The Editor's Roundtable: The 10Q Report—Advancing Women's Heart Health Through Improved Research, Diagnosis, and Treatment

Vincent E. Friedewald, MD[a,*], Sharonne N. Hayes, MD[b], Carl J. Pepine, MD[c], William C. Roberts, MD[d], and Nanette K. Wenger, MD[e]

Acknowledgment

This CME activity is supported by an educational grant from Gilead Sciences, Foster City, California.

Disclosures

Dr. Friedewald has no relevant financial relationships to disclose. Dr. Hayes has no relevant financial relationships to disclose. Dr. Pepine receives grant/research support from Amarin, Bedminster, New Jersey; Amgen, Thousand Oaks, California; Amorcyte, Allendale, New Jersey; Mesoblast, New York, New York; AstraZeneca Pharmaceuticals, Wilmington, Delaware; Baxter Healthcare, Deerfield, Illinois; Cytori Therapeutics, San Diego, California; Daiichi Sankyo, Parsippany, New Jersey; Gambro, Lakewood, Colorado; Genetech, San Francisco, California; GlaxoSmithKline, Philadelphia, Pennsylvania; Eli Lilly, Indianapolis, Indiana; Medtronic, Minneapolis, Minnesota; National Institutes of Health/National Heart Blood and Lung Institute, Bethesda, Maryland; and Sanofi-Aventis, Bridgewater, New Jersey and is a consultant for Amarin, Eli Lilly, Mesoblast, and SLACK, Thorofare, New Jersey. Dr. Roberts has no relevant financial relationships to disclose. Dr. Wenger receives research grants/contracts from and is part of Trial Steering Committee/Trial Adjudication Committee/Trial Data Safety and Monitoring Board of Abbott Laboratories, Abbott Park, Illinois; Gilead Sciences, Foster city, California; Merck, Whitehouse Station, New Jersey; National Heart and Blood Institute, Bethesda, Maryland; and Pfizer, New York, New York and is a consultant for Abbott Women's Advisory Board, Aboot Park, Illinois; Amgen, Thousand Oaks, California; AstraZeneca, Bridgewater, New Jersey; Gilead Sciences; Janssen, Titusville, New Jersey; Merck; and Pfizer.

[a]Associate Editor, *The American Journal of Cardiology*, Clinical Professor of Medicine, University of Texas−Houston Health Science Center, Houston, Texas, and Adjunct Research Professor, Indiana University School of Medicine, South Bend, Indiana; [b]Associate Professor of Medicine and Cardiovascular Diseases, Founder, Women's Heart Clinic, Mayo Clinic, Rochester, Minnesota; [c]Professor of Medicine, Division of Cardiovascular Medicine, University of Florida College of Medicine, Gainesville, Florida; [d]Editor-in-Chief, *The American Journal of Cardiology* and *Baylor University Medical Center Proceedings*, Executive Director, Baylor Heart and Vascular Institute, Baylor University Medical Center, and Dean, A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, Dallas, Texas; and [e]Professor of Medicine (Cardiology) Emeritus, Emory University School of Medicine, and Consultant, Emory Heart and Vascular Center, Atlanta, Georgia. Manuscript received September 9, 2013; accepted September 13, 2013.

*Corresponding author: Tel: (512) 417-5379; fax: (830) 798-0194.
E-mail address: vef@argus1.com (V.E. Friedewald).

Objectives

At the conclusion of this activity, the participant should be able to:

1. Better recognize presenting features of women with cardiovascular disease, with specific reference to differences from men
2. Design more effective strategies for primary and secondary cardiovascular disease prevention in women
3. Provide optimal assessment and treatment of chest pain due to ischemic heart disease in women

Target Audience

Cardiologists, internists, primary care providers, and healthcare professionals responsible for the diagnosis, treatment, or management of women with cardiovascular disease.

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http://dx.doi.org/10.1016/j.amjcard.2013.09.003

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Method of Participation

To receive credit for completing this activity, participants must:

1. Read the learning objectives, accreditation information, and faculty disclosures at the beginning of the activity.
2. Read the activity content.
3. Complete the online posttest and evaluation at http://elsevierme.com or mail/fax the answer sheet/evaluation to the address listed on the evaluation form.

Physicians who receive a grade of 70% or better on the posttest and who complete the evaluation will receive a CME certificate.

All other participants who receive a grade of 70% or better on the posttest and who complete the evaluation will receive a certificate of participation.

Introduction

The updated 2011 10Q Report (10Q) by the Society for Women's Health Research and WomenHeart: The National Coalition for Women with Heart Disease highlighted 10 unanswered research questions about prevention, diagnosis, and treatment of heart disease in women.[1] The need for the 10Q Report is based on the fact that cardiovascular disease (CVD) is the most common cause of death in women in the USA; yet, despite important known sex differences about many features of CVD, features unique to or predominant in women are generally not addressed. The goal of 10Q is to raise awareness of the need for more research that will provide better guidance to clinicians in CVD prevention and treatment for women.

The questions addressed by 10Q are:

1. What factors influence or explain disparities in cardiovascular disease epidemiology and disease outcomes between men and women?
2. What are the best strategies to assess, modify, and prevent a woman's risk of heart disease?
3. What are the most accurate and effective approaches to assess and recognize chest pain and other symptoms suggesting coronary heart disease in women?
4. What role does a woman's reproductive history and menopausal hormone therapy play in the development of heart disease?
5. What are the risk factors for cardiovascular disorders associated with pregnancy and how are they best treated?
6. What is the best method for studying sex differences in vascular injury so that cardiovascular repair therapies may be improved?
7. What are the most effective treatments for diastolic heart failure (heart failure with preserved pumping function of the heart) in women?
8. Why are young women more likely than men to die after a heart attack or after surgical revascularization procedure?
9. How do psychosocial factors affect cardiovascular disease in women?
10. What biological variables are most influential in the development and clinical outcomes of heart disease and what can be done to reduce mortality rates in women?

In this *Editor's Roundtable*, these questions and their ramifications for both researchers and practitioners are discussed by the faculty.

Discussion

Dr. Friedewald: Why was 10Q written?

Dr. Wenger: Heart disease in women has been understudied, under-recognized, and undertreated, with consequent sub-optimal outcomes for women.[2] The 10Q Report addresses a research agenda, with a focus on information that likely would improve women's CVD outcomes. There are 2 sponsoring organizations for the 10Q Report: *WomenHeart*, which is a coalition for women with heart disease; and the *Society for Women's Health Research*, which is an advocacy, research, and educational group. They brought together a group of expert clinicians and scientists to generate a consensus recommendation that the answers to the 10 questions in 10Q would advance women's cardiovascular (CV) health. 10Q recommendations target clinician-scientists, research funders, government officials, policy makers, and, most importantly, women and their families.

Dr. Friedewald: Where did the idea for 10Q originate?

Dr. Wenger: 10Q originated with The Society for Women's Health Research and WomenHeart, with the first report published in 2006. The first 10Q, however, required a more contemporary focus, so the 2011 Update was prepared.

Dr. Hayes: We believed a new report could help frame and focus on priority research questions which, if answered, would be most likely to have the greatest impact on women's heart health. We also wanted to influence funding priorities from government agencies and other organizations.

Dr. Pepine: Why do you believe that the original enthusiasm for more emphasis on CVD research in women did not continue?

Dr. Wenger: When a concept is new, as were the National Institutes of Health (NIH) Heart Truth campaign and the American Heart Association Red Dress campaign, it generates great excitement. However, despite the plateau in activity, there has been greatly increased awareness about women and CVD due to these educational campaigns. The public now knows that heart disease is no longer only a man's disease, with awareness among women of heart disease as their major health problem increasing from 30% to >50% since the initial release of 10Q. Prior to the year 2000, the decline in CVD mortality in the USA was solely in men. Since 2000, there have been annual declines in CVD mortality in both sexes, and the decline is steeper in women than men. Nonetheless, women continue to have greater CVD mortality. One-half of this decline is attributable to improved therapy of established disease—which takes into

account some of the early elucidation of sex and gender differences—and the other one-half of the mortality decline is due to increased preventive therapy. But there is a new warning sign: the subset of women aged 35-54 years now has an increase in CVD mortality, likely due to an epidemic of increasing obesity, sedentary lifestyle, diabetes mellitus (DM), hypertension, and the metabolic syndrome.

Dr. Hayes: That is correct. Through 10Q's focus on gender and sex differences in people with CVD, several entirely new fields of study have developed.

Dr. Wenger: When we address differences beyond gender we find that women are not a homogeneous group; the women who have the worst outcomes are those of racial and ethnic minorities and those who are economically, socially, and educationally disadvantaged. These minorities have limited access to care. Thus, although we must highlight sex and gender differences, we must also specifically address these high at-risk subpopulations of women.

Dr. Roberts: The same male subpopulations are also at greater risk, are they not?

Dr. Pepine: Yes, they are.

Dr. Wenger: Perhaps a bit less, possibly because men more often have job-related health insurance. Many more women are either not employed, depend on their husbands' insurance, or work in part-time jobs that do not provide the insurance needed for access to health care.

Dr. Friedewald: Are women under-represented in clinical trials?

Dr. Wenger: Yes. Because of under-recruitment women in CV research studies, we cannot appropriately translate research into clinical care of women. Government, nonprofit agencies, and industry must pay greater attention to the recruitment of adequate numbers of women in trials, and insist on reports of sex-specific results. Food and Drug Administration (FDA) device studies grossly under-represent women; yet, such devices are marketed for women. Congress has instructed the FDA to require representation in studies for device licensure that should reflect the population using these devices, but these instructions are largely ignored.

Dr. Friedewald: Dr. Roberts, what differences do you see between male and female hearts at necropsy?

Dr. Roberts: Women's and men's hearts differ in several ways. In general, women's hearts are smaller and contain more subepicardial adipose tissue. Women's coronary arteries are smaller, which I believe has implications for coronary artery bypass grafting (CABG) and percutaneous transcatheter coronary angioplasty (PTCA). Women's aortic valves require less calcium to produce the same gradient in aortic valve stenosis than in men. Thus, there are clear differences. When I look at hearts at necropsy, I believe that I correctly guess the gender about 80% of the time.

Dr. Wenger: Dr. Roberts, as a journal editor, do you ask authors of submitted manuscripts to abide by the recommendation from the Institute of Medicine that they require the reporting of sex-based analyses in their publications?

Dr. Roberts: I do not ask authors to do that very often. A common problem is for a manuscript to be heavily weighted toward men—as much as 90% men. This can be viewed in a number of ways, but if you generalize, in a study with 90% men, the 10% women component is a contaminant. I would prefer that a study be limited to 90 men and get another study of 90 women; such data are much more meaningful.

Dr. Wenger: Or, even better, conduct the same study with 90 women and 90 men so there can be appropriate comparisons.

Dr. Hayes: That is at the heart of some of the recommendations in 10Q. Researchers need to design their protocols in advance to achieve robust data for gender-specific results. Journal editors can help greatly in getting investigators to pay more attention to these recommendations.

Dr. Pepine: Unfortunately, what happens is they reproduce a table showing the influence of their treatment or whatever they are studying by covariates, and submit only what is mandated by the editor. They show no interaction relative to sex, and they conclude that treatment strategy X is not influenced by sex, even when inappropriate, because there are too few women in the study to reach meaningful conclusions.

Dr. Wenger: The National Institutes of Health guidelines for clinical trials define the appropriate representation of women and of minorities, but it is more expensive to enroll women and aged patients in clinical trials than to enroll middle-aged men. It is important for investigators to design strategies that minimize barriers to enrollment. Also, any trials with upper age restrictions limit women's participation in trials—particularly for coronary artery disease (CAD)—that use certain symptoms characteristic of the male population as entry criteria, will have an underrepresentation of women.

Dr. Roberts: Why is it more expensive to enroll women in trials than men?

Dr. Wenger: Study populations typically must come to the researcher, and fewer women drive, so they depend on other means for transportation. Many women are also caretakers of children, of grandchildren, and other family members, so other arrangements have to be made for women to participate. However, having conducted trials over the decades with sizable numbers of women, I have found that recruiting women, although challenging, is doable. The Society for Women's Health Research has had a program called "Some Things Only a Woman Can Do," citing that to obtain information on health outcomes for women, women must be in the trials. The women whom I have enrolled in clinical trials at Emory frequently told me that they want to help obtain the same types of disease information for their daughters and granddaughters that are already available for their sons and grandsons.

Dr. Hayes: Altruism is a powerful motivator for women's participation in research. Another barrier to enrolling women into CVD clinical trials, despite Go Red and Heart Truth education campaigns, is that women have not embraced heart disease as the number 1 woman's health issue that it clearly is. Women are underrepresented in CVD trials, but will stand in line for a hormone or breast cancer prevention trial. Women must "own" heart disease for us to make progress.

Dr. Friedewald: Women are traditionally the caretakers of family health, so once they understand the magnitude of the problem in women, it is logical for them to want to participate.

Dr. Pepine: There are some CV trials where women are recruited in appropriate numbers, including studies of hypertension, obesity, diabetes mellitus, and angina pectoris.

A particularly difficult research area for recruiting women is heart failure (HF) with left ventricular systolic dysfunction, mainly because women tend to preserve their myocardial contractile function.

Dr. Hayes: So they do not meet ejection fraction criteria.

Dr. Pepine: That is correct, and the reason is unknown. Perhaps this is related, in part, to increased fat around the heart, which Bill mentioned earlier. Adipocytes are a rich source of cytokines, hormones, and growth factors, which may have both local and central effects that may help preserve cardiomyocyte contractile function. Left ventricular diastolic dysfunction studies, however, are overwhelmed with women, who are so disabled by symptoms that they are ready to participate in trials in hopes of getting better relief.

Dr. Wenger: We still lack any evidence-based information about how to best treat diastolic HF. Everyone has a favorite drug, everyone has a favorite approach, but none are scientifically documented or compared for diastolic HF.

Dr. Roberts: With more and more women practicing medicine, surely this problem of lack of attention to women will improve.

Dr. Pepine: That is true only if the axiom is true that men do not pay attention to women, and women pay more attention to women's diseases. I am not sure that is true, either. Most of the gynecologists in this country are men.

Dr. Roberts: Yes, but that is changing.

Dr. Pepine: I agree that this is changing but I am concerned that this may not solve the problem of getting more women into clinical trials. In Russia and in the United Kingdom >70% of physicians are women, yet these countries also have difficulty studying CVD in women.

Dr. Wenger: The few studies that have examined provider gender differences have not seen changes in referral, management, or guideline-based therapy. Rather, it is much more the character of the physician, so our main challenge is the translation of knowledge from the cardiology community to primary care physicians. The Australian medical community is paying a huge amount of attention to coronary disease in primary care, especially with regard to women. In the CADENCE (Coronary Artery Disease in General Practice) Study in Australia, women appear to have more episodes of angina and more severe angina, causing more impaired life quality and physical activity, and women's angina is more often precipitated by emotional stress than by physical activity.[3]

Dr. Friedewald: What factors influence or explain disparities between men and women in CVD epidemiology and disease outcomes?

Dr. Hayes: Understanding what causes the persistence of disparities in outcomes, care, and access prompts several overarching questions. How does sex-based biology influence outcomes? Is there a difference in care or access? Is it a disparity, i.e., are we not applying what we know adequately to women? We must look far beyond gonadal sex differences. Women experience many different exposures to risk and differential experiences of related conditions that may help explain this. For example, hormonal fluxes between puberty, pregnancy, and menopause have huge effects on the vascular system. This is well illustrated by pregnancy and the attendant neovascularization with the uterus going from fist-sized, to carrying a baby, and then returning to its previous size. Some studies have shown that women may actually respond better to stem cells and other vascular promoters. Women are more likely than men to have vasospastic, autoimmune, and inflammatory conditions. They also have pregnancy-specific conditions such as peripartum cardiomyopathy. Such conditions may explain some of the sex and gender differences in CVD.

Dr. Friedewald: If you remove hormonal effects, is there still a difference in CVD between men and women?

Dr. Hayes: Yes, because hormonal differences do not entirely account for women's having more migraine headaches, autoimmune diseases, and vasospastic conditions. We prescribe hormones for women with these disorders.

Dr. Roberts: But there are also certain advantages for the female gender. In males, serum cholesterol levels start rising at puberty, but women's cholesterol stays down until menopause. After menopause, however, cholesterol rapidly rises to levels of men.

Dr. Hayes: Blood pressure trends are similar. I agree that women have some advantages. On average, women live longer than men, and they get atherosclerotic CVD 10 years later than men.

Dr. Roberts: That was not always true. In 1900, men and women had about the same lifespan.

Dr. Wenger: The basic question is whether the differences are due to biology or bias. Much of it, I believe, is a combination. A difference is not a disparity, so we must be careful about how we use these terms, as disparity has a negative connotation.

Dr. Hayes: A "difference" is neutral. A "disparity" is when a "difference" leads to a poorer outcome. The other important words often misused are "sex" and "gender." Sex does not equal gender. Sex is biological, and a lot of our discussion has been about sex differences. Gender, however, includes the psychosocial behavioral part of being a man or a woman, and that is where depression, lifestyle, personal priorities, and other entities enter the discussion.

Dr. Wenger: Every journal has its style preferences for these terms, and many change "sex" to "gender." When research involves cells in a petri dish, it is about sex. Unfortunately, most cells in a petri dish are male, and even when female cells are used, there is very little discernible information provided as to hormonal influences, age, cell source etc. So this is not just an issue for the clinician. It is also critical for the basic scientist to define the sex of the cells that are being used in experiments.[4]

Dr. Hayes: The more we learn about the differences between men and women, the more we realize that assumptions about the efficacy of a drug prescribed for a man may be different from that in a woman. That is where understanding the biology of these gender differences is important in preventing provider-related disparity.

Dr. Wenger: Women comprise one-half of the population. Government regulations state that they must be studied, but these regulations are not enforced, either for drug or device studies.

Dr. Friedewald: I do not recall different cautions for men and women in package inserts.

Dr. Hayes: That is correct. We went for years with women having disproportionately more cough secondary to angiotensin coenzyme (ACE) inhibitors for hypertension,

because this was not analyzed during early trials. Now we know that ACE inhibitor-related cough occurs 2-3 times more often in women than in men. Another example is the many women who died from *Torsades de Pointes* before we recognized their disproportionate risk from taking drugs that prolong the QT interval.

Dr. Friedewald: Do you approach women differently from men in risk factor control?

Dr. Pepine: No, not in evaluation of traditional risk factors. Although women are relatively protected from hypertension and hypercholesterolemia until their middle to older ages, systolic blood pressure and low-density lipoprotein cholesterol (LDL-C) continue to rise throughout their lifetime without any particular age threshold. When risk factors appear, the treatment strategies are the same for both genders. But non-traditional risk factors that are unique to women should be sought.

Dr. Wenger: The answer hinges on whether you are addressing short-term risk, 10-year risk—such as the Framingham risk score—or lifetime risk. Prevention must be for the long term. Risk factors, however, do not impact men and women to the same degree. Cigarette smoking, for example, conveys a 25% greater risk for women than for men in every study and in all of the meta-analyses of CAD. Diabetes mellitus also selectively disadvantages women. Far more women than men have diabetes at the time of an initial myocardial infarction, independent of age at the time of infarction. Thus, identifying diabetes in women is particularly important because they have greater risk and because patients with diabetes have lower goal thresholds for other risk markers, such as blood pressure and serum lipids. Another important feature is cultural, because prevention is not perceived as important in many non-white ethnicities. In some cultures obesity is viewed as a sign of success rather than as a sign of illness, and physical activity may be regarded as something appropriate for children and not for sensible adults. Education is a key component of risk reduction in racial and ethnic minority communities.

Dr. Hayes: Therein is the real opportunity, however, because women are more often than men the decision makers, and often they are community leaders, particularly in terms of health and well-being of their families. Thus, if you can educate and promote health in women, the effort reaps many times the benefit in terms of the impact on both their own families and their communities.

Dr. Pepine: The main problem is that risk reduction has little effect in the short term. People want instant gratification, and we cannot show short-term results, except, perhaps, for systolic blood pressure reduction and stroke.

Dr. Roberts: I believe that physicians should stress to both men and women the importance of numbers—cholesterol and blood pressure—and throwing away the cigarettes, slimming the waist, and for women to have these numbers in their purses, and men in their wallets. I would also stress the importance of proper exercise, especially the "push-aways" from the table.

Dr. Wenger: Physicians generally prescribe more extensive and intensive CV preventive interventions for men than women.

Dr. Hayes: This bias is compounded by the fact that preventive medications have not been tested enough in women to give us confidence that they are effective.

Dr. Wenger: And they may be correct. The Physicians' Health Study data on aspirin efficacy in men were initially available in the 1990s,[5] but it was not until many years later that it was found that although aspirin decreased myocardial infarction but not stroke risk in men, and the reverse was true in women. Again, to learn about preventive data for women, you have to study women.

Dr. Hayes: Like Dr. Roberts, I am a big proponent of "know your numbers," and believe those numbers should also be in our smartphones.

Dr. Wenger: We will have to learn how to use the smartphone not only in clinical practice, but in research studies as well, because this may help decrease the cost of research and increase accessibility. We have not paid enough attention to emerging technologies in research. They have much more to offer than only social media applications.

Dr. Pepine: I agree. Earlier apps transmitted pictures of electrocardiograms for ST-elevation myocardial infarction (STEMI) diagnosis in the field. Now patients can capture their electrocardiogram by holding a smartphone and simply touching the sensors to 1 finger of each hand. Other apps provide a more complete electrocardiogram by placing the device on the anterior chest wall.

Dr. Hayes: There is research to support using text messages to support health and healthy behaviors. We increasingly will cross the digital divide and figure out ways that we can interface with our patients, both for research and in clinical practice.

Dr. Friedewald: Let's focus now on angina pectoris in women.

Dr. Wenger: Too often physicians ascribe chest pain in women—especially in younger women—to a psychological, gastrointestinal, or musculoskeletal origin, with cardiac causes far down the list of possibilities. Women help reinforce this diagnostic prioritization with their descriptors. For example, a man with chest pain might tell a physician, "I'm having a heart attack." A woman, however, is more likely to say, "I'm having indigestion." The physician is more inclined to follow him or her down their suggested path. Women must realize that they are vulnerable to heart disease. More women than men with chest pain are sent home from emergency rooms and subsequently appear in the coronary care unit later after a missed acute myocardial infarction. An important reason for such missed diagnoses is that chest pain characteristics correlate better with obstructive CAD in men than in women. Women are more complicated, having myocardial ischemia due to both obstructive disease of the epicardial coronary arteries and to microvascular disease. Women with chest pain and/or evidence of myocardial ischemia in a variety of tests, and who are not treated for myocardial ischemia, have increased morbidity and mortality.

Dr. Hayes: A big knowledge gap is a full characterization of the symptoms of myocardial ischemia in women. Head-to-head comparative studies of chest pain in women and men are needed. We do know that both men and women—60-80% of study subjects, depending on the study—have some type of chest symptom, which is not always described as "pain," as the presenting symptom of CAD. This means that as many as 40% of patients have symptoms other than chest discomfort as their primary presenting symptom of CAD, including both angina pectoris and acute myocardial infarction (AMI).

Dr. Pepine: This is a complex topic that I have been studying since 1996, beginning with looking at symptoms in women with obstructive CAD. Our main finding was that the only descriptor predictive of obstructive CAD, microvascular disease, extent of disease, or any other measure, was discomfort above the waist. A recent survey of data from the National Registry of Myocardial Infarction, however, found no evidence that women present with more or less unstable angina pectoris or atypical symptoms than men.[6] This surprised us because our *a priori* hypothesis was that women's symptoms were often atypical, but this study found that unstable and atypical angina pectoris are directly related to age. The main problem with studying previous publications was the lack of uniformity in capturing data from different studies. Thus, we still believe that women have different symptoms upon initial presentation with CAD, but this has not been proven. Clearly, however, gender differences in chest pain disappear with increasing age.

Dr. Wenger: The National Myocardial Infarction Registry data showed that about 20% of men and >30% of women had no chest pain upon initial presentation with CAD. The BARI 2D study[7] found an equal prevalence in women and men of angina equivalents and of true Heberden's-type angina, so symptoms are not always typical. I believe that men are probably "noun people" and women are "adjective and adverb people." Thus, a man says, "I'm having chest pain" and a woman says, "I'm having headache, weakness, dizziness, nausea, back pain, arm pain, shoulder pain," and her chest pain becomes lost in such recitation. We teach our students at Emory that any symptom from the umbilicus to the jaw can be caused by myocardial ischemia.

Dr. Hayes: This is a major challenge. Women have more symptoms—*period*—regardless whether in the primary care setting or presenting with an acute myocardial infarction in the emergency department. Women also perceive pain differently from men, and much earlier. Another factor that underscores these disparities is that women get less CVD care, despite greater access. They visit physicians far more than men do, whether for obstetric, gynecologic, or preventative services. There are also differences in pain perception, with women perceiving pain much earlier.

Dr. Roberts: Women have pain every month for many years and have babies. Labor is real pain, which men cannot appreciate.

Dr. Wenger: Judged by comparable coronary computed tomography and other measures, women rate their angina as being more severe and much more likely to be stabbing or throbbing, and they are much more likely to limit their activity as a result of these symptoms.

Dr. Pepine: Women's pain thresholds are lower, particularly if they have coronary heart disease, and this applies to both obstructive and microvascular CAD.

Dr. Wenger: Clinical trials for acute coronary syndrome involving patients presenting with symptoms severe enough for hospitalization find that more women than men have unstable angina pectoris in the acute coronary syndrome population that does not have STEMIs. Fewer women than men have STEMI, but in the unstable angina pectoris groups, women's in-hospital prognoses are better. At 6-12 months, however, in these patients not having positive biomarkers and often not having coronary angiography, preventive intervention is neglected. We must pay more attention to women hospitalized for unstable angina pectoris because eventually they have the same adverse outcomes.

Dr. Hayes: Women are more challenging to diagnose for all the reasons we have discussed. Cardiologists, however, are coming under increasing scrutiny for ordering imaging and other tests. We need more research guiding us to order tests with the lowest risk, highest accuracy, and best predictive value. The Women's Ischemia Syndrome Evaluation (WISE) study[8] took us a long way toward helping us with that, but there is still considerable uncertainty on how best to assess both risk and symptoms.

Dr. Wenger: New guidelines recommend the treadmill stress test for women and men with a normal resting electrocardiogram, provided they can exercise to adequate intensity. The treadmills stress test is a relatively inexpensive test and a good first step in evaluation.

Dr. Pepine: A significant problem with the treadmill stress test is the concept of the "false-positive" test. I recently saw a 40 year-old woman with classic angina pectoris and 3 mm ST depression on the treadmill stress test, which was wrongly dismissed as a so-called "false-positive."

Dr. Hayes: That requires re-education of our own colleagues.

Dr. Wenger: "False positive" is a term that needs erasure from the vocabulary.

Myocardial ischemia kills, whether it is related to obstructive disease or to microvascular disease.

Dr. Hayes: Another phrase I want to get rid of is "atypical symptoms," because it is so often applied to women, with male symptoms being the "reference value." Rather, let's say "non-chest pain" or "other" symptoms.

Dr. Friedewald: What is the role of the reproductive history and hormone replacement therapy (HRT) in heart disease?

Dr. Wenger: We must begin the discussion by excluding countries other than the USA, because the USA was the epicenter of menopausal HRT as a "solution" to all problems of menopause. HRT was not overused elsewhere as much as in the USA. HRT was once considered the solution to all of a woman's symptoms, and it falsely eliminated worry about disease, because it was advertised to keep women young forever. HRT was probably the greatest experiment without informed consent that was ever conducted in women, but after evidence-based medicine appeared, the use of HRT in clinical practice changed radically. The HERS (Heart and Estrogen/progestin Replacement Study) trial[9] showed that in women with CAD, HRT did not provide benefit and was associated with increased risk. The hormone trials in the Women's Health Initiative,[8] which studied unopposed estrogen in women with hysterectomy and estrogen-progestin in women with an intact uterus, also did not show benefit. Although there may be subsets of women who benefit from HRT—and the last chapter certainly has not been written on the topic—both the trial data and our clinical practice guidelines and guidance from the FDA indicate that HRT should not be used for primary or secondary prevention of CAD. A large number of HRT preparations are currently in use, particularly the transdermal preparations, but they have never been studied for CAD prevention. There is an extensive area of bio-identical hormones, but the FDA has

removed them from the lexicon because they do not allow companies to advertise bio-identical hormones. Relief of menopausal symptoms, however, is not part of this discussion.

Dr. Pepine: A major dilemma is our advice to the many women who took hormones prior to menopause, because there is evidence that premenopausal HRT protects against CAD. Thus, women now want to know if it is safe to *restart* HRT, and we do not have any data to help answer the question.

Dr. Hayes: There were many people who thought the WHI results ended the discussion about HRT, but that did not occur for many reasons. For example, few perimenopausal women were included in WHI, leaving a real void in our ability to counsel young women about HRT risks and benefits. They are the ones with vasomotor symptoms who need treatment advice and also have the potential to experience both the greatest risks and benefits from HRT use. The results of HRT studies in perimenopausal women such as KEEPS (Kronos Early Estrogen Prevention Study) will be very helpful, but are unlikely to provide definitive guidance to physicians and women making HRT decisions.[10,11]

Dr. Pepine: This is a very important question in daily practice. Women do not want menopausal symptoms, but they are afraid of HRT.

Dr. Hayes: This is a quality of life issue. We know more about estrogen than we know about many drugs that we prescribe much more often.

Dr. Pepine: Gynecologists do not want to prescribe Premarin, which is the drug women liked, and the drug about which we have the most long-term data. The newer drugs, which the gynecologists prefer, do not have similar long-term data. It is difficult to know what to advise.

Dr. Wenger: We are now seeing a different population of women than the population studied in HERS, because many contemporary women were on oral contraceptives and they just transitioned to HRT. Thus, they were never truly hormone-free. I do not believe that a meaningful trial can be conducted today because most women have made up their mind: either they want to be symptom-free and will take HRT, or they are afraid of HRT and will not take it. It was easy to enroll women in hormone trials in the past, but today it is not. This is a very important clinical problem that needs evidence-based data, which we do not have.

Another issue involves women who have undergone CABG and who were on prior hormone therapy and tolerating it well. Appropriately, surgeons stop the hormone therapy prior to CABG because of the thromboembolic risk. After CABG these women return to me in clinic and ask to be restarted on HRT, because their hot flashes are worse than their angina was. The FDA directive is that the lowest doses for the shortest possible time should be prescribed. CAD patients are now better treated for risk factors than in prior years, so they are a different population than studied before.

Dr. Friedewald: Let's discuss the risk factors for CVD associated with pregnancy.

Dr. Hayes: Some events during pregnancy have long-term CV effects, or at least signal potential long-term risk. Pregnancy is a woman's first cardiometabolic stress test. If she fails this test by becoming hypertensive or diabetic during pregnancy, this indicates less cardiometabolic reserve, and is an early risk indicator. Preeclampsia, hypertension, and diabetes mellitus of pregnancy are the best examples. Thus, a history of these events during a prior pregnancy is very important in assessing CVD risk.

Pregnancy-related cardiometabolic abnormalities also have lifetime implications for the health of the offspring. Children of women who develop diabetes mellitus during pregnancy are more likely to be obese and have elevated serum cholesterol levels in childhood. Finally, there are the less common complications of pregnancy, such as peripartum cardiomyopathy, coronary artery dissection, and either diagnosed or undiagnosed congenital heart disease or valvular heart disease that is unmasked or made worse during pregnancy. All of these conditions associated with pregnancy are greatly understudied, largely because pregnant women were excluded from clinical trials because of concerns about harm. They are important because they disproportionately affect young women, but also impact women in their later years and their offspring.

Dr. Friedewald: Does diabetes mellitus control during pregnancy help prevent adverse effects on the child?

Dr. Hayes: Our only current evidence is epidemiological, based on a database of multiple pregnancies, so we do not have an answer. Very tight control of diabetes mellitus in pregnancy, however, is not recommended, largely because hypoglycemic episodes can harm the unborn baby.

Dr. Wenger: Preeclampsia and CAD share a great deal of common pathophysiology. Prior to a pre-eclamptic pregnancy, women tend to have a higher CVD risk profile—i.e., hypertension or prehypertension, diabetes mellitus or prediabetes, and hyperlipidemia—so it is a "chicken and egg" issue. The most important aspect is that gynecologists serve as primary care physicians for many women, and they are very prevention-oriented, so they are in a particularly good position to treat risk factors for CVD in their patients.

Dr. Friedewald: What do we know about the long-term effects of peripartum cardiomyopathy?

Dr. Hayes: Peripartum cardiomyopathy is a type of cardiomyopathy diagnosed in the last trimester of pregnancy or in early postpartum. What we know is mostly from studies of African-Americans and Africans, in whom the prevalence is higher than in whites, so there may be a genetic or environmental predilection. Some patients develop progressive left ventricular dysfunction requiring a cardiac transplant or ventricular assist device, and many recover completely or almost completely. We do not know about long-term outcomes, another area in need of research. Another possible marker for future CVD in the mother is when her newborn baby is labeled "small for dates." These women may lack the robust neovascularization reserve needed to build new blood vessels in the placenta or for vascular repair later in life.

Dr. Wenger: Following peripartum cardiomyopathy—even with apparent recovery of systolic function as measured by ejection fraction—there remains a measurable decrease in cardiac reserve. Subsequent pregnancies are sometimes characterized by recurring peripartum cardiomyopathy and worse outcomes, but some women do well. We have no predictive markers for women who will sustain another pregnancy safely and those who will not.

Dr. Friedewald: What is the best method for studying sex differences so that CVD therapies may be improved?

Dr. Pepine: We have no answer at this time. Which biomarkers are best is unknown and is a ripe area for research. The current focus is on the bone marrow, because the bone marrow is under sympathetic control and controls the egress of stem cells, which ultimately maintain and repair the vasculature and perhaps the heart as well. Studies of the Chernobyl incident suggest that about 40% of cardiomyocytes are replaced in a lifetime.

Dr. Friedewald: Stem cell injection for generation of new cardiomyocytes could have great implications in the future treatment of heart failure.

Dr. Pepine: And the implications may be even bigger for women. Research by Doris Taylor's group suggests that there are some sex differences in the body's ability to use these repairer cells.[12] This work is early, however, and has not been replicated. It could directly pertain to much of what we have discussed today, including pregnancy, pregnancy-related myopathy, pregnancy-related coronary dissection, aortic dissection, and even the hypertension of pregnancy.

Dr. Friedewald: What do we know about the treatment of women with angina pectoris due to microvascular disease?

Dr. Pepine: We can use the WISE cohort as a model where we studied about 1000 consecutive women with signs and symptoms of coronary heart disease.[8] The entry-level step was referral for a coronary angiogram; thus, their signs and symptoms had to be severe enough to justify coronary angiography. In that cohort, two-thirds of the women did not have obstructive CAD, defined as a lesion with $\geq$50% intraluminal diameter obstruction, interpreted by a core lab. The other one-third of women had "garden-variety" coronary arterial plaque obstruction. Women with obstructive CAD did not do well in follow-up, which was not a surprise and consistent with many other studies. What was surprising, however, is that the women with so-called "normal" coronary angiograms—or nonobstructive CAD—had a substantial adverse event rate over time (i.e., death, AMI, stroke, or hospitalization for angina pectoris or HF). For example, their 5-year follow-up death/AMI rate was >13% (2.6% per year), and by 9 years 20% had died. Among these, 75% had had coronary angiograms interpreted as "normal coronary arteries."

Dr. Roberts: Did they have repeat coronary angiograms?

Dr. Pepine: No. It is striking that all-cause mortality is becoming quite prominent in those women, which tells us that nonobstructive lesions—and I believe this is true in men as well as in women—are linked with some type of vascular disorder that results in myocardial ischemia and adverse outcomes. The question is whether a nonobstructive plaque is a site for fissures, erosions, and ruptures, which provides a nidus for thrombus formation that leads to these events. Alternatively, it could lead to a more distal abnormality, within the microvasculature, or even to sudden arrhythmic death. In WISE, more than half of deaths were "sudden." Another interesting hypothesis is that a microvascular disorder *precedes* obstructive plaque formation upstream in the larger arteries. This could be the result of limiting the ability of the epicardial artery to undergo its normal adaptive dilator and metabolic responses to changes in flow because flow is restricted downstream by microvascular dysfunction. Perhaps microvascular disease in mid-life promotes the development of obstructive plaque that is seen with aging.

An additional question of clinical relevance concerns the two-thirds of women who had nonobstructive plaque on coronary angiography; among these, one-third to one-half of patients were interpreted as having "normal coronary arteries." These women have increased adverse outcomes the same as those with obstructive lesions. Using intravascular ultrasound we found that 80% of the study patients with "normal coronaries" had plaque in a sampling of only a small part (10 mm) of the proximal left anterior descending coronary artery. This finding led to a halt in our interpreting angiograms as "normal," because that determination cannot be made from an angiogram.

Dr. Roberts: It is a lumenogram.

Dr. Pepine: Yes, that is correct.

Dr. Wenger: Thus, the unanswered question is how to treat patients with symptoms of myocardial ischemia who have no demonstrable obstruction in the epicardial coronary arteries. Different centers have different answers. In my practice, I treat these women as if they had a coronary event, with careful attention to precise control of risk factors and prescribing every antianginal drug at my disposal to see if I can decrease or eliminate their ischemic symptoms.

Dr. Pepine: We are now conducting a randomized, double-blind sub-study (called R-WISE and funded by Gilead) in which we use ranolazine as the primary treatment for these women. There is also a preliminary report from Noel Bairey Merz's group suggesting that ranolazine is beneficial in ameliorating angina as well as restoring perfusion abnormalities identified on perfusion magnetic resonance imaging.[13]

Dr. Friedewald: Is there a difference in LDL-C levels in patients with obstructive CAD compared to patients with nonobstructive CAD?

Dr. Pepine: No.

Dr. Roberts: What is the average LDL-C in your study?

Dr. Pepine: The average LDL-C is elevated. Thus, it appears likely that as the LDL-C rises, the earliest abnormality is at the microvascular level, which is probably both a combination of endothelial dysfunction and vascular smooth muscle dysfunction.

Dr. Hayes: I view nonobstructive CAD and obstructive CAD as different phenotypes of the same disease process, including the role of virtually all CVD risk factors.

Dr. Pepine: My view is the same: they are a continuum of the same vascular disease. Nonobstructive CAD is not a new disease. Microvascular dysfunction in the absence of coronary atherosclerosis has long been associated with hypertension, hypercholesterolemia, and DM. Virtually all of the major risk factors have been associated with microvascular dysfunction in both experimental models and in young people without obstructive CAD.

Dr. Roberts: Intramural coronary arteries are usually anatomically normal except, in my experience, in patients with amyloidosis, hypertrophic cardiomyopathy, and 3 neurological diseases—Friedreich's ataxia, progressive muscular dystrophy, and myotonia congenita. And their walls are relatively thin, which makes it difficult for me to imagine their constricting very much.

Dr. Wenger: We know that all of the major risk factors for CAD impart oxidative stress, so the basic problem is an abnormal endothelium. The endothelium in these small vessels may be more the culprit than vasoconstriction. Furthermore, it is likely that loss of the ability of the endothelium to dilate is the problem resulting from oxidative stress.

Dr. Pepine: That is important. The vessel bed probably does not get smaller under basal conditions; rather, it fails to dilate to its maximal capacity with stressors. That robs the upstream vessel's ability to have large changes in blood flow, so that the normal mechanism for flow-mediated dilation is not available.

Dr. Friedewald: What is the most effective treatment for HF with preserved ejection fraction (HFpEF) in women?

Dr. Hayes: One of the challenges in treating HFpEF is the absence of proven effective therapy. There is no specific drug that helps the myocardium to relax. And while this is the disproportionate manifestation of HF in women, clinical trials have not been designed based on HF symptoms. Rather, in many HF trials, inclusion criteria were based on a low ejection fraction, which eliminated, by definition, this large group of patients. Population-based studies of patients with HFpEF have shown that morbidity and mortality are similar to HF patients with reduced ejection fraction.[14] Both women and men with HFpEF are understudied.

Dr. Pepine: The median left ventricular end-diastolic pressure (LVEDP) at rest in the WISE enrollees at baseline was 16 mm Hg, which is well above the normal limit of 12 mm Hg, and they had normal ejection fractions. It is known that with effort, in patients with diastolic dysfunction, the LVEDP rises abruptly so these resting pressures markedly underestimate the proportion of women with diastolic dysfunction. This means that a large pressure burden is transmitted to the left atrium and, ultimately, to the lungs. The pulmonary veins are inside a bronchiole-arteriole venous sheath, and as the veins distend they compress the airways. Pulmonary venous congestion also causes the lungs to stiffen. The patient senses these changes as dyspnea, which occurs mainly with effort, not while reclining.

Dr. Wenger: There are probably 2 major features that contribute to HFpEF: first, long-standing hypertension with a resultant thick left ventricular wall and small left ventricular cavity; and second, aging. The first feature causes the heart to lose the ability to relax. Some of our therapy also contributes to the problem because early on, patients are dyspneic due to florid pulmonary edema, which is treated with diuretics. The main issue, however, is not volume overload; rather, it is a fluid maldistribution such that normal intravascular fluid volume is redistributed into the lung. Certainly, diuretics are appropriate treatment early in the course of HF, but extensive diuresis worsens the symptoms because the small left ventricular cavity needs volume to maintain cardiac output. As a result, continuing to treat with diuretics after the initial stages of HF is likely to worsen the dyspnea. Once HFpEF is severe enough to require hospitalization, mortality is comparable to HF with reduced ejection fraction. A drug that perhaps should be studied for treating patients with HFpEF is ranolazine. The late inward sodium current, with the sodium-calcium exchanger and myocyte calcium overload, causes myocardial stiffness in HF. Thus, if you could interfere with the late sodium current, there will be an enhancement of the ability of the heart to relax, allowing the ventricle to better fill, thereby increasing cardiac output. With ventricular relaxation, there is also less mechanical compression of the microvasculature. The hoped-for effect of ranolazine would be to improve the oxygen supply and decrease the demand, but this needs to be studied before the drug is considered for this indication.

Dr. Pepine: Diuretics also worsen the metabolic status, promoting dysglycemia. Ranolazine, on the other hand, does just the opposite, improving glycemic control,[15] which is another reason for further study of ranolazine in patients with diabetes and prediabetes, most of whom are women, who are at high risk for or have HFpEF. Ranolazine does not carry this indication at this time.

Dr. Friedewald: What is the role of hypertension in women with HFpEF?

Dr. Hayes: One reason that women disproportionately develop HFpEF is under-treatment of hypertension. One thing that I have found particularly useful in assessing blood pressure is the treadmill stress test. Some persons with only minor diastolic dysfunction, but not overt HF, have marked blood pressure elevations with exercise, starting from as low as 120 mm Hg systolic at rest to $>$200 mm Hg within 2-3 minutes of exercise, with the symptom of dyspnea reproduced at that time. I am more aggressive in treating the BP in such patients. Sometimes such persons are written off as being simply deconditioned.

Dr. Wenger: Exercise is an important part of the management of these patients, because deconditioning is an important component of elevated BP response. I tell my patients to walk for 5 minutes and when they get breathless, to sit down and rest for 5 minutes, then to repeat the sequence. Some of the hypertensive response can be modified with regular exercise.

Dr. Roberts: Do you instruct patients to take antihypertensive drugs in the morning or at night?

Dr. Wenger: Patients whose hypertension is difficult to control often require multiple medications more than once per day. When possible, I recommend BP medications in the morning. For patients with secondary hypotension, I recommend them at night. Ambulatory BP recorders have been very helpful in deciding which drugs to prescribe and when to take them, because patient responses to drugs widely differ. Even though beta-blockers are not great antihypertensive drugs, among all classes of antihypertensive agents, they are alone in not causing orthostasis. Thus, for hypertensive patients with prominent orthostasis, beta-blockers are particularly important.

Dr. Hayes: Often, there is a hyperdynamic component of hypertension, with a rapid heart rate and reduced left ventricular filling time, which are counteracted by beta-blockers. Whether beta-blockers improve long-term outcomes, however, is unknown.

Dr. Pepine: Patients with hypertension and a hyperdynamic component are typically young. Another consideration is the effect of hypertension on the coronary microcirculation. Coronary microvascular dysfunction is well-documented among patients with hypertension and is another mechanism, along with obstructive CAD, for myocardial ischemia, which further promotes left ventricular dysfunction.

Dr. Friedewald: Why are young women more likely than men to die after AMIs and after coronary revascularization procedures?

Dr. Wenger: We do not know. Typically, we think of the young patient with an AMI as having less risk because of lesser comorbidity and lesser polypharmacy than the older patient. Young women with AMI and after CABG very often have disproportionate smoking histories compared to men. Smoking, however, does not entirely account for the outcome disparity. Heart size also may be important. Women have thicker ventricles and smaller intracavitary sizes, so they are particularly sensitive to volume and pressure shifts during surgery and percutaneous coronary intervention.

Dr. Hayes: Young women are also more likely to have inflammatory, vasospastic, and autoimmune disorders that may contribute to this difference from men. The outcome difference between men and women, however, disappears by about age 70 years, so perhaps there is something unique about the biology of CAD at younger ages.

Dr. Roberts: The size of the coronary arteries in women is definitely smaller than in men, and the smaller the artery, the more difficult the surgical anastomosis. They also rupture more readily. The only ruptures of coronary arteries associated with coronary angioplasty that I have seen have all been in women with small, calcified arteries.

Dr. Pepine: A given plaque volume will result in more obstruction in a smaller coronary artery, further disadvantaging women with CAD.

Dr. Friedewald: What about higher mortality in nonvascular-type cardiac surgery, particularly cardiac valve surgery?

Dr. Wenger: In all surgical settings women have increased bleeding risk, which contributes to mortality. Bleeding imparts oxidative stress. Why women with various types of presentation of CAD—whether in the catheterization laboratory, at cardiac surgery, even during hospitalization—have increased bleeding risk, is unknown.

Dr. Hayes: Antithrombotic dosing in older, smaller women may be a factor. We may be overdosing many of these women.[16]

Dr. Friedewald: Are women with CVD more likely to have comorbid conditions that may account for some of the disparity?

Dr. Hayes: Women with CVD in comparable age groups with men are more likely to have arthritis, restricted mobility, and other factors such as deconditioning that at least indirectly interfere with recovery.

Dr. Pepine: Systemic lupus erythematosus, which is an important cause of arthritis in young women, is linked with CAD.[17]

Dr. Wenger: Women with angina—more often than men—have hypertension, hyperlipidemia, DM, and obesity, all part of the CAD spectrum.

Dr. Friedewald: How do psychosocial factors affect CVD in women?

Dr. Hayes: Prior to puberty, boys and girls have the same rates of depression, but after puberty, the rates almost double for women; this difference persists for life. This is important for women because depression and anxiety are both associated with an increased risk of heart disease.[18] After onset of heart disease, the presence of depression portends a poorer outcome. This could be another reason why young women have worse outcomes after AMI. Another important factor is that women more often live in poverty and alone, are less insured, and have reduced access to medical care. Better understanding and addressing the social determinants of health that disproportionately affect women are vitally needed.

Dr. Wenger: Responses to anxiety and depression are lifestyle behaviors that relate to CAD risk. Anxiety and depression are often associated with overeating, underactivity, substance abuse, and overuse of alcohol. Childhood abuse may much more strongly influence women and their subsequent anxiety and depression, and the cycle of CAD.

Dr. Friedewald: Depression is also associated with increased cytokine levels, so there may be an inflammatory link to CAD.

Dr. Hayes: Post-traumatic stress disorder, especially among individuals returning from military service, and particularly women who have suffered an acute cardiac event, appear to increase risk for CAD as well.[19]

Dr. Wenger: There is a sizable body of psychosocial publications showing that social support systems are very important in improving outcomes after an acute coronary event, but, again, the research is virtually restricted to men. In social support networks, women more often *give* rather than *receive* support.

Dr. Roberts: From what you are saying, it appears that marriage is good for men but not for women as it relates to CAD risk!

Dr. Wenger: That is true. Framingham data support that notion.

Dr. Hayes: There are a few small studies that looked at cardiac rehabilitation programs tailored specifically for women,[20] structured to guide problem-solving for them. They show some promise by focusing on aspects that are particularly relevant to women by helping them make appropriate lifestyle changes and providing social support.

Dr. Wenger: Social support is a large part of what women want in cardiac rehabilitation programs, helping them to better cope with stress. The responses to anger and fear include increased heart rate, increased BP, and increased myocardial contractility, all of which cause increased myocardial oxygen demand and angina/ischemia. When physical activity stops, myocardial oxygen demand abruptly decreases. Response to fear and anger, however, are much more protracted, because they cannot be halted rapidly and angina may be more prolonged.

Dr. Pepine: In WISE, we found that women who got social support had fewer adverse events than those who did not.

Dr. Friedewald: What biomarkers are best predictors of heart disease?

Dr. Wenger: We have examined a huge number of biomarkers and imaging studies in both women and men. Few rise to the level of where they are more predictive or raise risk beyond that of traditional risk factors.[21] Many markers, however, have not been investigated, such as vascular reactivity and inflammatory markers. Genomics is another exciting area that remains to be explored.

Dr. Friedewald: Statins are equally effective in women and men, so if we reduce women's LDL-C

sufficiently—say, under 50 mg/dl—can we lessen our concern for other factors?

Dr. Wenger: Some lipid enthusiasts might take that position, and I am a lipid enthusiast, but I do not believe that cholesterol is the be-all and end-all answer to CAD prevention. Even when cholesterol is well-controlled according to standard guidelines, significant CAD residual risk persists. These are likely imparted by associated risk factors, including elevated BP, smoking, and physical inactivity. CAD is a multifactorial disease and requires a multifactorial approach.

Dr. Roberts: Yes, but most studies showing residual risk after cholesterol lowering last only 5 years. If cholesterol levels were lower for a longer period of time, there may be less residual risk.

Dr. Wenger: The challenge is that the patient who is adherent to one drug regimen is characteristically the patient who is also adherent to multiple regimens. We cannot lower only lipids and not pay any attention to BP.

Dr. Roberts: What percent of the population taking statins are women?

Dr. Wenger: We do not know, but statin data suggest that 40% of patients who fill an initial statin prescription are not taking the drug at the end of a year. Thus, while we know the number of prescriptions, we do not know the level of adherence.

Dr. Friedewald: Adherence is a major problem with all medications that do not provide immediate symptom relief.

Dr. Wenger: The usual patient with angina pectoris is prescribed multiple drugs, including, at a minimum, aspirin, dual antiplatelet agents particularly after percutaneous coronary intervention, a statin, a beta-blocker, and an ACE inhibitor. Many patients are also taking other BP medicines and drugs for DM. Often, patients are selective of what drugs they take each day, taking one drug one day and others on another day. They refill their prescriptions, but in variable intervals. This problem has generated discussions about the polypill.

Dr. Roberts: I like the concept of a polypill.

Dr. Wenger: Even with suboptimal doses of multiple medications in 1 pill, will patients do better over the course of a year? I believe that remains to be determined. Patients with HF more often take their medicines because they know that if they do not, they will be symptomatic the next day. People who are well, however, get bored and often do not adhere to their medications if there is no symptom to prompt them, so I agree that the potential for polypills should be addressed.

Dr. Friedewald: The other side of the equation of disparities between men and women is that men may be *over*-diagnosed and *over*-treated for CAD.

Dr. Hayes: This is an important point. In the early days when there were huge disparities between the numbers of coronary angiograms being done on women versus men, the question was often raised, "Are we not doing enough angiograms on women or are we doing too many on men?" Both answers are probably correct.

Dr. Wenger: I believe that some of the changes in health care reimbursement will be driven not by volume, but by quality. And using quality measures for reimbursement is potentially a way of returning control to the physician. Requirements for failure to meet appropriateness criteria for procedures will result in lower reimbursement. With more use of electronic records in test and procedure use outliers will be easier to detect. I strongly believe that appropriateness criteria will change the way we practice medicine. They will change the relationship between hospital business administrators and the medical staff because we, as members of the medical staff, can help gauge quality, and if quality guides reimbursement, quality of care should improve.

Dr. Hayes: Through the electronic medical record, sharing of records with patients allows them to become fully informed participants in diagnostic and treatment decisions. If I had diabetes mellitus and were having a coronary angiogram, I would hope to have had a pre-procedure discussion, in person or electronically, that included the fact that my outcome might be improved by having coronary artery bypass grafting instead of percutaneous coronary intervention if 3-vessel CAD were found. We sometimes do not fully involve patients in these important decisions, particularly in emergency settings or where the timing of a decision may be more a *physician* emergency than a true *medical* emergency. I have patients in my practice who have made decisions whether to undergo high-risk therapies based on quality of life. If I do not hear them myself, and only look at a guideline, I am not providing optimal care.

Dr. Roberts: Cardiology fellows use their iPads to view guidelines for everything.

Dr. Wenger: But remember: these are *guidelines*. That is what the term states, and the level of evidence in any guideline is very important. For me, the highlights of some of these guidelines are the class III recommendations—the "do not use" recommendations—which say a drug or procedure is not beneficial and may even be harmful. I believe the guideline "do not's" are improving care. I am enthusiastic about the class I recommendations because they have substantial evidence, but the reason for a class IIa and IIb means "here is where the evidence can be weighed," and obviously that will vary with many other patient factors, including comorbidities, multiplicity of medications, and patients' personal desires. All such factors are even more important at advanced age.

Dr. Roberts: How long did it take to write 10Q?

Dr. Hayes: It took about 18 months of multiple phone calls, e-mails, and many small-group meetings.

Dr. Wenger: Much of the 10Q Report was written electronically. Our authors spent an enormous amount of time generating this document, so they deserve the credit.

Dr. Friedewald: And they should be credited with an outstanding document, well worth the time for reading by every physician.

Dr. Roberts: I agree. Thank you.

1. The 10Q report. http://www.womenshealthresearch.org/site/DocServer/10Q_FINAL_REVISED_6_28_11.pdf?docID=7301. Accessed February 20, 2013.
2. Wenger NK. Women and heart disease: a century after Herrick. Understudied, underdiagnosed, and undertreated. *Circulation* 2012;126: 604−611.
3. Beltrame JF, Weekes AJ, Morgan C, Tavella R, Spertus JA. The prevalence of weekly angina among patients with chronic stable angina in primary care practices. The Coronary Artery Disease in General Practice (CADENCE) Study. *Arch Intern Med* 2009;169: 1491−1499.

4. Taylor KE, Vallejo-Giraldo C, Schaible NS, Zakeri R, Miller VM. Reporting of sex as a variable in cardiovascular studies using cultured cells. *Biol Sex Differ* 2011;2:11.
5. Physicians' health study. http://phs.bwh.harvard.edu/, Accessed February 25, 2013.
6. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CL, Frederick PD, Sopko G, Zheng Z- J, for the NRMI Investigators. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 2012;307: 813−822.
7. Krishnaswami A, Hardiso R, Nrsto RW, Sobel B, BARI 2D Investigators. Presentation in patients with angiographically documented coronary artery disease and type II diabetes mellitus (from the BARI 2D Clinical Trial). *Am J Cardiol* 2012;109:36−41.
8. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM, Zineh I, Kelsey SF, Arnsdorf MF, Black HR, Pepine CJ, Merz CNB. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 2009;169: 843−850.
9. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E, for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605−613.
10. Harman SM, Vittinghoff E, Brinton EA, Budoff MJ, Cedars MI, Lobo RA, Merriam GR, Miller VM, Naftolin F, Pal L, Santoro N, Taylor HS, Black DM. Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes. *Am J Med* 2011;124: 199−205.
11. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA* 2002;288:321−333.
12. Zenovich AG, Panoskaltsis-Mortari A, Caron GJ, Kolb AG, Fremming R, Nelson WD, Taylor DA. Sex-based differences in vascular repair with bone marrow cell therapy: relevance of regulatory and Th2-type cytokines. *Transpant Proc* 2008;40:641−643.
13. Mehta PK, Goykhman P, Thomson LE, Shufelt C, Wei J, Yang Y, Gill E, Minissian M, Shaw LJ, Slomka PJ, Slivka M, Berman DS, Bairey Merz CN. Ranolazine improves angina in women with evidence of myocardial ischemia but no obstructive coronary artery disease. *JACC Cardiovasc Imaging* 2011;4:514−522.
14. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. *Circ Heart Fail* 2008;1: 91−97.
15. Chilsom JD, Goldfine, Dhalla AK, Braunwald E, Morrow DA, Karwatowska-Prokopczuk E, Belardinelli L. Effect of ranolazine on A1C and glucose levels in hyperglycemic patients with non-ST elevation acute coronary syndrome. *Diabetes Care* 2010;33: 1163−1168.
16. Ahmed B, Dauerman HL. Women, bleeding, and coronary intervention. *Circulation* 2013;127:641−649.
17. Karrar A, Sequeira W, Block JA. Coronary artery disease in systemic lupus erythematosus: a review of the literature. *Semin Arthritis Rheum* 2001;30:436−443.
18. Hayes SN. Broken-hearted women: the complex relationship between depression and cardiovascular disease. *Women's Health* 2009;5: 709−725.
19. Edmondson D, Richardson S, Falzon L, Davidson KW, Mills MA, Neria Y. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review. *PLoS ONE* 2012;7:e38915.
20. Orth-Gomér K, Schneiderman N, Wang H-X, Walldin C, Blom M, Jernberg T. Stress reduction prolongs life in women with coronary disease: the Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). *Circ Cardiovasc Qual Outcomes* 2009;2: 25−32.
21. Desai CS, Ayers CR, Budoff M, Erbel R, Kavousi M, Khera A, Lehmann N, Liu K, Mohlenkamp S, Ning H, Witteman J, Greenland P. Improved coronary heart disease risk prediction with coronary artery calcium in low-risk women: a meta-analysis of four cohorts. *J Am Coll Cardiol* 2013;61:A245.