Clinical Lipidology Roundtable Discussion

JCL Roundtable: Gender differences in reduction of CVD in response to lipid-lowering drugs

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Abstract: The Roundtable in this issue of the journal has to do with a very important topic that has generated much debate and confusion over the years. Do women and men need and receive the same type and intensity of drug therapy to appropriately reduce the incidence of major vascular events? Second, do women respond to lipid-lowering medications with similar changes in lipoprotein levels and with equivalent reduction in major cardiovascular clinical events? I am very pleased to have 3 experts in different aspects of this issue. Dr Rachel Mackey is a cardiovascular epidemiologist in the University of Pittsburg who is now actively involved in analyzing large data sets from community-based observational studies. Dr Thomas Pearson has many years of cardiovascular experience in clinical trials and observational studies that go to the issues faced by physicians in practice. He is the current Executive Vice President for Research and Education at the University of Florida Health Science Center. Dr Carl Orringer is a professor at the University of Miami School of Medicine who has years of experience in teaching preventive cardiology.

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Dr Brown: The Roundtable in this issue of the journal has to do with a very important topic that has generated much debate and confusion over the years. Do women and men need and receive the same type and intensity of drug therapy to appropriately reduce the incidence of major vascular events? Second, do women respond to lipid-lowering medications with similar changes in lipoprotein levels and with equivalent reduction in major cardiovascular clinical events? I am very pleased to have 3 experts in different aspects of this issue. Dr Rachel Mackey is a cardiovascular epidemiologist in the University of Pittsburg who is now actively involved in analyzing large data sets from community-based observational studies. Dr Thomas Pearson has many years of cardiovascular experience in clinical trials and observational studies that go to the issues faced by physicians in practice. He is the current Executive Vice President for Research and Education at the University of Florida Health Science Center. Dr Carl Orringer is a professor at the University of Miami School of Medicine who has years of experience in teaching preventive cardiology.
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I would like to start our conversation with the question, which I believe was most contentious until very recently. That is, have we approached clinical trial design to provide equivalent information regarding the benefit of drug therapy in both genders? If not, how do we assure that this problem is solved in future studies?

Dr. Mackey, would you care to comment on that question?

Dr Rachel Mackey: Yes, comparing men and women in clinical trials is complicated because both the risk of cardiovascular events and the underlying burden of subclinical atherosclerosis in women lags about 10 years behind men. Therefore, to obtain similar event rates, clinical trials would need to enroll women who are older or who have higher risk than men.

Dr Brown: We are limited in the number of participants and the duration of trials by a variety of practical issues such as adequacy of funding. Does it not come down to the fundamental issue that enough end points must be accumulated during a trial to do an appropriate analysis?

Dr Mackey: Yes. Especially in primary prevention trials, we would need a larger number of women than men to provide the statistical power for subgroup analyses. Of course this difference between women and men in event rates is narrower in secondary prevention trials, where the women are selected based on existing CVD or diabetes.

Dr Carl Orringer: As a first step, we would need to know baseline and steady-state lipid and lipoprotein levels of participants allocated to placebo or control vs those on less or more intense drug therapy. Then, we would need to assure that the effects of allocation to drug therapy are assessed among women and men at similar levels of baseline risk of vascular disease. This would require documentation of risk factors, including age, diabetes, smoking, hypertension, family history of premature atherosclerotic vascular disease, and personal history of atherosclerotic CVD (ASCVD).

Dr Thomas Pearson: Certainly, what we would want to do is come up with a reliable risk score, and then, stratify, so that we have similar-risk individuals of both genders. You do not want to have decrepit men and healthy women, and then, try to make the case for differences being gender-related, so you would like some stratification by risk, etcetera.

In recruiting to a trial, you must get the numbers you need for a meaningful analysis. There is always a drift to that group that is easy to recruit vs not. So you must pay attention to risk and need for therapy in both genders in order to have a true comparison of therapeutic effectiveness. This interpretation of risk can be different in men and women.

I wrote an editorial related to dealing with an aspect of this issue that occurred in the HERS trial, a secondary prevention trial of estrogen in women. It was a paper looking at statin use in women in that trial. There were remarkable differences in divorced, single, vs married women, with the married women having far less participation in their own preventative care. The point there is, set things up so that not only recruitment rates, but your compliance and your dropout rates are the same, so that you have a chance to have the equal number of events in both arms, so that your analysis has adequate statistical power.

The differences in women and men with respect to preventing vascular disease are more than age. The environmental influences can be different and powerful. I do not think that is usually taken into account in the recruitment or in the analysis of data from trials. This can become a big problem, and we have just not given it enough attention.

Dr Brown: We certainly continue to hear from skeptics that we have not proven benefit of lipid reduction in women. In particular, they argue that benefit is specifically not proven in primary prevention trials for women. In many of our older trials, women often make up only 20% to 25% of the cohort and they are in the same age range as the men.

In more recent studies in which we have equal numbers, we do not have sufficient event rates to answer the question.

Dr Pearson: Rather than recruiting the right group of women, the pressure is to accept more men as the recruitment is closed out just so that the sample size will be adequate for statistical power. I think this is something that is got to be planned in, really engineered right into the trial.

Dr Brown: I believe we now realize we have a very serious problem. We must not be simply politically correct, just tipping our hat to women. We need adequate and trustworthy data to answer these questions. I agree that we have not considered all the real issues in the planning process.

Dr Mackey: Absolutely. It is important that clinical trials not only enroll an adequate sample size of women but also enroll women who are actually at elevated risk of cardiovascular events. Specifically, earlier primary prevention clinical trials that used elevated low-density lipoprotein cholesterol (LDL-C) to determine eligibility likely included some women with low CVD risk, if their high LDL-C was discordant from normal apoB or LDL particle concentrations. As shown in several studies, this discordance of LDL-C >LDL-P concentrations is more common among women than men and is associated with lower event risk and lower levels of atherosclerosis.
It is not possible to demonstrate a benefit of lipid-lowering treatment among women whose CVD event risk was very low prior to randomized treatment. This could explain the larger benefit of statins among women in clinical trials such as JUPITER, which included a higher proportion of women, but also enrolled people with lower LDL-C levels, greatly reducing the possibility of including women with high LDL-C discordant from normal or low apoB or LDL particle concentrations, who are not at elevated risk. Dr Brown: We must also remember that in JUPITER, an elevation in the inflammatory marker, hs-CRP was required for inclusion so that there was a selection for women with occult disease. Some could argue that this was not true primary prevention.

Dr Mackey, you have a current experience with new and old risk factors that should help us understand risk in both genders in the 21st century. You have data from a variety of different techniques that can add to the classical measures from the Multiethnic Study of Atherosclerosis (MESA) study. The population has changed because the data acquisition in Framingham and we must take that into consideration in future studies. It seems we can do better in choosing high-risk women, and choosing the best target of treatment that will affect their risk.

Dr Pearson: The first principle of science is that you do not rely on a single experiment, and the first thing we teach in epidemiology courses is that you do not rely on one trial. There could have been some issues with that trial such as those which we have just described. There seems to be this constant referring to the negative trials vs looking at the meta-analysis or the big trials. For example, the Heart Protection Study did, in fact, have adequate numbers of women in it. In meta-analyses of low-risk individuals, over 50% of those lowest-risk strata were, in fact, women, and they all showed statin efficacy.

I think we need to do a little Epidemiology 101 training about looking at the totality of the data and being very interested in those trials that may or may not have come up with the “right answer.” Many of these trials did not reach a statistically significant level, but still gave the same direction and magnitude of result. They did not have the power because of the number of events. These did not prove that women do not benefit. They demonstrated inadequacy of the power of the trial. There is a lot of misreading of the trial literature, which generates this myth of lipid unresponsiveness in women.

Dr Brown: It is very difficult to progress in effective prevention efforts when you cannot provide confirmatory evidence. There are those who say that we are spending inappropriately with statin treatment of women because no one has proven that we can really prevent the initial presentation of heart disease in our mothers and sisters.

Dr Pearson: Choosing the appropriate end points must be considered. I think consideration of a composite cardiovascular end point is justified in some cases, especially bringing in measures of stroke, both as a predesignated end point subgroup with both fatal and nonfatal incidence. In early studies, we found, probably clearly wrongly, a 10:1 ratio of coronary events compared to strokes. As more data in women have become available, it is almost 1:1.

The stroke end point is something very important, particularly in older women. No one’s going to tell me that a stroke is more or less important than a heart attack. These are both things we want to prevent. The epidemiology and pathophysiology of stroke appears to have some interesting issues not fully defined. For example, in the aspirin studies, which show surprising stroke benefit in 45-year-old women but the coronary disease reduction is limited to women aged 65 years and older. Perhaps there are different mechanisms involved in the 2 diseases that relate to thrombosis. In attempting to measure benefit for women, the stroke end point is very important.

Dr Brown: One of the major issues that affects women and men is the question of benefit of reducing triglycerides. From observational data and from subgroup analysis of clinical trials, this is particularly important in those with low high-density lipoprotein (HDL) and triglyceride concentrations above 200 mg/dL. Statin treatment to reduce LDL cholesterol into desirable ranges by recent guidelines still leaves this population at increased risk. Perhaps non-HDL cholesterol, apoB, or LDL particle number would be appropriate targets in these individuals?

Is this a particularly important group for therapy in women?

Dr Mackey: We know that individuals (men or women) with high triglycerides and low HDL-C (ie, metabolic syndrome and diabetes) have a high prevalence of discordance between concentrations of LDL-C (low or normal LDL-C) and LDL particles or apoB (ie, LDL-C < LDL-P and/or apoB.) Among individuals with this type of discordance, for whom CVD risk is related to apoB or LDL-P rather than LDL-C. Non–HDL-C is considered by some to be the “poor man’s apoB,” and in discordant individuals, non–HDL-C also predicts better than LDL-C. Compared with age-matched men, women have lower mean levels of triglycerides, LDL-C, and non–HDL-C, prior to menopause, but higher mean levels of LDL-C and non–HDL-C postmenopause. In contrast, concentrations of LDL-P and apoB increase in women around menopause but tend to remain lower than among age-matched men. Therefore, the strong correlations of diabetes, metabolic syndrome, and high triglycerides with higher levels of apoB and LDL-P are particularly noticeable among women, given lower levels of apoB and LDL-P (and associated atherosclerosis and clinical CVD) in the reference group without diabetes, metabolic syndrome, or high triglycerides. This underscores how gender differences in baseline absolute risk between reference groups complicates comparisons of relative risks for men vs women.

Dr Brown: One consideration is to adjust the age of enrollment to generate a more equal incidence of end points during the trial. For example, enroll the men aged between 40 and 60 years and women aged between 50 and 70 years.
Dr Pearson: Even 20 years ago, it was obvious that we were ignoring a subgroup of the population with substantial risk, and there were no data from intervention studies. Fibrate studies such as the VA-HIT study and the Helsinki Heart Study, the Lipid Research Clinic Coronary Primary Prevention Trial all incorporated men only while ignoring women.

The other issue I wanted to raise is that we should not be lumping people together. When we start talking about some of our minority groups, Latinos, and African Americans, who have accentuated burdens of obesity often accompanied by a large prevalence of triglyceride disorders. Many of them are diabetic or prediabetic, and so, I think that a clinical trial in women with hypertriglyceridemia is particularly needed. I have been saying this for 20 years or more.

Dr Brown: The rise in population mean triglyceride concentration in men starts in the early-to-mid 30s and really peaks out by the time men are 50 years. Women show a similar rise at about 50 with a peak mean concentration in the late 60s.

If you recruit women who are 50 years old and who have high triglycerides, are they more like men who have already experienced this for 15 years at that point?

Dr Mackey: Well, I am not sure that we have adequate longitudinal data to evaluate that question. Typically, at a given age and triglyceride level, men will have longer duration of exposure to elevated triglyceride levels, as well as correlated high levels of apoB and LDL-P, and therefore, correspondingly higher levels of atherosclerosis and consequently, event rates. However, as you know, some studies suggest that triglycerides are more predictive in women than men. We have also recently published data from the Multi-Ethnic Study of Atherosclerosis that showed higher baseline levels of LDL particle concentration were associated with incident diabetes over approximately 7 years of follow-up among women but not men. Again, the stronger relative risks among women than men may be due to lower levels of atherogenic particles in the reference group among women than men.

Dr Brown: If we did a particle number trial in women, which included metabolic syndrome, elevated blood glucose, not necessarily diabetes, would we be able to reduce the impact of age range differences and help deal with this issue of primary prevention in women?

Dr Mackey: I think that there are ample data supporting use of LDL-P or apoB to identify women with increased atherosclerosis and therefore increased CVD risk. And women with metabolic syndrome and elevated blood glucose would be likely to have elevated concentrations of LDL-P and apoB, making them more similar to men of a similar age.

Dr Orringer: As I considered the possible differences in ASCVD in men and women, I began to wonder whether we were looking at the same biologic process, but with a different time clock or whether there are more fundamental differences in lipoproteins and other nonlipid risk factors that have not yet been fully appreciated.
morbidity and mortality in women. The hesitance to order calcium scoring likely relates to limited or no insurance reimbursement for the coronary calcium procedure; to concerns regarding downstream testing related to incidental findings; and to the lack of definitive data demonstrating that ordering the test is associated with improved outcomes.

Dr Pearson: We all dealt with the slippery slope. A high calcium score leads to putting the person on a treadmill.

Then they are in the cath lab, and then an angioplasty.

I think these calcium scores can help identify a person you want to treat aggressively with lifestyle change, to educate regarding risk, and to treat risk factors that are amenable to diet and exercise. Of course more aggressive lipoprotein reduction may also be indicated when the calcium score is elevated.

Dr Orringer: For those clinicians choosing to order the test, extremes of coronary calcium scoring in women may provide useful information. Women with no detectable coronary calcium have an exceedingly low risk of CHD events over the ensuing 10 years, an observation that would favor nonpharmacologic strategies for lipid management. Those found to have a coronary calcium score of 300 Agaston units or greater have extensive subclinical atherosclerosis, a finding that would favor more intensive lifestyle management approaches and may serve as indicator for consideration of pharmacologic therapy for prevention.

Dr Pearson: For many people with abnormal scans, or high risk scores, I certainly agree that they need treatment. This includes women. Some would be at sufficient risk to admit to our phase II cardiac rehab program. That is expensive and unfortunately not reimbursed.

Dr Brown: Well, do we have evidence that in women that we can select a group that we would benefit? Would we benefit women with the calcium score of 300 in a cardiac rehab program?

Dr Pearson: The cardiac rehab program should always be looked at as a platform for intensive lifestyle management. The exercise is only one component. There is a paucity of planned and supervised programs for patients who need that type of support. The cardiac rehab program is something currently available. When a woman on the treadmill talks to women exercising beside her, and one talks about her bypass surgery and the other talks about her resuscitation, you have a strong behavioral change environment.

Dr Brown: What I am concerned about is our ability to select the women for whom we could design therapy that will truly prevent the first event.

Is the statin story fully told? If so, what do we need to intervene on? What are the tools that will intervene on that particular target that is appropriate in the younger woman because again, we have 60-year-old women having heart attacks?

Admittedly, it is smaller group, but after 65 years, the incidence begins to really accelerate. We know the disease is there, preparing for its ugly presentation 20 years later. We are missing something here that we have not investigated in both men and women.

Dr Mackey: I would be interested to see how many women at risk are not identified by elevated LDL particle or ApoB concentration.

Dr Brown: We have never tested that. We have never selected a population based on particle number for prospective observation. Is that what we should be doing?

Dr Mackey: Well, it depends on the question. The meta-analyses do show a reduction in CVD risk with statin use among women without clinical evidence of atherosclerosis. However, if the question is how to improve the identification of women to treat, to avoid undertreatment or overtreatment, that is a different question, and may require either measuring atherogenic particles (LDL-P or apoB) or coronary artery calcification or both.

Dr Brown: Is the amplification of risk sufficient to have a practical clinical trial addressing that issue?

Dr Mackey: Well, another issue in women is that given the substantial changes in lipid and lipoprotein levels over their lifespan and especially across menopause, and the long incubation period for atherosclerosis, among postmenopausal women may be more correlated with premenopausal than postmenopausal lipid and lipoprotein levels. Therefore, levels of lipids and lipoproteins may be less informative about lifetime exposure for postmenopausal women than for similar age men.

Dr Brown: You get into a time factor there. I mean, we may know that a very important risk factor often shows up at age 70 years or later, but it may not be practical to intervene on that particular factor until they are 50 or 55 years because of the duration of time of exposure that is necessary to produce a clinical event.

Dr Pearson: But Dr Mackey, don’t you think that there have been a lot of imaging studies? There have been a lot of biomarker studies, a lot of the standard risk factor studies. Don’t you think everyone could get together and come up with an algorithm that would identify, say 50-year-old women who would be at risk of a coronary event by age 65 years?

Dr Mackey: Absolutely.

Dr Pearson: Yes, we have significant data in hand now that could set the inclusion criteria for a trial.

Dr Mackey: However, the most accurate way to determine a 50-year-old woman’s 15-year CVD event risk is probably to measure coronary artery calcification, and that may not be feasible or cost-effective.

Dr Orringer: I believe that the evidence from currently available statin studies indicate that men and women whose nonlipid risk factors are equally controlled enjoy similar benefits from statin therapy. Although randomized controlled trials have not shown clear differences in statin-related side effects in men vs women, a subanalysis of the USAGe study, an Internet-based survey of 10,138 current and former statin users, indicated that women were more likely than men to experience new or worse 500
muscle pain on a statin. There are multiple potential explanations for this finding.

Dr Brown: There are clues in phase III studies as part of drug development. The studies of rosvastatin included many older women, women in their 80s. They seemed to be particularly prone to myopathy, even rhabdomyolysis. It may have to do with the muscle mass or their renal status.

Dr Orringer: Women do get started on 80 mg of atorvastatin following acute coronary syndromes.

Dr Brown: And the great majority do well with high-intensity statin therapy. Rhabdomyolysis caused by statins is still quite uncommon in all age groups and in both sexes.

Dr Pearson: There are other issues that should be addressed in women. Number one is rheumatologic diseases, rheumatoid arthritis being the most frequent, which are far more common in women than in men, 3- to 4-fold so. Of Americans with RA, three-quarters of them are women, so we have got a sizeable number of individuals there who should be identified and, almost like diabetics, put in a category that really draws special attention to lipid management.

Hypothyroidism is much more common in women. I am concerned that we have forgotten about doing the baseline screening for this. This needs to be emphasized. The hyperlipidemic woman with occult hypothyroidism is a frequent finding. You fix that, and the hyperlipidemia goes away. Hypothyroidism alone can cause myopathy, and it sets the patient up for statin myopathy. These are real gender differences, with prevalence multiples of 3-, 4-, or 5-fold. When a clinician talks to a woman vs a man these differences should be kept in mind.

These comorbidities can be confused with statin effects. But if a woman with a high coronary risk, stops the statin because of myalgia that is caused by other factors, she is inadequately treated for her coronary risk because of the failure to recognize the true cause of the myalgia syndrome.

Dr Brown: Whether you stop it or she stops it, it still removes the therapeutic effect.

Dr Pearson: Another concern is the dose responsiveness of myalgia due to statin therapy. The starting of high-dose statins is really going to exacerbate that. If you are going to have a gender-based problem, it is going to show up early. Rather than starting a low dose and gradually increasing this monitoring its efficacy in order to reach a desired lipid level at the lowest effective dose. Starting a maximal dose may quickly result in a person with a myopathic syndrome and an aversion to statins that may extend to fear of all doses.

Dr Orringer: I agree. Many of the clinicians have had concerns about beginning high-intensity statins in women, based upon the clinical impression that women may be more prone to statin-related side effects than men.

Dr Pearson: There are ethnic issues in this consideration. There are reasonably good data in Asians, particularly Japanese that there is different metabolism of statins and higher dose responsiveness. These may lead predispositions to myalgias. These are very gender-oriented issues, with higher myalgia rates in women in these groups.

Dr Brown: Lupus erythematosus is not rare. Women have 7- to 8-fold higher prevalence of this disorder than men. There is an immune difference here that may also play into risk of a cardiovascular syndrome.

Dr Pearson: Again, they are all much higher in women, 6- to 10-fold higher.

Dr Orringer: Psoriasis occurs in both men and women, and some studies have suggested a higher incidence of subclinical atherosclerosis in these patients.

Dr Pearson: As is polymyalgia rheumatica.

Dr Brown: This issue of inflammation from a variety of sources is of great interest. The subclinical inflammation of arteriosclerosis itself is a potential target of treatment.

This was the subject of a Roundtable last year in this journal. Dr Paul Ridker discussed the rationale for 2 studies that are currently underway and that are going to address the pharmacologic suppression of inflammation with vascular end points.

Dr Pearson: We reviewed autoimmune diseases and vascular disease incidence several years ago in a monograph in the American Journal of Medicine. The rate of coronary events increased in those 45- to 65-year-old women with these inflammatory disorders at a time when they remain low in unaffected women. In women with RA, the risks were 2-fold higher. These data are from the Olmsted County, and San Antonio studies, which provided observational data showing that this is a high-risk group not otherwise identified by a risk calculator.

Dr Brown: Now, we have got a lot of genome-wide association studies out there that show genetic linkage to some of these rheumatologic disorders and, not only to diabetes but also to several components of the metabolic syndrome. The coalescence of the components of the metabolic syndrome also seem to have genes that bring these together. You see lipid disorders or triglyceride elevation and diabetes associated with the same set of genes.

Do you think we may be able to define high-risk women through genetic indicators or predictors of rheumatologic disorders or metabolic syndrome characteristics?

Dr Pearson: One of the problems with genome-wide association studies of rheumatologic disorders is the association with whole major histocompatibility complexes. This is an enormous bank of genes and you may have many associations, which probably have to do with inflammation, and not necessarily what is inflamed. The sorting out of all those associations to find only those associated with cardiovascular disease, I think, would be daunting.

Dr Orringer: The Reynolds Risk Score was developed as a global risk scoring system for women and was the first such tool to include a marker of inflammation.

Dr Brown: The C-reactive protein (CRP) component.

Dr Pearson: True. Well, interestingly, if your CRP is over 10, you look for other diseases such as psoriasis or...
RA. What you probably ought to continue to be concerned about is the cardiovascular risk.

Dr Brown: As we noted before, the JUPITER study required elevation of CRP for enrollment. Women experienced an equivalent risk reduction to men. Do you think that may indicate that we should pay more attention to markers of inflammation in women when assessing vascular risk?

Dr Pearson: I think about the National Lipid Association (NLA) recommendations, perhaps we should have made some gender-specific comments regarding the use of a risk calculator. One might give special consideration to the Reynolds Risk Scoring for women, over other risk calculators that were mentioned in the NLA recommendations.

Dr Brown: I am not sure that we would have a lot of strong evidence to support that. However, it is certainly a reasonable consideration.

Dr Pearson: Well, again, there are risk scores that do or do not include diabetes. As diabetes was considered a risk equivalent, it was taken out of the scores and I think we lost something there.

Dr Brown: If we look to the future now and think about the extension of our therapeutic options beyond statins, perhaps we have not fully studied the benefits of fibrates or other triglyceride-lowering drugs, in particular, those of the peroxysomal proliferator activator receptor alpha subset?

Dr Pearson: I think what you say is true. All those interventions, could favor a female audience as being at least as benefiting in women as in men or maybe more so.

Dr Orringer: ACCORD-LIPID demonstrated that type II diabetic women allocated to simvastatin plus fenofibrate had worse outcomes than those allocated to simvastatin monotherapy.

It is important to point out that this finding was not confirmed in any of the other fibrate trials, and there was a relatively small number of women in the study.

Dr Brown: That is right, this was a small subset and all with long standing diabetes on statins.

Dr Orringer: I do not think that that occurs in any of the other fibrate trials that I know of and I wonder whether that is just an outlier, but this has been noticed by those raising caution about treating women.

Dr Pearson: Others did not have any women.

Dr Brown: Finally, let us go back to the diabetes issue. There is concern regarding the statins a sufficient rise in glucose to convert prediabetes and those with the metabolic syndrome into those with the diagnosis of type II diabetes? Yet, if you look at the other side of that coin, statin trials in diabetics have been the most effective therapy in preventing vascular events. We have not shown benefit of aggressive lowering of glucose except for slowing renal disease progression and possibly retinal complications.

Dr Pearson: We have made no difference in terms of macrovascular disease with glucose control. But perhaps there is some benefit with the neuropathies and microvascular disease end points.

Dr Brown: There is a better trend with fenofibrate in microvascular disorders. In several studies of type II diabetics, fenofibrate has been found to lower retinopathy, proteinuria, and neuropathy more effectively than does glucose control, so we do not understand microvascular disease very well.

Let me turn to the stroke issue raised earlier by Dr Pearson. Are we assessing stroke appropriately in these trials? Should we focus more on thrombotic stroke and try to get rid of the atrial fibrillation issues and certainly the hemorrhagic causes? Should we spend the money necessary to really define stroke by magnetic resonance imaging, if we are going to do a trial in women because I agree that stroke is really the most interesting end point there? Is one of our failings not to define atherosclerotic stroke?

Dr Pearson: Versus embolic stroke or hemorrhagic stroke?

Dr Brown: Embolic stroke has implications for an atherosclerotic vessel as the source but are there many other causes of atrial fibrillation?

Dr Pearson: We do not fully understand why the Women’s Health Study showed a doubling of stroke with estrogen and progesterone therapy and that aspirin seemed to make little difference. I believe the prevalence of atrial septal defects and patent foramen ovale is higher in women than in men. Many of these women that have been looked at clinically, after they have these strokes, have normal vascularities. Some of them were apparently very healthy.

So, with aging, there may be some episodic reversal of flow with atrioseptal defects and patent foramen ovale. Obviously, those women may have otherwise low coronary risk. Clinical trials have shown fixing them surgically is not significantly beneficial, but aspirin does usually work.

Dr Brown: Some have pointed to evidence that there is an anti-inflammatory component in the vasculature with statins. However, there is also evidence that lowering LDL with lipoheresis produces rapid reduction in inflammation in arterial lesions. You can demonstrate this with positron emission tomography scanning within a few hours after physically lowering LDL dramatically. Women do seem to be particularly prone toward thrombotic events. This was demonstrated with the risk of stroke in young women who smoked cigarette while taking those early contraceptive drugs with their high estrogen levels?

Dr Pearson: Peripheral venous disease is also much more common in women.

Dr Brown: Do you believe the propensity to inflammation and to thrombosis may be related in women? Do studies with aspirin or other anti-inflammatory treatments need to be continued?

Dr Pearson: As you now, there are a number of aspirin trials underway.

Dr Brown: Yes, that is true. I hope we are monitoring for all pertinent changes that may relate to vascular end points.

Dr Pearson: Many of those trials are within the moderate-risk category. They are not very low-risk
individuals, but they need to have enough end points in order to have statistical power. I think some of those trials will have an answer. Generally, I think the imaging after a cerebrovascular or neurologic event is good enough. We will find now that they will at least be able to sort out the hemorrhagic from the atherothrombotic.

Dr Orringer: The American Heart Association/American Stroke Association Guideline on Stroke Risk and Prevention did not even list lipids as a risk factor for stroke. That is particularly interesting, especially because stroke is often the first manifestation of ASCVD in women, and when it occurs in an older woman, they are in trouble because they are often widowed and they are living alone. They do not have a good support system and the consequences are most devastating.

Dr Pearson: It is a bizarre oversight. Coronary disease is the leading cause of death in stroke survivors. It is always been that way and it is going to continue to be that way. So, what you have is a strong coronary risk issue to which we are not alerting our neurology colleagues. They need to be either referred or managed for this well-documented treatable risk determinant. I thought it was a huge oversight.

Dr Brown: Myocardial infarctions can lead to strokes. This includes silent infarctions because of the embolic phenomenon off the endocardium.

Dr. Mackey, with regard to stroke in women, is there enough data on particles from Mesa or from other studies to say that they are a predictor of this vascular event?

Dr Mackey: In a nested case–control study of stroke in the Women’s Health Initiative, stroke was associated with higher LDL-P, but not LDL-C, concentrations, accounting for age and race. However, the association of LDL-P with stroke was attenuated and not statistically significant after adjustment for a range of covariates including diabetes. The study did not report whether the association existed if limited to women without baseline diabetes.

Dr Brown: We know if you lower LDL cholesterol with statins, stroke rates go down. It remains a puzzle because the lipoproteins have been such poor predictors of stroke.

Dr Pearson: In SPARKLE even, the increase in hemorrhagic stroke, which we are all anxious about, was more than taken up by the reduction in the atherothrombotic stroke in a poststroke cohort.

Dr Brown: Hemorrhagic stroke remains a perplexing disorder. Weak but recurrent evidence of a relationship to low cholesterol is puzzling. Reduction in blood pressure is the one effective therapy.

Dr Orringer: I think that we need to look carefully at statin dosing in these studies.

Dr Brown: The adverse event rate was low in TNT, where we did compare 80 mg to 10 mg of atorvastatin. Do we know if there was a difference in the incidence between the women and men in that study?

Dr Orringer: One major limitation of these trials is that they did not employ validated instruments that focused on side effects. This is a common problem in statin randomized controlled trials.

Dr Pearson: I would have to go back and look at the guidelines. We know that with the initiation of statin therapy, you get this amazing bang with the first dose, and then, you get the rule of 6s. Every time you double it, you get another 6%.

What needs to be paired with that curve is some sort of side effect assessment. This is what I think is missing—the incidence of side effects, which are dose-responsive. I have never seen that done. We have all seen this rule of 6s. I think that would be something to call for because I think you could probably find a different relationship of dose in men than in women. If in fact, lipid levels get into the therapeutic ranges of just going with 80 mg, but by backing off to 40 mg or 20 mg, you could escape side effects and still get the vast majority of benefits of lipid management that is essentially an endorsement for dose scaling of statins.

Dr Brown: This raises the question again of optimum therapy. Is it simply the maximum-tolerated dose of statin or is it treatment to a range of lipoprotein values. We have recommended that we reduce LDL cholesterol and non–HDL-C into specific ranges depending on the level of estimated risk. Otherwise, judging success in reducing risk in your patient is based only on whether they are adhering to a given regimen. We now have a lot of data relating rates of major events to the concentrations of LDL and non–HDL-C sustained for months or years after instituting treatment. In terms of change in atheroma volume or in reducing event rates, LDL cholesterol less than 70 mg/dL is more effective than 100 and 50 mg/dL is more effective than 70 mg/dL. Are these adequate goals of therapy? Are such values worthy goals to pursue in everyone with consideration of benefit vs potential harm?

Dr Mackey: By LDL, you mean LDL-C, not LDL particle concentrations?

Dr Brown: Yes, the numbers I gave were LDL-C values. I would like to have particle numbers in everyone. The problem is not many studies have acquired that data. I am very pleased that a growing number do. We do not have the kind of interventional studies showing particle change that we would like to have in order to inquire regarding the desirable goal ranges that we could define and recommend to our colleagues. At present, it would be difficult to define goals with the measure of particles that would gain wide agreement.

I know that LipoScience has taken data from a variety of observational studies and clinical trial cohorts and provided relationships between baseline measures and clinical events. This of course focuses on LDL particle number (LDL-P) as derived from nuclear magnetic spectral analysis. However, there are little data comparing changes in LDL-P with therapy and the outcomes. They have proposed that a desirable level of LDL-P is less than 1000 micromoles per liter. But again, we have very little data on events as they relate to achieved particle number with any therapy. Is the therapeutic goal adequately set by experimentation? Is it the same thing as the values from observational data?
Dr Mackey: Well, I wanted to come back again to RA and the issue of inflammation. Statins are powerfully effective in reducing LDL particles as well as LDL cholesterol. However, when our focus turns to inflammation, and inflammatory diseases, lipid levels often have paradoxical associations with CVD risk, but accumulating data suggest that concentrations of atherogenic particles, that is, LDL-P or apoB, remain predictive of CVD. For example, a recent meta-analysis of tumor necrosis factor alpha inhibitors in RA patients found that apoB and the apoB/apoA1 ratio were more predictive of CHD events than LDL-C. With increasing focus on inflammation and inflammatory diseases, I expect increasing recognition that cholesterol estimates of lipoproteins may be discordant from particle concentrations and also be poorer estimates of CVD risk.

Dr Pearson: I think we have all had about 100 to 120 years of practice experience here. I think we probably all put RA patients on statins, and on occasion, they said that their RA was better. There is that whole literature of the consolidative influenza, pneumonia, and statins. Although poorly sorted out, there are a lot of hints that statins are not neutral, relative to immunologic issues. As a result, I am a bit more aggressive with statins in a patient with RA.

Dr Brown: One of the intriguing things is that when you give certain anti-inflammatory drugs in rheumatoid arthritis, you find a rise in LDL-C and HDL concentrations of 15% and 20%. We are still puzzling over that one.

Dr Orringer: Have you seen any signals to suggest that women experience more side effects related to nonstatin agents than men?

Dr Brown: I can not quote any studies that might address the rates of adverse events with fibrates or niacin in women vs men. There are relatively few studies of these drugs in adequate numbers of women for such a comparison.

Dr Pearson: We looked at thousands of ezetimibe patients, adding it to statins or not, and there was additional benefit documented in terms of LDL reduction and now with the IMPROVE-IT, there is evidence of vascular benefit.

Dr Brown: The IMPROVE-IT trial is the first to ask the question with adequate numbers of patients to give us an answer with regard to added benefit with ezetimibe plus statin when tested against an equivalent dose of statin alone. Ezetimibe has been found to have almost no significant adverse effects so benefit regarding vascular endpoints is a very valuable contribution to our theory that it is the LDL, not the dose of statins that determines benefit.

Dr Pearson: Truly.

Dr Brown: It is hard to attribute anything bad to it.

Dr Pearson: I think the other issue that is relevant to this discussion in women is the approach to the elderly. There are many more women in the 9th and 10th decades of life, and they are experiencing a very high incidence of morbidity and mortality from vascular disease. The American College of Cardiology/American Heart Association guidelines are not very helpful with this problem. I was on the PROSPER Data Safety Monitoring Board, which Dr Brown chaired. Perhaps we should comment on this data.

Dr Brown: It was a short study, only 3.5 years, with pravastatin 40 mg/d vs placebo. We found reduced coronary events in those who were between ages 70 and 82 years on entry. Unfortunately stroke rates were not reduced.

Dr Pearson: There was no difference in dementia after careful assessment during the trial, including magnetic resonance imaging measures of brain. No harm but no evident benefit with the statin therapy. I know some colleague proposed a proper study in elderly for the National Institutes of Health to fund, both in men and women, with a very great interest in stroke in elderly women. The study was not funded.

If you have a vibrant elderly woman that is an 80-year-old grandmother chasing around her grandchildren, playing golf, and volunteering, most physicians are going to say I would like to help sustain 10 more years of that.

Dr Brown: Well, I absolutely could not agree more. I think that may be one group in which we do a study in women only.

Dr Pearson: Yes.

Dr Brown: I’m going to treat every 75-year-old man or woman with any risk factors who comes to my office and asks my advice. I am not going to stop at 75, 80, or 85 if they are otherwise expecting several more years of productive life. I know their risk is terribly high of losing that life.

Dr Mackey: But a few studies suggest that women might have a higher risk than men of developing statin-related diabetes, and in epidemiology studies, we see women in that age group who have zero or very low levels of coronary artery calcification and correspondingly low risk of events. Those women could have high LDL-C that is discordant from LDL-P and their CVD risk, but be treated on the basis of their high LDL-C, and might get diabetes on the statin.

Dr Pearson: But there are different protocols you could go on. You could do that, but that is part of any trial. Most of the adverse effects that we considered documented were not from case reports, but from the analysis of large data sets derived from the bigger trials.

Dr Brown: I believe the data are now clear that the people who get diabetes on statins entered the trial with the classical predictors of type II diabetes. They have “prediabetes” (blood glucose >100 mg/dL, obesity, high triglycerides, and high blood pressure). These are the very patients who benefit most from statin therapy. Virtually all patients with type II diabetes should be on statin therapy according to the American Diabetes Association and the NLA agrees.

Dr Mackey: But at the same time, if we are talking about someone with zero calcification, who are at very low risk, but then statins push them over the threshold.

Dr Brown: What if they have got a high particle number?
Dr Mackey: That is a different story. I am talking about individuals with discordant levels (LDL-C > LDL-P).

Dr Pearson: There is this polypharmacy issue in the elderly. They are frequently on a bunch of other drugs, and I think it needs to be resolved in more of a practical trial where these people may be on all these drugs.

Dr Brown: The question is how would you select the high-risk 75-year-old woman? You would not just throw every 75-year-old woman into a trial. You would select them, based on what you believe their risk factors to be and you would treat those with a risk estimate that is high. I do not believe that statins are not going to raise their risk of vascular disease at that age. Watching for the presence of competing drugs that may interfere with statin metabolism is an issue that must be considered in this group.

Dr Mackey: Agreed. And most older women, as well as older men, will have subclinical atherosclerosis regardless of their risk factor levels measured at that older age.

Dr Pearson: I am much more interested in a practical trial, which not only may identify the efficacy of whatever the intervention was but also may identify the subgroups that should not be treated. If you put everybody in as high risk, you are never going to know that.

Dr Brown: I would like to see a clinical trial in elderly women with the high HDL-C/high LDL-C phenotype, examining the impact of coronary calcium scoring on risk prediction of coronary events.

Dr Pearson: All of us have not been aggressive enough, in terms of pushing comparative effectiveness studies. The issues in these are those of real-life settings. So, if you are going to spend $100 and receive radiation, what do you get back for it?

Patient-centered outcomes research needs emphasis. We also have not been strong enough to get things to really help the doctor. So, some clinicians are providing these things on a commercial basis, rather than on a scientific basis.

Dr Brown: But stroke is a very expensive disease, and the benefit there may be very impressive. The British have been leaders in studying interventions such as lipid lowering in a broad cross section of patients, and these have shown benefit even with quite low LDL-C. However, as in the Heart Protection Study, they include those with clinical risk factors such high blood pressure and diabetes.

Dr Pearson: Considering stroke prevention is of interest to the elderly patient. It is the substance of a terror campaign for preventive cardiology. A heart attack on the golf course does not seem to scare people, but contemplating an aphasic, hemiparetic, wheelchair-bound person in the nursing home, can motivate people to prevent that.

Dr Orringer: That is because many people are more afraid of a disabling stroke than of sudden cardiac death.

Dr Pearson: I have looked at some editorials, position statements, or whatever that women are overtreated.

Dr Brown: Physicians in practice seem to be ignoring this argument. In the NHANES data on the prevalence of state use, women over 60 years are treated just as frequently as men at the same age. Women are clearly more health conscious. We men are likely to be treated because our wives insisted that we take proper care.

Dr Pearson: This is this editorial that I wrote in JAMA once that why do divorced and single women have better compliance with prevention than married women? The answer is the married woman is the care provider for everyone but herself. Moms always look after the kids and the hubby, so some of this is not just noncaring providers. It is getting mom in to care, too.

Dr Brown: I want to thank Drs Mackey, Orringer, and Pearson for joining me today and sharing their knowledge and experience on this important issue of defining the gender differences in risk. Most importantly, I appreciate their discussing the ways in which we could improve the scientific information needed to better guide treatment of risk of vascular disease in women.

Gender differences in reduction of CVD in response to lipid-lowering drugs: Recommended reading