November 2001 Volume 17 Supplement D

THE CANADIAN JOURNAL OF
CARDIOLOGY
JOURNAL CANADIEN DE
CARDIOLOGIE

The Journal of the Canadian Cardiovascular Society
Journal de la Société canadienne de cardiologie

Canadian Cardiovascular Society 2000 Consensus Conference: Women and Ischemic Heart Disease

Publication of this supplement was sponsored by unrestricted educational grants from Aventis Pharma Inc and Pfizer Canada Inc

PULSUS GROUP INC

THE CANADIAN JOURNAL OF
CARDIOLOGY

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The French version of this Supplement is available on the Canadian Cardiovascular Society Web site at http://www.ccs.ca

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Chapter 1
Introduction

Stephanie J Brister MD FRCSC, Michele A Turek MD FRCPC

Ischemic heart disease (IHD) is the leading cause of morbidity and mortality for women in Canada, and in most developed countries. In developing countries, it will be the leading cause of death in the next 20 years.

As well, in women, mortality from IHD at presentation is approximately twice that of men. There is evidence for disparities between men and women in the prevention, diagnosis and management of IHD, which may contribute to the poorer overall prognosis in women. In addition, public perception about IHD in women is still evolving, and this issue continues to engender misinformation and neglect.

Previous official documents and scientific statements on women and heart disease have been few, likely because it has taken time for enough research data and clinical trials to accrue. The American Heart Association/American College of Cardiology (AHA/ACC) scientific statement on cardiovascular disease in women in 1997 (1) and the AHA/ACC statement on primary prevention in women in 1999 (2) are two statements produced in the United States. In Canada, there has been a report on cardiovascular disease in women published by the Heart and Stroke Foundation of Canada (3), and there have been sections in previous Canadian Cardiovascular Society (CCS) Consensus Conferences pertaining to women. There is a need, however, for a Canadian perspective and, most importantly, to identify areas that need more research.

This Consensus Conference is designed to provide a current assessment of IHD in women, using extensive literature review, expert opinion and consensus. The importance of prevention will be highlighted because there is abundant evidence that IHD is largely preventable (for both sexes). Differences between men and women pertaining to prevention, diagnosis and management will also be discussed. Nevertheless, the emphasis is that established clinical guidelines are applicable to both men and women. Such guidelines have been published in previous CCS Consensus Conferences, particularly pertaining to the prevention and management of IHD, and the prevention of sudden death.

Since the publication, 10 years ago, of two sentinel studies detailing differences between men and women in the delivery of care of patients with heart disease (4,5), there has been a heightened awareness in the health care community of particular issues germane to the assessment, management and research of IHD in women. One issue is the use of the terms 'sex' and 'gender' in the medical literature. Sex indicates biological differences between men and women (such as those related to hormones, developmental biology), whereas gender implies a social and cultural context, and is more of an external force on the patient. Often, there is an interaction between the two that can combine to affect health. Unfortunately, sex and gender are often used interchangeably in the medical literature. For example, research detailing underdiagnosis or misdiagnosis may indicate gender-based differences. More precise research methods may be able to define whether pathophysiology or biology are important sex-related differences. This Consensus Conference will attempt to adhere to a more appropriate use of these terms.

The other issue is the androcentric focus of much of cardiovascular research and the necessity to generalize this type of research to the female population. Only in recent years have women been included in sufficient numbers in clinical trials and databases or has there been a requirement for sex-based analysis of data (6), despite the importance of IHD for women as detailed above. Much of this increase is due to large clinical trials of coronary artery disease funded by the National Heart, Lung, and Blood Institute. However, a substantial amount of cardiovascular research is either not federally funded or peer reviewed and fails to include women. There should be increased efforts to enhance the enrollment

TABLE 1
Categories of quality of evidence

Level of evidence	Definition
I	Evidence from at least one properly randomized, controlled trial or one large epidemiological study
II	Evidence from at least one well-designed clinical trial without random assignment, from cohort of case-control analytical studies, preferably from more than one centre, from multiple time series or from dramatic results in uncontrolled, nonrandomized experiments
III	Evidence from opinions of respected authorities on the basis of extensive clinical experience, descriptive studies or reports of expert committees

TABLE 2
Categories for strength of recommendations

Category	Definition
A	Good evidence to support recommendation for use
B	Moderate evidence to support recommendation for use
C	Poor evidence to support recommendation for or against use
D	Moderate evidence to support recommendation against use
E	Good evidence to support recommendation against use

of women where appropriate. The dual research criteria of scientific validity (best achieved with a homogeneous population) and generalizability are not mutually exclusive. This Consensus Conference will provide data on female enrollment in trials or research studies, where available.

As with previous Consensus Conferences, the clinical practice recommendations presented in this Supplement are graded by quality of evidence (Table 1) and strength of recommendation (Table 2) (7). Ranking (in brackets) follows each recommendation, where appropriate.

Despite impressive gains in combatting cardiovascular disease, there is still much to be done to accelerate these gains. The research and health care communities must rise to the challenge of IHD in women to increase knowledge about, and understanding of, this important disease, to promote good heart health through effective and evidence-based prevention strategies, and to support the provision of appropriate cardiovascular services for women. There are critical knowledge gaps and opportunities in research. This document should be only one part of an integrated approach. The understanding of particular issues relevant to IHD in women only enhances our ability to offer the best care for women and men.

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Chapter 2
Sex-related differences in the pathophysiology of cardiovascular disease: Is there a rationale for sex-related treatments?

Michael R Buchanan PhD, Stephanie J Brister MD FRCSC

Cardiovascular disease is a major cause of morbidity and mortality in both men and women (1,2). Nonetheless, the diagnosis of and treatment practices for cardiovascular disease differ markedly between men and women (3,4). A number of possibilities have been suggested to explain these differences, including social and psychological perceptions, and sex-related differences in symptom presentation, lifestyles and body size. There is also a body of evidence that suggests that a number of sex-related biological differences exist. These biological differences not only affect the pathogenesis of cardiovascular disease, but also affect the relative risks and the benefits of different treatment strategies. Below is an overview of the basic understanding of the underlying genesis of vascular disease as it relates to our current treatment strategies; the exacerbation of cardiovascular disease by comorbid risk factors; and how some of these risks and benefits may be sex-related. This overview is not meant to be 'all-encompassing', but rather is to be used to highlight examples of sex-related differences to engender the concept of developing more effective 'tailor-made therapies' to benefit patients, irrespective of sex.

PATHOGENESIS OF CARDIOVASCULAR DISEASE

Cardiovascular disease begins in early adulthood and progresses with age. Its progression is enhanced in genetically predisposed patients; in patients suffering hypertension, diabetes and/or hyperlipidemia; and in patients who smoke or who eat an unhealthful diet.

The disease process itself is complex and involves continuous interactions of injured or dysfunctional vessel walls with activated blood components. As a result, these blood vessels become less resilient, constricted and/or occluded, thereby causing ischemia and poor blood perfusion to the vital organs, including the heart.

The healthy vessel wall is biocompatible with the circulating blood. However, when the vessel wall is injured, it becomes highly reactive and thrombogenic. Specifically, injured veins and arteries express tissue factor, the expression of which increases over time after injury (5). Tissue factor expression is enhanced further by polymorphonuclear leukocytes (PMNs) and/or monocytes/macrophages that invade the injury site. This enhancement depends on the expression

of adhesive molecules in PMNs and/or monocytes/macrophages such as CD18 (5,6). The invading monocytes differentiate into macrophages that, in turn, ingest lipids, calcium and other blood-derived constituents, thereby forming a more complex lipid-laden atherosclerotic plaque (7,8).

Vessel wall tissue factor expression activates prothrombin that is widely distributed throughout vascular tissue rich in smooth muscle cells (9). Thrombin, in turn, upregulates endothelial cell platelet-derived growth factor (PDGF) receptor expression, thereby facilitating platelet activation and smooth muscle proliferation (10,11). Activated platelets secrete thromboxane A_2, which is vasoconstrictive, and PDGF, which is mitogenic for smooth muscle cells; activated platelets also act as a template for the assembly of procoagulants, which further exacerbates coagulation (12,13). Platelet-related Factor Xa/Va activity bound to the injured vessel wall also renders the vessel wall highly thrombogenic. This latter effect persists for longer than 96 h (14). Thus, there is a multiplicity of cell cell interactions that trigger thrombus formation and initiate intimal hyperplasia. This, in turn, leads to vessel wall constriction, lumen narrowing and occlusion (9-16). Our understanding of the multiplicity of these events forms the basis of the rationale for using antithrombotic therapies that target coagulation, platelet function and fibrinolysis. However, there also is a rationale for using an antithrombotic therapy that targets vessel wall thrombogenicity. To date, this latter approach is almost nonexistent.

The injured vessel wall itself also plays an active role in modulating vascular reactivity and its interactions with the circulating blood components. Vessel wall cells release nitric oxide, prostacyclin and endothelin, which regulate vasoconstriction and vasodilation. Vessel wall cells release other constituents that inhibit thrombus formation or facilitate fibrinolysis. Vessel wall cells also express receptors that influence the dynamics of the vessel wall/blood cell interactions, and the selective transmigration of macromolecules across the endothelial barrier. Dysfunction of any of these can lead to vascular constriction, and blood cell or blood constituent accumulation onto the blood/vessel wall interface. This leads to the accumulation of unwanted substances within the vessel wall, such as oxidated low density lipoproteins (LDLs), or to the constriction of the vessel wall lumen. Thus, there is a rationale for targeting vessel wall function as an approach to enhance antithrombotic therapy and/or to attenuate vascular ischemia.

CURRENT ANTITHROMBOTIC THERAPIES

Heparin and its low molecular weight derivatives are given to accelerate thrombin inhibition by antithrombin-III, thereby preventing fibrinogen cleavage to fibrin and subsequent fibrin clot formation. Acetylsalicylic acid (ASA) is given to acetylate platelet cyclooxygenase, thereby inhibiting thromboxane A_2 synthesis and rendering platelets less reactive to prothrombotic stimuli. Oral anticoagulants such as the coumarins, eg, sodium warfarin, are given to decrease the level of vitamin K-dependent procoagulants, thereby decreasing the amounts of procoagulant substrates available for thrombus formation.

All current antithrombotic approaches used to treat cardiovascular disease *impair* coagulation and/or platelet function.

The only antithrombotic approach currently used to affect the vessel wall is the use of lipid-lowering agents that are thought to attenuate atherosclerotic lesion formation. Interestingly, while these treatments provide an immediate benefit to the patient with cardiovascular disease, the effects are reversible, and the treatments must be continued to maintain a beneficial effect, ie, the disease process is simply delayed, but the disease is not prevented. Current treatment strategies focus primarily on altering blood cell interactions with the vessel wall, thereby rendering the patient hemostatically dysfunctional. Little attention focuses on fixing the vessel wall, other than acute interventions such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting.

ANTICOAGULANT THERAPY AND VESSEL WALL RESTENOSIS

A number of studies have demonstrated that heparin inhibits experimentally induced smooth muscle cell proliferation in vitro and in vivo (17-19). These data suggest that clinically, heparin should be effective in preventing smooth muscle cell hyperplasia and subsequent restenosis. However, restenosis occurs clinically despite heparin treatment. It is now recognized that thrombin is protected from inhibition by antithrombin-III and the acceleration of that effect by heparin when thrombin binds to fibrin or to other constituents on the injured vessel wall surface (20-23). Moreover, the surface-bound thrombin remains active, contributing to systemic hypercoagulation despite anticoagulant therapy in various experimental and clinical settings (14,24-26). Consequently, surface-bound thrombin can activate platelets and further coagulation, and promote smooth muscle cell proliferation unchecked. There also is evidence that the smooth muscle cells that proliferate in response to repeated injury are less sensitive to heparin treatment than the smooth muscle cells that proliferate in response to a first injury (27,28).

ANTIPLATELET THERAPY AND HYPERPLASIA

Clearly, ASA is beneficial in reducing the risks of stroke, myocardial infarction and transient ischemic attacks in patients with a variety of cardiovascular diseases (29). However, the overall risk reduction with ASA is only about 25%. Moreover, there is little evidence that antiplatelet therapy reduces smooth muscle cell hyperplasia. Finally, ASA may benefit only certain subgroups of patients (30-32). This may be due, in part, to the wide variation in platelet responsiveness to assorted stimuli after ASA ingestion (33) .

Alternate antiplatelet agents that block the platelet glycoprotein IIb-IIIa (GPIIb-IIIa) receptor have been proposed to be superior alternates to ASA. In the Evaluation of PTCA

to Improve Long-term Outcome by c7E3 GPIIa-IIIa Receptor Blockade (EPILOG) study, a GPIIb-IIIa receptor agonist, c7E3, decreased acute ischemic complications in patients undergoing PTCA (34). Similar results were obtained in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study using tirofiban, a nonpeptide GPIIb-IIIa antagonist (35). However, there is little clinical evidence to indicate that long term hyperplasia is inhibited by these platelet GPIIb-IIIa inhibitors, suggesting that platelet inhibition alone for finite periods of time is unlikely to have any long-lasting effect. Antiplatelet therapy does not prevent chronic intimal hyperplasia.

ANTI-INFLAMMATORY THERAPY AND HYPERPLASIA

As early as 1939, inflammation was recognized as playing an integral step in the cardiovascular disease process (36), yet 'anti-inflammatory' agents are not included in the rationale of standard antithrombotic therapy. There is convincing evidence that attenuating certain inflammatory responses actually provide a significant benefit. For example, monocytes/macrophages and PMNs express the integrin CD11/CD18 or intracellular adhesion molecule, and these cells release cytokines when activated (37). The cytokines, in turn, stimulate: $beta_3$ integrin expression in other cells such as platelets, endothelial cells and smooth muscle cells (38,39); tissue factor activation (6); and PDGF expression (40,41). Platelet-derived lipid fractions augment these responses by inducing monocyte/macrophage differentiation and growth (42). Macrophages sequestered within the injured vessel wall accumulate lipid, leading to the formation of a more complex atherosclerotic lesion (15,43). Blocking monocyte/macrophage intracellular adhesion molecule expression reduces monocyte/macrophage adhesion to the vessel wall, thereby significantly reducing fatty streak formation and vessel wall hyperplasia (43-45). Similarly, radiation treatment in doses that selectively impair monocyte/macrophage function decreases vessel wall hyperplasia in both experimental and clinical settings (40,46,47). These data provide direct evidence that altering inflammation has a significant beneficial effect on intimal hyperplasia and subsequent vessel wall restenosis. Attenuation of acute inflammatory responses after vessel wall injury decreases chronic intimal hyperplasia.

DECREASING VESSEL WALL THROMBOGENICITY AND INTIMAL HYPERPLASIA

Lonn et al (48) suggest that inhibitors of the renin-angiotensin-aldosterone pathway, such as ramipril, may restore endothelial cell function, thereby reducing the risk of progressing cardiovascular disease. This approach appears to have significant promise (49), but the mechanism by which the beneficial effect of ramipril is achieved is not clear. One suggestion is that ramipril re-establishes 'vessel wall quiescence', possibly by elevating vessel wall cyclic adenosine monophosphate levels, which renders the vessel wall more biocompatible. Regardless of which mechanism, one of the effects of angiotensin-converting enzyme inhibitors appears to take place at the level of the vessel wall. This is further support for the concept that the vessel wall is an appropriate target for antithrombotic therapy, independent of other antithrombotic agents that compromise blood coagulation and/or hemostasis.

There are a number of experimental studies indicating that decreasing vessel wall thrombogenicity alone can ameliorate vessel wall disease without compromising hemostasis or coagulation. Vessel wall biocompatability can be re-established directly by elevating vessel wall cyclic adenosine monophosphate or by downregulating vessel wall integrin expression, thereby decreasing acute platelet/vessel wall interactions at the time of vessel wall injury (50-52). Alternatively, vessel wall thrombogenicity can be decreased after injury by inhibiting thrombin, which is bound to the damaged vessel wall surface at the time of injury (14,53). These treatment approaches also result in the attenuation of chronic vessel wall hyperplasia after injury despite discontinuation of these treatments (53,54). These latter results indicate that these effects are irreversible. This contrasts markedly with the effects of our current antithrombotic treatments, which are reversible and, therefore, require continuous long term use to sustain any beneficial effect. While the former studies are experimental in nature, preliminary clinical studies indicate that similar approaches can be used to decrease acute vessel wall thrombogenicity in patients undergoing cardiac surgery (55). There is experimental evidence that blood/vessel wall interactions that lead to cardiovascular disease can be attenuated without compromising hemostasis and coagulation by acutely altering vessel wall thrombogenicity.

SEX-RELATED DIFFERENCES IN THE PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE

Most antithrombotic treatments currently used are prescribed as a standard dose, despite that men and women differ from many perspectives. The obvious example is the recommended dose of ASA: 80 to 325 mg daily or every other day, depending on the clinician's bias. Regardless, a 77-year-old woman weighing 49 kg receives at least twice the dose of ASA as a 42-year-old man weighing 96 kg. Perhaps such a difference does not really matter. However, can that difference alone explain the high risk of cerebral bleeding in the elderly woman? There are data from both human and animal studies that indicate that ASA is absorbed more rapidly in women than men; ASA is distributed in a larger apparent volume in women than men; and ASA is hydrolyzed more rapidly in women than men (56-59). Such differences support the consideration of sex-related differences in antithrombotic therapy. Given the multiplicity of interactions of many blood cells and plasma constituents with the vessel wall, is it not possible that sex-related differences in these factors may influence the risk and pathogenesis of cardiovascular disease, and/or the relative effectiveness of the various antithrombotic therapies?

There are obvious sex-related differences in pharmacokinetics and pharmacodynamics that should be understood when implementing any therapeutic regimen.

HYPERLIPIDEMIA

Hyperlipidemia is considered to be a major risk factor in the progression of cardiovascular disease. In particular, an overall high plasma lipid level or a high LDL to high density lipoprotein (HDL) ratio is thought to increase a patient's risk of cardiovascular disease. Oxidized LDL ingested by macrophages within the extracellular vascular space results in foam cell formation and vascular fatty streak formation. Studies in both humans and animals indicate that men and women differ significantly in these lipid ratio profiles. For example, women have higher HDL levels and lower triglyceride levels than men (3,4,60,61). Moreover, the LDL particle size is larger in women (62,63). Some investigators have suggested that these differences are due, in part, to differences in lifestyle and diet (61). However, controlled animal studies indicate that these lipid level differences are, in part, sex-related. Specifically, when hamsters were fed a hypercholesterolemic diet for 12 weeks, female hamsters had lower total cholesterol plasma levels, higher HDL levels and larger LDL particle size than their male counterparts. These differences were associated with less fatty streak formation in the female hamsters (62). Thus, metabolism of the same lipid diet and subsequent fatty streak formation are sex-dependent. This sex-related difference may be due to a number of factors, including hormone and vessel wall and/or monocyte/macrophage interaction differences (discussed below). Lipid metabolism differs between men and women, thereby suggesting that the treatment of hyperlipidemia also should differ between men and women.

DIABETES

Diabetes exacerbates cardiovascular disease. The sex-related difference seen between the prevalence of cardiovascular disease in men and premenopausal women disappears if premenopausal women have diabetes (63). This appears to be associated, in part, with a diabetes-induced dyslipidemia, ie, diabetic premenopausal women have lower HDL levels, and higher triglyceride and oxidized LDL levels than nondiabetic premenopausal females (64). The higher triglyceride and oxidized LDL levels are associated with increased platelet responsiveness and increased cardiovascular risk. Gaillard et al (65) suggest that the increased cardiovascular disease risk in diabetic premenopausal women is due to a genetic predisposition rather than a diabetes-mediated increased risk. They found that nondiabetic, obese first-degree relatives with type 2 diabetes mellitus had similar metabolic and anthromorphic risk factors to their type 2 diabetic relatives.

If so, further studies are required to understand better the genetic predisposition of premenopausal diabetic women and their first-degree relatives to determine the need for alternate or adjunct therapies and whether this genetic predisposition is sex-specific.

COAGULATION

Fibrinogen and total coagulation factor VII (VIIc) concentrations are higher in patients with cardiovascular disease who are at increased risk of acute ischemic events (66). Increased thrombin levels seen in cardiovascular disease patients undergoing PTCA, cardiac surgery or carotid endarterectomies also are thought to be predictive of increased cardiovascular thrombotic events (24-26). However, there is little evidence to suggest that the levels of these procoagulants differ significantly between men and women. In fact, it is difficult to make any conclusion about the importance of a hypercoagulable state or hyperactive platelets as predictors of cardiovascular disease. Clearly, procoagulant zymogens and/or platelets become activated after vessel wall injury, and in a diabetic or hyperlipidemic milieu, exacerbate thrombus formation and/or cardiovascular disease. But, it is difficult to determine whether the hypercoagulable state exists before, thereby acting as the underlying stimulus for injury or for the onset of the disease, or whether the hypercoagulable state is the result of ongoing injury or disease. This issue has yet to be resolved. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, the baseline fibrinogen levels in postmenopausal women who suffered an idiopathic venous thromboembolic event were, in fact, lower than the baseline fibrinogen levels seen in the postmenopausal women who did not suffer a venous thromboembolic event (67). Surrogate markers of hypercoagulation are not sex-specific, nor do they necessarily indicate a predisposition to thrombotic or ischemic events.

HORMONES

The majority of evidence suggests that sex-related differences in cardiovascular disease are due to sex-related hormones. First, men between 30 and 50 years of age are at a higher risk of cardiovascular disease than premenopausal, nondiabetic women of the same age (68). Second, the rate of increase in atherosclerotic lesions is higher in women aged 50 to 70 years than in men of the same age. This sex-related difference is thought to be due to an effect of plasma estrogen on the lipid profile in men and women (3,4,60-62). Consequently, hormone replacement therapy has become a recommended therapy to attenuate the increased risk of cardiovascular disease in postmenopausal women (3,4,69). However, recent studies, particularly the Heart and Estrogen/progestin Replacement Study (HERS), have challenged this recommendation. HERS suggested that there is an increased risk of cardiovascular events in postmenopausal women within the first year of hormone replacement therapy (70). However, it should be noted that HERS was conducted mainly in women with known coronary artery disease. Thus, one cannot conclude that hormone replacement therapy is contraindicated in the prevention of cardiovascular disease in the general population of postmenopausal women.

Other clinical and experimental studies indicate that both testosterone and estrogen exert multiple effects on

homeostatic processes independent of lipid metabolism, the relative advantages and/or disadvantages of which have yet to be established (71). Studies in transsexuals indicate that hormone replacement therapy affects vessel wall calibre and blood flow. When female-to-male transsexuals received high dose testosterone, not only did their HDL levels decrease analogous to the sex-related differences in HDL baseline levels, but vascular reactivity (measured as sublingual nitroglycerin-induced brachial artery flow) was severely depressed (72). Vascular reactivity in response to nitroglycerine is lower in men than in women (73). It has been suggested that the higher resting and stress response vascular reactivity in women preserves myocardial blood flow better (60). In contrast, when male-to-female transsexuals were given long term estrogen therapy, vascular reactivity increased to a level comparable with that of similar age-matched premenopausal women (74). Similarly, vascular reactivity that became impaired in postmenopausal women was restored to near premenopausal levels when these women were given hormone replacement therapy (73). Vascular reactivity facilitates reperfusion of ischemic tissue. Hormone replacement therapy, particularly estrogen-related therapy, which enhances vascular reactivity, thereby facilitating reperfusion to ischemic tissue, is beneficial for postmenopausal women.

However, other data are inconsistent with the above conclusion. For example, while some studies confirm a beneficial effect of hormone replacement therapy on lowering plasma lipid levels, particularly LDLs under baseline conditions, any beneficial effect in this regard may be lost in more pathogenic states. Specifically, Holm et al (75) found that female rabbits fed a cholesterol-rich diet accumulate at least 50% less cholesterol in segments of uninjured aorta compared with the amount of cholesterol that accumulates in segments of uninjured aorta in male rabbits fed a cholesterol-rich diet. However, the cholesterol accumulation in segments of balloon-injured aorta obtained from the same female rabbits was equal to or higher than that in the males. Similar results have been seen in primates. In normolipidemic female cynomolgus monkeys, coronary artery reactivity was higher than in their male counterparts, suggesting that the female monkeys were at less risk of vascular disease. However, when female monkeys were fed an atherogenic diet for 12 weeks, a lipid-lowering agent reduced the cholesterol plasma levels in a dose-related manner, but had no effect on fatty streak plaque formation compared with their male counterparts (76). The explanation for the inconsistency has yet to be explained, but may provide a partial explanation for any apparent increased cardiovascular event rate in HERS.

A number of other studies suggest that estrogen inhibits c-*jun*, c-*fos* and transforming growth factor-beta inducible early gene expression, thereby inhibiting various aspects of smooth muscle cell proliferation (77), and inhibits vascular cell adhesion molecule expression, thereby inhibiting monocyte/macrophage adhesion onto the vessel wall (78). The negative results of HERS cannot be extrapolated to the general postmenopausal female population. More studies are required to understand better the sex-related advantage(s) of premenopausal women over men concerning the risk of cardiovascular disease, and to elucidate better the potential beneficial and/or adverse effects of hormone replacement therapy in postmenopausal women.

DRUG PHARMACOKINETICS AND PHARMACODYNAMICS

As mentioned above, absorption, distribution and clearance of ASA differs significantly between women and men (56). Similarly, there are sex-related differences in the pharmacokinetics of heparin that may explain the predisposition of women to bleeding complications when treated with heparin (57). This difference may be due, in part, to a sex-related difference in postheparin lipase activity (79). Thrombin fragment 1 levels (a measure of the hypercoagulable state) are decreased more effectively with pravastatin in female patients than in male patients (58). Atorvastatin, a coenzyme A reductase inhibitor that reduces plasma cholesterol level by inhibiting cholesterol synthesis, has a 36% longer half-life in elderly women than in elderly men. This difference is associated with a 45% higher plasma level in women than in men (59). It is important to recognize that sex-related differences in both the pharmacokinetics and pharmacodynamics of any drug therapy are likely to exist in cardiovascular disease patients, particularly when most of these therapies involve more than one drug and various routes of administration. Understanding these differences and treating disease accordingly may significantly affect not only subsequent outcomes, but also secondary comorbidity.

POSSIBLE RESEARCH DIRECTIONS

First, there is no doubt that premenopausal women are at less risk of cardiovascular disease and postmenopausal women are at the same or greater risk of cardiovascular disease than men of the same age. Differences in estrogen-testosterone hormone levels may explain some of these differences. The observed beneficial effects of hormone replacement therapy on plasma lipid profiles and vascular reactivity in both postmenopausal women and transsexuals are consistent with that possibility. However, comorbidity, particularly dyslipidemia (either diabetic- or hypercholesterolic-induced), appears to compromise the estrogen-related benefit. Notwithstanding, there are a number of other effects of hormone replacement therapy that are independent of any lipid-lowering effect and may contribute to the lower risk of cardiovascular disease in premenopausal women. Thus, more studies that help to reveal the various mechanisms of action of different hormones may provide a better targeted antithrombotic therapy for both men and women at risk of cardiovascular disease. These studies should be stratified for comorbidity.

Second, a better understanding of the sex-related differences in drug pharmacokinetics and subsequent pharmacodynamics must be obtained to optimize the treatment

regimens for both women and men with cardiovascular disease. Women are generally smaller than men, and dosing should be administered with this in mind. The higher bleeding risks seen in women receiving antiplatelet and/or anticoagulant therapy may be due simply to a size rather than a sex difference.

Finally, there is no evidence that there are any sex-related differences in surrogate markers of thrombosis that affect overall treatment strategies for cardiovascular disease in men and women. However, the recent experimental and clinical data indicating that targeting the vessel wall as a therapeutic approach to prevent chronic vessel wall hyperplasia and cardiovascular events deserve further attention. These approaches may circumvent the significant hypocoagulant and dysfunctional bleeding side effects associated with our current therapies. These latter effects are more apparent in women and may be due to significant differences in drug treatment pharmacokinetics. Thus, more studies are warranted to understand better the sex-related differences between the risks of cardiovascular disease, and the sex-related differences in therapeutic strategies to prevent or treat cardiovascular disease.

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Chapter 3
Epidemiology of ischemic heart disease in women

Eva Lonn MD MSc FRCPC

CARDIOVASCULAR DISEASE IS THE MAJOR CAUSE OF DEATH FOR CANADIAN WOMEN

Despite major advances in the diagnosis and management of ischemic heart disease (IHD) and stroke, cardiovascular disease (CVD) is the leading cause of death for both women and men in Canada, and throughout most of the industrialized world. In 1997, there were 79,457 deaths attributed to CVD in Canada, 39,619 among women and 39,838 among men (1). Of these, IHD accounted for the largest proportion of deaths in women, and acute myocardial infarction (MI) was the leading cause of death among Canadian women. The proportion of deaths due to CVD in women increases significantly after menopause and continues to increase with advancing age (Figure 1, Table 1). Deaths from cardiovascular causes largely exceeded deaths related to all forms of neoplasms combined; it exceeded deaths from infectious diseases, respiratory diseases, complications of pregnancy and all other major categories of diseases in women (Figure 2).

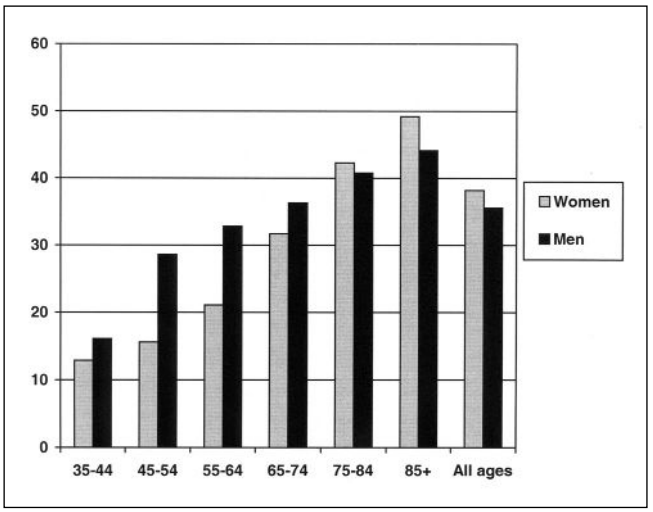

Figure 1) *Percentage of total deaths due to cardiovascular diseases by age group and sex in Canada, 1997. Source: Heart and Stroke Foundation of Canada: The Changing Face of Heart Disease and Stroke in Canada. Ottawa, Canada, 1999 (reference 1)*

Age-standardized mortality rates from CVD overall, from IHD and from acute MI have declined steadily over the past three decades among Canadian women and men (Figure 3). This decline may be explained by a reduction in the prevalence of smoking and other risk factors, and by improved therapies for people who develop CVD. Similar trends are expected to continue into the next century. However, the decline in age-standardized mortality rates from CVD in general, from IHD and from acute MI in women has been less pronounced than that in men (1). Despite the documented decline in age-standardized mortality rates, both in women and in men, the actual number of deaths related to CVD has increased. Thus, in 1990, there were 36,266 deaths from cardiovascular causes among Canadian women, and this number increased to 39,619 in 1997. While the number of actual deaths from cardiovascular causes overall has increased, the number of IHD deaths has decreased for men and has reached a plateau for women over the past three decades, with a marked decline in deaths from acute MI in men and a less pronounced decrease in acute MI deaths in women.

The overall increase in cardiovascular deaths and the projected increase in deaths from IHD in the next decade is related mainly to Canada's aging population. Life

TABLE 1
Number and percentage of deaths due to cardiovascular diseases by sex in Canada, 1997

Age (years)	All deaths (n)	All cardiovascular diseases* n	All cardiovascular diseases* % of all deaths	Ischemic heart disease† n	Ischemic heart disease† % of all deaths	Acute myocardial infarction‡ n	Acute myocardial infarction‡ % of all deaths	Cerebrovascular disease§ n	Cerebrovascular disease§ % of all deaths
Women									
<35	2982	150	5.0	13	0.9	9	0.3	37	1.2
35-44	2416	314	12.9	101	4.2	59	2.4	112	4.6
45-54	4563	712	15.6	325	7.1	208	4.6	198	4.3
55-64	8111	1708	21.1	903	11.1	518	6.4	345	4.3
65-74	18,040	5711	31.7	3155	17.5	1791	10.0	1100	6.1
75-84	31,989	13,531	42.3	7030	22.0	3713	11.6	3185	10.0
≥85	35,567	17,488	49.2	8172	23.0	3171	8.9	4398	12.4
All ages	103,668	39,614	38.2	19,699	19.0	9469	9.1	9375	9.0
Men									
<35	5947	226	3.8	50	1.0	33	0.6	38	0.6
35-44	4361	702	16.1	447	10.2	261	6.0	92	2.1
45-54	7384	2113	28.6	1439	19.5	895	12.1	241	3.3
55-64	13,466	4419	32.8	3050	22.6	1808	13.4	503	3.7
65-74	27,560	9999	36.3	6380	23.1	3473	12.6	1428	5.2
75-84	33,915	13,846	40.8	8094	23.9	4197	12.4	2585	7.6
≥85	19,338	8529	44.1	4362	22.6	1821	9.4	1786	9.2
All ages	111,971	39,834	35.6	23,822	21.3	12,488	11.2	6673	5.9

**International Classification of Diseases Ninth Revision (ICD-9) 390-459; †ICD-9 410-414; ‡ICD-9 410, acute myocardial infarction is a subcategory of ischemic heart disease; §ICD-9 430-438. Source: Heart and Stroke Foundation of Canada: The Changing Face of Heart Disease and Stroke in Canada. Ottawa, Canada, 1999 (reference 1)*

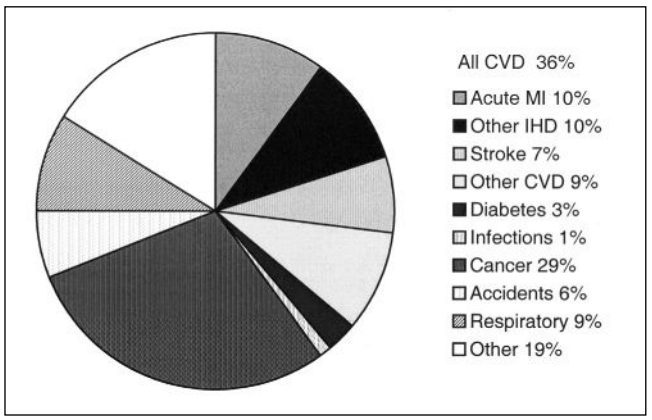

Figure 2) *Leading causes of death in Canada, 1997, by percentage. Total number of deaths 215,999. CVD Cardiovascular disease; IHD Ischemic heart disease; MI Myocardial infarction. Source: Heart and Stroke Foundation of Canada: The Changing Face of Heart Disease and Stroke in Canada. Ottawa, Canada, 1999 (reference 1)*

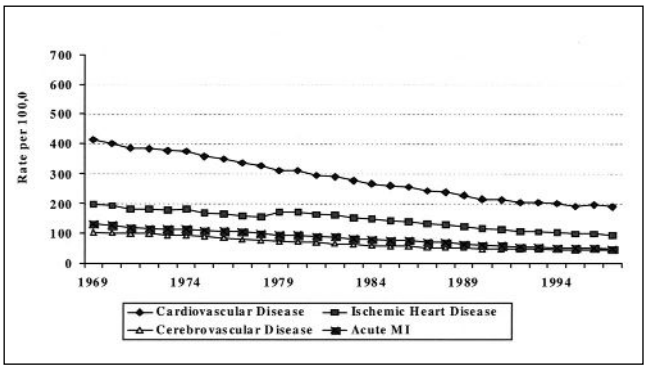

Figure 3) *Age-standardized mortality rate per 100,000 women in Canada, 1969 to 1997. Age was standardized to 1991 Canadian population. Source: Heart and Stroke Foundation of Canada: The Changing Face of Heart Disease and Stroke in Canada. Ottawa, Canada, 1999 (reference 1)*

expectancy in Canadian women was estimated to be 81.3 years in 1995, and 13.7% of Canadian women were aged 65 years or older in 1995. It is expected that the percentage of elderly women will increase further, and by 2041, close to one-quarter of the total Canadian population will be aged 65 years or older (2). As women tend to live longer than men and as there are higher CVD rates among elderly people, it is expected that the number of deaths from cardiovascular causes among women will likely surpass those among men in the near future; thus, it is also projected that, while CVD deaths for men in Canada will not change significantly over the next two decades, the numbers for women will increase by 28% between 1995 and 2016 (Figure 4) (1). This projected future increase in CVD deaths among Canadian women is expected to result from higher numbers of deaths both

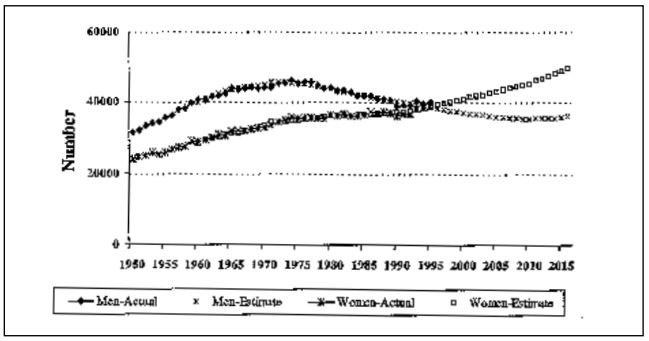

Figure 4) *Number of cardiovascular disease deaths by sex, actual and projected, in Canada, 1950 to 2016. Source: Heart and Stroke Foundation of Canada: The Changing Face of Heart Disease and Stroke in Canada. Ottawa, Canada, 1999 (reference 1)*

from IHD and stroke. At present, the number of deaths from cerebrovascular disease (stroke) is already higher for women than for men, and this trend is likely to continue in the future.

There are significant regional differences in mortality rates from IHD in Canada, both for women and for men. In 1995, the highest rate of death from IHD in women was noted in Newfoundland, and the lowest rates were noted in British Columbia. Similarly, IHD and overall CVD mortality and morbidity rates vary within provinces among different regions (1,3).

CVD is the leading cause of death worldwide, but rates vary considerably by country. Statistics provided by the World Health Organization comparing 22 selected countries in the mid 1990s rated Canada 11th for age-standardized mortality rates from IHD overall (women and men) and 12th for women. The highest age-standardized mortality rates from IHD in women were documented in the Russian Federation at 271.6 deaths/100,000 women compared with 94.5/100,000 women in Canada, 33.8/100,000 women in France and 26.6/100,000 women in Japan (Japan and France were the countries with the lowest mortality rates from IHD) (1).

MORBIDITY ASSOCIATED WITH IHD IN WOMEN

Precise rates of nonfatal IHD are difficult to ascertain. The 1996 to 1997 National Population Health Survey evaluated self-reported heart disease rates among Canadians. Overall, 4% of the Canadian women who responded to this survey reported that they had a diagnosis of heart disease, with increasing rates by age. Thus, in the age group of women aged 75 years and older, 22% responded that they had heart disease diagnosed (1).

Heart disease and stroke are the leading causes of hospital admission for women in Canada, with the exception of childbirth, and the leading cause of hospital admission for men. Hospitalization rates for CVD accounted for 13% of all hospital admissions for Canadian women in 1996 to 1997, with higher rates with increasing age. Of these, hospitalizations for IHD represented a large proportion. A trend toward increasing hospital admission rates for IHD has been documented over the past three decades, and it is projected that this trend will continue in the next 20 years.

Hospital admissions for IHD is a major health problem in women aged 55 years and older, while hospital admissions for heart failure and stroke affect mostly elderly women, primarily those aged 75 years or older. Admissions to hospital for IHD are more frequent for men than for women; however, length of hospital stay for women surpasses, on average, that for men. Diagnostic and therapeutic interventions are frequently used in the management of CVD, and additionally, a large number of cardioactive drugs are prescribed. IHD has, therefore, a huge economic impact in Canada. In 1993, health care costs related to coronary heart disease (CHD) in women and men combined were estimated to be $7.8 billion (4).

WOMEN'S PERCEPTION OF THE IMPORTANCE OF CVD FOR THEIR HEALTH

While CHD is a major cause of mortality and morbidity in women, heart disease is still widely viewed as a health problem of middle-aged men. Both the general public and, frequently, physicians fail to recognize IHD as a major health problem in women. The Heart and Stroke Foundation National Omnibus Survey taken by Environics Research reported that 60% of women polled regarded breast cancer as the leading cause of death among women in Canada, while only 17% recognized heart disease as the major cause of mortality in Canadian women (5). Similarly, in a national telephone survey of American women, 58% "believed they were as likely or more likely to die of breast cancer than coronary artery disease", and close to 50% of women included in this survey who were older than 45 years of age reported that their physicians had "never talked to them about heart disease" (6), suggesting that physicians' acceptance of the importance of coronary artery disease (CAD) in women is also frequently inadequate.

RISK FACTORS FOR IHD IN WOMEN

The major risk factors for CHD in women are increasing age, cigarette smoking, hypertension (including isolated systolic hypertension), dyslipidemia, diabetes mellitus, sedentary lifestyle and a premature family history of IHD. Several additional potential risk factors that are currently under investigation and are commonly referred to as 'emerging' risk factors, as well as psychosocial factors, are also likely to play important roles. Although most risk factors for CAD are similar in women and in men, gender differences have been documented, particularly in the prevalence and magnitude of the effect of certain risk factors such as hypertension, diabetes and dyslipidemia. Some risk factors, such as the use of oral contraceptives and menopause, are unique to women.

The Canadian Heart Health Surveys conducted between 1986 and 1992 acquired information on the prevalence of major risk factors (smoking, high blood pressure, elevated cholesterol, physical inactivity and obesity)

from 23,129 Canadian women and men across all 10 provinces. A total of 11,753 women and 11,376 men aged 18 to 74 years were evaluated. This study found that 62% of Canadian women aged 18 to 74 years had one or more modifiable risk factors for CHD, and 33% had two or more major risk factors (7).

NONMODIFIABLE RISK FACTORS

Nonmodifiable risk factors for CHD in women include advancing age, postmenopausal status and family history.

Age: In both sexes, the risk of CHD increases markedly with age (8-10). Age is a particularly strong risk factor for CHD in women (11,12). The dramatic influence of age on the development of CAD in women was first shown conclusively in the Framingham study (12). This study reported significantly lower morbidity and mortality rates from CHD in women than in men. However, in the advanced age groups, the rates of women with CAD was close to that of men (12). The Framingham study also found a very marked sex-associated disparity in the incidence of CHD for the younger age groups, and this gap diminished progressively during the middle-age years and almost disappeared in elderly individuals. Furthermore, when incidence rates of CHD for men and women were grouped according to age, there was a striking 40-fold difference between the oldest (75 to 84 years) and the youngest (35 to 44 years) age groups for women, whereas the difference across these age groups in men was only sixfold. The clinical onset of CAD in women who undergo natural menopause is, on average, 10 years later than that for men, with MI occurring as much as 20 years later. Death rates from CHD in women also lag behind those in men by about 10 years. Similar findings were reported by other studies, and the dominant influence of age on CHD risk in women is also documented by Canadian statistics. The effect of aging on CHD risk in women may be related, at least in part, to menopause. Thus, premenopausal women display a much lower incidence of CAD compared with age-matched men, and after menopause, the incidence of CAD among women increases rapidly. In the Framingham study, there was a 10-fold increase in CHD risk in women 55 years of age and older, while the increase in CHD risk in men over the same age span was only 4.6-fold. This change was thought to be related largely to the onset of menopause, which occurs at an average age of 51.4 years. It remains unclear, however, whether the influence of menopause on CHD is related primarily to changes in estrogen levels or to the other age-associated changes in risk factors (13,14).

While younger women have substantially lower rates of CAD, identifying young women at high risk is important. Young women with CAD are more likely to have a history of tobacco exposure, obesity, diabetes, hypertension, early menopause and (less often) cocaine abuse (15,16).

Genetic predisposition and family history of premature CHD: CHD tends to cluster in families, and a positive family history of premature CHD is an important risk factor both in women and in men (17). The family history is considered positive if clinical CHD or sudden death is documented in first-degree male relatives before the age of 55 years or in first-degree female relatives before the age of 65 years. The Framingham study reported an increased relative risk of 1.6 among women with a parental history of premature death due to CHD, after adjusting for other major risk factors (18). A number of other epidemiological studies found similar associations between a family history and CHD risk even after accounting for other risk factors (19-22). Factors contributing to the frequent occurrence of CHD in families relate both to shared lifestyle characteristics (eg, cigarette smoking, eating habits, physical inactivity) and to genetic factors (eg, familial dyslipidemias affecting lipoprotein[a], low density lipoprotein [LDL] pathways, apoproteins, high density lipoprotein [HDL] apoproteins, apoprotein E variations, polymorphisms such as the angiotensin-converting enzyme D/D polymorphism, etc). Promising research into genetic determinants of IHD and gene-specific therapies is ongoing. At the present time, however, it remains unclear to what extent the research into genetic determinants of IHD will further our understanding of the occurrence of heart disease and its prevention, because complex interactions between multiple genetic and environmental factors are likely to contribute to CHD.

Gender-specific nonmodifiable risk factors: The incidence of CHD in women increases dramatically in middle age. This has led to speculation that menopause is a risk factor for CHD; this likely relates to changes in ovarian hormones, which are presumed to be cardioprotective (12). Women who experienced early and abrupt menopause as a result of bilateral oophorectomy, and who did not receive hormone replacement therapy were found, in the Nurses Health Study, to have a 2.2 times higher risk of CHD than premenopausal women of the same age (23). It remains uncertain, however, whether natural menopause is also a risk factor for CHD, and whether the increase in incidence of IHD in middle-aged and elderly women is caused by lower estrogen levels or is an overall manifestation of advancing age (24,25).

MODIFIABLE RISK FACTORS

Cigarette smoking: Cigarette smoking is the leading preventable risk factor for IHD in women. Contrary to popular belief, smoking is responsible for more deaths due to heart disease and stroke than cancer. A large body of evidence has consistently indicated that the risk of CHD is two to four times higher in women who are heavy smokers (usually defined as those who smoke 20 or more cigarettes/day) than among women who do not smoke (26,27). In the Nurses Health Study, there was a dose-response relation between smoking and the risk for angina, nonfatal MI and fatal CAD, but even 'light' smokers, defined as women who smoked one to four cigarettes daily, more than doubled their coronary risk (28). Some studies suggest that smoking is a stronger risk factor for MI in middle-aged women than in men (29). Cigarette smoking triples the risk for MI among premenopausal women and is also an important

contributor to sudden cardiac deaths in young women (30). Additionally, smoking lowers the age of menopause, on average, by one and one-half to two years, with the longer duration of menopausal status possibly augmenting coronary risk. The risk associated with cigarette smoking is further enhanced in premenopausal women who use oral contraceptives. This synergistic effect of smoking and oral contraceptive use was originally demonstrated in earlier studies evaluating the use of oral contraceptives containing more than 50 μg of estrogen (31). Subsequent studies of oral contraceptives containing lower doses of estrogen also showed a significantly increased risk of CAD (32). Smoking remains an important risk factor among elderly women (33). In the Systolic Hypertension in the Elderly Program (SHEP) study, both women and men older than 60 years of age who smoked experienced 73% more CAD events than nonsmokers (34). There is no evidence that smoking cigarettes with reduced nicotine or tar levels lowers the risk for coronary events associated with smoking. Passive exposure to tobacco is also deleterious (35,36).

Canadian statistics show a decline in smoking rates in the 1970s and 1980s, with an apparent plateau in the 1990s (1). Thus, there has been little change in overall smoking rates since 1991. From 1996 to 1997, 29% of Canadians aged 15 years and older smoked cigarettes; 24% were daily smokers and 4% were occasional smokers. In Canadian teenagers aged 15 to 19 years, however, there is an alarming increase in smoking rates both in women and in men, from 16% in 1991 to 22% in 1996 to 1997, with higher smoking rates among young women (23%) than young men (21%). More men than women were daily smokers in all other age groups (except in the age group under 20 years) (1).

Smoking rates differ among Canadian provinces, with the highest smoking rates among women in Quebec (1). A higher proportion of women and men in lower income groups are current or former smokers (1).

The Canadian Heart Health Surveys reported that women who smoke more than 25 cigarettes daily have a markedly greater prevalence of additional risk factors, including high blood pressure, diabetes mellitus and sedentary lifestyle (37).

Diabetes mellitus: Diabetes is a more powerful coronary risk factor for women than for men, essentially negating the gender protective effect even for premenopausal women, so that diabetic women have a risk of CHD similar to that of diabetic men (38,39). Women older than 45 years are also twice as likely as men to develop diabetes. Based on data from the Nurses' Health Study, maturity-onset diabetes mellitus confers a three- to sevenfold increase in the risk for cardiovascular events (40). In the Framingham cohort, the risk of a coronary event in a diabetic versus a nondiabetic woman was increased 5.4-fold compared with a 2.4-fold increase in risk in a diabetic versus a nondiabetic man (41).

Diabetes is often associated with a cluster of cardiovascular risk factors, including hypertension, dyslipidemia, physical inactivity, obesity and abnormalities of fibrinolysis.

Type 1 or insulin-dependent diabetes mellitus occurs primarily in young individuals and is related to abnormalities in insulin production. Type 2 or adult-onset diabetes, also called noninsulin-dependent diabetes (NIDDM), comprises about 90% of overall diabetics and almost all diabetic patients older than 45 years of age. Type 2 diabetes, which is much more prevalent in middle-aged and older adults, and is associated with insulin resistance, contributes considerably to morbidity and mortality from CHD. In addition to women with overt NIDDM, women with impaired glucose tolerance are also at increased risk for CHD and adverse cardiovascular outcomes (42,43). Furthermore, recent data show an exponential and continuous relationship between glucose levels and cardiovascular events in women and in men extending to the ranges of 'normal' glucose concentrations, and suggesting that even nondiabetic persons with high normal fasting glucose levels are at increased risk (44).

Diabetes is also associated with a less favourable outcome of clinical coronary events. Both in-hospital and long term prognoses of MI are substantially worse for diabetic women than for diabetic men compared with their nondiabetic counterparts. Diabetic women who have an MI incur a higher risk of death, a double risk of reinfarction and a fourfold increase in the risk of development of heart failure (45-49). Among patients who undergo myocardial revascularization procedures, both coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty, more women than men are diabetic. Diabetes contributes to their less favourable outcome from such procedures.

The prevalence of diabetes is difficult to evaluate. There are many women and men who have diabetes without having been diagnosed. Some studies suggest that up to 50% of cases of diabetes in North America are undiagnosed and, therefore, unreported. The limitations in the evaluation of the true prevalence of diabetes among populations suggest that available data greatly underestimate the prevalence of diabetes among Canadian women. The National Population Health Surveys reported a prevalence of 3% of diabetes in Canadian women in 1996 and 1997, with a significantly higher prevalence in older age groups, reaching 9% in women aged 65 years or older (1).

Gestational diabetes mellitus refers to glucose intolerance of varying severity first detected during pregnancy. Women with gestational diabetes mellitus are at a high risk of developing future diabetes (primarily type 2) or glucose intolerance (50,51). Thus, studies from the United States using the National Diabetes Data Group criteria for gestational diabetes mellitus suggest that 50% to 60% of women with prior gestational diabetes develop type 2 diabetes during their lifetime (52). Women with prior gestational diabetes who developed diabetes are at an increased risk of CHD by virtue of being diabetic. There are no good prospective data, however, to suggest that women with gestational diabetes who do not develop diabetes are at an increased risk of CHD; the relation between gestational diabetes and CHD risk is not well studied and requires further exploration.

Polycystic ovary syndrome (PCO) is a condition specific to women that is associated with insulin resistance and hyperinsulinemia, and with an increased risk of developing NIDDM. Women with PCO frequently display a cluster of metabolic abnormalities, including central ('android') obesity, elevated levels of circulating androgens, glucose intolerance and hyperinsulinemia, high plasma triglycerides, low HDL cholesterol (primarily HDL_2), high intermediate density lipoproteins and small, dense LDL cholesterol (53-56). It is likely, therefore, that women with PCO are at an increased risk of developing CHD. To date, however, there are only very limited data on CHD risk associated with PCO. One cross-sectional study in women undergoing coronary angiography suggests that women with PCO have more extensive CAD than women with normal ovarian function (57). There are, however, no good prospective data on CHD incidence in women with PCO.

Dyslipidemias: A large number of epidemiological studies show that elevated concentrations of total cholesterol and LDL cholesterol are important risk factors for CHD in women (58-62). The association between total and LDL cholesterol and CHD risk is stronger in younger and middle-aged women than in older women. A National Heart, Lung, and Blood Institute workshop that collected data from 25 prospective cohort studies on approximately 86,000 women reported that in women younger than 65 years of age, the pooled relative risk for CAD mortality in women with total cholesterol levels 6.2 mmol/L or higher compared with those with total cholesterol levels lower than 5.2 mmol/L was 2.44, and the relative risk for CAD mortality in women with LDL cholesterol levels higher than 4.1 mmol/L compared with those with LDL cholesterol levels lower than 3.6 mmol/L was 3.27. In women aged 65 years and older, the relative risk of CAD mortality associated with these total cholesterol and LDL cholesterol levels was 1.12 and 1.13, respectively (63). Low levels of HDL cholesterol also place women at particularly high risk (58,64,65). Based on Framingham data, an increase of 0.26 mmol/L in HDL cholesterol confers a 40% to 50% decrease in coronary risk for women (58). The role of elevated triglyceride levels as an independent coronary risk factor remains somewhat controversial. Some cohort studies have shown elevated triglycerides to be an independent risk factor for CHD in women (58,66), while others have not (67,68). Elevated triglycerides are often associated with other CAD risk factors such as obesity, glucose intolerance and low HDL levels, making it more difficult to estimate the independent increased risk conferred by hypertriglyceridemia. Some studies suggest that, while hypertriglyceridemia may not be an independent risk factor for men, it is more significant for women (68-70).

Other lipid moieties such as lipoprotein(a) and small, dense LDL particles have been associated, in some studies, with an increased risk of CHD in women, although the significance of these findings is not yet entirely clear. Elevated lipoprotein(a) level was associated with an increased risk of CHD in the Framingham Offspring Study, which reported that the attributable risk associated with lipoprotein(a) excess in women was similar to the risk associated with hypercholesterolemia and low HDL cholesterol levels (71). A smaller study did not find an association between lipoprotein(a) and CHD risk in women (72), and it was suggested that the increased CHD risk observed in individuals with excess lipoprotein(a) may be at least in part related to the concomitant excess of LDL cholesterol (73). The relationship between lipoprotein(a) and CHD risk in women requires further investigation, especially because lipoprotein(a) levels can be substantially lowered by estrogen replacement therapy; a recent report from the Heart and Estrogen/Progestin Replacement Study (HERS) suggested that elevated lipoprotein(a) levels may identify a subset of women that may derive benefit from hormone replacement therapy (74).

Premenopausal women have lower LDL and higher HDL cholesterol levels than men. After menopause, LDL cholesterol levels in women rise progressively with age, so that elderly women have, on average, higher levels of LDL cholesterol than elderly men. HDL cholesterol levels decrease after menopause, although on average, HDL cholesterol levels remain higher in women than in men.

Dyslipidemias are prevalent among Canadian women. According to the 1986 to 1992 Canadian Heart Health Surveys, 42% of Canadian women aged 18 to 74 years have a total blood cholesterol above the desired level of 5.2 mmol/L, 32% of women have elevated LDL levels, defined as higher than 3.4 mmol/L, and 4% of women have depressed HDL cholesterol levels lower than 0.9 mmol/L. In fact, 27% of women were in the moderate risk group based on total cholesterol level (5.2 to 6.1 mmol/L), and 17% were in the highest risk group, defined as total cholesterol level higher than 6.2 mmol/L. The proportion of women with high cholesterol levels increased with age, almost doubling from the 35- to 44-year age group to the 45- to 54-year age group. After the age of 64 years, women were found to have appreciably higher triglyceride concentrations than men.

Hypertension: High blood pressure, defined as a systolic blood pressure of 140 mmHg of higher or a diastolic blood pressure of 90 mmHg of higher, is a major risk factor for CAD, stroke, peripheral vascular disease and congestive heart failure in women. The Framingham study reported that hypertensive women have a 2.2-fold higher risk for CHD than normotensive women, and the study also suggested that hypertension carried the greatest population-attributable risk for the development of congestive heart failure (75,76). These findings were confirmed by other observational studies (77-79). A systematic overview collected data from nine large prospective cohort studies, of which three studies included women, and reported that a 7.5 mmHg difference in diastolic blood pressure was associated with a 29% increase in this risk of CHD, similar in men and women (80). Isolated systolic hypertension and increased pulse pressure are important risk factors for CHD in elderly women and men (81-83). Blood pressure levels increase with age in both women and men; however, after the age of 55 years, high blood pressure is more common in women than in men (84).

Left ventricular hypertrophy, a sequela of hypertension, is an independent risk factor for fatal and nonfatal CHD both in women and in men, as identified in the Framingham Study and confirmed subsequently in other cohorts (85-87).

The Canadian Heart Health Surveys found that 22% of adult Canadians, 18% of women and 26% of men had high blood pressure (88). Older women had the highest prevalence of hypertension, 58% in the age group 65 to 74 years. In both sexes, isolated systolic hypertension was more common in the older age groups, and 38% of women aged 65 to 74 years had this condition. The prevalence of hypertension in women increases with age more quickly than in men. Hypertensive women also have a higher prevalence of high cholesterol, high body mass index, sedentary lifestyle and diabetes mellitus than nonhypertensive women, and are, therefore, at particularly high risk for adverse cardiovascular outcomes.

Physical inactivity: The United States Surgeon General has identified physical activity as a major modifiable risk factor for heart disease (89). In a seven-year follow-up of a large cohort of over 40,000 postmenopausal women, a graded relationship between physical activity and all-cause as well as cardiovascular death was observed (90). A large number of studies, mostly in men, showed an association between reduced levels of physical activity and risk of CHD, and a meta-analysis of such studies estimated that physically active individuals have a 50% lower risk of developing CAD (91). Several prospective cohort studies and case-control studies have analyzed and presented data on women separately, and support, in general, an inverse relationship between the risk of fatal and nonfatal CHD and increased levels of physical activity and fitness (92-95).

In 1988, the Survey of the Well-Being of Canadians found that only 10% of women aged 20 to 64 years engage in regular aerobic activity, defined as 30 min or more every other day at 50% or more of individual capacity (96). The Canadian Heart Health Surveys reported that 36% of Canadian women aged 18 to 74 years are physically inactive, and statistics from 1996 to 1997 based on self-reporting of physical activity found that 57% of Canadian adults were physically inactive (1). In general, Canadian women tend to be more commonly inactive than men, and physical inactivity increases for both women and men with age. Physical inactivity is more prevalent in populations with lower educational and socioeconomic levels (97).

Obesity: Being overweight has been defined as having a body mass index greater than 25 kg/m^2, while obesity is frequently defined as a body mass index greater than 30 kg/m^2. Direct positive associations between obesity and risk of CHD in women have been demonstrated in a number of large prospective cohort studies (98-100). In the Nurses' Health Study, obesity increased the risk of nonfatal CAD, cardiovascular death and total death even after adjustment for other risk factors (101,102). After 16 years of follow-up, the women in this study who had a body mass index greater than 32 kg/m^2 and who had never smoked had a relative risk of death from cardiovascular causes of 4.1 compared with those with a body mass index less than 19 kg/m^2.

Obesity frequently occurs in association with other risk factors such as hypertension, diabetes mellitus, dyslipidemia, smoking, sedentary lifestyle and low socioeconomic status. The presence of a combination of these risk factors identifies women at a particularly high risk for CHD.

Obesity is highly prevalent among Canadian women. The Canadian Heart Health Surveys conducted between 1986 and 1992 reported that 41% of Canadian women aged 18 to 74 years were overweight, defined as having a body mass index greater than 25 kg/m^2, and obesity, defined in this survey as having a body mass index greater than 27 kg/m^2, was evident in 27% of women aged 18 to 74 years (103). The prevalence of obesity in this survey was shown to increase steadily with age. Five per cent of women surveyed were found to be massively obese, with a body mass index greater than 35 kg/m^2, and these women were identified primarily in the elderly 55- to 74-year age groups. Similar data are provided by other surveys. Most studies also suggest little change in age-distributed weights among Canadian women, although there have been extensive attempts to promote healthy weights for nearly two decades.

Psychosocial factors: Psychosocial factors reported to be associated with increased CHD risk in women include low socioeconomic status, social isolation, hostility, anger, type A personality, depression, anxiety and stress. Observational studies consistently show an increased risk of IHD in lower socioeconomic groups and in people who lack social support systems (104,105). Hostility, anger, type A behaviour and depression were also shown to increase cardiac risk (105), although the evidence for the independent contribution of these factors to cardiac risk is less robust.

Several social and economic factors are particularly relevant in women. Women have increased life expectancy and, as seniors, are therefore at high risk for low income and social isolation. In 1991, 13% of all Canadian women were aged 65 years or older, but by 2016, an estimated 18% of women will be seniors, increasing to 25% by 2041.

Other social changes that have affected Canadian women dramatically include the rise in female employment, the multiple role responsibilities of women and the changes in family structure. The effects of these social changes on IHD is under investigation.

Emerging risk factors: Additional mechanisms in the pathogenesis of atherosclerosis and potential risk factors for CHD are under investigation. These include increased oxidative stress, hyperhomocysteinemia, infectious and inflammatory agents, elevated fibrinogen levels and activation of other prothrombotic mechanisms (106-108). The role of these emerging risk factors and of preventive therapies directed toward their modification remains unclear and is under investigation.

ETHNICITY AND HEART DISEASE

Approximately one in five Canadians is a first-generation immigrant. In addition, many Canadians born in Canada are descendants of immigrants from various regions, with different cultural, nutritional, social and genetic backgrounds. South Asian-born Canadians have higher mortal-

ity rates from heart disease and stroke compared with Canadians of European descent, while Chinese-born Canadians have been identified to have lower mortality rates from heart disease and stroke (109,110). South Asian women have the highest rate of IHD among women, almost three times the rate for women of Chinese background. Aboriginal Canadians, women and men, have also been identified to be at a high risk of CHD and stroke (111).

The prevalence of risk factors for IHD also varies among different ethnic groups in Canada. For example, First Nations and Inuit adults report much higher rates of diabetes, particularly in women, reaching over 30% in those aged 55 years or older (1). Canadians of South Asian origin also have high rates of diabetes, impaired glucose tolerance, hypertriglyceridemia and low HDL cholesterol levels. Migrant groups from China, who generally have lower rates of IHD, also have a lower body mass index, and lower total cholesterol and LDL cholesterol levels (112).

CLINICAL PRACTICE RECOMMENDATIONS

- Clinicians should be aware that IHD is the major cause of mortality and morbidity in women in Canada.
- Clinicians should be aware of the relevance of different classical and emerging risk factors in women.
- Clinicians should be aware of the racial and ethnic variations in risk factors, clinical manifestations and outcomes of IHD in women.

RESEARCH RECOMMENDATIONS

Ongoing research is needed to further our understanding of the determinants of risk for IHD in women. Such research is essential to devise improved prevention strategies. Suggested areas of epidemiological research include:

- The study of emerging biological risk factors for IHD;
- The study of genetic determinants of IHD;
- The study of the relationships between behavioural and psychosocial factors and IHD risk;
- The study of environmental factors and risk for IHD;
- The study of racial and ethnic variations in risk factors, clinical manifestations and outcomes of IHD;
- The study of factors specific to women that may contribute to increased risk of IHD including effects of abnormalities detected during pregnancy (eg, gestational diabetes, pregnancy-related hypertension), effects of menopause (including premature menopause and those factors that may predispose patients to this such as smoking) and effects of PCO syndrome; and
- Ongoing surveillance data of risk factors in the Canadian population, including emerging risk factors.

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Chapter 4
Risk factors and primary prevention of ischemic heart disease in women

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Lifestyle modification is important in the prevention of ischemic heart disease (IHD) in both men and women. Mortality from vascular disease has declined over the past two decades, largely from improved rates of smoking cessation and other lifestyle modifications, in addition to advances in medical management. Primary prevention of IHD in women through diet, exercise and abstinence from smoking has been shown to reduce event rates in large cohorts of women (1); however, from a primary prevention perspective, healthy habits must start at a young age and continue throughout adulthood. There are gender-specific societal pressures in young women that may lead to unhealthy behaviour (eg, the desire to be thin and the unhealthy body images of fashion models encourage increased smoking in young women). Prevention efforts should, therefore, address social influences and motivation toward unhealthy behaviours, and some should show sex differences (eg, concerted messages to avoid smoking during and after pregnancy should be directed at women).

Essentially, all of the risk factors for IHD and the strategies for preventing disease among men are also important for women (2-4); however, this issue requires a 'gender lens', because the magnitude of risk factor effects may be different in men and women. In addition, there are risk factors and preventive strategies that are unique to women.

The presence of multiple risk factors greatly increases a person's level of risk. For example, a woman with a markedly elevated cholesterol level may have two times the risk of other women of the same age. Her risk doubles again if she smokes and doubles yet again, up to eight times the risk of other women, if she also has hypertension (5).

SMOKING

Cigarette smoking is the main preventable heart disease risk factor in women (6). As in men, long term cigarette smoking impairs endothelium-dependent coronary arterial vasodilator function experimentally in women (7). Cigarette smoking increases the risk of IHD by two to four times and accounts for a greater than 70% excess rate of death from IHD and an elevated risk of sudden death (8). Cigarette smoke contains more than 4000 active compounds, and many of these contribute to IHD risk (9). Importantly, however, it has been shown that, within two years of smoking cessation, women who are former smokers decrease their excess risk of all-cause mortality by 24% (10,11). Within three to five years of smoking cessation, cardiovascular risk approaches that of nonsmokers. This latter benefit occurs regardless of the duration or intensity of smoking, or the age at which smoking cessation occurred, which reinforces recommendations for smoking cessation, even for older women. Benefits associated with smoking cessation have been demonstrated in women without prior manifestations of IHD, as well as in those with prior myocardial infarction (MI) and coronary artery bypass graft

surgery (12). A recent analysis of the Nurses' Health Study found that a decrease in smoking prevalence resulted in a 13% decline in the incidence of coronary artery disease (CAD) (13).

Historically, increased rates of female smoking have coincided with concerted tobacco advertising campaigns that are aimed at women. Today's images of tobacco advertising are still focused on women and children. Although smoking is a problem for all youth in Canada, in addition to the epidemic seen in developing countries, there are gender-specific issues that must be addressed to decrease the rates of smoking in young girls and women. For example, the possibility of weight gain after cessation of smoking may represent a significant barrier to quitting in women (14). There is much qualitative research to suggest that boys and girls begin smoking for different reasons, and the development of this process begins at as young as 10 years of age. Girls may continue to smoke for different reasons than boys. More girls than boys report that they smoke to make friends and as a way to rebel. Smoking may have unique meaning to women, such as organizing social relationships (bonding, equalization of power and, for some, respite from child care activities), controlling emotions, creating an image, and forming and feeding one's identity. The different reasons why girls and women begin (and continue) to smoke must be undersood if the problem is to be adequately tackled in a way that is meaningful for girls and women.

The strongest evidence of efficacy includes a combination of pharmacotherapy and behavioural counselling (15), as well as exercise programs (16). Women have been included in clinical trials of pharmacotherapy for smoking cessation, and the effectiveness and safety of these products have been demonstrated in the female population (17).

ALCOHOL CONSUMPTION

Moderate alcohol consumption is associated with a lower risk of CAD in women (18), although heavy alcohol use increases the risk of death from cardiovascular causes. Previous studies that assessed the association between IHD and alcohol in women, however, had methodological concerns (19) and were, at one time, often based on self-reporting. The Nurses' Health Study failed to show a correlation between alcohol consumption and incidence of coronary disease, largely because this particular variable was stable over the period of time in which this analysis occured (13). Moderate alcohol consumption has also been linked to hypertension, and there are concerns about increased hemorrhagic stroke and breast cancer with alcohol (2). Additionally, heavy consumption of alcohol is a leading preventable cause of death.

EXERCISE

Women have been grossly under-represented in the many epidemiological studies that have been conducted to assess the relationship of exercise to CAD (20), although some prospective and case-control studies have separately analyzed data on women (21-26). These analyses indicated that physically active women have a 60% to 75% lower risk of IHD than inactive women. For the most part, these studies have been small, and the best estimate may be the 50% reduction in risk that was derived from a meta-analysis of studies that were based largely on men (27).

A cross-sectional analysis from the Healthy Women Study showed associations between physical activity and reduced weight, lower blood pressure, and favourable lipid and insulin profiles in perimenopausal women (27). After three years of follow-up, the women who exercised gained less weight and had a smaller drop in high density lipoprotein cholesterol (HDL-C) levels than the more sedentary women. Physical activity, however, was not linked to blood pressure, triglyceride, low density lipoprotein cholesterol (LDL-C) or insulin levels, as it was in the cross-sectional analysis (28). Walking, compared with vigorous exercise, had similar effects in the prevention of CAD in women in the Nurses Health Study Cohort (22). There is less direct evidence that physical activity reduces the incidence of CAD in women (13), but there is still fair evidence that physical activity improves coronary risk factors and decreases cardiac events in women.

OBESITY AND DIET

A number of large, prospective cohort studies of women have shown an association between obesity and the risk of IHD. Women who maintain their ideal body weights have a 35% to 60% lower risk of MI than women who become obese (29-31). Although a large part of the excess risk is attributable to the influence of adiposity on lipids, blood pressure and glucose tolerance, a moderate association persists after adjustment for these variables (31-33). Excess abdominal and upper body fat is associated with a particularly high risk of CAD and the risk rises steeply among women whose waist-to-hip ratio is higher than 0.8 (34). Cross-sectional studies of women have shown that abdominal adiposity is positively associated with cigarette smoking, lifestyle and reproductive factors (35,36).

Recently, results of several cohort studies have looked at the association of diet and IHD in women. In the 14-year follow-up of the large (greater than 80,000 women between the ages of 35 and 59 years) Nurses' Health Study, women who ate more than 142 g of nuts per week had a significantly lower risk of total CAD than women who rarely ate nuts. Further adjustment for intakes of dietary fats, fibre, vegetables and fruits did not alter these results. The inverse association persisted in subgroups that were stratified by levels of smoking, use of alcohol, use of multivitamin and vitamin E supplements, body mass index (BMI), exercise, and intake of vegetables or fruits (37). This same group showed a trend for reduction in IHD and whole grain consumption and a higher intake of alpha-linolenic acid (found in polyunsaturated fats) (38,39). An improvement in diet (low intake of trans and saturated fats, coupled with a higher intake of folate, marine n-3 fatty acids, cereal fibre and polyunsaturated fats) accounted for a 16% decline in the incidence of CAD over a 15-year period among women in the Nurses' Health Study (13).

ANTIOXIDANTS

The role of dietary antioxidant vitamins in preventing IHD has aroused considerable interest because of the knowledge that oxidative modification of low density lipoprotein may promote atherosclerosis. Kushi et al (40) published the results of a seven-year prospective cohort study that evaluated 34,486 postmenopausal women with no cardiovascular disease, and the effect of dietary and supplemental vitamins. In analyses that were adjusted for age and dietary energy intake, vitamin E consumption appeared to be inversely associated with the risk of death from IHD. This association was particularly prominent in the subgroup of 21,809 women who did not consume vitamin supplements. There was little evidence that the intake of vitamin E from supplements was associated with a decreased risk of death from IHD, but the effects of high dose supplementation and the duration of supplement use could not be definitively addressed. This study suggested that, in postmenopausal women, the intake of vitamin E from food is inversely associated with the risk of death from IHD, and such women can lower their risk without using vitamin supplements. By contrast, the intake of vitamins A and C was not associated with lower risks of death from CAD. Obviously, there are potential limitations and confounding variables to a nonrandomized study design. The observational studies of vitamin C are far less consistent, especially when analyses are adjusted for the use of other antioxidants. There are very few data on beta-carotene as primary prevention in women. The only large, randomized trial involving women that was at least partially focused on primary prevention was the Heart Outcomes Prevention Evaluation (HOPE) study of high risk patients with vascular disease, and this failed to show a conclusive benefit of vitamin E supplementation after a mean follow-up of five years (41).

HIGH BLOOD PRESSURE

As blood pressure increases, so does the risk of IHD. As in men, the strong association between elevated blood pressure and CAD in women has been demonstrated by a number of prospective studies (42-45). Treatment of hypertension has been shown to be effective in both women and men (46). A meta-analysis of randomized drug treatment trials involving a total of 37,000 subjects, 47% of whom were women, evaluated therapy of three to six years' duration for mild to moderate hypertension. A mean decrease of 6 mmHg in diastolic pressure significantly reduced overall mortality from vascular disease by 21%, fatal and nonfatal stroke by 42%, and fatal and nonfatal CAD by 14% (47,48). Randomized trials of drug treatment for mild to moderate hypertension, in which women were separately assigned to treatment, have reported a 9% to 30% reduction in the incidence of all cardiovascular events among women, and one trial reported a decrease in the incidence of CAD (49). Isolated systolic hypertension (ISH) is a particular problem in women. Clinical trials have shown that treatment of ISH reduces morbidity and mortality (50). There are few data that confirm whether the side effects of antihypertensive drugs are the same in women and men (51). Dietary intervention and weight loss have been moderately successful in treating high blood pressure. In several studies, 30% to 60% of the patients were women (52-54). In the Nurses' Health Study, modest adult weight gain substantially increased the risk of hypertension in women, and weight loss reduced that risk (55).

LIPID LOWERING IN WOMEN FOR PRIMARY PREVENTION

The majority of research on cholesterol and IHD has involved middle-aged men, among whom a 2% to 3% decline in the risk of IHD has been associated with every 1% reduction in the serum cholesterol level (56). Extrapolation of these findings to women has been questioned because estrogens affect the lipid profile (57). The majority of many prospective observational studies have reported a positive association between total cholesterol levels and IHD in women (58-65). An increased level of HDL-C is a strong predictor of a decreased risk of IHD in women (58-60). Only age was a greater predictor of cardiovascular death than HDL-C among women in the Lipid Research Clinics Follow-up Study (60).

The data on primary prevention of IHD by modification of the lipid profile in apparently healthy women are limited; however, the pathophysiology of lowering LDL-C for cardioprotection is the same in men and women. Until recently, less than 20% of the more than 30,000 participants enrolled in primary prevention trials of cholesterol reduction have been women (66,67). Elderly patients over the age of 75 years are particularly under-represented (57).

The first randomized, placebo-controlled, primary prevention trial of lipid lowering to include women was published in 1998 (68). The Air Force/Texas Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial used lovastatin in healthy patients with high LDL-C levels. Included in the study were almost 1000 women over the age of 55 years with low HDL-C levels (less than 1 mmol/L) and high LDL-C levels (greater than 3.9 mmol/L). After an average follow-up of 5.2 years, lovastatin reduced the incidence of first major coronary events in both men and women (68). The study was not designed or powered for mortality, and unfortunately, there are no mortality data on the primary prevention of CAD via lipid lowering in women. There is also no information on the role of lipid-lowering drugs for the primary prevention of CAD in women with normal or high HDL-C levels. The overall risk in this population, however, is likely to be lower than those with low HDL-C levels. In contrast to the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial (a secondary prevention trial that included approximately 1500 women), in which 34 patients would need to be treated over six years to prevent one acute MI, 435 patients would need to be treated over five years to prevent one MI if extrapolating the AFCAPS/TexCAPS data (68,69). Although the primary prevention of IHD by lowering LDL-C levels has been shown to be effective at reducing cardiac events in women

and men, the decision to use pharmacotherapy in either sex is one that may need to be weighed from a cost effectiveness perspective at a societal level. Additional mortality data are needed in this important area.

ACETYLSALICYLIC ACID

In a collaborative overview of randomized trials of antiplatelet therapy (70), acetylsalicylic acid (ASA) was found to be of benefit in the 70,000 'high risk patients', including secondary prevention and 'high risk' primary prevention subjects (eg, diabetics). Additionally, approximately 30,000 'low risk' subjects from the general population were studied, although women were not adequately represented. In this group, benefit from antiplatelet agents was not evident (4.4% antiplatelet therapy versus 4.8% control; five-year benefit was only approximately four of every 1000 patients treated [not significant]). The authors concluded that, as yet, there is no clear evidence on the balance of risks and benefits of antiplatelet therapy in primary prevention among low risk subjects, including women. The data on ASA for the primary prevention of IHD in women are limited. There are four observational studies and one recent randomized trial with inconsistent findings. Two studies demonstrated a reduced incidence of MI among women who took ASA (71,72), one demonstrated a possible adverse effect on IHD (73) and one demonstrated no effect (74). The Hypertension Optimal Treatment (HOT) trial of hypertensive women and men did not show any additional benefit of low dose (75 mg) ASA in women, although this strategy was significantly effective in men (75). More recently, the Primary Prevention Project included 2500 women and randomly grouped patients with one or more risks for cardiovascular disease. There was a reduction in cardiovascular events, although it was not statistically significant (RR 0.71 [0.48 to 1.04]). Additionally, 70% of the patients in this study had two or more risk factors, and almost 20% of these were diabetic (76). The United States Preventive Services Task Force recommends ASA for the primary prevention of MI in men 40 years of age and older in whom the risk of MI is sufficiently high to warrant risking the possible adverse effects of the drug (77). No similar recommendation has been made for women due to a lack of data to date.

DIABETES

Diabetes is a stronger risk factor for IHD in women than in men. Although it is not yet proven that tight glycemic control reduces the risk of IHD, there is evidence that intensive treatment of insulin-dependent diabetes slows the development of other diabetic complications in both women and men (78). Diabetes worsens the effects of other coronary risk factors and may impair estrogen binding, which negates the protection against IHD that is evident in premenopausal women (79,80). As diabetes obviates the protective effects of female sex hormones in premenopausal women, the utility of hormone replacement therapy for cardioprotection in postmenopausal women with diabetes mellitus is not clear. Very few diabetics have been included in studies that have assessed hormone replacement therapy for cardioprotection (79).

Gestational diabetes, which develops in approximately 3% of pregnant women in North America, may be a marker for an increased risk of IHD. Because this risk in gestational diabetics may be related to the development of frank diabetes later on, young women with gestational diabetes may be ideal individuals at whom to target early preventive efforts (81,82).

APPROACHES TO PRIMARY PREVENTION

Two complementary approaches are available to address modifiable cardiac risk factors in the population. The clinical approach identifies individuals who are at high risk and who need intensive intervention efforts. The population approach aims to shift the distribution in the entire population to a lower level, and relies on a combination of public policy tools (eg, higher tobacco taxes or restricted cigarette advertising) and community health promotion programs.

With respect to clinical prevention, many clinical guidelines have been published that simultaneously address single factors or multiple risk factors. Most of these guidelines urge a case-finding approach based in the family physicians' office, emphasizing the need to address the global risk of IHD by simultaneously considering multiple risk factors. Unfortunately, payment mechanisms in primary care provide few incentives for physicians to spend large amounts of time on this strategy for risk modification. Limited availability of dieticians in many parts of the country remains a barrier to optimal preventive care. As well, some patients with limited incomes and no drug insurance have difficulty affording lifelong therapy with antihypertensive or cholesterol-lowering drugs.

It seems unlikely that clinical prevention, in itself, can address the persistence of substantial social inequalities in IHD risk and the resultant burden of the disease. Similarly, no evidence suggests that conventional health promotion programs can claim major successes in blunting income- and education-related inequalities in CAD burden. As long as major socioeconomic inequalities persist in Canadian society, it is plausible that the biggest payoff from community-based 'heart health' prevention will come from outreach programs that are targeted at disadvantaged neighbourhoods or communities.

Nevertheless, adherence to published guidelines can make a substantial difference in overall risk. The Nurses' Health Study found, after 14 years of follow-up in over 84,129 women, that those who engaged in healthier lifestyles (encompassing only 3% of the population studied), including daily moderate to vigorous physical activity, not smoking, a normal BMI, better dietary habits and mild to moderate alcohol consumption, had an 83% lower risk of IHD events (1). In addition, data from the same group indicated that a reduction in smoking and an improvement in diet, coupled with an increased postmenopausal hormone

use, accounted for a 21% absolute decline in the incidence of coronary disease during the period from 1980 to 1994 (13). Unfortunately, an increased prevalence of obesity attenuated this trend.

The prevention of heart disease is a matter of social, economic and political policy. Treatment, preventive care, community health promotion and a healthy social policy are interlocking parts of a single strategy for better heart health.

IHD is the leading cause of death and an important contributor to morbidity and disability among women. It is largely preventable, and the epidemiology of the disease indicates that there are particular opportunities to target risk reduction in women. These opportunities include the time near pregnancy and the so-called 10-year 'window of opportunity' afforded to women near menopause. Women should receive counselling about lifestyle on an ongoing basis, with an emphasis on the profound beneficial effects of lifestyle modifications, as demonstrated by the Nurses' Health Study. The following clinical and research recommendations are provided to build on this general advice and on that of the American Heart Association/American College of Cardiology Consensus Panel Statement (4).

CLINICAL PRACTICE RECOMMENDATIONS

Smoking

- Even brief, but intense, interventions by physicians can reduce smoking in women (level II B).
- Advocate for national fiscal and legislative changes that aim at reducing smoking in all groups, including women and youth. This may include a smoking cessation payment plan (level III C).

Alcohol

- Although moderate alcohol consumption lowers the risk of IHD in women, its effects on the incidence of coronary disease appear not to be as important as other dietary and lifestyle changes, especially weighed against the risk of excessive alcohol intake (level II B).
- In women, the beneficial effects of low to moderate alcohol consumption must be balanced against the risk of breast cancer (level II B).

Exercise

- Regular moderate physical activity is effective in reducing cardiac events (level I B).
- Encourage fitness for health reasons (as opposed to body image) in young women (level III C).

Obesity and diet

- Provide dietary counselling, especially to women with other risk factors and to young women (level III C).
- Reinforce BMI goals at all ages, but especially in early life, in addition to the higher risk postmenopausal years. Prevention of obesity should be encouraged because subsequent weight loss is difficult to achieve and maintain (level III C).
- An improvement in diet (lower intake of saturated fats, coupled with a higher intake of folate, marine n-3 fatty acids, cereal fibre and polyunsaturated fats) may reduce the incidence of CAD in women (level I B).

Antioxidants

- Encourage a diet that is high in antioxidant nutrients rather than supplements (level III C).
- As yet, there is no evidence for a primary prevention role for vitamin E, C or beta-carotene supplements (level I B).

Hypertension

- Particular attention should be given to the lowering of blood pressure in women with risk factors for IHD, especially diabetics. ISH should also be treated (level I A).

Lipid lowering

- Lipid-lowering therapy in primary prevention in women has been proven to lower cardiovascular events (level I A).
- Women at high risk for IHD (diabetics, women with vascular disease elsewhere) should be treated with pharmacotherapy as per guidelines (83) (level II A).

ASA

- There is no evidence that ASA is beneficial in the low risk, healthy woman (level I A).
- ASA should be strongly considered in diabetics and other high risk individuals (level III C).

Diabetes

- Aggressive risk factor modification, especially hypertension and lipids, is necessary (level II B).
- Women with gestational diabetes should be monitored over the long term (level III C).

RESEARCH RECOMMENDATIONS

Smoking

- Investigate the relative efficacy of various smoking cessation aids in women (eg, behavioural counselling, pharmacotherapy, exercise programs, etc).

- Assess the role of pharmacotherapy in young women (younger than 18 years of age), because over 90% of current smokers start to smoke before the age of 18 years.
- Assess differences between women, with respect to smoking, that account for ethnic differences, especially in aboriginal women.

Exercise

- Understand why women are less active and provide methods to encourage active living (especially in the workplace).

Obesity and diet

- Assess dietary trends across ethnic and aboriginal populations, especially the 'westernization' of diet.
- Randomized, controlled trials are needed to assess dietary supplements and dietary changes in women.

Antioxidants

- Encourage well-designed primary prevention trials of antioxidant supplements, especially in high risk patients such as diabetics and postmenopausal women.

Hypertension

- Given the importance of hypertension as a risk factor and its increased prevalence, especially in postmenopausal women, clinical trials should continue to include women, with an emphasis on older women.
- Sex differences in pharmacotherapy and side effects that are particular to women should be investigated.

Lipid lowering

- Mortality data are needed for the use of lipid lowering for primary prevention of CAD in women.
- Trials in primary prevention to assess therapies such as statins are needed in women with high LDL-C and HDL-C levels.
- Trials in primary prevention to assess therapies such as fibric acid derivatives are needed in women with normal LDL-C levels and low HDL-C levels.
- Clinical trials should also be performed on women with multiple risk factors and no established CAD.
- Long term effects of lipid-lowering agents on women, especially sex-specific side effects such as breast cancer, should be monitored.
- The role of high HDL-C levels in preventing IHD needs further investigation.

ASA

- Trials establishing the risk and/or benefit of ASA in women without CAD are needed.

Diabetes

- Diabetes in women from different ethnic groups must be considered, and inclusion of such women in clinical trials is necessary.
- Evaluation of sex hormones in diabetic women should be addressed.

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Chapter 5
Hormone replacement therapy and cardiovascular disease

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Coronary artery disease (CAD) is the leading cause of death and a significant cause of morbidity for both women and men (1). One in nine women between the ages of 45 and 64 years has cardiovascular disease, and this ratio increases to one in three women over the age of 65 years (2). Menopause, and the attendant loss of ovarian estrogen, has unfavourable effects on lipid metabolism and endothelial function, which may contribute to an increased risk of coronary disease (3). Following natural menopause or premature ovarian failure, women have a greater than twofold elevation in the relative risk of CAD compared with age-matched premenopausal women (4). Observational studies suggest that hormone replacement therapy (HRT) regimens are associated with a 40% to 50% lower CAD risk (5). This may be related, in part, to healthier risk factor profiles in women who use estrogen.

Oral estrogen has a number of effects on plasma lipoproteins, oxidative processes, fibrinolysis (6) and endothelial function, which might be expected to provide protection from CAD. On the other hand, oral estrogen significantly increases thrombosis risk and increases plasma concentrations of C-reactive protein (CRP) – effects which might enhance the risk of acute coronary events.

EFFECTS OF ESTROGEN ON PLASMA LIPOPROTEINS

After menopause, there is a decrease in high density lipoprotein cholesterol (HDL-C) and an increase in low density lipoprotein cholesterol (LDL-C) concentrations (4). These changes may be related to estrogen withdrawal and to other menopause-associated factors such as weight gain. HRT has been shown to have an overall beneficial effect on lipid risk factors. Oral estrogen replacement increases HDL-C and decreases LDL-C by 10% to 15%, in part dependent on the level of estrogen and type of progestin in the HRT regimen (7).

The Postmenopausal Estrogen/Progestin Interventions (PEPI) study was a multicentre, randomized, double-blind, placebo controlled trial designed to assess the effects of estrogen/progestin regimens on CAD risk factors in postmenopausal women (8). In a three-year trial, 875 women between the ages of 45 and 64 years were randomly assigned to placebo, conjugated estrogen, estrogen plus cyclic medroxyprogesterone acetate (MPA), estrogen plus consecutive MPA, or estrogen plus cyclic micronized progesterone treatments. All treatment regimens of oral HRT lowered LDL-C levels by 0.37 to 0.46 mmol/L and increased triglycerides by 0.13 to 0.15 mmol/L. The PEPI study showed significant differences in the magnitude of the HDL-C response among the various regimens. MPA, but not micronized progesterone, markedly attenuated the HDL-raising effects of oral estrogen. Unopposed oral estrogen was the optimal regimen for elevation of HDL-C levels, but because it was also associated with a significantly increased risk of endometrial adenomatous or atypical hyperplasia, estrogen alone should be used only in women who have undergone a hysterectomy. Conjugated estrogen with cyclic micronized progesterone had a favourable effect on HDL-C levels without any excess risk of endometrial hyperplasia.

TABLE 1
Effects of various hormone replacement therapy regimens on plasma lipoproteins

Regimen	LDL-C (% change)	HDL-C (% change)	Lp(a) (% change)	TG* (% change)
Oral estrogen†	–14	+11	–19	+15
Oral estrogen + MPA	–12	+3	–19	+15
Oral estrogen + MP	–12	+8	–19	+15
Transdermal estrogen‡	–5	No change	No change	No change
Raloxifene†	–12	No change	–7	No change

**Triglycerides (TG) may increase much more significantly in response to oral estrogen in patients with underlying hypertriglyceridemia; †Both oral estrogen and raloxifene increase the risk of venous thromboembolism (VTE) threefold; ‡Transdermal estrogen has not been shown to increase VTE risk significantly, but few data are available; HDL-C High density lipoprotein cholesterol; LDL-C Low density lipoprotein cholesterol; Lp(a) Lipoprotein(a); MP Micronized progesterone; MPA Medroxyprogesterone acetate*

The effects of estrogen on plasma lipoproteins are most evident when estrogen is orally administered. High concentrations of estrogen reaching the liver by the portal circulation result in increased expression of the LDL receptor and apolipoprotein A-I, and decreased expression of hepatic lipase, leading to a reduction in LDL-C and lipoprotein(a) and an increase in HDL-C (7). Oral estrogen also increases hepatic triglyceride synthesis and can markedly aggravate hypertriglyceridemic states. Transdermal estrogen has minimal beneficial effects on HDL-C concentrations (9), but is the preferable route of administration for women with hypertriglyceridemia. Raloxifene is a selective estrogen modulator – a nonhormonal agent that binds with high affinity to the estrogen receptor and may exhibit either estrogen agonist-like or estrogen antagonist-like effects, depending on the target tissue. Raloxifene lowers LDL-C and does not alter plasma triglycerides, but is less effective than estrogen in increasing HDL-C (10). The effects of different HRT regimens on plasma lipoproteins are summarized in Table 1 (8-10).

ENDOTHELIAL FUNCTION

There is accumulating evidence that estrogen improves endothelial function (11). The endothelium plays an important role in atherosclerotic cardiovascular disease by synthesizing and releasing several vasodilating factors, the most important of which is nitric oxide (12,13), and thus regulates vascular tone, inhibits platelet adhesion and maintains a balance between thrombosis and fibrinolysis. In postmenopausal women, endothelial function is impaired (14). Estrogen replacement increases nitric oxide production and is associated with decreased endothelin-1 (12). Estrogen may also augment endothelium-dependent vasodilation mediated by non- nitric oxide factors in postmenopausal women (15), and may mitigate age-related changes in arterial structure and function in postmenopausal women (16).

Endothelium-dependent, flow-mediated dilation can be assessed by brachial blood flow studies using a simple physiological method that causes the release of endogenous nitric oxide, leading to arterial dilation in response to increased flow. In healthy women, there is an increase in brachial artery diameter in response to increased blood flow – a response that is significantly diminished in healthy postmenopausal women. Several studies that investigated the effects of estrogen and its benefits on flow-mediated dilation and vasomotor function have found improved vascular reactivity with oral, but not transdermal, estrogen replacement in postmenopausal women (17-22).

HRT, INFLAMMATION AND HEMOSTASIS

CRP is a hepatically derived acute phase reactant protein (23). CRP has been associated with future coronary events in healthy middle-aged and elderly men and women (24-26). The relationship between CRP and atherosclerosis is not well understood, but may be related to arterial wall inflammation due to preclinical atherosclerosis, low grade infection, or genetic or environmental factors. In a report from the Cardiovascular Health Study, use of HRT in women older than 65 years was associated with higher levels of CRP and lower levels of albumin, consistent with increased inflammation (27). This study demonstrated a significant increase in factor VIIc in HRT-treated women. Other studies have reported an increase in prothrombin activation peptide F1+F2 and a decrease in antithrombin-III activation (28,29), which may explain the observed threefold increase in venous thromboembolism (VTE) in women undergoing oral HRT. Raloxifene increases VTE risk to an extent similar to that of oral HRT and cannot be considered an alternative for women with risk factors for thromboembolism. A number of studies have demonstrated a significant decrease in plasminogen activator inhibitor-1 and a smaller decrease in fibrinogen in estrogen-treated women (8,27,30). Thus, HRT has complex effects on coagulation, which appear to both enhance thrombosis risk and improve fibrinolysis. Transdermal administration of estrogen results in much less hepatic exposure to estriol or estradiol. Scarabin et al (31) demonstrated that oral, but not transdermal, estrogen significantly increased the mean value of prothrombin activation peptide (F1+F2) and decreased mean antithrombin activity compared with no treatment. Oral estrogen was associated with a significant decrease in both mean tissue-type plasminogen activator concentration and plasminogen activator inhibitor-1, and a significant rise in global fibrinolytic activity compared with both placebo and transdermal estrogen (31). Clinical data on the effect of transdermal estrogen on VTE risk, however,

TABLE 2
Effects of oral estrogen on cardiovascular disease risk factors

Beneficial effects	Detrimental effects
Lipoproteins	Proinflammatory
Increased HDL-C	Increased C-reactive protein
Decreased LDL-C	Procoagulant
Decreased Lp(a)	Increased factor VII antigen
Fibrinolysis	Increased prothrombin
Decreased PAI-1	activation peptide F1+F2
Antioxidant	Decreased antithrombin-III activity
Endothelial function	

HDL-C High density lipoprotein cholesterol; LDL-C Low density lipoprotein cholesterol; Lp(a) Lipoprotein(a); PAI-1 Plasminogen activator inhibitor-1

are lacking. One case-control study showed a nonsignificant increase in thrombotic risk in women using transdermal therapy, but this was based on only five cases of women currently undergoing transdermal HRT (32). The absolute risk of VTE remains low for healthy postmenopausal women on HRT (33), but until further data are available, estrogen and raloxifene are contraindicated in women at risk for VTE or arterial thrombosis, irrespective of the route of administration. Overall, a number of positive and negative effects of HRT on cardiovascular risk factors have been documented (Table 2).

HRT AND CAD

The Nurses' Health Study (34) used a very large population to examine the relationship between the use of postmenopausal hormone therapy and mortality. Data were collected by biennial questionnaires between 1976 and 1992 from women aged 30 to 55 years at baseline. There were 3637 documented deaths from 1976 to 1994. Results indicated that hormone users had a lower risk of death than subjects who had never taken hormones (RR 0.63; 95% CI 0.56 to 0.70). In addition, hormone users with coronary risk factors (69%) had the largest reduction in mortality (RR 0.51; 95% CI 0.45 to 0.57). Overall, the Nurses Health Study generated a great deal of enthusiasm for HRT use. Women who were taking estrogens in this and other observational studies, however, were also less likely to be obese or to smoke and were more likely to be physically active. A recent Canadian population survey found that women with unfavourable lipid and nonlipid risk profiles had a lower prevalence of HRT use (35), suggesting that differences in education, socioeconomic status or rates of compliance may be additional factors to consider. The results of The Healthy Women's Study were similar in that premenopausal women who chose to take HRT after menopause were better educated and had fewer risk factors for CAD, such as dyslipidemia, hypertension, sedentary lifestyle or obesity (36). Although statistical approaches have been used to compensate for such differences, it remains very difficult to control for all known confounders and impossible to control for unknown confounders. Randomized clinical trials represent the only approach that can provide a definitive answer to the question of HRT and its relationship to CAD risk.

The Heart Estrogen/progestin Replacement Study (HERS) recruited 2763 postmenopausal women with CAD (37). Women were randomly assigned to one tablet daily of MPA (Prempro [Wyeth-Ayerst Inc, USA]), which contained both conjugated equine estrogens 0.625 mg and MPA 2.5 mg, or an identical placebo. Women were between the ages of 44 and 79 years, with a mean age of 66.7 years. The majority of participants had advanced CAD: 42% of women enrolled had a history of coronary artery bypass graft (CABG) surgery, 45% had previous angioplasty and 10% had significant congestive heart failure (CHF). Women were at high risk for cardiovascular events: 62% were past or current smokers, 59% had hypertension, 90% had serum LDL-C levels of 2.6 mmol/L or higher, and 23% had diabetes mellitus. There was no difference between the two treatment groups in the combined primary end point of CAD death and nonfatal myocardial infarction (MI) at five years. The analysis by year since randomization, however, showed that there were more CAD events during the first year in the HRT group than in the placebo group (risk hazard 1.57). The evolution of this trend reversed during the trial, to the point that the risk hazard during the last two years of the trial was 0.67 with HRT (P=0.009). Although a random variation over time is possible, this hypothesis appears to be very unlikely. An early prothrombotic effect may explain the apparent harm of HRT during the first year. The benefit observed later may then be a true effect of HRT on progression of atherosclerosis. Alternatively, it is possible that high risk patients had HRT-induced events early in the study, which then resulted in the creation of a lower risk group. As expected, the risk hazard for deep venous thrombosis and pulmonary embolus in HERS was increased by HRT to 3.18 and 2.79, respectively. Of some concern was that the medical treatment of HERS women was not in accord with current practice guidelines, with only 78% of women taking acetylsalicylic acid, 32% taking beta-blockers and only 10% achieving the LDL-C target for patients with CAD (less than 2.6 mmol/L). In addition, significantly more women who were randomly assigned to placebo were started on lipid-lowering treatment (mainly statins), which have been shown to reduce CAD events in women. It remains possible that longer follow-up may have demonstrated an overall benefit of HRT in women with CAD. In conclusion, HERS showed that the daily use of conjugated equine estrogens plus MPA for more than four years in women with CAD did not reduce overall CAD risk and increased the risk of VTE events threefold. A number of genetic factors may predispose certain women to the prothrombotic effects of HRT. In a group of postmenopausal hypertensive women, Psaty et al (38) reported that the prothrombin 20210 guanine to adenine variant was a risk factor for MI in HRT users. Compared with nonusers of HRT with the wildtype genotype, current users of HRT with the

prothrombin variant had a 10.9-fold (95% CI 2.15 to 55.2) increase in the risk of a nonfatal MI.

Unopposed estrogen, other HRT regimens and women without CAD were not evaluated in HERS. Several other ongoing clinical trials are assessing the value of HRT. The Women's Health Initiative (WHI) enrolled 27,438 women (age 50 to 79 years) between 1993 and 1998, most without a history of heart disease (39). Of these women, 60% still had a uterus and were randomly assigned to combined HRT or placebo, and 40% had undergone a hysterectomy and were randomly assigned to estrogen-only or placebo treatments. Preliminary observations from WHI suggest that the risk of MI, stroke and VTE events was increased in the early years of the trial in women taking HRT. As was the case in HERS, these risks appear to decrease over time. In a randomized, controlled trial involving 321 postmenopausal women, oral HRT did not reduce progression of atherosclerosis as measured by carotid intima-media thickness over a two-year period (40). In another recent study, oral estrogen did not reduce mortality or the recurrence of stroke in women with cerebrovascular disease (41). Another study similar to WHI, the Women's International Study of Long-Duration Oestrogen after Menopause (WISDOM) is currently recruiting 34,000 women without pre-existing heart disease. The Estrogen Replacement and Atherosclerosis (ERA) investigators recently presented their findings of 309 women with pre-existing heart disease (42). These women were randomly assigned to the same HRT regimens used in WHI. There was no difference in the progression of atherosclerosis on angiography in active hormone groups and placebo groups. There are three other angiographic trials of HRT in women with pre-established heart disease in progress (Women's Lipid Lowering Heart Atherosclerosis [WELL-HEART], Women's Angiographic Vitamins and Estrogen [WAVE], Estrogen And Graft Atherosclerosis Trial [EAGAR]). All of these randomized trials are crucial to define the role of different HRT regimens in postmenopausal women with varying risk profiles.

A cardiovascular outcomes trial is also currently underway to assess the effects of raloxifene in postmenopausal women with, or at high risk for, CAD. The Raloxifene Use for the Heart (RUTH) trial will enroll 10,000 high risk, postmenopausal women. This multinational study will compare the effects of raloxifene with those of placebo on cardiac deaths and nonfatal MIs.

EFFECTS OF HRT ON BREAST CANCER RISK AND OTHER CLINICAL OUTCOMES

HRT has a number of noncardiovascular effects that are important in decision-making. HRT is most often prescribed by physicians to improve a woman's quality of life, especially to alleviate the vasomotor symptoms associated with menopause, such as hot flushes, night sweats and heat intolerance. HRT may have positive effects on mood, cognition and fatigue (43). HRT has an established role in osteoporosis prevention and treatment (44). Ongoing studies suggest that HRT may attenuate the risk of Alzheimer's disease and colon cancer, and improve oral health (45-48), but randomized, controlled trials are needed to address these important issues. Women at increased risk of VTE are not candidates for HRT as discussed above.

Increased risk of breast cancer with long term HRT remains a major concern for many women. In the Nurses' Health Study, the benefit of HRT decreased with long term usage due to a 30% increase in breast cancer mortality among current estrogen users and a 45% increase after use for more than five years (34). Recent data from the National Cancer Institute's Breast Cancer Detection Demonstration Project (BCDDP) support the findings from the Collaborative Group (49), as do the results from the Nurses' Health Study (50). The Collaborative Group on HRT and Breast Cancer reanalyzed data from 51 observational studies, including 52,705 women with breast cancer and 108,411 women without breast cancer, and reported no increased risk for HRT use of short duration (less than five years). For women who had used HRT for five years or longer, the average relative risk of breast cancer increased by approximately 2% per year of use (49). This reported relative risk for breast cancer with HRT would account for an excess of two, six or 12 cases per 1000 HRT users after five, 10 or 15 years of use, respectively. Within five years of discontinuation of HRT, the increased RR virtually disappeared. Breast cancers diagnosed in women who have used HRT tend to be less advanced and less aggressive clinically than those in women who have never used HRT. Furthermore, HRT does not seem to increase mortality rates from breast cancer. It is noteworthy that, although estrogen increases the incidence of breast cancer, the absolute risk involved, even with long term use, is much less than the risk associated with postmenopausal weight gain, alcohol consumption and a sedentary lifestyle (51).

CONCLUSIONS

Although evidence from many observational studies has supported the use of oral HRT regimens to prevent cardiovascular events and improve outcomes, HERS was the first randomized study to assess the cardioprotective effects of estrogen on coronary events. Information on the long term benefit of various HRT regimens on CAD and non-CAD outcomes for women without a previous history of CAD (WHI) will not be complete until the year 2005 (39). The results of HERS may not directly apply to the use of oral estrogen in healthy postmenopausal women. HERS does, however, suggest that conjugated estrogen in combination with MPA should not be initiated in postmenopausal women with advanced CAD, particularly in those with unstable angina, acute MI or CHF. It also should not be initiated in postmenopausal women before, and for 12 months following, percutaneous transluminal coronary angioplasty (PTCA) or CABG. For women currently taking HRT, estrogen should be withheld one week before major surgery and restarted when recovery is complete. For these women, and for others with poor mobility, the early prothrombotic effects of oral HRT may outweigh any longer term antiatherosclerot-

ic benefits. HRT may be prescribed to increase HDL-C concentrations in high risk women without CAD. HRT may also be considered when clinically indicated for menopausal symptoms or osteoporosis prevention in women with stable, early CAD who are mobile and have not had a recent infarct, thrombotic event or bypass surgery. Definitive data on the long term cardiovascular risks or benefits of HRT in either of these groups are not yet available. The increased risk of VTE and breast cancer in women on HRT should be weighed against the potential benefits.

For all women with CAD or risk factors for CAD, treatment regimens should focus on proven therapies such as statins, beta-blockers, angiotensin-converting enzyme inhibitors and antiplatelet agents. There is clearly a need for randomized, clinical trials with cardiovascular end points to define the effects of HRT on coronary events in women with varying risk profiles.

CLINICAL PRACTICE RECOMMENDATIONS

Primary prevention

- HRT is not recommended in any formulation for the sole purpose of preventing ischemic heart disease (IHD) in healthy women or women with multiple risk factors for IHD until results of randomized trials are available (level III C).

- Established preventive strategies as discussed elsewhere in this document are recommended (level I A).

- Different formulations of HRT or selective estrogen receptor modulators may be used depending on proven non-IHD indications (treatment of menopausal symptoms, osteoporosis) and established risks (such as VTE, endometrial cancer and breast cancer) (level III C).

Secondary prevention

- The initiation of conjugated estrogen with or without MPA in women with established IHD is not recommended for the prevention of future cardiac events or to slow the progression of coronary disease (level I A).

- Other HRT regimens are also not recommended, pending results of randomized trials (level III C).

- Stable IHD patients already using HRT may continue this treatment if they have been on HRT for more than one to two years and have had no history of unstable angina, MI, CHF, PTCA, CABG or cerebrovascular accident within the previous 12 months (level I A).

- For stable IHD patients who are not yet on HRT but who require estrogen, consider using the lowest tolerable doses and monitor closely for the first six months and annually thereafter (level III C).

- For women on HRT who are scheduled for CABG, PTCA or other major surgery, or admitted to hospital with acute MI, unstable angina or CHF, or with lower extremity fractures or prolonged immobilization, discontinue HRT during this period of time due to a small excess absolute risk of VTE (level I A).

RESEARCH RECOMMENDATIONS

- The biochemical and clinical characteristics of patients at risk for procoagulant, proinflammatory effects of HRT;

- The comparative effects of different regimens of oral HRT, transdermal HRT and selective estrogen receptor modulators on coagulation markers, and on short and long term clinical end points;

- The effects of concomitant medical therapy, including statins, antiplatelet agents and angiotensin-converting enzyme inhibitors on clinical outcomes in women with CAD on various HRT regimens;

- Long term (five to eight years) randomized, controlled trials on HRT and clinical end points in women with and without clinical evidence of CAD.

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Chapter 6
Clinical evaluation of women with ischemic heart disease: Diagnosis and noninvasive testing

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ARE WOMEN'S SYMPTOMS DIFFERENT AT PRESENTATION?

Chest pain in women is common and often nonischemic. Conversely, atypical and nonchest pain presentation of coronary artery disease (CAD), including acute myocardial infarction (MI), is more common in women than men. It has been suggested that clinical presentation and risk factor analysis are of less value (and are less likely to be accurate) in predicting the presence of angiographically significant CAD in women than in men (1-3).

Chest pain is the most common presentation of CAD in both sexes; however, the initial presentation of chest pain occurs in the setting of acute MI more frequently in men than in women (4-6). In patients who presented to the emergency room with symptoms suggestive of acute coronary syndromes, MI was twice as likely in men than in women. The presence of ST elevation eliminated the sex difference, however, as did the presence of clinical congestive heart failure. Women presenting with acute MI tend to be older and have more comorbidities than men. Specifically, the presence of hypertension or diabetes increases the likelihood of diagnosis of acute MI (4).

Even in the setting of acute MI, women's presenting symptoms differ from those of men. Women are more likely to experience back, jaw, abdominal and neck pain; nausea; shortness of breath; and congestive symptoms; and are less likely to complain of diaphoresis (4,7-12). While some series have suggested than women present later after symptom onset during acute MI than men (13,14), other series have found no difference in time to presentation between women and men (7,15). Women have an increased incidence of silent or unrecognized MI compared with men (10).

Chest pain in women accounts for a significant number of visits to primary care physicians and subsequent referral to cardiovascular specialists, outside the setting of suspected acute coronary syndromes. In fact, women are much more likely to present with angina as their initial symptom of CAD than with MI. Chest pain has many potential etiologies, and women have a greater prevalence of noncoronary causes of chest pain than men. Chest pain, whether typical or atypical, is associated with less angiographically significant CAD in premenopausal women (1,16). The presence of atypical features in women, however, does not decrease the likelihood of CAD to the same degree as it does in men (6,17). Women may present with a mixed picture of both typical and atypical features such as pain in locations other than the anterior chest, or chest pain equivalents such as dyspnea, palpitations, fatigue, nausea or presyncope (1,12). Features such as rest angina, nocturnal angina and angina with mental stress are more commonly seen in women than men with chronic stable angina (17).

There are also differences in the ways that men and women interpret cardiac symptoms and the ways in which these symptoms are conveyed to health care workers. Women are more likely than men to ascribe their symptoms to noncardiac etiologies, even in the setting of acute MI (10,18), and may bias their care by suggesting that their pain is something other than cardiac (symptom attribution) (7,13,14). Women are less likely than men to recognize their risk for the development of CAD and are even less likely to recognize their risk of dying from this disease (19). The presence of atypical features on presentation, along with possible symptom attribution by the patient herself, may lead to less probing of symptoms and risk factors by health care workers. There is some evidence, as well, that both race and sex affect the way that physicians manage patients who present with chest pain. For example, women, in particular black women, are less likely than men to be referred for cardiac catheterization, even when they present with identical clinical characteristics (20).

APPROACH TO DIAGNOSIS OF WOMEN WITH SUSPECTED CAD

Chest pain and other symptoms that may be associated with CAD occur commonly in women. These symptoms often have atypical features, and the challenge is to establish whether there is evidence of significant CAD. While it is true that estimating the likelihood of CAD can be guided by assessment of the patient's clinical characteristics and coronary risk factors, there is evidence to suggest that this prediction is more easily and accurately accomplished in men than in women (1). The prevalence of CAD, particularly multivessel disease, in women, except in the older age group (older than 65 years), is lower than that in men (2,21,22); therefore, the predictive value of any symptom or noninvasive test is lower in women than in men (23-25). Because the utility of diagnostic testing is related to pretest probability of disease, a careful assessment of risk, including symptom characterization and risk factors, is required to guide the choice of diagnostic modality (or to determine whether any testing is required at all).

Despite that women tend to have more atypical features than men when they present with CAD, the presence of typical chest pain is associated with a higher prevalence (60% to 75%) of angiographically significant CAD than an atypical presentation (2,22,26,27). Patients with some atypical features ('probable angina') had a less than 50% (30% to 40%) prevalence, and women with nonspecific chest pain syndromes (only atypical features) had a very low (2% to 7%) prevalence of significant occlusive CAD on angiography. Therefore, as one aspect of risk stratification, pain characteristics should be assessed and pain should be classified as typical, atypical or nonanginal. Typical chest pain is associated with three or more typical features, atypical chest pain is associated with two of the typical features and nonischemic pain is associated with one or none of the typical features (Table 1).

While classic risk factors play a role in CAD risk in women, some are of greater significance than others (Table 2).

TABLE 1
Classification of chest pain

Typical features
Substernal
Squeezing, burning, heavy
Exertional or precipitated by emotion
Promptly relieved by rest or nitroglycerin
Atypical features
Left chest, abdomen, back, arm, without midchest pain
Sharp or fleeting
Repeated or very prolonged
Unrelated to exercise

Data from references 22 and 40

TABLE 2
Determinants of likelihood of coronary artery disease (CAD) in women

Major
Postmenopausal status (without HRT)/age older than 65 years
Diabetes
Peripheral vascular disease
Intermediate
Hypertension
Smoking
Lipid abnormalities
Minor
Obesity
Sedentary lifestyle
Family history of CAD
Other risk factors for CAD

HRT Hormone replacement therapy. Data from reference 40

The presence of any type of chest pain, whether atypical or typical, is associated with a lower risk of CAD in premenopausal women than in age-matched men; however, CAD likelihood increases after menopause (3). Therefore, a woman's age and menopausal status should be taken into consideration when assessing risk of CAD. Aside from age, diabetes is one of the most important risk factors for CAD because it eliminates the age advantage in women over men and confers a substantially greater CAD mortality than in nondiabetic females. Diabetes is, therefore, an important predictor of the presence and prognosis of CAD in women. In an assessment of women who underwent coronary angiography for chest pain assessment, diabetes was the only risk factor to discriminate accurately between patients with angiographically significant CAD and patients with normal coronary arteries (1).

The algorithm shown in Table 3 is proposed for the classification of patients into high, intermediate or low probability of CAD. This algorithm takes into consideration

TABLE 3
Algorithm for investigation of chest pain

High probability of CAD (greater than 80%)
Typical angina and any of the following:
• Postmenopausal status and/or age older than 65 years
• Diabetes
• Peripheral vascular disease
• Two intermediate determinants
Atypical angina and any of the following:
• Postmenopausal status and/or age older than 65 years and one or more intermediate determinants
• Diabetes plus one or more intermediate or minor determinants
• Three intermediate determinants or two intermediate determinants plus one minor determinant
Intermediate probability of CAD (20% to 80%)
Typical angina and one intermediate or two or more minor determinants
Atypical angina and postmenopausal status and or age older than 65 years
Nonischemic pain and either of the following:
• Postmenopausal status and/or age older than 65 years
• Diabetes and two or more intermediate and/or minor determinants
Low probability of CAD (less than 20%)
Typical angina and premenopausal with no determinants
Atypical angina and no major determinants
Nonischemic pain and no major determinants

CAD Coronary artery disease. Data from references 3, 22, 40 and 108

TABLE 4
Causes for lower sensitivity and specificity of exercise testing in women

Lower prevalence of multivessel disease
Reduced functional capacity in older women
Inadequate exercise duration
Resting baseline electrocardiography ST-T wave abnormalities
Increased likelihood of comorbidity (such as hypertension and left ventricular hypertrophy)
Effect of estrogens on exercise electrocardiographic ST changes
Similarity of estrogen's chemical structure to digitalis
Different chest wall anatomy
Methods for performing thresholds for abnormal exercise electrocardiography were established almost exclusively in men

chest pain characteristics, age and/or menopausal status, diabetes and the presence of other risk factors.

DIAGNOSTIC EVALUATION OF WOMEN WITH CHEST PAIN

The diagnostic evaluation of chest pain in women with suspected, but undiagnosed, CAD is challenging and problematic. The critical role of noninvasive testing in women is to diagnose accurately CAD in a population with a lower prevalence of disease before the development of more severe clinical manifestations. Due to the rising costs of health care and the limited resources available, it is imperative to find an integrated and cost effective approach to evaluating women with chest pain. Recent advances offer the potential for improving the quality and efficiency of evaluation of women with chest pain and are reviewed.

Exercise electrocardiographic stress testing: Exercise electrocardiography (ECG) remains the most readily available and least costly tool for risk stratification of patients with chest pain and suspected CAD, yet it is often less predictable in women than in men. A meta-analysis performed by Kwok et al (28) found that exercise ECG testing is less accurate in women than in men, with a sensitivity of 61% and a specificity of 70%. This result is compared with a similar meta-analysis that involved predominantly male participants, in which the sensitivity was 68% and the specificity was 77% – both values significantly different from those in women (29). Although the precise reason for the decreased accuracy of stress testing in women is not known, it is likely that differences in autonomic function, hormonal milieu, function of small coronary vessels and heart size may play a role (see below).

Mechanisms to explain a higher false positive rate in women include a lower prevalence of disease in women. Several studies using coronary angiography have demonstrated that women have a lower incidence of multivessel disease than men (22,27,30,31). This, in turn, affects both the sensitivity and specificity of the ECG response. Nevertheless, some studies in which the prevalence of CAD was similar in men and women showed lower exercise test accuracy (22,32,33).

Possible mechanisms for the lower sensitivity of exercise treadmill testing in women are shown in Table 4. In addition to sex differences in the prevalence and extent of disease, women are less likely than men to achieve adequate heart rate response and are more likely than men to have repolarization abnormalities. Compared with men of the same age, women are more likely to be deconditioned and incapable of achieving an adequate exercise heart rate. Women are generally older than men at the time of diagnosis, and comorbidities associated with age, such as hypertension with electrocardiographic criteria for left ventricular hypertrophy, are also likely to affect the utility of noninvasive testing.

An additional mechanism resulting in false positive studies is the effect of estrogen on the ST segment. Estrogen has molecular similarities to digitalis and can cause a digitalis-like false-positive ECG response (34). The response of exercise ST segment changes to estrogen replacement is heterogeneous because of different study designs (35-38). Specificity appears to be lower in nonischemic, postmenopausal women

who take estrogen than in premenopausal women (35). As a result, the sensitivity of the ECG stress test has been shown to vary both during the menstrual cycle (39) and in response to estrogen therapy (38).

The optimal strategy for diagnosing ischemic heart disease (IHD) in women has yet to be defined. Cost effectiveness of a first-line diagnostic strategy varies according to the pretest probability of the disease. Before testing, patients should be clinically stratified into low, moderate or high probability categories for CAD based on the symptoms, age and cardiovascular risk factors discussed in the previous section (40).

For patients who can exercise, the value of the Duke Treadmill Score (DTS) has been recently tested in women (976 women). The DTS is a weighed index that combines ST segment deviation, treadmill time and exercise-induced angina, and has been shown to provide accurate diagnostic and prognostic information for the evaluation of female patients with clinically suspected IHD (41). A low risk DTS was better at excluding IHD in women than in men. The results support the routine initial use of the exercise treadmill test in suitable candidates of both sexes who present with suspected IHD (41-43).

In women with a low probability (less than 20%) of CAD, noninvasive testing may yield false-positive results and should be avoided (40). This population includes young, premenopausal women with chest pain and no risk factors for CAD. They are at such low risk for CAD that performing a stress test of any kind would probably not be indicated and could lead to multiple unnecessary tests because of false-positive results. Conversely, if a stress test is performed in these low risk women, a negative exercise test result will have a high negative predictive value, and imaging procedures will not be required (24). These patients should be reassured, and, in this subgroup, a negative test result should be trusted.

On the other hand, in women with a high likelihood of disease (greater than 80%), the most cost effective strategy may be to proceed directly to cardiac catheterization (44). Exercise stress testing may still be performed initially, and if the results are negative, patients should be observed and followed closely. If the test results are positive or nondiagnostic, then direct referral for coronary angiography is indicated.

If the pretest likelihood of disease, and the sensitivity and specificity of the diagnostic procedure are known, then the post-test likelihood of disease can be calculated. An important implication of Bayes' theorem (3) is that a diagnostic test is most helpful if the pretest likelihood of disease is an intermediate level of probability. Most women belong in the intermediate/moderate risk group (risk between 20% and 80%). There are controversial opinions as to how they should best be managed.

Douglas and Ginsburg (40) believe that women with an intermediate likelihood of disease should undergo exercise ECG. The negative predictive value in this subset of patients is good. The likelihood of a false negative test is lower for women than for men (45). The current American College of Cardiology/American Heart Association guidelines for exercise testing suggest that some form of imaging should be added when there are baseline ECG abnormalities, the patient is taking digoxin or the goal of the test is to determine the location and extent of ischemia (46).

Exercise testing in women – Prognostic value: Three studies have assessed the prognostic value of stress testing in women and have achieved conflicting results. The Coronary Artery Surgery Study (CASS) registry (47) underscored the prognostic value of exercise capacity in women by showing that the use of exercise testing is a better predictor of cardiac events in men than in women. A total of 3086 men and 747 women underwent maximal treadmill exercise testing and coronary angiography, and were prospectively followed for up to 16 years. Among women, neither medical nor surgical therapy resulted in an improved 12-year survival rate in any of the subgroups tested (high, intermediate and low risk, on the basis of exercise testing). Survival rates at 16 years were significantly better in women than in men. Exercise testing was shown to be helpful in assessing long term survival in men and women; however, only exercise testing in men could identify a high risk subset whose survival was enhanced by coronary artery bypass graft surgery.

The Olmsted County retrospective cohort study (48) was undertaken to assess the prognostic value of exercise testing of both men and women between 1987 and 1989. It revealed that exercise capacity was the treadmill variable that exhibited the strongest association with all cause mortality and cardiac events. The protective effect of exercise capacity was observed in both sexes. An increase in one metabolic equivalent in workload was associated with a 17% decrease in risk in men and a 23% decrease in risk in women. The differences between the CASS report and these data are likely related to differences in the two populations, because CASS patients had undergone coronary angiography and many had a history of MI.

Finally, data derived from selected groups who were self-referred to a preventive medicine facility showed that the only significant independent predictors of mortality in women were low fitness and smoking (49).

Nuclear imaging: Myocardial perfusion imaging (MPI) with ^{201}thallium or ^{99}technetium sestamibi is performed widely, and there are good data supporting the added benefits over conventional exercise ECG testing (50). These techniques not only identify the presence or absence of CAD, but also provide prognostic information by identifying patients with more severe disease who may benefit from invasive diagnostic testing and possible therapeutic interventions. Patients with low risk perfusion studies are at low risk for future ischemic events and may be medically managed without requiring more expensive and invasive tests (51).

Exercise ^{201}thallium: Data from the meta-analysis by Kwok et al (28) on five studies that used thallium imaging reported a sensitivity of 78% and a specificity of 64% (872 women studied) (27,52-55). A false-positive rate for

^{201}thallium imaging was noted in the range of 35% (52,56), particularly with single vessel disease (57,58).

Attenuation of activity from the heart is highly dependent on body habitus, breast density and tissue characteristics. Tomographic algorithms, which lead to lower specificities, may accentuate breast artifact in women, a sex-specific issue. Soft tissue attenuation in women often results in defects in the anterior and septal distributions, which, in turn, result in fixed ^{201}thallium defects and the possible erroneous reporting of infarction. The shifting of breast tissue may lead to the mistaken conclusion that redistribution has occurred. Various approaches to alleviating this artifact include taping the breast upward to minimize left ventricular overlap and strapping the breast against the chest wall so that the attenuation is more evenly distributed.

Recent data suggest that women have less accurate study results because of smaller left ventricular chamber size (59). When exercise thallium results were adjusted for ventricular size, there was no difference in accuracy between men and women. Lower accuracy in women may be accounted for by greater amounts of image blurring in smaller hearts. Also, tomography may magnify the increased blurring noted in smaller hearts, thereby explaining the improved specificity with thallium planar imaging (89%) compared with tomographic imaging (56%).

Taillefer et al (60) found that interpreting the end-diastolic images to summed images from gated single photon emission computed tomography (SPECT) acquisitions improved sensitivity in 53 consecutive women, especially in those with small hearts.

^{99m}Technetium sestamibi: The introduction of ^{99m}technetium sestamibi in the early 1990s enhanced the diagnostic accuracy of myocardial perfusion SPECT in assessing the physiological significance of CAD in women (57,61). It has become the radiotracer of choice for women. SPECT ^{99m}technetium sestamibi facilitates the evaluation of both myocardial perfusion and left ventricular function with gated SPECT and improves specificity for detection of CAD.

Imaging studies using newer, higher energy radioisotopes (^{99m}technetium sestamibi) decrease the problem of breast attenuation. In a selected group of 85 patients who were referred for coronary angiography, Taillefer et al (57) recorded a similar sensitivity, but a higher specificity (82% improved to 92% with ECG gating compared with 67%) for the diagnosis of CAD in women with ^{99m}technetium sestamibi SPECT imaging than with ^{201}thallium imaging. ^{99m}Technetium sestamibi also offers several advantages over ^{201}thallium, such as less attenuation, the ability to measure first pass ejection fraction and gated acquisition. Similarly, in a study that evaluated the diagnostic accuracy of ^{99m}technetium sestamibi SPECT in women (63 women) and men, Santana-Boado et al (61) reported a specificity of 91%.

Because breast attenuation artifacts are the predominant soft tissue artifacts in women, any improvement in interpretation in women may be due to reduction of breast attenuation (62). Recent advances in nuclear imaging technology designed to reduce imaging artifacts from soft tissue attenuation have noted significant improvements in the normalcy rate in men and women, without a decline in overall sensitivity, but with a reduction in detection of extensive coronary disease (63).

Nuclear imaging – Prognostic value: Pancholy et al (64) identified an independent and incremental prognostic value of SPECT exercise ^{201}thallium imaging in women. The extent of the perfusion defect was the most important predictor of prognosis.

Hachamovitch et al (65) identified 4136 consecutive patients (2742 men and 1394 women) who underwent rest ^{201}thallium/exercise ^{99m}technetium sestamibi SPECT. Follow-up was 20±5 months for events (cardiac death or nonfatal MI). The women were older, presented with more atypical symptoms and had more risk factors than the men. Women with a 'definitely abnormal' perfusion scan had a greater than twofold event rate than men (13.9% compared with 6.6%, P=0.001). Perfusion imaging also effectively risk-stratified the patients, regardless of their clinical risks. Dual-isotope MPI was found to yield incremental prognostic value in both men and women. Although this modality identified low risk women and men with equal effectiveness, this type of perfusion imaging more effectively stratified high risk women than men.

In a prospective cohort study, Lauer et al (66) followed 1318 women with no prior history of invasive cardiac procedures for 1.8 years. These women had all been referred for treadmill thallium testing. They were as likely as men to be referred to coronary angiography once they were stratified for thallium results. There was no association between sex and referral for angiography. During follow-up, an abnormal thallium scan increased the risk of death for men and women, but women were at less risk than men.

Travin et al (67) reported similar findings in a study using ^{99m}technetium sestamibi SPECT in 1151 women. Men and women with abnormal images had similar event rates (19.6% and 18.2%, respectively), although men more often had MI or cardiac death than women (7.6% compared with 4.1%, P<0.05). Women had a higher likelihood of unstable angina or congestive heart failure than men (11.5% compared with 7.6%, P<0.05). Normal images predicted a low yearly rate of MI or death (1.7% for men and 0.8% for women). Image findings, particularly defect extent, were independent predictors of events in both groups.

Using a nonrandomized design, the Economics of Noninvasive Diagnosis (END) study group (68) prospectively assessed 4638 women. These women were either referred for diagnostic evaluation of stable chest pain directly to coronary angiography (n=3375) or they underwent stress MPI using predominantly ^{99m}technetium sestamibi first, followed by coronary angiography if at least one reversible myocardial perfusion abnormality was detected. Both groups had an intermediate pretest probability (56% for MPI and 48% for direct catheterization). MPI, followed by selective coronary angiography in patients with at least one perfusion abnormality, minimizes the near-term

composite cost per patient compared with a direct catheterization-first strategy, regardless of pretest CAD likelihood. The 30% average difference in composite cost was accrued regardless of pretest probability.

The END study group recently published an article on the noninvasive prediction (exercise or pharmacological MPI) of cardiac mortality in 3402 women and 5009 men who were followed up for a mean of 2.4±1.5 years (69). The clinical risk index and number of territories with perfusion defects were associated with cardiac mortality in women and men. In women who underwent exercise MPI, the number of abnormal territories remained the strongest correlate of mortality after adjustment for exercise variables. The results of MPI are, therefore, important independent predictors of survival in both women and men.

Dipyridamole and adenosine nuclear imaging: Sex-specific data on dipyridamole nuclear imaging are limited. In a small study of only 43 women, there were no significant sex differences in sensitivity and specificity using dipyridamole-induced hyperemia in combination with planar ^{201}thallium imaging (70). However, dipyridamole side effects were more common in women than in men (62% compared with 38%).

The use of adenosine ^{99m}technetium sestamibi myocardial perfusion SPECT for the detection of CAD was assessed in 201 female patients, 130 of whom underwent coronary angiography (71). For patients with a low pretest likelihood of disease, the normalcy rate was 93%. In the 103 patients without prior MI, the sensitivity, specificity and predictive accuracy were 91%, 78% and 86%, respectively, for detecting 50% or greater coronary artery diameter stenosis. This diagnostic technique was shown to have a high sensitivity, despite presenting symptoms or pretest likelihood of CAD. The same authors, using the same diagnostic technique, further described a sensitivity of 91% and a specificity of 70% for the diagnosis of severe or extensive coronary disease in women (72). These results are comparable with those of previous studies that used similar methodologies and were performed in predominantly male cohorts (62).

Using adenosine for pharmacological stress in 4166 women, Cerqueira (34) showed that women experienced a statistically significant increase in the occurrence of chest pain, shortness of breath and several other adverse events related to peripheral vasodilation. The observed increase in side effects for women has been attributed to the higher adipose body composition in women and smaller intravascular volume of distribution. Because both adenosine and dipyridamole doses are weight adjusted, women may achieve higher serum levels than men, which results in greater potency and more side effects. The occurrence of atrioventricular nodal block, MI or hemodynamic changes was similar in women and men.

Exercise radionuclide ventriculography – Diagnostic and prognostic value: Changes in left ventricular systolic function during exercise have been used for the noninvasive detection of CAD. Several investigators have demonstrated sex differences in the response of the ejection fraction to exercise (73-76). Women may have a marked increase in end-diastolic volume during exercise that increases cardiac output without resulting in an increase in ejection fraction (77). Men are more likely to decrease end-systolic volume and to manifest an appropriate augmentation in ejection fraction of five or more units at peak exercise. The poor specificity of the exercise ejection fraction in female patients markedly limits the diagnostic and prognostic applicability of stress radionuclide ventriculography in women and is not recommended as a clinical tool (78).

Investigational: Pilot studies using stress F-18 deoxyglucose positron emission tomography imaging have been completed and have assessed the role of this modality in predominantly obese women (79). Larger trials are planned to assess the role of F-18 deoxyglucose SPECT imaging.

Exercise echocardiography: Exercise echocardiography is more accurate than exercise ECG for the diagnosis of CAD in men and women. A recent meta-analysis of both sexes revealed a sensitivity of 85% and a specificity of 77% (80). In the four published studies that involved at least 50 women, for a total of 384 patients, the overall reported sensitivity ranged from 79% to 88% (weighted by sample size, sensitivity: 81%) (81-84). Specificity ranged from 81% to 86% (weighted by sample size, specificity: 75%), except for one study in which the specificity was 37% (83). When corrected for post-test referral bias, the specificity increased to 86%. The positive predictive value, negative predictive value and overall test accuracy were 72%, 84% and 72%, respectively. A smaller meta-analysis also revealed higher sensitivity and specificity for exercise echocardiography than for either exercise thallium or exercise ECG testing (28). A negative stress echocardiogram test result will continue to have important reassurance value, particularly in the prediction of future cardiac events (85). Additional studies are nevertheless needed with more patients.

Exercise echocardiography prognosis: The prognostic value of a normal exercise echocardiogram has been assessed in three studies. Sawada et al (86) followed 71 women and 77 men for a mean of 28.4±8.5 months. Overall, events occurred only in patients who exercised to workloads less than six metabolic equivalents or who achieved less than 85% of the age-predicted maximal heart rate. A normal exercise echocardiogram in a patient with good exercise capacity was predictive of an excellent prognosis, even in patients who had abnormal exercise ECGs. A larger study by McCully et al (87), in which 1325 patients (52% women) were followed for a median of 23 months, also reported excellent prognosis for patients with normal exercise echocardiography, even those with a clinically intermediate or high pretest probability of CAD. Sex was not an independent predictor of subsequent cardiac events. Heupler et al (88) followed 508 women for 41±10 months after exercise echocardiography. Cardiac events occurred in 31% of women with echocardiographic evidence of ischemia, compared with 4% of women without ischemia. Exercise-induced wall motion abnormality was an independent

TABLE 5
Advantages and disadvantages of stress imaging in women

Technique	Advantage	Disadvantage
Stress echocardiography	Less costly than nuclear imaging	5% to 10% poor or incomplete imaging
	Better specificity than nuclear imaging	Interobserver variability
	Global and regional assessment of left ventricular function and cardiac structures	
Nuclear imaging	Highly accurate in women	Breast attenuation artifacts
	Powerful prognostic predictor	Cost

predictor of cardiac events and was also a better predictor than exercise capacity or ST segment changes. An abnormal echocardiographic result added incremental prognostic value to that provided by clinical and exercise ECG variables.

Pharmacological stress echocardiography – Diagnosis: Tong and Douglas (89) reviewed pharmacological echocardiography for the diagnosis of CAD. Eight studies, with sample sizes of at least 50 women, revealed a sensitivity and specificity (weighted by sample sizes) of 86%, and positive predictive value, negative predictive value and overall accuracy of 85%, 86% and 86%, respectively (90-97).

The Women's Ischemia Syndrome Evaluation (WISE) trial is a National Heart, Lung, and Blood Institute-sponsored study designed to address issues surrounding IHD recognition and diagnosis. Pilot data on dobutamine stress echocardiography in 92 women have been published (98). To be eligible, women had to have symptoms suggestive of MI and clinical indications for coronary angiography. The prevalence of disease was only 27%. The sensitivity for detecting multivessel disease was 81% if inadequate heart rate responses were excluded. The sensitivity for detecting single vessel disease (50% or greater coronary stenosis) was low at 40% to 50%. There was an association between the angiographic extent of CAD and inducible ischemia as detected by wall motion abnormalities.

Pharmacological stress echocardiography – Prognosis: The prognostic value of pharmacological stress echocardiography with either dipyridamole (n=305) or dobutamine (n=151) has been assessed in one study of 456 women who were referred for chest pain and who were followed for 32±19 months (99). Echocardiographic evidence of ischemia was found as the only independent predictor for cardiac events (death and MI). A negative stress echocardiographic test predicted a cardiac event rate of less than 1% over a three-year follow-up. Patients who developed ST segment depression in the absence of new wall motion abnormalities had an excellent prognosis (no cardiac events). These results were similar to and expanded the data obtained by Heupler et al (88) for exercise echocardiography.

A large trial at the Mayo clinic assessed the prognostic value of dobutamine stress echocardiography in predicting outcome in 860 patients with known or suspected CAD (100). This trial included 381 women and, although results were not stratified by sex, it showed that dobutamine stress echocardiography provided significant incremental value compared with clinical and rest echocardiographic variables in predicting cardiac events. The one-year and two-year event-free rates of patients with normal study results were 98% and 97%, respectively. In contrast, a positive dobutamine study was associated with a fourfold higher risk of cardiac events.

Finally, in a smaller study of 72 women with an intermediate pretest likelihood of CAD, the probability of CAD was reduced to 14%±10% with dobutamine echocardiography (101). No cardiac events were noted during follow-up. The results emphasized the importance of achieving at least 85% of the maximum predicted heart rate to reduce false-negative rates.

When possible, exercise echocardiography should be chosen instead of dobutamine echocardiography; however, because many women are unable to exercise to maximum aerobic capacity, pharmacological stress echocardiography or nuclear imaging should be considered in these women (102).

Comparison of stress echocardiography with perfusion imaging: Both MPI and stress echocardiographic techniques have evolved tremendously during the past decade and now play a major role in the evaluation and management of patients with known or suspected CAD. Each method requires clinical experience and technical expertise, and each has potential advantages and disadvantages that, in a given institution or practice setting, may make one or the other perform more accurately, efficiently or cost effectively (Table 5). Stress echocardiography offers a relatively cost effective method for cardiac imaging, and this technique is often viewed as a lower cost alternative to MPI. The available data reported in the literature for both sexes indicate that stress echocardiography and MPI provide comparable results for the diagnosis of CAD (103,104).

Ultrafast computed tomography in women: In a multicentre trial (105), ultrafast computed tomography has been shown to be a sensitive method for the detection of coronary calcification associated with atherosclerotic disease. There are conflicting data in women (106). The sensitivity of coronary calcium for the detection of atherosclerotic disease in women younger than 60 years of age was 50%, which was significantly less than the 97% sensitivity in

women older than 60 years of age and the 87% sensitivity in men younger than 60 years of age. The reduction in sensitivity for women may be related to estrogen. Atherosclerotic lesions in women are less likely to have coronary calcium than lesions with a similar degree of lumen narrowing in men.

In summary, ECG stress testing should not be abandoned in women, but the results need to be carefully interpreted and integrated. Optimal practice requires estimation of pre- and post-test probability, recognition of the limitations of routine stress testing, evaluation of the adequacy of the exercise and consideration of the use of adjunctive imaging. A positive test in a postmenopausal woman with risk factors should be trusted, but a negative test in the same woman who did not achieve an adequate exercise heart rate should be regarded with less confidence. Selecting the correct initial test and considering the costs, availability and local expertise in test performance and interpretation are all very relevant issues to consider (107).

In a study of 161 women, exercise echocardiography stratified significantly more patients of intermediate (20% to 80%) pretest disease probability into the high (greater than 80%) or low (less than 20%) post-test probability group than exercise ECG, despite normal baseline tracings (84). This study and another (44) recommended exercise echocardiography as a cost effective approach to the diagnosis of CAD in women because of the avoidance of inappropriate angiography. In patients with at least one perfusion abnormality, it was suggested that MPI, followed by selective coronary angiography, minimizes the near term composite cost per patient compared with that of a direct catheterization-first strategy, regardless of pretest CAD likelihood (68).

In the past few years, diagnostic techniques have been refined to improve the accuracy of CAD detection in women compared with that achieved by clinical assessment and stress ECG alone. Combined clinical and noninvasive imaging assessment can identify women at very high and very low risk for future cardiac events. The reduction in unnecessary coronary angiography accomplished by improved specificity, and the accurate determination of cardiac risk, provide the most cost efficient use of medical resources in the female population with known or suspected CAD. Further research is needed to assess sex-specific responses.

CLINICAL PRACTICE RECOMMENDATIONS

- Physicians should be aware that women are more likely to have angina than MI as their initial presentation of CAD. Typical features of CAD, both in the acute and chronic situation, occur in women; however, women have a higher likelihood of presenting with atypical symptoms than men. Women are less likely than men to attribute their symptoms to cardiac disease, even in the setting of acute MI (level III C).

- Before exercise testing, patients should be clinically stratified into low, moderate or high probability, based on the chest pain algorithm (Table 3). The cost effectiveness of a diagnostic strategy varies with the pretest probability (level III C).

- Women with a low probability profile (less than 20% likelihood of CAD) should not undergo stress testing (level II B).

- Women with an intermediate probability profile (20% to 80% likelihood of CAD) who can exercise with a normal baseline ECG should undergo exercise testing with the DTS. Stress imaging (nuclear or echocardiography) should be performed if the patient cannot exercise maximally, has a nondiagnostic exercise test or has baseline ECG abnormalities (level II B).

- Women with a high probability of disease (greater than 80% likelihood of CAD) should undergo stress testing with the DTS or coronary angiography (level II B).

- Physicians should consider that the indications for stress imaging are similar in men and women. Electrically positive ECG stress tests in women taking estrogen may be considered a sex-specific indication for stress imaging (level III C).

- The algorithm shown in Figure 1 should be considered in the clinical evaluation of women with chest pain (level III C).

RESEARCH RECOMMENDATIONS

Exercise ECG in women: Suggested areas of research include the following:

- The role of hormones in the genesis of exercise-induced ST changes;

- The relationship between exercise ST response and different routes of administration of estrogens alone or in combination with progesterone;

- The role of synthetic estrogen modulator receptors on exercise ST response;

- The value of DTS in a predominantly outpatient female setting;

- The optimal strategy for diagnosing obstructive CAD in women;

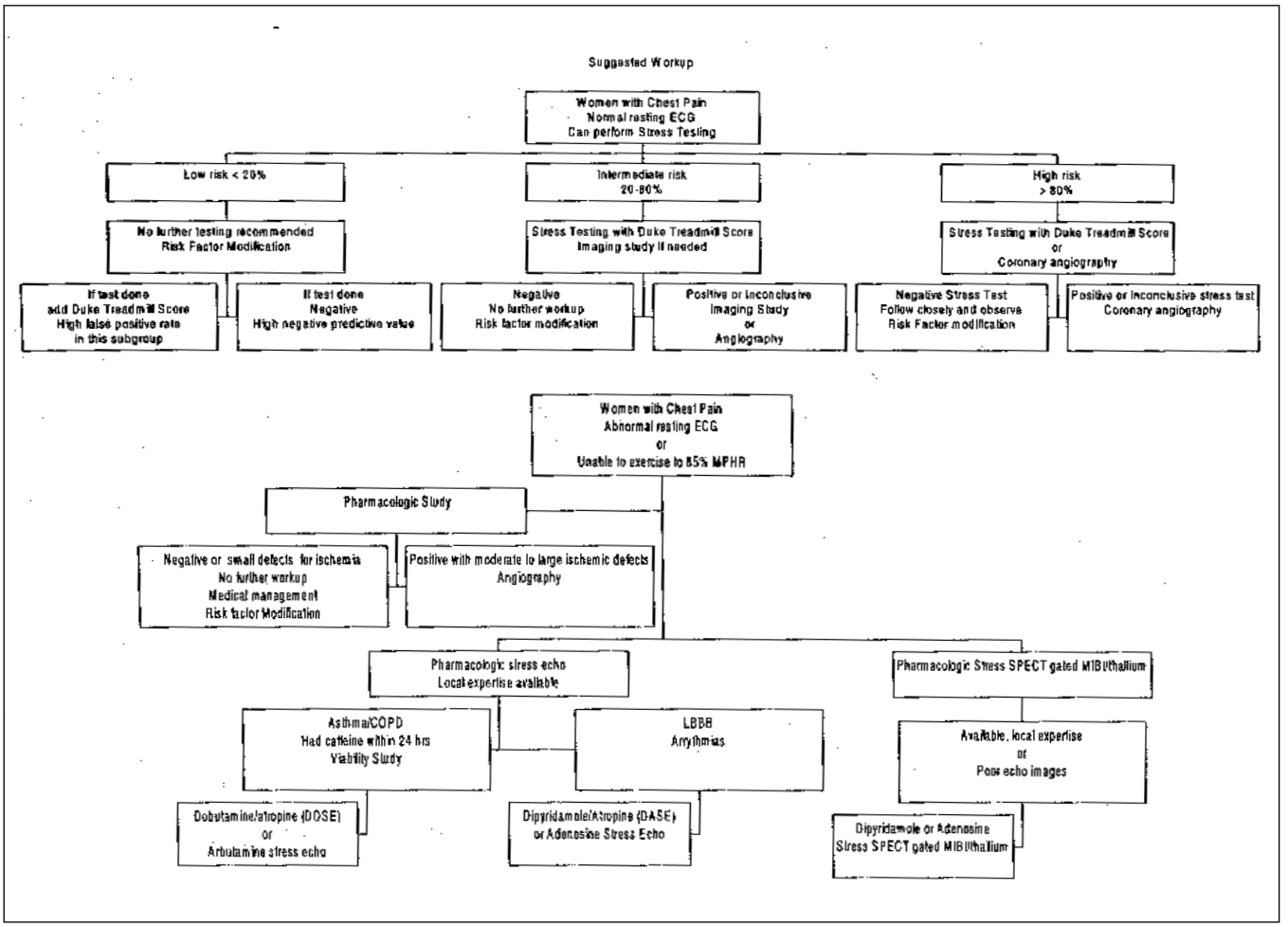

Figure 1) *Work-up of women with chest pain. COPD Chronic obstructive pulmonary disease; ECG Electrocardiography; LBBB Left bundle branch block; MPHR Maximal predicted heart rate; SPECT Single photon emission computed tomography*

- The value of right precordial leads V3R-V4R-5R in addition to 12-lead ECG testing in women.

Nuclear imaging in women

- Further studies in women using ^{99m}technetium sestamibi are needed to confirm the advantage for CAD in women in general.
- Randomized trials of the cost effectiveness of noninvasive stress imaging versus direct coronary angiography are needed.
- The prognosis in women with symptoms and abnormal diagnostic tests with no or noncritical coronary stenosis need to be better defined.
- Diagnostic testing modalities for microvascular dysfunction ('syndrome X') need to be better defined.
- The role of nuclear imaging versus stress echocardiography in women, including women with hypertension, needs to be studied.
- The role of metabolic imaging in women needs to be studied.

Stress echocardiography in women: Additional research is required:

- To confirm and improve the accuracy of stress echocardiography and to compare the accuracy of stress echocardiography with intravascular ultrasound and fractional flow reserve in noncritical lesions by angiography;
- To compare the magnitude of ischemia precipitated by both treadmill exercise and dobutamine stress echocardiography for the same patient in a crossover study; and
- To assess the accuracy of viability studies in women.

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Chapter 7
The medical management of acute coronary syndromes and chronic ischemic heart disease in women

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Myocardial infarctions (MIs) are more often lethal in women than in men, regardless of age or comorbidity (1-3). In Lerner and Kannel's (1) 26-year follow-up of the Framingham population, the overall case fatality rate was 32% in women compared with 27% in men. Even in the current thrombolytic era, both 30-day and one-year crude mortality rates in women after MI are approximately double the rates in men (4-6). The risk of death is greater in women at either end of the age spectrum, especially in younger women (40 to 49 years of age) (7,8). The World Health Organization-Monitoring Trends and Determinants in Cardiovascular Disease (WHO-MONICA) project reported that younger women with acute MI had higher mortality rates than men of comparable age, likely because overall event rates are low and more women than men are underdiagnosed because the index of suspicion is even lower in women than in men. Women are older, and have more comorbidity (eg, diabetes, hypertension and hyperlipidemia) and more complications (eg, reinfarction, strokes, pulmonary edema, shock and cardiac rupture) than men (9-11). Other factors that contribute to increased morbidity and mortality in women include delayed presentation to the emergency room and a reduced perception of risk of MI by health care providers (12). These factors are compounded by atypical, more transient symptoms at presentation (13). Once these confounding variables (especially age) are taken into account, adjusted mortality rates for women who have a clear indication for thrombolytic therapy in such trials are approximately 15% higher than the rates for men (4,6). A more recent analysis of a United States Medicare population of patients who were deemed suitable for treatment after MI did not show any apparent differences between the sexes with respect to early mortality (14).

Women are more likely to present with non-ST segment elevation MI and unstable angina than with ST elevation MI (15). These syndromes are more difficult to diagnose and can take longer to diagnose than in men, and may be missed in the emergency room (16), which may contribute to higher mortality for women. Women with the same symptoms as men were less likely to be admitted to a coronary care unit, particularly at older ages (13,17). The coronary care unit or its equivalent is the environment in which thrombolytic treatment and other evidence-based therapies are more likely to be used.

Women with acute coronary syndromes have more complications than men, despite having less clinically significant and less multivessel diseases (15). Differences in coronary artery disease (CAD) severity are less marked in

female patients with MI than in those with unstable angina. Women also have more congestive heart failure (CHF) than men, despite better left ventricular systolic function and equivalent myocardial damage (9,10).

The pattern of increased mortality in women after MI is present from the time of discharge and persists for at least two years (9). In the Manitoba Health Reform Impact Study, the level of physical functioning one year after MI decreased in women, but increased in men (18).

THERAPY OF ACUTE CORONARY SYNDROMES

The beneficial effects of thrombolytic agents, acetylsalicylic acid (ASA), beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and other adjunctive therapies on morbidity and mortality appear to be equal in men and women (19-21); however, these therapies may be used less frequently in women than in men (9,14,22,23). Data derived from clinical trials (wherein all eligible patients receive the planned treatment, regardless of sex or age) may underestimate mortality for women in registry studies. Sex differences in coronary angiography and revascularization are discussed in the chapters on revascularization (Chapter 8, pages 53 to 56) and access to care (Chapter 10, page 63 to 67).

Thrombolytics: Infarct artery patency rates after thrombolysis are equivalent in men and women; however, women are less likely than men to receive thrombolytics, even when indicated. Results from the Myocardial Infarction Triage and Intervention (MITI) registry showed that thrombolysis was given to only 55% of women in whom it was indicated compared with 78% of men (24). Patients who did not receive thrombolytic therapy had longer hospital stays than those who did, which added to health care costs (25). Women experienced increased bleeding after thrombolysis (4,17,25,26), which may have been related to a lack of adjustment of heparin and other weight-based adjunctive therapies. In addition, older age and a previous history of hypertension are important comorbid risk factors for hemorrhagic stroke (27). Menstruation is not a contraindication to thrombolysis, but the risk of bleeding may be slightly increased. There are no data on thrombolysis and pregnancy. Although women of child-bearing potential have been excluded from the majority of trials, there is no reason to doubt the efficacy of thrombolytics in this group of women. Possibly because of such exclusions, thrombolytic trials have enrolled only 18% to 25% women.

Other adjunctive therapy: Following admission to the hospital, women are less likely to receive standard medical therapy, including ASA, beta-blockers and heparin, despite evidence of benefit in clinical trials (see above). For example, reported ASA use was 55% in women compared with 70% in men (18). Women received more nitrates and calcium channel blockers, despite that these drugs have not been shown to decrease mortality (12,18). ACE inhibitors, however, have been shown to reduce mortality and morbidity in women and men after an acute MI (24,28,29). A number of studies (28,29) have shown comparable use of ACE inhibitors in both sexes, possibly due to a higher incidence of heart failure in women than in men.

Low molecular weight heparins have shown comparable benefit to unfractionated heparin in recent trials involving women, although the percentage of women enrolled has been low (approximately 20%) (30). Studies comparing glycoprotein IIb/IIIa inhibitors with standard antiplatelet regimens in patients with unstable angina have been small, have enrolled approximately 20% women and have provided little data on sex-based differences (31). Given problems in previous trials with thrombolytics and bleeding, especially in elderly women, it is important that such trials provide these types of data with respect to women. Many newer trials are using a combination of weight-adjusted or lower dose regimens.

Neither antiarrhythmic drugs nor magnesium are standard or routine therapy following acute MI and, therefore, are not discussed here. However, the Fourth International Study of Infarct Survival (ISIS-4) trial, which studied magnesium therapy along with captopril and oral mononitrate, included 26% women and analyzed the results by sex (28).

CHRONIC ISCHEMIC HEART DISEASE

The medical management of chronic ischemic heart disease in women parallels that of men, with similar overall benefits. The evidence for secondary prevention is much stronger than that of primary prevention. However, few data are available that compare specific medical therapies in men and women, likely because earlier trials either failed to enrol women or did not conduct separate analyses of men and women. Six weeks after entry into the Thrombolysis and Myocardial Infarction (TIMI II) trial (32), women were more likely than men to be prescribed a calcium channel blocker, and were less likely than men to receive a beta-blocker. The use of ASA was similar in women and men. Lifestyle modification and control of risk factors (such as hypertension and diabetes) assume heightened importance and are appropriate, especially given the higher rate of mortality for women than for men with acute coronary events.

ACE inhibitors are standard therapy in post-MI patients and in patients with CHF. More recently, these agents have been shown to decrease mortality in patients with established vascular disease (including CAD) diabetes, and in patients with risk factors without CHF or a recent MI. The Heart Outcomes Prevention Evaluation (HOPE) Study, which enrolled 28% women, showed equal benefit of ACE inhibitors in women and men (33).

Lipid-lowering trials for secondary prevention have shown a reduction in major coronary events (including CAD death and total mortality in the Cholesterol and Recurrent Events [CARE] trial) in women (34-36). Thus, lowering low-density lipoprotein cholesterol is important. Secondary prevention guidelines from the Lipid Working Group should be used for the treatment of hyperlipidemia (37).

The role of hormone replacement therapy is discussed in a separate chapter.

SPECIAL SITUATIONS

Syndrome X: Between 10% and 30% of patients who undergo coronary angiography for evaluation of chest pain are found to have normal coronary arteries. The term 'syndrome X' was introduced a number of years ago to describe patients with angina and normal coronary arteries. There is a preponderance of women in this group. Microvascular dysfunction has been proposed as a possible mechanism for the chest pain and for ischemic ST depression on exercise; however, other more objective evidence of ischemia has been difficult to find. Endothelial dysfunction has been proposed as a mechanism for microvascular dysfunction. In one study, the abnormal endothelial-dependent response was improved in postmenopausal women with transdermal estrogen administration (38). A more recent study that used phosphorus-31 nuclear magnetic resonance in a small number of women with chest pain and normal coronaries demonstrated an abnormal metabolic response to stress (39). The therapeutic and prognostic implications of these findings have yet to be defined.

The above results are of interest because women who have undergone catheterization in the setting of acute coronary syndromes (including MI) have a higher likelihood of insignificant stenosis than men (15). In an autopsy study of women with sudden coronary death, plaque erosion with minimal occlusive disease was more common in premenopausal women who smoked than the more severe occlusive disease with plaque fissures and healed infarcts seen in postmenopausal women and in men (40).

The paradigm of significant obstructive disease as the most important pathophysiological finding in the setting of angina, acute coronary syndromes or sudden death may need to be re-examined in women.

Oral contraceptives: Early case reports showed an association between oral contraceptive use and acute MI. Newer third-generation oral contraceptives are associated with less risk, and this risk is essentially confined to women older than 35 years of age who smoke. Venous thrombosis is the most important contributor to overall risk in younger women (younger than 35 years). On the other hand, smoking is associated with higher mortality than oral contraceptive use at any age (41).

Perioperative risk assessment: Morbidity and mortality due to cardiac complications are the major contributors to overall risk for men and women who undergo noncardiac surgery. There are no sex-specific data on the management of women with CAD or at risk for CAD who undergo noncardiac surgery (42). Overall prevalence of disease is lower in women than men, which decreases the overall risk (except in patients with vascular disease and perhaps diabetes). In one important randomized trial that showed the benefit of beta-blockers perioperatively, the enrolment consisted of only 12% women, and there was no separate sex analysis (43).

CLINICAL PRACTICE RECOMMENDATIONS

- Physicians should review practice guidelines and beneficial therapies in acute coronary syndromes and should ensure their implementation in appropriate patients of both sexes (level II A).

- Earlier triage and recognition of acute MI and unstable angina in the emergency room should be accompanied by prompt administration of evidence-based therapies (level I A).

- Given the higher mortality of womenwith acute coronary events (higher than men), the use of established therapeutic regimens and the control of risk factors in women with chronic ischemic heart disease assume greater importance (level III C).

RESEARCH RECOMMENDATIONS

- In any ongoing and/or future clinical trials, there should be adequate representation of women. Sex-specific analysis of outcomes related to therapies must be undertaken.

- The pathophysiology and treatment of noncritical or minimal coronary stenosis should be investigated.

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Chapter 8
Revascularization strategies in women with ischemic heart disease

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PERCUTANEOUS STRATEGIES IN WOMEN: CURRENT STATUS

Management strategies for women remain somewhat speculative because many large trials of coronary artery disease (CAD) diagnosis and treatment have not included women or have included them in very small numbers. Thus, the applicability of these trial results to women is controversial for pharmacological and interventional management strategies. In addition, fewer women than men are referred for invasive testing and/or interventional strategies, which further compromises the ability to evaluate treatments effectively.

In 1987, Tobin et al (1) first reported a gender bias in the referral for coronary arteriography. Later studies, including the Survival And Ventricular Enlargement (SAVE) study, continued to report a higher level of symptomatology in women, yet a lower referral rate for coronary angiography (2).

In 1996, the Thrombolysis in Myocardial Ischemia (phase III) (TIMI III) registry reported that women were less likely than men to receive anti-ischemic therapy and were less likely to undergo coronary angiography (3). However, in this study, women had less severe and less extensive coronary disease than men, although both had a similar risk of experiencing an adverse event within six weeks. Thus, the study was somewhat controversial.

In 1998, a report from the National Registry of Myocardial Infarction revealed data consistent with other studies, in that women with acute myocardial infarction in the United States were older than men, had a higher mortality rate than men (even when controlled for age), and had lower rates of cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) surgery than men (4).

Although there are specific data on the rates of cardiac catheterization, PTCA and CABG in Canada, these data were not broken down into sex differences (5). Information presented in this supplement by Slaughter and Bondy (pages 63 to 67) suggests that referral rates for these procedures in Ontario are lower for women than for men.

Reasons for the lower rate of referral for coronary angiography among women are unclear, but possibilities include difficulties in diagnosis due to atypical presentation; poor sensitivity and specificity of noninvasive testing; poor access to resources; and misperceptions that CAD rarely affects women, or that women tend to have advanced coronary disease and, therefore, are unlikely to benefit from interventions.

Further work is required to better delineate these possibilities.

Registry data: Early studies suggest that women do not fare as well as men following both PTCA and CABG for ischemic heart disease (IHD). Results of percutaneous interventions in women in the 1985 to 1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry revealed female sex to be an independent risk factor for death (risk ratio of 4.53) (6). Women in this registry were older, and had more risk factors and more severe angina than men. They did not have more extensive CAD than men, but did have higher initial complications and a higher procedural mortality rate. Several other registries, including a 1982 to 1986 Registry from Emory University (7), and a 1984 to 1989 Registry combining data from Emory, the San Francisco Heart Institute and the University of Michigan (8) have confirmed female sex to be an independent risk factor for poor outcome.

The Mayo Clinic Registry described almost 4000 interventions from 1979 to 1990 (9), and the Cleveland Clinic described over 5000 interventions from 1980 to 1985 (10). Both of these registries found female sex to be a risk factor for death, but felt that it was related to body surface area and was not an independent variable.

Virtually all registries, which may be the best reflection of 'real life', have shown significantly higher mortality and

complication rates in women than men. In all studies, the women were older than the men and had more comorbidities and lower body surface area. Some studies reported sex as an independent factor, while others found it to be associated with the other variables.

Hypothesized reasons for the poor outcome of interventions in women include impact of comorbidities and older age, late presentation leading to more advanced CAD and smaller vessels associated with small body surface area.

Randomized trials: Randomized trials of interventions in IHD have historically included a very small percentage of women. Review of the vast majority of large interventional trials, even those published more recently, reveals that the average inclusion rate for women is between 20% and 30%. Nevertheless, the randomized trials generally fail to show evidence of a difference between men and women in terms of referral and/or revascularization outcomes.

The Second Primary Angioplasty in Myocardial Infarction (PAMI II) trial study group found no difference in mortality rates between men and women, nor did they find any differences in the angioplasty success rates, or the incidence of reocclusion or reinfarction in the 1100 patients who underwent primary angioplasty for acute myocardial infarction (11).

Looking at the differences between men and women in the management of unstable angina, the Global Unstable Angina Registry and Treatment Evaluation (GUARANTEE) Registry study evaluated almost 3000 consecutive patients (39%) admitted to 35 United States hospitals in 1996 (12). The GUARANTEE study continued to show that cardiac catheterization, coronary angioplasty and bypass surgery were performed less often in women than in men. Women also had different epidemiological profiles than men – a result that is consistent with that of other studies. The GUARANTEE study then controlled for clinical severity between men and women by applying the Agency for Health Care Policy and Research unstable angina guidelines and the TIMI IIIB criteria for catheterization and revascularization. When using these clinical guidelines, they found that women and men were appropriately referred to angiography at a similar rate. However, fewer women than men underwent bypass surgery. There was no difference in the rate of recurrent angina, in-hospital myocardial infarction or death between women and men undergoing all interventional procedures.

Similarly, a recent report from the Bypass Angioplasty Revascularization Investigation (BARI) study, which evaluated 1829 patients with symptomatic multiple vessel CAD who were randomly assigned to either coronary artery bypass surgery or angioplasty (27% women), found consistent results (13). Women in BARI were older with more comorbidities, and interestingly, in the interventional arm, women assigned to angioplasty had more intended lesions successfully dilated than men. At an average of 5.4 years' follow-up, mortality rates were similar in women and men, and contrary to previous reports, female sex was an independent predictor of improved five-year survival after control for multiple risk factors.

A 1999 report by Leape et al (14) also failed to show any gender bias for referral to revascularization procedures. Interestingly, this study suggested that referral rates to invasive procedures were significantly lower in hospitals that did not provide revascularization procedures.

An interesting aspect of this topic was highlighted by Saha et al (15), where willingness to undergo invasive procedures was reviewed as a possible explanation for the lower rates of diagnostic cardiac catheterization and interventions seen in women in previous studies. Unadjusted analysis revealed a trend toward greater reported willingness to undergo cardiac catheterization among women than men; however, similar proportions of women and men stated that they would be willing to undergo a cardiac catheterization. Women and men were similar in their reported willingness to undergo angioplasty and coronary bypass surgery. This suggested that differences in patient preferences do not explain any disparities between the sexes seen in the use of cardiac catheterization, angioplasty or bypass surgery.

Further data from the present era (when stent and glycoprotein IIb/IIIa inhibitors are frequently used) specific to sex differences need to be further evaluated, but will likely result in even better outcomes for percutaneous intervention in both men and women.

In summary, early registry reports indicate a poor outcome with percutaneous interventions in women, but more recently, randomized clinical trials have suggested that, although epidemiological and angiographic differences continue to exist between men and women, outcomes of percutaneous interventions in women and men may now be similar.

AORTOCORONARY BYPASS GRAFTING FOR IHD IN WOMEN: CURRENT STATUS

In most reported series of coronary artery grafting, there has been a large preponderance of male patients. In the past, female sex in itself has been considered a risk factor for coronary bypass surgery (16-23). This may have, in part, led to the bias that appears to exist against the referral of women for angiography or bypass surgery (24-27).

It is clear that the clinical characteristics of females presenting for revascularization differ from those of their male counterparts. There is almost universal agreement that women presenting for CABG are older and have more comorbid conditions, including diabetes, hypertension and peripheral vascular disease (24,28-34). Women present with more severe anginal symptoms than men and require surgery more often on an urgent basis (13,14,16,20,24,28-31). On the other hand, women tend to have less extensive CAD than men (28,35) and have better preservation of left ventricular function than their male counterparts (28,29,35,36). Men are more likely than women to have a history of smoking (30). Some series report an increased incidence of congestive heart failure (30,36,37), renal failure (30) and obesity (30,37) in women compared with men. Obviously, the risk profile and anatomic substrate at the time of presentation are different between men and women.

What are the results of aortocoronary bypass grafting in women? In many previously reported series, higher hospital mortality has been reported after bypass grafting in women than men (16-23). Explanations for this difference have included the smaller size of women's coronary arteries, which presents a technical challenge at the time of surgery and may translate into incomplete revascularization or decreased graft patency. Others have suggested that there is a referral bias that causes women to present for revascularization at a more advanced stage of the disease than men (11,12,24-27,38-40). In recent studies, some of the increased risk has been attributable to comorbid factors (advanced age) and decreased body size (27,28,31,35,41,42). Several recent series have reported no significant difference in operative mortality between men and women (28,43,44). The significance of sex as an independent risk factor for coronary artery bypass grafting is, therefore, debatable.

The single largest registry of results for coronary artery bypass grafting is the Society of Thoracic Surgery database. It contains information on over 300,000 patients, of which 97,000 (28%) are women (29,45). A multivariate analysis of these data found that risk factors for men and women were virtually identical, although the relative weight of some of the risk factors was quite different, depending on sex. They found that sex was an independent risk factor related to operative mortality. Body size (surface area) was also clearly related to operative mortality. Mortality increased with decreasing body size. For small people (body surface area of less than 1.8 m^2) there was no difference in operative mortality between women and men. For those with a body surface area greater than 1.8 m^2, risk in women was greater than in men.

A consensus conference (46) identifying preoperative variables associated with increased operative mortality following CABG identified acuity, prior heart operation, age and ejection fraction as the most important factors to consider, which provide one-half or more of the total predictive information. Sex was not one of these key variables. Clearly, body size and other differences in risk factor profiles are more important determinants of operative mortality.

In most reported series, women receive fewer arterial grafts than men, and in particular, women have fewer left internal mammary artery grafts to the left anterior descending coronary artery (28,29,31,47). The reasons for this may include advanced age in women, increased diabetes or concern over quality of bone in postmenopausal patients and perceived increased risk of sternal wound infection or dehiscence if the mammary artery is used.

Do women receive the same benefits from aortocoronary bypass grafting as men? A recent study by Stewart et al (48) showed that, although women function at a lower level both pre- and postoperatively, the improvement in functional status after surgery is similar to that seen in men. However, several studies have shown that, in women, there is an increased incidence of angina or recurrent myocardial infarction over time (30,49). Whether this is due to incomplete revascularization, decreased graft patency related to small size of distal vessels or acceleration of atherosclerosis in native vessels is debatable. A recent study by Tan et al (43), which analyzed graft patency and clinical outcome at one year, showed that early graft occlusion was related to factors including diabetes, high cholesterol, location and type of distal anastomosis, and size of distal vessel. One-year graft patency was not related to sex.

Several studies have shown that, in spite of increased recurrence of angina, fewer female patients are referred for repeat revascularization procedures. The reason for this apparent bias is not clear.

Several recent studies have shown comparable long term survival following aortocoronary bypass grafting in men and women (35,36,49,50). Long term survival appears to be more related to other factors such as age, congestive heart failure, diabetes and peripheral vascular disease than to sex.

We conclude that differences in risk factor profiles between men and women presenting for revascularization are more important in determining operative mortality and long term survival than sex itself. More studies with larger numbers of female patients are needed to provide specific information regarding completeness of revascularization, vessel size and graft patency to clarify the relationship between specific risk factors and sex with respect to both short and long term results. The decision to proceed with revascularization in women should be made with the expectation of short term results and long term survival comparable with that achieved in men.

CLINICAL PRACTICE RECOMMENDATIONS

- Outcomes for percutaneous interventions in women are comparable with those in men. Referrals for invasive testing and subsequent intervention should be based on evaluation of significant disease and known benefit (level II A).

- Short term and long term survival in women undergoing surgical revascularization is comparable with that of men. Referrals for surgical revascularization should be made following evaluation of the disease and with regard for the known benefit of the procedure (level III A).

- Differing risk factor profiles in men and women presenting for revascularization are more important in determining operative mortality and long term survival than sex itself (level III A).

RESEARCH RECOMMENDATIONS

- In all ongoing and future clinical trials, adequate representation of women must be ensured to facilitate evaluation of revascularization strategies in both men and women.

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Chapter 9
Rehabilitation

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The focus of this chapter is cardiac rehabilitation as part of secondary prevention in women with ischemic heart disease. For the most part, the evidence of the past decade has been emphasized; however, older studies have been included when either the methodology was particularly strong or the work remains seminal in the field. As much as possible, the focus is on studies of women, although restricting the review in this way severely limits the portrait of what has been done in the area of cardiac rehabilitation, and studies of women are very few in number. Therefore, investigations that have included both male and female participants are included in which reasonable extrapolations from the female subsample can be drawn.

PROGRAM PARTICIPATION

Referral: In general, many more people stand to benefit from cardiac rehabilitation than are currently referred. In a study of predictors of referral to cardiac rehabilitation, Burns et al (1) found an overall (men and women combined) referral rate of 35% (74 of 213 patients) after myocardial infarction (MI), coronary artery bypass graft (CABG) surgery or both. This is similar to the overall 23.9% referral rate reported in a Canadian sample of 955 men and 290 women who were seen after MI, CABG surgery or angioplasty (2). In the United States, estimates indicate that between 15% and 30% of patients who have had MI or CABG surgery are referred for cardiac rehabilitation, and that men are referred almost twice as often as women (3). Halm et al (4) found that although 90% of the male and female patients (mostly post-MI) in their study were eligible for cardiac rehabilitation, men were more likely than women to receive orders from their physicians to attend outpatient cardiac rehabilitation (66% of men compared with 48% of women; $P<0.01$). Referral patterns and exercise response to cardiac rehabilitation in men (n=228) and women (n=98) aged 62 years and older who had been hospitalized with either acute MI or CABG surgery were compared in another study (5). Older women were less likely than older men to enter the rehabilitation program (15% compared with 25%; $P=0.06$).

In general, although referral to cardiac rehabilitation is low in both sexes, research suggests that women are referred in lower numbers than their male counterparts, and the evidence appears to converge on a rate that shows men being referred at least 50% more often than women.

Predictors of referral: There is consistent evidence that younger patients are more likely to be referred for cardiac rehabilitation than older patients, and the threshold for reduced likelihood of referral appears to be around age 70 years (2,6,7). Evidence is mixed, however, with respect to sex as a predictor of referral. A number of studies published in the 1980s and early 1990s reported that women were less likely to be referred for cardiac rehabilitation than men (5,8,9). More recently, Bittner et al (6) and King et al (2) found no difference in referral according to sex, whereas Melville et al (7) found that women were less likely to be referred.

Surprisingly, data related to socioeconomic status (SES) have not been consistently collected in studies that have examined predictors of referral. However, of those that have assessed SES, there is a common finding that low SES is associated with decreased referral (6,7,10).

Good premorbid functional status and physical activity have been shown to be predictors of referral in two studies (1,11).

Rural residents are consistently less likely to be referred for cardiac rehabilitation than urban dwellers (2,6,12). Cannistra et al (13) reported that 90% of their patients travelled less than 16 km to participate.

Generally speaking, clinical characteristics such as obesity, hypercholesterolemia and hypertension are associated

with higher likelihood of referral, presumably because these factors may be modified by the education, exercise and dietary components of cardiac rehabilitation.

In summary, although female sex has been a less consistent single predictor of decreased referral in recent studies, using sex alone to describe the referral picture is incomplete. A number of other predictors are likely to interact with female sex, resulting ultimately in fewer women referred. Women are more likely to be older, and to have lower SES and lower functional status than men at the time of their cardiac event. These factors, when combined, reduce the chance of referral for women.

Predictors of uptake: Once a patient is referred to cardiac rehabilitation, there are several factors that contribute to program uptake. Of these, the most powerful predictor of both male and female participation in cardiac rehabilitation is physician recommendation (5,14,15). Unfortunately, physicians recommended participation more strongly to men 62 years of age or older than to women of the same age group ($P<0.05$), despite that clinical profiles were similar (5). Similarly, Johnson et al (12) examined rural residents' use of cardiac rehabilitation by patients (n=254) who had been hospitalized for MI, CABG surgery or angioplasty. In that study, of the 100 patients who had no intention of attending a rehabilitation program, 34 indicated that their physician had not recommended it. Of those who did attend rehabilitation, one of the most important predictors was the 'powerful others' subscale of health locus of control. The 'powerful others' scale typically represents the influence of key people, often physicians, who the respondent views as having a role in his or her decision to undertake health maintenance activities. Thus, physician recommendation plays a pivotal role in patients' intent to participate, whether they live in rural or urban settings.

There is consistent evidence that older age is an important predictor of program uptake. Again, most studies report that, after age 70 years, there is a lower probability of patients electing to undergo cardiac rehabilitation (2,3,7,16). Lower functional capacity is one significant explanatory variable with respect to enrolment in rehabilitation programs (11). Patients with lower functional capacity were substantially less likely to enrol in such programs, and although univariate analysis identified other factors associated with program uptake, most of those factors disappeared in multivariate analysis. Only functional status and education remained as significant predictors of uptake.

Sex has not been found to be a consistent predictor of rehabilitation program uptake. One study found that, after referral, significantly fewer women than men enrolled in cardiac rehabilitation (3). Some have confirmed this finding (5,11), but others have not (2,12,16). The more recent studies found no difference, suggesting a change in both the practice of health professionals and the views of patients regarding cardiac rehabilitation for women.

In terms of SES, higher levels of education and income have been found to be independent predictors of program uptake in multivariate analysis (11). Rehabilitation participants tend to be more educated, more likely to own and drive a car, and more likely to have a white-collar job than nonparticipants (5). Similarly, social deprivation has been reported to be a significant predictor of program uptake, although no difference was found in invitation rates according to deprivation scores (7).

Once again, living in a rural setting is associated with lower uptake of cardiac rehabilitation (2,12), a factor that has as much to do with distance from available programs as with transportation problems, time of the program, program duration and financial concerns.

When social support has been considered as a variable, it has been found to influence program uptake positively (12). Lieberman et al (14) described male/female differences in the type of support that promoted enrolment in cardiac rehabilitation. Men were more likely to attend if they had spousal support, whereas women were more likely to attend if they had the support of their adult children.

In summary, when it comes to actual enrolment in cardiac rehabilitation following referral, several clear predictors exist: strong physician support, age younger than 70 years, good preprogram functional status, good socioeconomic status and/or education, living in an urban environment and perceived social support. Once again, although sex has been an inconsistent single predictor, women are less likely to be represented by these positive predictors of enrolment; therefore, the actual number of women in cardiac rehabilitation programs is lower than the number of men.

Dropout: Dropout from cardiac rehabilitation (no analysis by sex) has been reported to be in the range of 40% to 60% over a six-month program (12,16). Balady et al (17) found an equivalent 36% dropout rate in both men and women over an average program duration of 10 weeks. A number of authors, however, have reported higher dropout rates for women than for men (18,19). In a women-only study, the dropout rate was 43% over three months (13), and this rate has been confirmed in other mixed-sex series (4,20). The highest dropout rates (48%) were among patients whose baseline exercise capacity was less than five metabolic equivalents (METs) (17). Although the number of men versus women in this subset was not identified, it is a reasonable hypothesis that women are more likely to enter rehabilitation programs with an exercise capacity of less than 5 METs. The most frequently cited reasons for female dropout are concurrent medical illness, transportation problems, psychosocial difficulties such as anxiety and depression, family commitments and inconvenient timing of the program.

Summary: There is room for improvement in referral of women to cardiac rehabilitation programs, and accomplishing this should be relatively straightforward. Clearly, the two most difficult areas to address are adoption, followed by maintenance, not just of exercise, but of the many lifestyle changes that are recommended as part of rehabilitation. Social cognitive theory proposes that both intra- and extrapersonal factors are determinants of behaviour (21). Biological (age, sex) and psychological (specific beliefs, past

experiences) variables are the primary intrapersonal factors. Many of these are apparent in the literature reviewed above. External factors such as persuasion (eg, physician recommendation) and the physical environment (eg, access to programs) are also important influences on behaviour. Theoretical formulations suggest that different processes guide the adoption and maintenance of many behaviours (22). In fact, adoption of exercise in previously sedentary women (the typical female cardiac patient) could be predicted by education, self-efficacy, and friend and/or family support, whereas maintenance was predicted by education alone (23). Initial efforts should be directed to increasing referral and promoting adoption of cardiac rehabilitation in women.

PROGRAM OUTCOMES

Morbidity/mortality: A significant and frequently quoted contribution to the literature is the study by O'Connor et al (24), which was a systematic review of 22 randomized, controlled trials of rehabilitation after MI. All trials included in this analysis were published between 1973 and 1985, and the interventions were either exercise only, or exercise plus other educational and/or behavioural components. Of the 4554 patients represented by these combined trials, only 3% were women. Briefly, the main findings from this review were a 20% reduction in overall mortality that persisted for three years following the intervention and a reduction in sudden death in the first year. There were no significant differences between groups in nonfatal reinfarction over the three years. More recently, the morbidity and mortality outcomes in a sample of post-MI patients who had been part of a case-control study of multifactoral cardiac rehabilitation 10 years earlier were reported (25). Women represented 15% of the sample. There was a reduction in all-cause and cardiac mortality after 10 years, as well as a reduction in nonfatal reinfarction in the intervention group. No male/female differences were found. Similarly, a lower cardiac mortality and sudden death in the intervention group (at 15-year follow-up) was found in a sample of 375 post-MI patients who had been part of a randomized, controlled trial of multifactoral cardiac rehabilitation (26). In this study, approximately 20% of the sample was female, and no sex differences in mortality were found. Other recent studies of long term survival following exercise and/or multifactoral cardiac rehabilitation have been published; however, women were not included in some samples (27). Limacher (28) suggests that "reductions in cardiovascular death rates [for women] have not been established, owing to the limited number and size of existing studies". However, despite the fact that most of the evidence related to mortality and morbidity as outcomes of cardiac rehabilitation comes largely from data on men, there appear to be similar benefits to women when they have been analyzed separately.

Exercise capacity: Many studies have examined exercise capacity as an outcome, although again, few of the initial studies included women. Between 1992 and 1997, a number of observational studies and a case-control investigation compared exercise capacity outcomes in men and women (29). Between 1995 and 1999, at least two randomized, controlled trials examined exercise and other outcomes of cardiac rehabilitation, but the numbers of women in these trials were 19% and 9%, respectively, and findings were not analyzed by sex (30,31).

Generally speaking, studies that have examined exercise capacity outcomes in men and women have included patients whose index event was MI, CABG surgery or percutaneous transluminal coronary angioplasty (PTCA). In some cases, patients with angina have also been included. Entry to most rehabilitation programs was between six and 14 weeks after the index event. The intervention in the majority of studies was the typical multidimensional cardiac rehabilitation, and the exercise component was, for the most part, a supervised program offered three times per week for 12 weeks. Various exercise capacity outcomes have been used, including peak volume of oxygen consumption per unit of time (VO_2), MET level, rate pressure product and percentage of maximum heart rate. Most frequently, findings have been reported in percentage increase in MET level.

Results from the studies comparing men and women are remarkably consistent, reporting more of an improvement in peak MET level for women than men (32,33). In one study, black women improved their peak MET level more than white women (13). Shiran et al (34) reported an equivalent 19% increase in exercise capacity for both men and women. In a study of elderly women (older than 65 years of age), a significant improvement in exercise capacity occurred after their 12-week program (35). Balady et al (17) compared exercise capacity outcomes according to sex and age strata. In the under 65 years of age group, men improved 36% and women improved 41%. In the 65 to 75 years of age group, improvements were 36% and 50%, respectively. In the over 75 years of age group, improvements were 36% for men and 32% for women. Finally, a case-control trial of exercise training in older patients with coronary disease (62 years of age or older) reported increases in peak VO_2 of 16% in women compared with 15% in men (29). In summary, there is clear evidence that women can expect significant gains in exercise capacity following an average three-month program of cardiac rehabilitation. These gains have been shown to range from a low of 11% to a high of 50%. On average, women can expect an approximate 20% improvement, with older women and those starting at the lowest levels of exercise capacity seeing improvements of even greater magnitude.

Lipid changes: In this chapter, only evidence related to lipid changes associated with the education and exercise components of cardiac rehabilitation is presented, not the evidence related to the use of lipid-lowering medications. In three studies of the effect of cardiac rehabilitation on lipid profiles where women were included and analyzed, no significant changes in lipids were found (13,32,33). In all three studies, the dietary intervention was poorly described, except to state that recommendations were given according to the American Heart Association Step 1 diet. Warner et al (36) examined changes in high density lipoprotein cholesterol

levels over a five-year cardiac rehabilitation program in which the dietary intervention consisted of general instruction for a low cholesterol, low saturated fat diet. Their initial sample consisted of 553 men and 166 women; however, by the five-year assessment point only 12% of the men and 8% of the women had completed the follow-up. Although both men and women showed an increase in high density lipoprotein cholesterol level after one year, only the women's levels continued to increase to the five-year point. Limitations, such as not accounting for the use of lipid-lowering agents or hormone replacement therapy, weaken the impact of these findings. LaFontaine (37) published a very helpful review article on lipid management by diet and exercise, and its effects on progression, stabilization and regression of atherosclerotic lesions. The majority of studies reviewed had overwhelmingly male samples; however, these findings can most likely be extrapolated to women. This review found that traditional cardiac rehabilitation programs are inadequate and ineffective in stabilizing or slowing the progression of atherosclerosis, because intensive diet and exercise intervention with aggressive monitoring is required to slow or reverse atherosclerotic changes. In addition, the daily diet should have no more than 20% to 27% of calories as total fat and 3% to 8% as saturated fat. A minimum of 1600 kcals per week of aerobic exercise is required for stabilization of lesions or a minimum of 2200 kcals per week for the possibility of regression.

Other studies have investigated the perceived barriers to changing eating habits among men and women and have found that women may have more difficulty avoiding fat, and that the workplace is especially challenging for women when it comes to making dietary change (38,39). Low socioeconomic status and/or education levels have consistently been found to be associated with difficulties in making diet and other lifestyle changes (40-42).

Finally, cardiac rehabilitation with 12 weeks of exercise training was associated with a 12% reduction in homocysteine levels in cardiac patients (14% female) who had normal lipid profiles and hyperhomocysteinemia (43). Further, nine months of exercise training after MI (27% females) improved fibrinolysis by reducing levels of plasminogen activator inhibitor (44).

Quality of life: Patient-based assessments of health-related quality of life (HRQL) are increasingly used as outcomes in the evaluation of health care interventions, and cardiac rehabilitation is a particularly pertinent case (45,46). In a meta-analysis of HRQL in cardiac patient research, only 7.1% of the studies examined cardiac rehabilitation as the intervention (47). Most of the evidence related to HRQL with cardiac rehabilitation is observational and is from studies including very few women. Given the paucity of data, the National Institutes of Health Consensus Conference on Physical Activity and Cardiovascular Health called for more rigorously controlled investigations with respect to HRQL and cardiac rehabilitation (48).

In cross-sectional investigations comparing male and female patients, women had consistently lower HRQL life scores after six months (49) and one year (50) of participation in cardiac rehabilitation. There is some evidence that, while there are point differences in HRQL scores between men and women, these can be accounted for by baseline differences between them, and the absolute gains made by women may be more than those for men (51). The best predictor of improved HRQL after MI may be poor HRQL at baseline (52). Women are likely to enter rehabilitation programs with lower levels of HRQL than men and thus have much to gain.

Psychosocial issues: The point prevalence of major depression has been documented to be 15% to 20% in patients with coronary artery disease (CAD). Several authors have reported higher rates of anxiety and depression in women than in men, particularly after MI (53-54). While Frasure-Smith et al (54) found that depression after MI was a risk factor for one-year cardiac mortality in both men and women, women were twice as likely to report post-MI symptoms of depression than men. A review of the literature on psychosocial factors and CAD in women examined nine studies comparing psychosocial adjustment post-MI in men and women, and six such studies related to CABG surgery or PTCA (55). Eight of the nine post-MI studies suggested that women do not cope as well psychosocially as men; they scored higher on psychosomatic symptoms, anxiety and depression. The vast majority of depressed patients remain depressed one year after MI (56). Reports comparing psychosocial adjustment after CABG and/or PTCA were inconclusive. It is worth noting that epidemiological studies have shown similar female to male ratios for depression in the general community.

Numerous authors have reported gender differences in patient-professional communication and the provision of information (57-60). Women receive less information about heart disease than men and have reported the perception that they are living with a man's disease in a man's world. In communication with their physicians, women have been found to be more passive and deferential than men. They perceive themselves as less powerful from both social status and gender perspectives, and the net result is a negative impact on communication and information exchange.

One study of the effect of a cardiac rehabilitation program on depression in women found that the prevalence of depression dropped from 23% to 12% after a 12-week exercise and education program (61). On the other hand, a meta-analysis of 37 studies of psychoeducational programs for patients with CAD reported that psychoeducational interventions do not generally succeed in reducing anxiety or depression (62). Women represented approximately 12% of the total number of subjects in these studies. This latter finding is in contradiction to an earlier meta-analysis that found a reduction in psychological distress and mortality in patients who received psychosocial interventions in addition to other typical components of cardiac rehabilitation (63). Neither meta-analysis compared men and women. Despite conflicting evidence, there is general agreement that psychoeducational interventions are successful when

their use is focused on the most distressed patients; thus, such patients should be identified upon entry to rehabilitation programs.

CLINICAL PRACTICE RECOMMENDATIONS

- In older women, the likelihood of referral to rehabilitation is less, but the expected gains are equal to or better than those expected for men. Access should not be restricted for older females (level II B).
- Women with low baseline functional ability can expect significant improvement. Access should not be restricted due to poor functional capacity (level I A).
- Strong physician recommendation and support are crucial to increasing enrolment and maintenance in rehabilitation for women (level II B).
- Women are less likely to have informal caregivers; therefore, information on community-based resources should be provided (level III B).
- Because gender differences exist in women with respect to communication patterns and styles in the patient-professional relationship, emphasis needs to be placed on information (level III C).
- Significantly distressed patients should be identified and referred for counselling (level II B).

RESEARCH RECOMMENDATIONS

- Prospective studies of psychosocial interventions for women (which control for pre-existing depression, anxiety and other symptoms of distress) are warranted.
- More study is needed regarding different approaches to programming, such as home-based rehabilitation or community support programs, which may be more suitable for women.
- Rigorous studies of HRQL changes in women as a result of participation in cardiac rehabilitation are required, particularly comparing different program modalities.
- Investigation of novel approaches to increasing women's participation in cardiac rehabilitation is needed.

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Chapter 10
Differences in access to care

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This chapter addresses the question of whether there are differences in access to care, specifically for noninvasive ischemic testing, coronary angiography, and percutaneous and surgical revascularization, for women with ischemic heart disease (IHD). The chapter complements and builds upon earlier chapters that address related issues, including sex differences in the prevalence of IHD, utility of diagnostic tests in women and men, and evidence of the efficacy of revascularization procedures in women.

Access to care encompasses differences in availability and use of health care services, and is indicated by varying rates of use that are inadequately explained by differences in disease rates and presentation or by the scientific evidence of the efficacy of a given intervention. Much of the research literature reviewed here is from the emerging field of health services research. Relevant studies of this type are constrained by the availability of data, particularly data that have population-wide relevance.

Extensive evaluation of sex differences for most phases of cardiac care has been undertaken internationally, confirming that the evaluation and treatment of coronary artery disease by physicians are different for women and men. Studies have shown that women with suspected IHD undergo fewer noninvasive and invasive diagnostic tests than men, while those with proven disease have fewer interventional procedures than men (1-14). Even in an experimental paradigm, the patient's sex has been shown to influence clinical decision-making. In this paradigm, female sex was associated with a lower perceived probability of IHD and had an effect in reducing the likelihood of ordering catheterization that was independent of clinical history (15).

For purposes of this statement, special emphasis has been placed on Canadian studies because of the differences inherent in Canada's universal health care system, queuing strategies and waiting list management for many components of cardiac care, and the influences of restructuring activities in this decade. Researchers in Canadian jurisdictions have investigated the use of invasive cardiac procedures, but these studies did not report sex-specific data (16,17). Smaller institution-specific datasets or collaborative initiatives also often lack sex-specific information, and unfortunately, some reports are available only in abstract form.

Several studies have been published in Ontario by researchers at the Institute for Clinical Evaluative Sciences (ICES). Information from *Cardiovascular Health and Services in Ontario: An ICES Atlas* (18) is also presented here as a window on current cardiovascular access patterns for women in Canada. Although this was an Ontario-based report, it was the first Canadian, population-based, comprehensive study of cardiovascular care, and it included sex-specific analyses in all instances.

STUDIES OF NONINVASIVE DIAGNOSTIC TESTING

Studies in the United States and elsewhere have reported that, among patients with suspected IHD, men are more likely than women to receive specific invasive and noninvasive investigations (2,4).

In Canada, the use of noninvasive ischemic testing (NIIT) was assessed in a single centre study by Jaglal et al (19), who reported referral patterns from primary care practitioners to cardiologists for patients with suspicion of IHD. Women were less likely than men to have had prior NIIT. Cardiologists referred a higher proportion of women for NIIT than men, and when stress testing was positive, were more likely to refer women for further testing than men.

Chan et al (20) reported population-based procedure rates for exercise stress tests, myocardial perfusion scans and radionuclide angiography (RNA) in Ontario between 1989 and 1992. In that study period, the ratios of male to female testing rates (age-adjusted, all ages) were 1.73 for exercise testing, 1.45 for perfusion scans and 1.25 for RNA. Over the same period, the sex ratios diminished somewhat, and glob-

TABLE 1
Ratio of male to female, age-adjusted diagnostic testing rates per capita: fiscal years 1989/90 to 1996/97*

Test	Fiscal year 1989/90	Fiscal year 1996/97
Exercise stress test	1.75	1.56
Myocardial perfusion scintigraphy	1.70	1.35
Radionuclide angiocardiography	1.27	1.28

**Age-standardized number of tests per capita for men, divided by the number of tests per capita for women. Adapted with permission from reference 21*

al expenditures for all three procedures increased more for women than for men. The authors of the study commented that the increase in utilization of these noninvasive tests probably reflects a growing awareness of the risk of IHD for women, who historically had been underevaluated. It was not possible to demonstrate that expansion of service in men or women represented appropriate increases in use. However, it was perceived as encouraging that the most rapid growth in utilization for women was in the form of scintigraphy, which is a particularly useful test in younger women as well as in women with atypical symptoms, where test results are influenced by prevalence.

In *Cardiovascular Health and Services in Ontario: An ICES Atlas*, Chan (21) updated, by five years, the previously published findings on noninvasive testing and expanded the list of procedures to study the newer technologies. Myocardial perfusion scans and RNA testing had the greatest increase in utilization. These updated data showed a continuation of the trend toward lower male to female testing ratios and probably indicate that IHD is being investigated more extensively in women. The ratios of male to female, age-adjusted diagnostic testing rates per capita between fiscal years 1989/90 and 1996/97 in Ontario are shown in Table 1. The changes may be attributable, in part, to the publication of clinical practice guidelines in both the United States and Canada in the 1990s, although this cannot be demonstrated directly.

STUDIES OF SEX DIFFERENCES IN INVASIVE CORONARY PROCEDURES

By the early 1990s, a number of American studies reported that men and women had different probabilities of receiving invasive procedures for IHD (1,6,7,9,10) as previously discussed.

Roos and Sharp (22) examined Manitoba data for the fiscal years 1977/78 to 1983/84 and found that utilization of invasive coronary procedures in older patients was less pronounced than reported in other jurisdictions. Rates of bypass, however, differed hugely for women and men in 1983/84, with rates of 27/100,000 and 93/100,000, respectively.

Early information on angioplasty was reported by Ugnat and Naylor (23) from a single centre, showing that rates for this procedure were higher in men than in women in all age groups in 1991. The same paper presented and discussed crude and age-adjusted rates of bypass and angioplasty per population for a period between 1981 and 1989 in Ontario. These data show a procedure ratio of approximately 3:1 in men compared with women during these years. What is more striking is the consistency of the 3:1 ratio when age subgroups are examined. A higher rate of procedures for men among patients younger than 50 years would be justifiable by differences in prevalence. However, the same 3:1 ratio was found even among patients older than 65 years where prevalence rates were comparable.

Another study that directly addressed sex differences retrospectively assessed sex-related differences in revascularization procedures in a consecutive group of patients referred for revascularization (24). The investigators found that, although women were more likely than men to have unstable angina when referred, more women than men were turned down for either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) surgery, even after controlling for the age of the patient and the referring cardiologist's expected procedural risk. Anatomy was the main determinant of selection, but sex was the only other significant variable. Referring physicians requested CABG more frequently for men than for women, and of those accepted, men underwent CABG procedures more often than women.

Other reports have presented rates of angiography, angioplasty and bypass surgery across Canada, derived from surveys of Cardiac Catheterization Laboratories (16,17), but unfortunately, these reports did not include data analyzed by sex.

Using Canadian hospitalization data, Jaglal et al (25) defined a cohort of all patients admitted for acute myocardial infarction (AMI) in Ontario during a six-month period in 1990 (approximately 7000 patient records in the analysis). They found that 18.4% of men underwent angiography compared with only 9.9% of women (odds ratio 2.2 [95% CI 1.8 to 2.4]). For bypass surgery, 3.3% of women underwent the procedure compared with 6.4% of men (odds ratio 2.0 [95% CI 1.6 to 2.6]). Angioplasty rates also differed by sex: 3.1% in women compared with 5.7% in men (odds ratio 1.9 [95% CI 1.5 to 2.5]). The sex difference in rates of angiography was significant after adjusting for age group, comorbidity and mortality in a logistic regression analysis (adjusted odds ratio 1.4 [95% CI 1.2 to 1.6]). After adjustment, the sex difference for angioplasty was no longer statistically significant; however, the sex difference in bypass surgery continued to be significant (adjusted odds ratio 1.6 [95% CI 1.2 to 2.0]).

Anderson et al (26) found sex and sex-related differences in patients who underwent angiography and bypass surgery in Ontario compared with those in British Columbia. In patients who underwent angiography in British Columbia, there was a slightly higher proportion of patients older than 65 years (36% compared with 32% in Ontario) and a higher proportion of women (37% compared with 25% in Ontario). Among patients in British

TABLE 2
Overall, and age- and sex-specific cardiac procedure rates after acute myocardial infarction in Ontario 1994/95 to 1996/97

	Women (age in years)					Men (age in years)				
Procedure	**20-49**	**50-64**	**65-74**	**≥75**	**Overall**	**20-49**	**50-64**	**65-74**	**≥75**	**Overall**
Angiography*	50.7	37.0	25.1	6.0	19.6	52.9	41.1	28.7	9.2	31.5
Angioplasty†	16.0	12.7	7.4	1.8	6.1	18.5	12.0	6.6	1.8	8.9
Bypass surgery†	8.1	11.3	10.1	1.9	6.4	12.1	15.6	13.4	4.0	11.6

**Mean six-month coronary angiography rates; †One-year angioplasty and bypass surgery rates. Reproduced with permission from reference 27*

TABLE 3
Overall, and age- and sex-specific cardiac procedure waiting times after acute myocardial infarction in Ontario 1994/95 to 1996/97

	Women (age in years)					Men (age in years)				
Procedure	**20-49**	**50-64**	**65-74**	**≥75**	**Overall**	**20-49**	**50-64**	**65-74**	**≥75**	**Overall**
Angiography*	22	18	18	17	18	22	23	19	18	21
Angioplasty†	7	5	4	4	5	7	7	6	6	7
Bypass surgery†	28	25	13	11	15	51	37	19	13	27

**Mean six-month coronary angiography rates; †One-year angioplasty and bypass surgery rates. Reproduced with permission from reference 27*

Columbia who underwent CABG, there was a similar difference in the proportion of patients older than 65 years (45% compared with 32% in Ontario), but the difference in the proportion of women was minimal (23% compared with 20% in Ontario). The differences may be due to the older population in British Columbia. Patients in Ontario were less likely to be older than 65 years and were less likely to have unstable angina.

Alter et al (27) also examined angiography, angioplasty and bypass surgery in the Ontario Myocardial Infarction Database, including more than 50,000 AMI patients. Women received statistically significantly fewer procedures than men ($P<0.0001$ in all instances). Once women have undergone angiography, their access to PTCA or CABG is the same as that of men. Women's overall rates of PTCA, however, are half that of men, while rates of CABG among women are slightly more than two-thirds that of men (Table 2). The most striking finding in Table 2 is the inverse relationship of procedure rates to age and to the prevalence of the disease. Procedure rates were highest for younger women, among whom the mortality from AMI was lowest, and lowest for older and elderly women, who had the highest mortality rates after AMI.

When women did receive angiography, their waiting times for revascularization were shorter than those of men ($P<0.0001$) (Table 3). This was interpreted as an indicator that cardiologists were triaging women in accordance to either a perceived or real difference in clinical urgency relative to men.

After AMI, the youngest age groups in both sexes have the highest procedural rates. In the oldest age category (75 years and older), although rates of angioplasty are similar for both sexes, men have significantly higher rates of angiography than women (9.2% compared with 6%), as well as bypass surgery (4% compared with 1.9%). Based on these data, it is difficult to determine whether this represents appropriate clinical judgement, ageism or sexism.

Slaughter et al (28) reported a summary of changes in population-based rates of both angioplasty and bypass surgery with reference to sex differences. They reported that overall rates for both angioplasty and bypass surgery in Ontario increased significantly between the fiscal years 1994/95 and 1997/98 in the general population, and not simply in those who had suffered an AMI. However, major sex-related gaps persist in the use of both PTCA and CABG in the most clinically relevant age categories (50 to 64 years, 65 to 74 years, and 75 years and older), despite that the incidence of IHD is generally similar across the sexes after the age of 65 years.

The rate of angioplasty in men 65 years of age and older is double that of women (Table 4). Women in this age group tend to have more complicated coronary disease, with increased comorbidity, which may argue for substitution of CABG for PTCA. However, the rate of CABG in women still substantially lags behind that of men, both between the ages of 65 and 74 years, and over the age of 75 years, when rates are consistently triple that of women (Table 5).

CONCLUSIONS FROM STUDIES OF SEX-BASED RATE DIFFERENCES IN CORONARY PROCEDURES

The studies presented in this chapter have been interpreted as demonstrating some degree of sex discrimination, in that women have been historically underserved in coronary procedures compared with men, although this differ-

TABLE 4
Age- and sex-specific angioplasty rates per 100,000 population aged 20 years and older in Ontario, 1994/95 to 1997/98

	Women (age in years)					Men (age in years)				
Year	20-34	35-49	50-64	65-74	≥75	20-34	35-49	50-64	65-74	≥75
1994/95	1	11	61	109	42	2	56	194	222	76
1995/96	1	12	66	115	45	2	57	197	207	94
1996/97	1	12	71	118	64	2	58	226	243	117
1997/98	1	13	86	136	73	2	61	247	270	151

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TABLE 5
Age- and sex-specific coronary artery bypass graft surgery rates per 100,000 population aged 20 years and older in Ontario, 1991/92 to 1997/98

	Women (age in years)					Men (age in years)				
Year	20-34	35-49	50-64	65-74	≥75	20-34	35-49	50-64	65-74	≥75
1991/92	0	8	61	134	41	1	50	286	432	141
1992/93	0	8	67	136	45	1	51	294	448	154
1993/94	1	7	61	139	49	1	48	292	468	188
1994/95	0	7	65	155	57	1	46	299	509	211
1995/96	1	7	63	165	69	1	47	297	503	226
1996/97	1	9	69	192	80	1	47	310	537	261
1997/98	1	9	71	197	103	1	46	339	601	326

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ence has been decreasing somewhat over the past decade (29). It appears that these observed differences originate not with surgeons' or interventional cardiologists' decisions when women are considered for revascularization, but rather with what Naylor et al (18) and Alter et al (27) have called "the referral funnel" (from symptoms to diagnosis), in which fewer women than men are positioned as candidates for angiography. Once women have had angiography, their access to angioplasty or bypass surgery is the same as that of men. Because of differences in referral to angiography, however, overall rates of PTCA and CABG in women remain dramatically lower than in men, even in age groups in which the IHD prevalence is not different for men and women.

What remains unclear is whether higher rates indicate that procedures are being applied appropriately. Similarly, the fact that procedure rates in women are increasing may be interpreted as better care for women or greater application of procedures to women that may have been overused in men.

The diagnostic challenges in IHD in women, as discussed in previous chapters, lie in the differing clinical presentation of the disease, the diminished accuracy of the diagnostic tools used and the skewed prevalence of IHD in women (because sentinel events generally occur a decade or more later than in men). Women's anginal symptoms are not always classical and are often vague or atypical in presentation, as previously discussed.

There are limitations to the data presented. Most of these studies are large, nonrandomized, epidemiological studies, and the representative data sources have known limitations. These sources lack clinical depth and are not prospectively collected for research. Nonetheless, it is critically important to do these kinds of analyses, because observed differences challenge assumptions, and can help to drive and shape research that focuses more intently on the appropriateness of clinical care. Health services research often cannot provide information about the clinical decision process, including how much the patient influences the treatment decisions made, or how physician beliefs or practice patterns mitigate clinical care.

Good clinical practice requires clear information on how best to assess women with both typical and atypical symptoms and to make appropriate and timely referrals for intervention. These patterns of care include understanding the effects of and outcomes associated with the attendant co-morbidity of older age (when more women suffer from IHD), so that women can be appropriately and effectively treated. This consensus statement, in specifically presenting information directed to this goal, is a step forward.

CLINICAL PRACTICE RECOMMENDATIONS

- Rates of referral for invasive diagnostic testing are lower for women than men; therefore, overall revascularization rates are lower. These differing rates of referral may influence outcome. Physicians should re-examine their treatment practices in light of this information (level II C).

RESEARCH RECOMMENDATIONS

- Evidence specific to women is needed about diagnostic testing and invasive cardiac interventions to further enhance understanding of these modalities and to inform clinical practice.

- The use and outcomes of coronary care services need to be tracked and critically evaluated in an ongoing fashion.

- Research is required to monitor differences in the care received by patients with respect to age and sex. Observed differences in access need to be critically examined to determine whether they are appropriate; whether they reflect differences in disease prevalence and presentation or proven differences in the efficacy of interventions; or whether they are due to misconceptions or lack of evidence.

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Chapter 11
Women and heart disease in Canada

Elinor Wilson RN PhD

In Canada, cardiovascular diseases (CVDs), including myocardial infarction, ischemic heart disease, valvular heart disease, peripheral vascular disease, arrhythmias, high blood pressure and stroke, are the leading causes of mortality for both men and women. For women of all ages, 38% of deaths in Canada are attributable to cardiovascular disease, which exceeds the corresponding value of 36% for men (1). Internationally, the World Health Organization Health Report (2) indicates that there were approximately 16.7 million deaths due to CVD for all ages in 1999, of which an estimated eight million were men and 8.7 million were women. Despite gains in treatment and prevention, CVD remains the number one killer of Canadian women and is a major public health problem for women in all countries.

Heart disease substantially affects the lives of Canadian women, significantly altering quality of life and affecting ability to return to work. Ischemic heart disease is associated with depression and anxiety, can increase a woman's concerns about a repeat heart attack or stroke, and is linked to chronic pain, physical disability and the inability to fulfill previous family roles. In addition, the costs associated with health problems related to heart disease include a financial strain to health care, a loss of productivity and an increased need for social services.

Prevention and management of these conditions are major public health priorities; however, a lack of awareness of the women-specific aspects of heart health has impeded progress in this area. Higher rates of heart diseases among young and middle-aged men have created the false perception among women and health care practitioners that heart disease is primarily a middle-aged, male disease. The rate of coronary artery disease among women increases with age, and as a result, when combined with the increased longevity of women, CVDs pose an equal threat to women and men.

The promotion of heart health and the prevention of heart disease can only be accomplished with attention to the realities of women's various roles within society, the family, the workplace and the community. The *2000 Victoria Declaration: Women, Heart Diseases and Stroke* (3) released after the First International Conference on Women, Heart Disease, and Stroke, 2000 called on a number of individuals and organizations who have an impact on the health and heart health of women to marshal their efforts and invest resources in the prevention and management of heart diseases and stroke.

Professional societies, researchers, cardiologists, clinicians and other health professionals can make significant contributions to the struggle against ischemic heart disease in Canada. Professional societies have a loud voice, and can act as strong advocates for women and heart health in Canada. Cardiologists, clinicians and other health professionals are instrumental in improving the heart health of women, and increasing awareness and education of the specific issues related to women and heart health.

The *Declaration* asks cardiologists and other health care providers to offer supportive psychosocial environments, and to encourage women to adopt heart healthy behaviours, including a tobacco-free lifestyle, health-promoting dietary habits and regular physical activity. Encouraging heart healthy behaviours will help reduce the prevalence of risk factors such as hypertension, diabetes and obesity. The steadily increasing rate of smoking among young women in Canada threatens to reverse the gains that have been made in combatting heart disease.

Development of programs and services that cater to the needs of women is essential to reduce heart disease in Canada. The *Declaration* calls for the development of programs and services such as primary prevention, screening,

diagnosis and treatment, prevention of recurrence, rehabilitation and support that are tailored to the needs of women. Primary prevention activities must be directed at the entire population, because all girls and women are potentially at risk of developing heart disease. The inclusion criteria for high risk screening programs must consider risk factors that are specific to women, such as gestational diabetes. Biological differences between men and women must be considered when providing diagnosis and treatment services for women. Appropriate diagnostic criteria, drug dosages and interventions that are effective for women must be identified and developed according to the needs of women. Rehabilitation and support services have a profound impact on an individual's return to full functioning and quality of life. Programs and services for heart disease patients must consider women's needs, and must involve women in the development, implementation and evaluation phases.

The *Declaration* also calls for cardiologists, clinicians and other health care professionals to be gender sensitive in communications, practices, skills and attitudes when delivering programs and clinical services. Educating patients and professionals about women and heart disease is essential for increasing awareness among women and the general public, and improving health care service and delivery to women.

More research focused on the issues relevant to women would form a strong foundation for action on heart disease and stroke. This includes research on risk factors, the effectiveness of prevention, preclinical and clinical interventions, and quality and responsiveness of health services.

Population surveillance and information monitoring would be more useful if they included whole and subpopulation sex-related indicators and analyses, as well as the collection and analysis of interventions and outcome data. Ongoing program evaluation, research and surveillance will help to tailor programs to the needs of women and provide the best possible care to this population.

An integrated approach to the prevention, treatment and management of heart disease is essential to combat heart disease in Canada. Collaboration among various health sectors, improved awareness about women and heart disease, advocacy for programs and services, preventive measures, and diagnosis and treatment that target the needs of women are required to improve women's heart health in Canada. The recommendations of the *2000 Victoria Declaration: Women, Heart Diseases and Stroke* are echoed in the present consensus document. The consensus document recognizes the multiple gaps in knowledge and identifies clear opportunities for the research of many unanswered questions. Armed with these recommendations, professional societies, researchers, clinicians, cardiologists and other health care professionals can improve the heart health of women in many ways, and together, they are an important and vital element to the solution of this problem in Canada.

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The Canadian Journal of Cardiology – the official journal of the Canadian Cardiovascular Society – is published 12 times a year by Pulsus Group Inc and is printed on recycled paper in Canada. Printed on acid-free paper. Circulation: 15,500.
ISSN 0828-282X. Date of issue: November 2001

Canadian publications mail product sales agreement no: 40062595. Postage paid at Winnipeg, Manitoba.

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