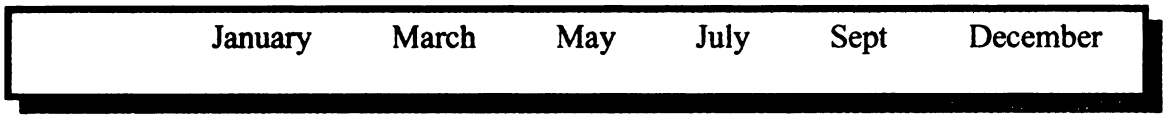
The diagnosis of myocardial infarction was confirmed by electrocardiographic(EKG) results (Q or QS finding + ST elevation or T-Wave inversion), by the typical symptoms of shortness of breath, nausea, dizziness, severe discomfort in the anterior chest, and by an elevation of enzymes (elevation of CK and MB fraction > 1.2 times the upper limit of normal or elevation of SGOT or LDH > 2 times upper limit of normal) within 48 hours of symptom onset.

All non-transferred patients meeting the criteria at presentation of chest pain, high enzymes, and positive EKG were included in the MICH study. The study criteria for Phase I patients were: any one typical symptom of MI plus elevated serum enzymes and EKG confirmation. The study criteria for Phase II patients were: elevated enzymes plus evidence of MI in the patient chart by symptoms or EKG confirmation. Patients excluded were those who were transferred from a non-MICH hospital, met enzyme criteria due to a scheduled surgery, met enzyme criteria due to angina and/or PTCA or CABG, or met enzyme criteria but were hospitalized due to other causes (e.g., pneumonia hypoxia, pancreatitis, or car accident). A total of 621 women met the MI criteria for MICH (407 from Phase I and 214 from Phase II)

Recruitment

Figure 1 is the time line of MICH implementation. Subjects were enrolled beginning in January 1994 until October 1997 (patient recruitment ceased during 1996 to conduct follow-up interviews). Recruitment occurred in two distinct phases. Phase 1

Phase I 1994 - 1996



Phase II 1997

Figure 1 - Time line of Subject Identification and Data Collection

began January 1, 1994 and recruited patients through April 30, 1995. Between May 1, 1995 and March 1, 1997 research activity focused on obtaining follow-up data. Phase 2 began additional patient recruitment during March 1, 1997 through September 30, 1997. The MICH study was approved by the University Committee on Research in Human Subjects (UCRIHS). Trained nurses identified eligible patients in-hospital and approached them for study consent. Potential participants were approached in the hospital prior to discharge, at which time they were informed about the MICH study and about subsequent interviews, both in the hospital and during follow-up after discharge. All eligible patients consenting to study inclusion were then interviewed prior to discharge. The MICH assistants conducted all chart abstraction on patients within the study and collected follow-up data for Phase 1 participants from subsequent 3-month, 6-month, and 9-month mail surveys and a close-out (1 to 3 year) telephone interview. Phase 2 follow-up included a 6-week post discharge telephone interview.

Data Collection

Figure 2 outlines women enrolled and interviewed for each phase of MICH. In addition to interview data, information was abstracted from patient charts by MICH nurses. The data collected included medical histories, hospitalization course, laboratory test results, medications, and procedures preformed. Women were interviewed in-hospital regarding demographic, health, lifestyle, and clinical information. The data was collected and entered into a MICH database. Data cleaning and subsequent data analyses were conducted by MICH assistants.

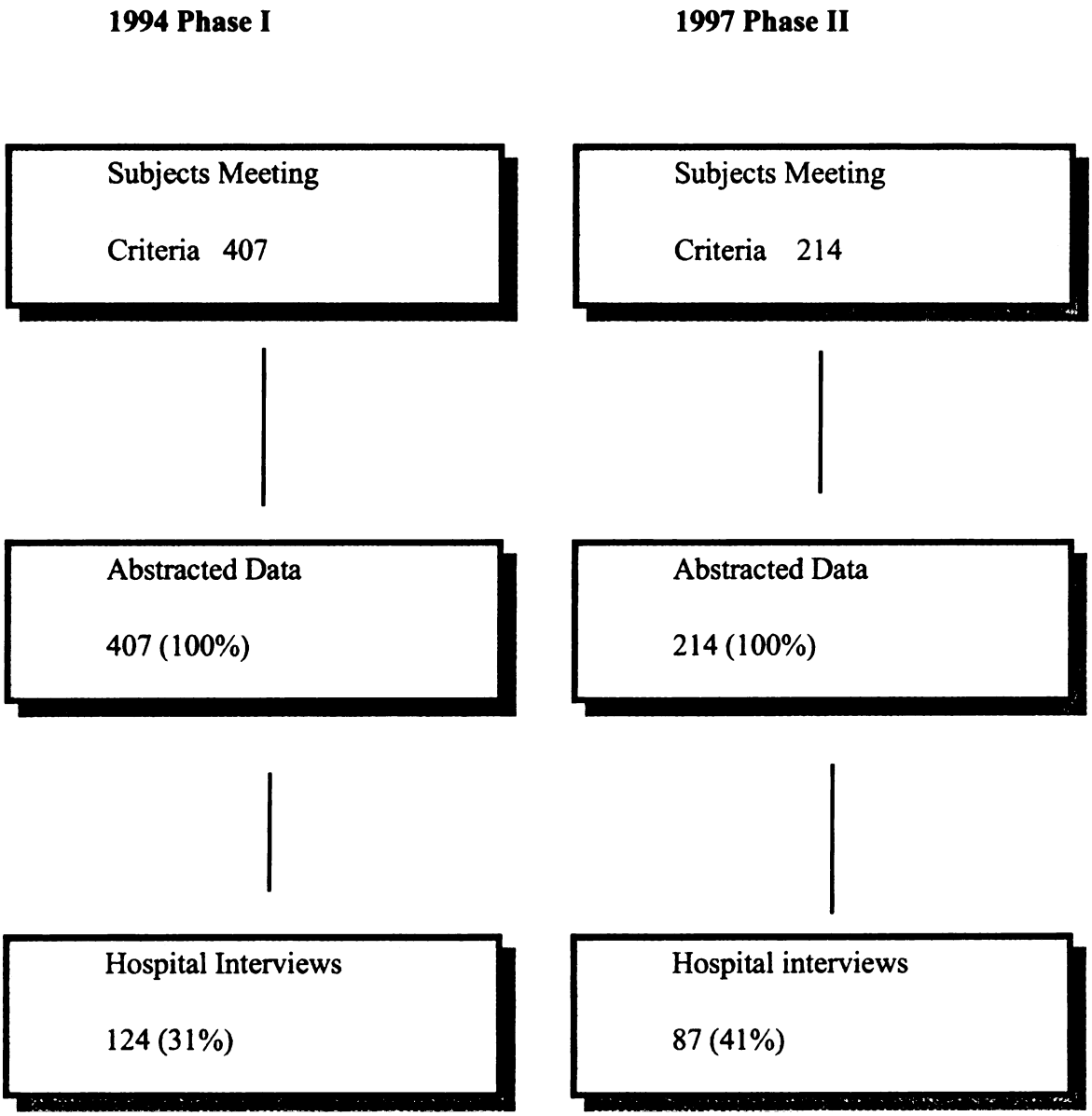


Figure 2 - MICH Study Sample Flow Chart

Thesis Study

Purpose

Limited information exists on HRT use among women with preexisting heart disease. The purpose of the thesis research was to describe the utilization of HRT among women experiencing an acute MI and the frequency of having discussed HRT with a physician. All postmenopauasal women recruited into the MICH study were eligible for the thesis research on HRT.

Eligibility

All MICH study women who were postmenopausal or who had a hysterectomy were eligible for the HRT study. Study participants were postmenopausal women recruited into the MICH study and completing follow-up telephone interviews during Phase 1 or in-hospital interviews during phase 2.

Human Subjects and Informed Consent

The original Institutional Review Board approval for the MICH consent form was not altered because it was consistent with collection of follow-up information obtained from MICH patients. Questions on HRT were added to the existing MICH interview instrument. This addition was formally approved by the University Committee on Research in Human Subjects (UCRIHS) on 3/27/97.

Recruitment

There were 124 Phase I women with completed in-hospital interviews. Follow-up telephone interviews which included questions on HRT (conducted 1 to 3 years post discharge) were completed for 68 women (56% of those with hospital interview). For Phase II recruitment, 214 women met study criteria. A total of 87 (41% of those meeting criteria) Phase II women completed in-hospital interviews which included questions on HRT. In some cases, interviews were conducted shortly after discharge. Table 5 lists the various reasons that MICH women were not interviewed during the in-hospital and follow-up surveys.

Table 5: Reasons MICH Women Were Not Interviewed

Reasons for Not Being Interviewed	Phase I (n,%) Eligible for In-hospital Total=407	Phase I (n,%) Eligible for Follow-up Total= 124	Phase II (n,%) Eligible for In-hospital Total= 214
Not meet criteria	4 (03)	00	00
Refused	00	5 (04)	60 (12)
Deceased	00	11 (09)	62 (12)
No answer	00	12 (10)	NA
Disconnect/wrong #	00	28 (23)	00
Discharg/unknown	00	00	79 (15)
Unable to interview	6 (04)	00	74 (14)
Reasons not specified	273 (67)	00	00
Total non-response	283 (70)	56 (45)	127 (59)
Completed interviews	**124 (31)**	**68 (55)**	**87 (41)**

This study includes 156 women; 69 who were interviewed at follow-up in Phase I and 87 who were interviewed close to discharge in Phase II.

Data Collection

At the follow-up interview (Phase I), a telephone survey was conducted by MICH nurses and medical graduate students regarding follow up information on lifestyle changes, health, symptoms, and HRT use. For Phase II participants, questions regarding HRT use and discussion with a physician were obtained during the in-hospital interview. Validated questions on HRT utilization and participant characteristics were obtained from the published literature. Questions specific to physician recommendation were developed myself. The survey was then pilot tested on 50 selected older women by telephone survey. The HRT questionnaire consisted of a 3-page structured survey with forced choice and open-ended questions regarding whether a physician ever recommended HRT to the patient, the specialty of those physicians who had recommended HRT, HRT use at the time of the heart attack, current use and compliance patterns, past HRT use and compliance patterns, reasons for noncompliance, and whether a physician had ever recommended withdrawing from HRT. Figure 3 shows a flowchart outlining HRT questions. These questions (with a slight variation in the query to reflect use 'at the time of the heart attack') were those used for Phase I women at the follow-up interview 1 to 3 years post discharge and for Phase II women during the in-hospital interview. The Appendix provides the instruments used to survey subjects about their exposure to HRT.

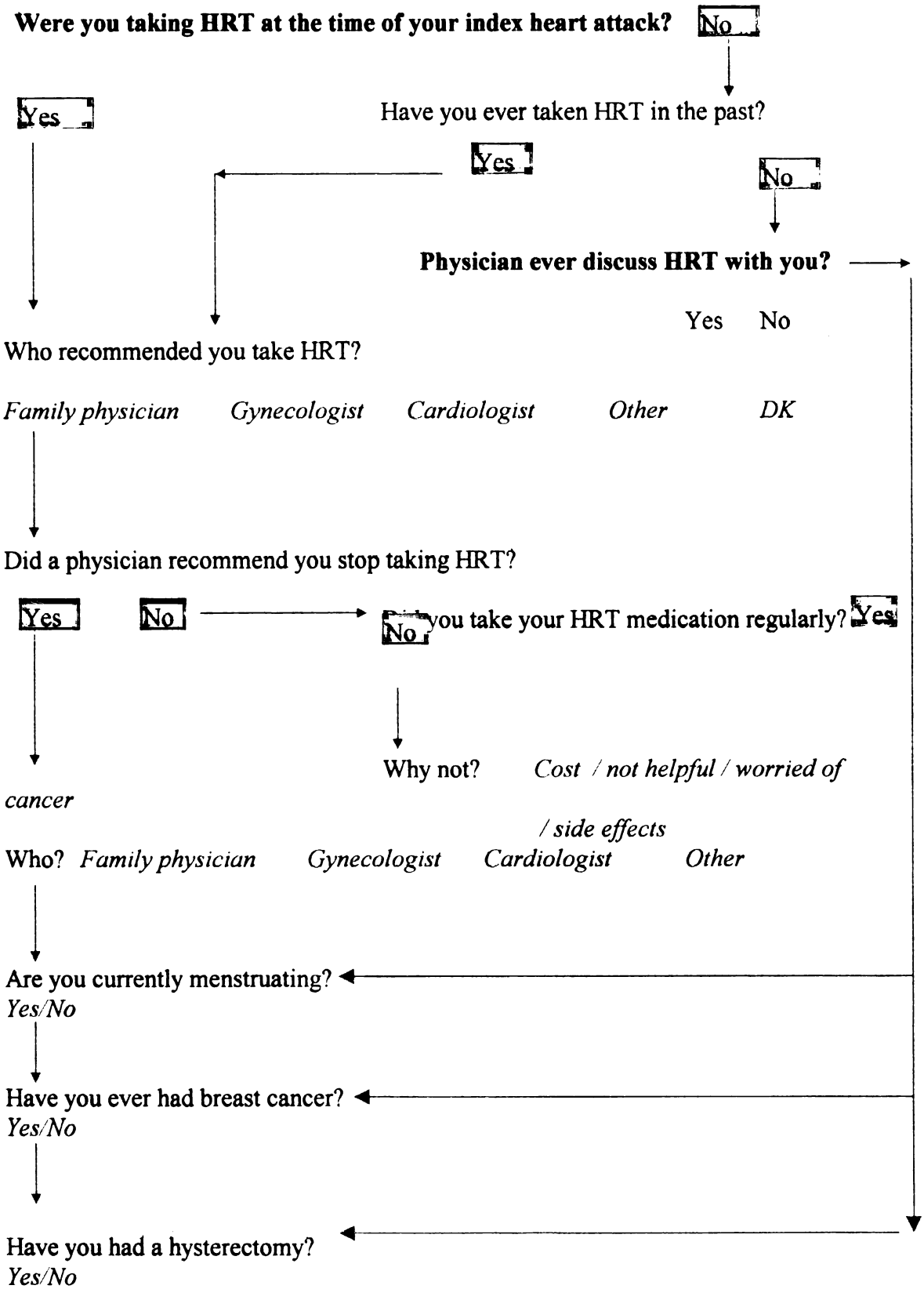


FIGURE 3: INTERVIEW FLOWCHART REGARDING HRT

Plan of Analysis

Demographic characteristics of study participants were grouped into categorical variables such as age (<45, 45-54, 55-64, 65-74, 75+), ethnicity (Caucasian, African American, Other), insurance status (Private, Medicare, Medicaid, HMO, None), income (<20,000, 20,001-40,000, >40,000), and education (< HS, HS degree, Post HS schooling). Smoking status and family history of CHD were expressed as dichotomous variables, present or absent. The main variables of interest, HRT use and discussion of HRT were scaled as dichotomized variables, yes or no.

Precision was calculated for estimates of HRT use and discussion of use with a healthcare professional from Phase I follow-up interviews. A calculation for the precision that could be achieved with a hypothesized point estimate of 12% for HRT use and 30% HRT discussion and a projected sample size of 200, assuming a 95% confidence level was performed (Table 6).

Table 6: Precision Based on Hypothesized Estimates for HRT Use /Discussion

Parameter	Value	
Hypothesized Prevalence	12% HRT Use	30% Discussion
Projected Sample Size	**200**	**200**
Confidence level	95%	95%
Precision	± 4.5	± 6.5
Confidence Interval	7.5 - 16.5	23.5 - 46.5

As time progressed we realized that the sample size was considerably less than the 200 projected initially and we prepared for increasing the sample size by incorporating the HRT questions into the Phase II in-hospital interview rather than waiting for additional follow-up interviews. When it was discovered that the sample size of both Phases would fall short of the 200 projected, we anticipated precision to be somewhat poorer. This is particularly true for data examined separately by Phase.

Time Line

An initial request was made to incorporate the hormone replacement therapy query into the MICH research project in January 19, 1996. The HRT related questions were developed and submitted to the MICH coordinator for revisions which was approved at a subsequent MICH meeting on March 15, 1996. An invitation for additional investigators interested in HRT to be co-investigators was put forth and three were identified. Additional questions from the new investigators were incorporated and a second revision submitted to the MICH committee was made on April 19, 1996. A request for pilot testing was made and then conducted on a convenience sample of 10 women. Results were presented at the June 21, 1996 meeting. At this time, recruitment of patients for Phase I was completed and the HRT questions could not be added to the Phase I in-hospital interview. A final vote on the questions for inclusion was made in December of 1996, at which time it was determined that the hour long telephone MICH instrument was too lengthy and HRT questions (as well as many others) had to be minimized. The HRT questions remaining were those essential to my inquiry (i.e., use, discussion with health provider, who recommended HRT, and

reasons for noncompliance). The Phase I close-out interviews were begun in February of 1997 and the HRT questions were included.

Phase II patient recruitment was begun on March 1, 1997. The HRT questions were revised to be incorporated into the in-hospital interview. Contacting women for HRT questioning prior to discharge would increase our sample size from that achieved at Phase I follow-up. Recruitment was scheduled for March through September 30, 1997 with an anticipated enrollment of over 200 women. However, recruitment stalled, ceasing at one location during the month of July, resulting in a total of 87 women interviewed in-hospital. Chart abstraction by medical volunteers and previous MICH recruiters was conducted from October 1997 through April 1998 with data entry completed in June 1998.

Chapter 3

RESULTS

Final Precision Levels

The combined total from both Phases resulted in 156 female participants with a prevalence of HRT use of 22% and prevalence of discussing HRT with a health care provider of 46%. The resulting precision for these point estimates is decreased from that anticipated and values are listed in Table 7. The precision values by phase are reported separately in Table 7 as well. The resulting precision by phase was considerably compromised due to the smaller sample sizes.

Table 7: Precision Based on Observed Estimates for HRT Use /Discussion

Parameter	Combined		Phase I		Phase II	
Observed Prevalence	23% HRT Use at time of MI	46% Discuss	17% HRT Use at time of MI	39% Discuss	26% HRT Use at time of MI	50% Discussion
Final Sample Size	156	156	69	69	87	87
Confidence level	95%	95%	95%	95%	95%	95%
Precision	± 6.6	± 7.8	± 9.0	± 11.5	± 9.2	± 10.5
Confidence Interval	16.4 -29.6	38.2 - 53.8	8 - 26	27.5 - 50.5	16.8 -35.2	35.5 - 60.5

Demographics

Of the 621 women enrolled into the MICH study with chart data abstracted, 156 completed interviews on HRT questions. Table 8 compares demographic data on the 466 women with chart data only compared to the 156 woman interviewed for HRT (Phase I follow up= 69, Phase II= 87).

Table 8: Demographics of MICH Women

Demographic	Chart Data Total= 466 n (%)	Interviewed Total= 156 n (%)
Primary Insurance		
Private	98 (21)	55 (35)
Medicare	331 (71)	67 (43)
Medicaid	19 (04)	06 (04)
None	14 (03)	07 (05)
Missing	5 (01)	21 (13)
Ethnicity		
Caucasian	401 (86)	134 (86)
African Am	56 (12)	17 (11)
Other	9 (02)	5 (03)
Age	μ= 67.9 yrs	μ= 66 yrs
44 and under	14 (03)	
45 thru 54	33 (07)	11 (07)
55 thru 64	79 (17)	21 (14)
65 thru 74	122 (26)	43 (28)
75 and over	168 (36)	35 (22)
Missing	56 (12)	46 (29)
		00

Women interviewed were less likely to be on Medicare and slightly more likely to have private insurance than women not interviewed (35% vs 21%, p=.0005). The younger

mean age of interviewed women may explain differences in insurance coverage (μ = 68 yrs vs μ= 66 yrs). Differences between the two groups may reflect a tendency for those of higher economic status and younger age to respond to surveys or reflect that older women are more likely to die before interviews can be obtained. The ethnic distribution was similar between the groups.

Demographics of study participants were examined according to their Phase status. Variables available for both Phases included age, ethnicity, and employment. Education, income, and marital status were available depending on the Phase. Table 9 outlines the demographic data according to Phase status.

Table 9: Demographics of Study Patients by Phase Status

Demographic	Phase I Total =69 n (%)	Phase II Total =87 n (%)
Age (μ)	64.2 yrs range: 42 - 88	68.9 yrs range: 28 - 92
Ethnicity		
Caucasian	62 (90)	73 (84)
African American	6 (09)	11 (13)
Other	1 (01)	1 (01)
Missing	00	2 (02)
Employment		
Employed	22 (32)	18 (21)
Homemaker	20 (29)	18 (21)
Retired	21 (30)	37 (43)
Un-employed	6 (09)	10 (11)
Missing	00	4 (04)
Education		
< H. S. Degree	-NA--	26 (30)
Have H.S. Degree		36 (41)
Some College		17 (20)
Assoc Degree or more		06 (07)
Missing		2 (02)
Income		
< $12,000/yr	17 (25)	-NA--
$12k to $19,999k	12 (18)	
$20k to $39,999k	23 (34)	
$40k to $59,999k	8 (12)	
$60k or more	5 (07)	
Missing	3 (04)	
Marital Status		
Married	-NA--	37 (43)
Divorced/Separated		9 (10)
Widowed		37 (43)
Single/never married		3 (03)
Missing		1 (01)

NA= not available

There were ethnic differences between the two Phase groups. Phase I women had fewer African Americans then Caucasians (9% AA vs 13% AA) but this difference was not statistically significant (p=0.6). Phase I women were more likely to be employed (32% vs 21%) while Phase II women were more likely to be retired (43% vs 30%). Again, these differences were not statistically significant (p=0.2). A majority (71%) of the Phase II women had a high school degree or less and 56% were single. Forty-three percent of Phase I women reported an annual income of less than $20,000. Although the mean ages were similar, Phase II women included those as young as 28 years while Phase I had a 42-year-old as their youngest.

Health Behaviors

Descriptors for health behaviors were examined between the two Phases. Table 10 presents the health behavior variables of smoking, history of MI, family history of MI, level of activity, and reported presence of diabetes. The variables differed depending on Phase status.

Table 10: Health Behavior Data

Health Factor Phase I (n=69)	Number (%)	Health Factor Phase II (n=87)	Number (%)
Told have Diabetes		**Family Hx MI***	
Yes	18 (26)	*Mother*	32 (37)
No	50 (73)	*Father*	36 (41)
Don't know	1 (01)	*Don't know*	11 (13)
Chol Checked	66 (96)	**History MI**	
Told Chol High	44 (64)	*Self*	23 (26)
Smoke Post MI		**Smoke Prior MI**	
Yes	5 (07)	*Yes*	48 (55)
No	63 (91)	*No*	39 (45)
Physically Active		**Physically**	
Yes	37 (54)	**Active**	49 (56)
No	31 (45)	*Yes*	38 (44)
		No	

* multiple responses and do not add to 100%

Information describing health behavior for the two phases were as follows; more than half (55%) of Phase II women interviewed in-hospital reported current smoking and 7% of Phase I interviewed post-MI reported current smoking. The difference is likely due to the timing of the question. Phase I participants were asked about smoking 1 to 3 years following their MI and Phase II were asked about smoking just prior to their

MI. Twenty-six percent of Phase I women reported having diabetes and 64% reported having high cholesterol. For Phase II women 77% reported either a mother or father or both as having heart disease. The percent reporting that they were physically active at the time of the interview were similar between the two groups (54% and 56%).

Hormone Use and Discussion

Women in both Phases were questioned about HRT use at the time of MI. Of the Phase I women who reported HRT use at follow-up (n=16), 7 (44%) had been placed on HRT post-MI discharge. Nine (75%) of the 12 women on HRT at time of MI remained on it at the time of follow-up interview and 3 (25%) had quit taking HRT after the MI. Table 11 provides further data on hormone activity.

Table 11: Hormone Use by Phase Status

Hormone Use	Phase I Total=69 n (%)	Phase II Total=87 n (%)	Combined Total=156 n (%)
HRT Use			
At follow-up	16 (23)	-NA--	
At time of MI	**12 (17)**	**23 (26)**	**35 (22)**
Prior to MI	-NA--	16 (19)	
Ever Discussed HRT (with HC provider)	27 (39)	44 (50)	71 (46)
Recommend by:			
Family Phys	11 (16)	26 (30)	37 (24)
Gynecologist	0	14 (16)	14 (09)
Cardiologist	0	0	0
Other doctor	1 (01)	0	1 (.01)
Does not apply	53 (77)	47 (54)	100 (64)
Advised Start HRT (Following MI, n=8)			
By Family Phys	3 (37)	--NA--	
By Gynecologist	2 (25)		
By Cardiologist	1 (12)		
Other doctor	2 (25)		
Hysterectomy	25 (36)	34 (39)	59 (38)
Still Experiencing Periods	7 (10)	8 (09)	15 (10)

The HRT data were examined by Phase. Prevalence of HRT use in Phase I was 17% (CI: 8 - 26) and 39% (CI: 27.5-50.5) for discussion. Prevalence of HRT use in Phase II was 26% (CI: 16.8-35.2) and 50% (CI:35.5-60.5) for discussion. Precision was poorer for each phase than for the combined total due to the smaller sample size. There was a lower prevalence of HRT use in Phase I than in Phase II which may be attributed to differences in when and how the data were obtained. The proportion of women having a hysterectomy were similar in the two groups (37% and 39%). However, more Phase II women reported hormone use at the time of MI (26% vs 17%). There were more Phase II women reporting recommendation of HRT use by a gynecologist (16% vs 0) and a family physician (16% vs 30%) than Phase I women.

The combined Phases total 156 women responding to questions on HRT. The prevalence on HRT use for the combined data (n=35) was 23 % (95% CI: 16.4 - 29.5) and prevalence on history of HRT discussion with health care provider (n=72) was 46% (95% CI: 38.2 - 53.8). The prevalence for the combined data, as well as physicians recommending HRT, is listed in Table 11.

Characteristics distinguishing HRT users from nonusers in the study sample were examined by Phase and for the total sample. Table 12 lists the demographic, medical, and health behavior variables available to compare users from nonusers. Although the numbers are small there were some interesting findings. Users overall were more likely to be younger (62 yrs vs 66 yrs, p=.21), to have private insurance (49% vs 32%, p=.10), to be employed (34% vs 23%, p=.27) but not significantly so. They were

significantly more likely to have had a hysterectomy (63% vs 32%, p.002). The HRT use by ethnicity differed for the two phases. The Phase I group had no African Americans reporting use of HRT at the time of MI while the Phase II group had a greater proportion of African Americans among HRT users (17%) than among non users (11%). Information on education and family history was unavailable for Phase I. The Phase II data showed that users were more likely to have a degree beyond high school (39% vs 21%, p=.16) and to have a family history of MI (48% vs 39%, p=.61) but these differences were not statistically significant.

Table 12: Proportions (%) of Selected Use and Nonuse Characteristics According to Sample Phase Status

Factor	Phase I Total= 69 n (%)			Phase II Total= 87			Combined Phases I & II Total = 156		
Subgroup Totals (n)	Users time of MI (12)	Nonusers (55) 1 missing	Total (69)	Users time of MI (23)	Nonusers (62) 2 missing	Total (87)	Users time of MI (35)	Nonuser (117)	Total (156)
Demo:									
Age (μ)	64.7 yr	63.5 yr	64.2 yr	59.4 yr	68.6 yr	64.0 yr	62.1 yr	66.1 yr	64.0 yr
Af Am	00	6 (11)	6 (09)	4 (17)	7 (11)	11 (13)	4 (11)	13 (11)	17 (11)
Priv Ins	6 (50)	24 (44)	30 (44)	11 (48)	13 (21)	43 (49)	17 (49)	37 (32)	73 (47)
Demo:									
Employed	5 (42)	16 (29)	21 (30)	7 (30)	11 (18)	20 (25)	12 (34)	27 (23)	41 (26)
≤ H.S.	NA	NA	NA	13 (57)	48 (77)	62 (71)	NA	NA	NA
> H.S.	NA	NA	NA	9 (39)	13 (21)	23 (26)	NA	NA	NA
Medical:									
Hysterec	9 (75)	16 (29)	25 (36)	13 (57)	21 (34)	34 (39)	22 (63)	37 (32)	59 (38)
Smoke:									
Post MI	1 (08)	4 (07)	5 (07)	NA	NA	NA	NA	NA	NA
Pre MI	NA	NA	NA	8 (35)	20 (32)	30 (34)	NA	NA	NA
Hx MI:									
Family	NA	NA	NA	11 (48)	24 (39)	36 (41)	NA	NA	NA
Self	NA	NA	NA	5 (22)	17 (27)	23 (23)	NA	NA	NA

Chapter 4

DISCUSSION

Coronary heart disease is a major contributor to morbidity and mortality in older women.[1] The prevalence of CHD during the postmenopausal years is high--33% among women over the age of 65 years.[3] African-American women are particularly vulnerable. Compared to Caucasian women, African Americans have a much higher prevalence of CHD risk factors such as hypertension and high cholesterol.[4] They are also at higher risk of death due to CHD than Caucasian women.[1] Although recent years have observed declines in CHD mortality rates, a postmenopausal woman currently has a 31% lifetime mortality risk from CHD.[5]

Hormone therapy is commonly prescribed for women experiencing symptoms of menopause. Among women 40 to 60 years of age, 30% to 40% are prescribed HRT.[10,12] However, more than 60% of those with an HRT prescription discontinue use within one year.[25] Unlike women who utilize hormone replacement for the relief of menopausal symptoms, older postmenopausal women on HRT for CHD or osteoporosis are in an age group that, as a whole, are more concerned about breast cancer[37] and object more to HRT side effects than younger women.[34] Prevalence of HRT use among postmenopausal women greater than 60 years of age is only 12%,[29,30,64] and a mere 6% among minority women.[30] Although research shows that women who have taken HRT in the past are more likely to take it again when older,

the prevalence of HRT use in older women remains half that of peri-menopausal women.[65,29] In addition, a majority of prevalence studies on current and past HRT use show half as many older women reporting current use as reporting past use. [17,33,42,48]

A preponderance of evidence suggest that HRT is effective as a preventative therapy in reducing the risk of MI in postmenopausal women. A 30% to 50% decreased risk of MI has been observed for current users of HRT and a smaller but still significant decreased risk of 15% to 35% for past users.[47,17,23,33] Although it does not explain the full impact of risk reduction, HRT use postmenopausally has been linked to higher SES, [32, 30] higher education, [12, 29] greater awareness of health issues,[29] and better access to medical care [32] in many studies and selection bias cannot be fully ruled out. However, other studies have observed no differences between HRT users and nonusers in SES, [28] education,[32] and access to medical care.[12,33]

Because half of all postmenopausal women are at risk of osteoporosis[15] and a third are at increased risk of CHD,[3] a 30% to 50% prevalence of HRT use among older women would not be unexpected. However, the literature emphasizes that HRT prevalence among older, postmenopausal women, who are at the greatest risk of MI and of osteoporosis, is currently very low (6% to 14% among those $\geq$ 65 yrs). The prevalence of HRT use was 17% among a select group of women who were members of a health organization in Puget Sound and had previously experienced an MI.[48]

MICH Data Findings

Prevalence

Among the 156 women of this study sample, less than half (46%) had ever discussed HRT with a health care provider. Because women with a hysterectomy accounted for almost 40%, few women in the study with natural menopause had ever discussed HRT with a physician. Although the level of HRT discussion is relatively low, reported use of HRT at the time of MI (22%) is higher than that of other studies involving postmenopausal women. In studies with women reporting a similar frequency of hysterectomy and in studies including only women older than 65 years, prevalence of HRT use was less than 15%.[32,64]

Unique to this study is that all women had experienced an MI. Compared to a historical cohort study conducted in Puget Sound involving only women with MI, prevalence of HRT use in our sample was slightly higher (22% vs 17% [48]). However, the confidence intervals of our sample do include the estimate of the Puget Sound study and these two studies may be similar in their prevalence. The two studies were similar regarding type of menopause (37% with hysterectomy) and ethnicity (86% & 92% Caucasian). The two studies differed in other ways. The Puget sound study included only postmenopausal women and had fewer than 9% under the age of 56 years. The MICH sample was younger and included 32% of women under the age of 55 years.

Phase II women reported a 31% greater prevalence of HRT use at the time of MI than

Phase I women and a 20% greater prevalence of HRT discussion. This difference may be explained by random sampling or differences in recall. Although both groups were asked similar questions about HRT use at the time of MI, they were queried at different time points. Phase I women were asked to remember 1 to 3 years in the past whether they were on HRT at the time of their MI and Phase II women were asked about their HRT use immediately following their index MI. The recency of the event could explain more women remembering and thereby reporting their prescription use, or 3) selection factors- - Women responding to the Phase I follow-up survey may be inherently different than those responding in Phase II who were queried in-hospital. They are a select group who survived long enough to be contacted 1 to 3 years post MI. While Phase II women were contacted near the time of their MI. Survivorship may be positively or negatively associated with the use of HRT. The use of HRT may improve the probability of survival or may be associated with other risk lowering factors. Alternatively, higher risk women placed on HRT may be less likely to survive long term. The Phase I prevalence of HRT use is lower than the 22% to 35% of other studies including women in their 40's.[11,33,47] The Phase II HRT prevalence of 26% is similar to other studies including women of similar age and frequency of hysterectomy. However, the decreased precision of our estimate
($\pm$ 9.2) prevents accurate conclusions. The differing methods of measurement, time frame differences in data collection, and small sample size make it difficult to compare or combine women from Phases I and II.

Characteristics

Although it reflects a select group of women willing and/or able to respond to the surveys, it is interesting to note the descriptive findings of this sample. The current study was quite heterogenous on SES and demographic factors. Half of respondents depended on Medicare and a third had private insurance. There were similar proportions reporting less than a high school degree (29%) and greater than a high school degree (26%). Similar proportions of older age groups were represented (20% 55-64 y, 27% 65-74 y, 37% $\geq$ 75y). The employment status most commonly cited was retirement (37%) and of those not retired, equal proportions were either employed or a homemaker (25%). A third (38%) reported having a hysterectomy. This heterogeneity has greater representation for the population than other studies confining generalizability to select groups of a single ethnicity or a single socio-economic status.

Frequency of HRT Discussion

Of concern is the large number of women (54%) reporting having never discussed HRT with a health care provider. Previous studies suggest that this high percentage of non discussion is explained by 'non-opportunity' or the lack of access to a primary care or cardiac physician. However, all the women in the current study had experienced an acute MI and were under the care of a cardiologist at some time during their hospital stay and 57% queried 2-3 years post discharge remained under the care of a cardiologist. It may be that at the time of the heart attack, the immediacy of treatment decisions and the concerns of rehabilitation over shadow the opportunity to discuss HRT during the hospital stay. However, when analyzing just the Phase I data

where women were interviewed one to three years post MI, the prevalence of never having discussed HRT with a health-care provider was still high (59%).

Although the cardiologist's role is important in influencing risk reduction following an MI, their involvement in discussing HRT for heart disease prevention remains low. Of the 8 (12%) Phase I women who discussed HRT use after the MI event, only 1 woman reported that a cardiologist discussed the issue with her. A nationwide inquiry of 1268 general practice physicians conducted by The Medical Research Council in the United Kingdom reported only half of physicians (57%) prescribed estrogen for the prevention of heart disease. [Wilkes 91] Studies have shown that patient willingness to consider hormone replacement is very much influenced by physician recommendation.[25] However, the current study showed few cardiologists involved in the discussion of HRT benefits and risks. This suggests missed opportunities to improve the health of at-risk postmenopausal women by way of risk reductions in osteoporosis and/or heart disease.

Characteristics Distinguishing HRT Users

Although the numbers are small, there are several observations of the current study consistent with that of the Puget Sound study among women experiencing MI. Users among the total group of 156 women were more likely to be younger, to have private insurance, to be employed, and to have had a hysterectomy than were nonusers. The data on education and history of MI were limited to the Phase II interview. Users were more likely to have a degree beyond high school and to have a family history of MI.

These findings were also consistent with the observations from the Puget Sound study. In addition, both studies found that users were less likely to have a history of MI (MICH sample) or history of heart failure (Puget sound) suggesting that women with existing disease are less likely to be placed on HRT following hospitalization for MI. These findings suggest the possibility of selection factors associated with HRT use among women experiencing an MI.

Limitations

Our study sample suffered considerably from low numbers. Although over 600 MICH women were identified prospectively at the time of MI, only 25% (n=156) completed HRT interviews. Exposure (HRT use at time of MI) was reported by only 35 women. This small sample size and low frequency of HRT use resulted in a lower precision (± 6.6) than expected with hypothesized numbers. For these reasons, findings on HRT use may not be generalizable to all women hospitalized with MI.

Conclusions

Use of HRT in elderly women remains especially low (6%-18%). This low prevalence of use was previously identified with women's concerns regarding endometrial and breast cancer, as well as, a commonly held belief by health care providers that HRT increased the risk of thrombosis. However, studies reported in the last five years have shown that breast cancer risk is not increased with HRT use of 5 to 10 years and that the risk of endometrial cancer is attenuated with combination therapy (estrogen/progestin) for women with intact uteri.[21] In addition, animal studies on

vasomotor effects and human studies using MRI imaging have shown no increase in thrombotic events for those exposed to HRT. [52,53]

The overwhelming evidence strongly suggests that long-term use of HRT is safe and impacts favorably on MI risk for peri and postmenopausal women. However, prevalence of use remains low. The trend appears to be toward an increase in HRT use among older women, but prevalence remains extremely low. Prescription rates of HRT for women with menopausal symptoms remained the same between 1989 and 1994 (40%, 38%), while the number of postmenopausal women without symptoms who reported use of HRT doubled during the same time period (3% to 7%).[67] The current study supports observations that HRT use among older women is low and that most cardiologists are not discussing HRT risks and benefits.

Strengths and Weakness of Current Database

The opportunity to access an existing database in its initial implementation phase for hypothesis generation and testing, in principle was a good one. Benefits included the saving of personal resources in designing and conducting all aspects of a prospective study. Benefits also included access to expertise in areas of hypothesis generation, question formulation, instrument construction, interviewer training, and telephone interviewing. Other benefits included professional contacts with others in the field, involvement in related grant and investigative projects, and experience at orally presenting research at a national level forum.

However, problems for the current research were evident throughout the project. Time delays existed, from incorporating new questions into the existing instrument to obtaining the data necessary for review. Much of the delays experienced are inherent in any collaboration where all members are provided opportunity and time to consider, discuss, and provide input on new questions for research. Because all collaborators were professionals, many of them clinicians, receiving feedback sometimes took months. Obtaining consensus on approval from all co-investigators required waiting on signatures which often took several weeks at each step of the process (added questions, revised questions, hypothesis, study design, and analysis). These approvals did not displace institutional review board approval through UCRIHS which together took many months to obtain full approval.

Because the HRT research was conducted through an existing database that was being implemented at the time of incorporation of study questions, this investigator underestimated the time involved for collecting final interviews, conducting chart abstraction, and entering and cleaning data into the database. At the same time a process for data access from investigators outside the MICH committee was being defined. All data requests were to be presented to the principal MSU- MICH investigators. These requests required a specific hypothesis, background and rationale, identification of the questions by interview labels (form name, question number, and test group), operational definition of all key variables requested and the evidence for those definitions, a description of the analytic approach, and calculation of power for answering the proposed question. The MICH data supervisor and statistician had

oversight approval authority for each step of the process. Any deficiencies were returned to the investigator for corrections. Upon final approval at the MSU site, the request was then to be sent to the other community MICH investigators for approval. This process was being developed at the same time that data was being requested for this descriptive study. Although an efficient, streamlined data request process has since been worked out, this created additional time delays for requesting and obtaining data on HRT questions.

The MICH population was ideal for the study question of HRT use among women experiencing MI. Cases of MI patients were being prospectively recruited and questioned in-hospital about health and lifestyle behaviors. However, in hindsight, incorporating new questions for a timely research project into a study that had already begun, and was in the middle of implementation, was less than ideal.

Approaches to Strengthen Existing Database Use

The benefits of using an existing database for conducting research far outweighs that of implementing research from scratch when acquisition of data is timely. The MICH database has observed a decrease in turn around time due to a streamlined data-request process and the use of electronic transfer of variables to other investigators. Having a single coordinator responsible for data entry, analysis, and data release is important for outside investigators to have the data they need and to understand the particulars of each variable (coding, value labeling, definitions, etc). The value of community involvement through multi-site approval of new research use and site rotation of the

monthly meetings can not be under estimated. The continued use and success of a collaborative research project depends on such activities because of the volunteer nature of community investigator time.

Future Directions for Research

The merits of determining HRT prevalence among post menopausal women or among women with CHD risks is important for understanding trends in heart disease prevention strategies. Due to the low interview response rate (41%) and resulting small sample size of the current study, this descriptive study lacked precision in estimating HRT prevalence in women suffering from MI. In future research, women should be interviewed prior to discharge from the hospital and then followed within one year post-MI to decrease attrition rates. The study would also require following all discharged subjects for mortality and subsequent medical record data collection for prescription use and/or proxy interviews.

The following is a list of suggested studies that may build on other descriptive research;

1) Physician Survey- - assessing the attitudes of cardiologists on the merits of HRT for older women and those suffering from heart disease. A random selection of cardiologists practicing throughout the United States could be surveyed on their reasons for or against counseling women who present with symptoms of heart disease,

2) Community Surveillance - - examining changes in HRT use of women with MI over time. Because use patterns are changing rapidly, previously collected data is not

informative, except to document change. Therefore, it is important to continually update prevalence studies and conduct prospective studies with periodic assessment of HRT use over time, and 3) Community Survey- -The attitudes of women regarding HRT utilization and their ability to access a system likely to provide important information on the risks and benefits of the therapy. Although one community survey including women up to 65-years found that HRT was not a high priority for prevention, few women in that study and in others correctly perceived their true risk of heart disease.[36, 37, 34] Determining the receptiveness of postmenopausal women to HRT for CHD prevention would help target information for public health campaigns.

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