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Atherosclerosis in Women: The Role of Gender

BY MARIE GERHARD-HERMAN, MD

Cardiovascular disease (CVD) accounts for over 40% of all deaths in women in the United States and is the leading killer of women in most developed countries. For many years, nearly all studies of coronary artery disease (CAD) excluded women. This was likely due to age bias, rather than gender bias, as men present with CVD at a younger age. The problem of CVD in women has therefore been masked by the protective effect from cardiac death in young premenopausal women. This issue of *Cardiology Rounds* reviews the role of gender in CAD with specific emphasis on the current understanding of the role that ovarian function and hormone replacement therapy (HRT) plays in atherosclerosis.

The female advantage in coronary artery disease

Men are more likely to die of CVD than women. Population studies demonstrate a male to female ratio in coronary disease mortality ranging from 2.5 to 1 to 4.5 to 1 in countries with different rates of CAD.¹ This virtually universal male excess in CAD implies a universal inherent female advantage that operates across populations with divergent rates of heart disease and lifestyles (Figure 1). An obvious explanation drawn from these data is that estrogen is good or that testosterone is bad. However, the wide differences in cardiac death rates between countries, together with the consistent differences in sex ratios, indicate that the female advantage in CVD is mediated by atherosclerosis risk factors that exert an effect on both men and women. In fact, the differences between countries are greater than the differences between sexes. This suggests that gender alone is not destiny with regard to CAD.

Female gender diminishes risk factor impact

Another observation regarding gender differences in CVD is that in women, the absolute level of CAD is lower for any given level of risk factor than in men.² The differences attributable to gender persist in studies that adjusted for risk factor differences³ or stratified by levels of risk factor.² Women have a similar dose response and relative risk for each risk factor, but their absolute risk of CAD is lower for any given level of that risk factor. This remains true even after menopause.

Gender may indeed influence the impact of specific risk factors. For example, Kesteloot and Sasaki⁴ used international lipid data to suggest that a cardiovascular advantage exists in women, in part, because they can raise their HDL cholesterol levels in response to a diet high in saturated fat, whereas men cannot. In fact, the same level of HDL cholesterol may confer greater cardiovascular benefit in women than in men.^{5,6}

The protection from heart disease conferred by female gender is, however, least apparent in individuals with diabetes mellitus. In the 36-year follow-up of the Framingham Study, female gender had little impact on moderating the risk of CAD from diabetes in individuals from 35- to 64-years of age.⁷ An increase in premature menopause in women with type I diabetes suggests that diabetes directly affects ovarian function.⁸ This further illustrates the complexity of interactions between gender and cardiovascular risk factors.

What aspect of gender imparts cardiovascular benefit?

Understanding why females are protected from CVD requires an understanding of what defines female gender and what distinguishes a female from a male. The differences between men and women start with the sex chromosomes. Sex chromosome status determines different *in utero* conditioning for females and



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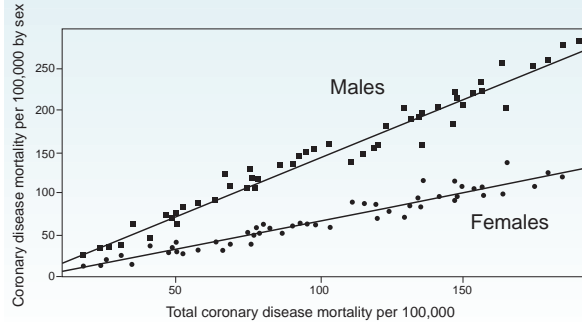
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Figure 1: Universal sex difference in coronary heart disease (CHD) death rates in 52 countries. The rate of CHD deaths per 100,000 persons differs for each country.¹



males. The result is obvious for reproductive anatomy, but more contested with regard to outcomes such as behavior. Premenopausal women are further defined as women with intact ovarian function. Natural and surgical menopause have been associated with an increased risk of atherosclerosis, suggesting that the premenopausal state confers cardioprotection. Studies of natural menopause and atherosclerosis are confounded by the increased risk of atherosclerosis with age. However, in women of the same age in the Framingham Study, the incidence of CVD was greater in women who were postmenopausal than those who were premenopausal.⁹ These data and others consistently confirm an association between menopause and increased cardiovascular risk. Similar observations have led to the hypothesis that the loss of estrogen may be the aspect of ovarian function that results in increased cardiovascular risk following menopause and that restoring estrogen levels would decrease this risk. This hypothesis has been supported by extensive, but not unanimous, observational evidence that estrogen therapy is associated with reduced cardiovascular risk.¹⁰⁻¹² Therefore, much research on the female advantage in cardiovascular disease has focused on estrogen production as the aspect of ovarian function that is responsible for cardio-protection.

Estrogen alters the basic biology of atherosclerosis

Estrogen production is one aspect of ovarian function that could explain the observed cardiovascular protection in women. For example, parenteral estrogen therapy markedly attenuates the development of atherosclerosis in female monkeys post-oophorectomy by directly modifying endothelial and vascular smooth muscle function. The healthy vascular endothelium provides a vasodilatory, anticoagulant, and antiadhesive surface for leukocytes and inhibits the proliferation of vascular smooth muscle cells.

The impact of estrogen deficiency on the endothelium has been evaluated by observing endothelial function following estrogen replacement. In these studies, exogenous estrogen enhanced endothelium-dependent vasodilation in normo-cholesterolemic animals post-oophorectomy, as well as in monkeys with dietary atherosclerosis post-oophorectomy.¹³⁻¹⁵ This improvement was associated with augmentations in nitric oxide and vasodilator prostaglandin levels. Restoration of endothelial health is also expected to decrease atherogenesis. Estradiol administration corrects coronary endothelium-dependent vasodilation in postmenopausal women, but not in men, with atherosclerosis.¹⁶ This observation suggests that estrogen receptors play an important role in the observed improvement in

vasodilation since these receptors are more abundant in women than in men. In women undergoing surgical menopause, there is impairment in endothelium-dependent vasodilation after oophorectomy that can be restored by estradiol administration.^{17,18} These findings indicate that estrogen has positive effects on the endothelium, effects that may be expected to decrease both the early and late manifestations of atherosclerosis.

Estrogen could benefit women in the setting of an acute coronary event via other mechanisms. Estrogen blunts vasoconstrictor responses to histamine, serotonin, angiotensin II, and norepinephrine.^{19,20} These responses are mediated by endothelial nitric oxide synthase and by free-radical scavenging. Estrogen may also moderate reperfusion injury through decreased inflammation within the infarct zone, decreased free-radical burst with reperfusion, and increased serum glutathione.²¹ Estrogen modifies vascular repair after injury, for example, blunting neointima formation after balloon injury.^{22,23} These animal and human studies elucidate mechanisms whereby estrogen could modify fatal CVD, and in combination with observational data, have led to randomized trials of estrogen therapy to decrease fatal CVD in women.²⁴ It is important to note that the Coronary Drug Project was the only randomized trial to examine the role of HRT in decreasing CVD prior to this time. The trial included only men and demonstrated an increased risk of myocardial infarction (MI) with high-dose conjugated equine estrogen. Therefore, many investigators were in a state of equipoise prior to the trials performed in women.

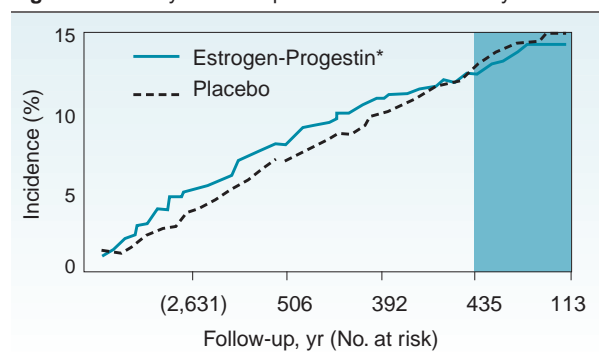
Randomized controlled trials of HRT in heart disease

The Heart and Estrogen/Progestin Replacement Study (HERS) was the first, major, completed, randomized trial of the effects of estrogen therapy on clinical outcomes in postmenopausal women with heart disease.²⁵ HERS randomized 2,763 postmenopausal women with CAD to receive 0.625 mg premarin with 2.5 mg medroxyprogesterone acetate (MPA) or placebo daily. No difference was found, since 13.0% (179/1380) of women in the hormone group and 13.2% (182/1383) in the placebo group experienced the primary endpoint of MI or cardiac death (Figure 2). One interesting observation in this trial was that the number of events in the first year was greater in the active treatment group, leading to the hypothesis that there is an increased early risk of cardiovascular events with the initiation of HRT.

Importantly, a similar worrisome trend was reported in participants of the Women's Health Initiative (WHI), a randomized trial of premarin and MPA.²⁶ WHI has enrolled 161,809 healthy, postmenopausal women, age 50- to 79-years, into a set of clinical trials testing postmenopausal hormone use, low dietary fat pattern, and calcium plus vitamin D therapy. As part of this extensive research program, 27,348 women were randomized to HRT or placebo. The 16,608 women who had not had a hysterectomy were randomized to either the combination of progesterone and estrogen (.625 mg conjugated equine estrogen plus 2.5 mg MPA) or placebo; 10,739 participants with a prior hysterectomy were randomized to either estrogen alone or placebo. On May 31, 2002, it was announced that the combination therapy in non-hysterectomy subjects was being prematurely terminated due to a worrisome net increase in adverse cardiovascular events.²⁶

The primary outcome of the WHI hormone therapy trial was coronary heart disease (CHD) (nonfatal MI and CHD death), with invasive breast cancer as the primary adverse event. The rate of CHD events was 29% higher in women receiving

Figure 2: Primary CHD endpoints in the HERS study²⁵

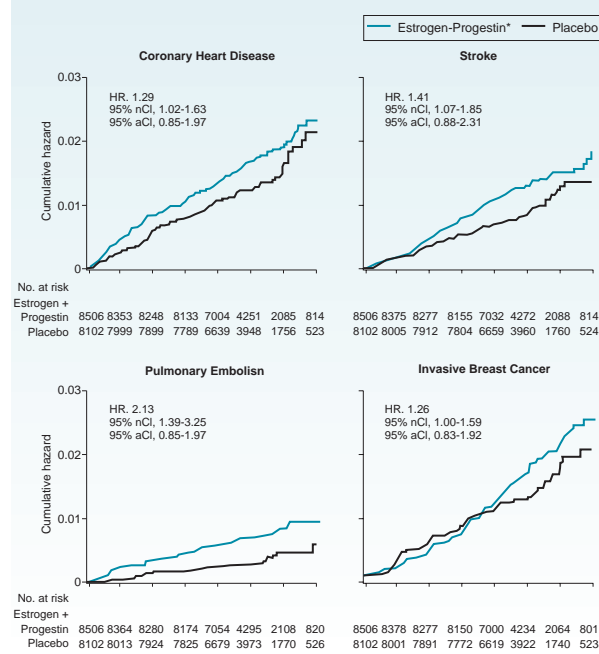


Log rank $P=0.91$

* Combined incidence of nonfatal MI and CHD death.

the combination therapy (Figure 3). In an attempt to sum up important aspects of benefit versus risk, a global index was utilized. This index addressed the issue that total mortality may be an insensitive indicator in this relatively healthy population. The global index was defined as the earliest occurrence of CHD, invasive breast cancer, endometrial cancer, pulmonary embolism, colorectal cancer, hip fracture, or death from other causes. Increased weight was given to the occurrence of CHD, invasive breast cancer, endometrial cancer, and pulmonary embolism compared to the weight given death from other causes in the calculation of the global risk index. Overall CHD rates were low, yet there was a 29% increase observed in women on active therapy ($P=0.05$). The majority of CHD events were nonfatal MIs. The global index demonstrated a 15% greater hazard in women on active treatment (Figure 4, panel A) that was not apparent when looking at death alone (Figure 4, panel B). For every 10,000 women treated per year, there was an excess of about 8 CHD events, 8 strokes, 8 pulmonary emboli, and 8 cases of breast cancer. Although there

Figure 3: Kaplan-Meier estimates of cumulative hazard for CHD, stroke, pulmonary embolism, and invasive breast cancer in the Women's Health Initiative (WHI) trial²⁶



were 6 and 5 per 10,000 per year fewer colorectal cancers and hip fractures, respectively, the Data Safety Committee recommended terminating the trial for excess risk from premarin in menopausal women with an intact uterus.

The results from WHI indicate that treatment with premarin/MPA should not be initiated or continued for prevention of CHD. Most importantly, these results reinforce the fact that all the effects of hormone therapy must be considered when contemplating its use as a therapeutic agent. For example, the risk of CHD and invasive breast cancer must be weighed against the benefit with regard to fracture in selecting agents for the treatment of osteoporosis.

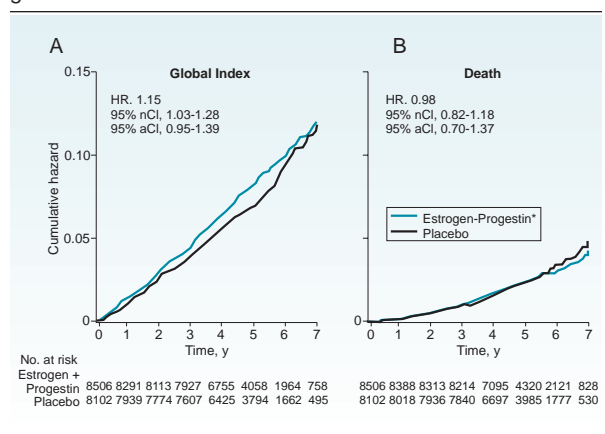
Where do we stand after the randomized trials?

Oral HRT has not provided cardiovascular protection to postmenopausal women. Oral HRT causes changes in thrombosis and inflammation, and these changes may contribute to the lack of observed benefit. There are clear differences between the net effects of oral HRT and parenteral or endogenous hormones. Therefore, the route of therapy may have contributed to the lack of observed benefit, and despite basic and observational data, estrogen may not be the aspect of ovarian function that is responsible for the evident cardioprotection in premenopausal women.

Estrogen therapy affects thrombosis

Oral estrogen clearly increases venous thromboembolic disease and could increase CHD events by increasing arterial thrombotic events. In several observational cohorts, women receiving HRT were about 2 to 3 times more likely to experience venous thromboembolic disease than nonusers.²⁷⁻²⁹ A similar increase in the risk of venous thrombosis was observed in women randomized to active treatment in trials of both estrogen with progesterone (HERS) and raloxifene.^{30,31} Activated protein C resistance, caused by factor V Leiden mutation, is a risk factor for venous thromboembolic disease in women during pregnancy and with oral contraceptive use, and may also increase the risk of deep vein thrombosis in women taking HRT. However, the pathology of venous thrombosis is clearly distinct from that of arterial thrombosis at the site of plaque rupture. Venous thrombi are fibrin-rich and platelet-poor, while arterial thrombi are platelet-rich. However, in light of the finding of an increased propensity for venous thrombosis with HRT, the hypothesis that there may also be an increased propensity for arterial thrombosis with HRT has sparked further investigation.

Figure 4: Kaplan-Meier estimates of cumulative hazards for global index and death in the WHI trial²⁶



One possibility that may explain increased cardiovascular risk with HRT is that prothrombotic mutations present in individuals may modify the association between hormone therapy and MI. This was examined in a population-based, case-controlled study in women aged 30- to 79-years with a first nonfatal MI between 1995 and 1998.³² The outcome measure was risk of first nonfatal MI based on current use of estrogen therapy and the presence or absence of prothrombin 20210A and factor V Leiden among cases and controls, stratified by hypertension. Among postmenopausal hypertensive women, the association between estrogen therapy and MI risk differed between those with and without the prothrombin 20210 variant. These findings suggest that screening for this variant may allow a better assessment of the risks and benefits of estrogen therapy in postmenopausal women.

Estrogen alters inflammation via multiple pathways

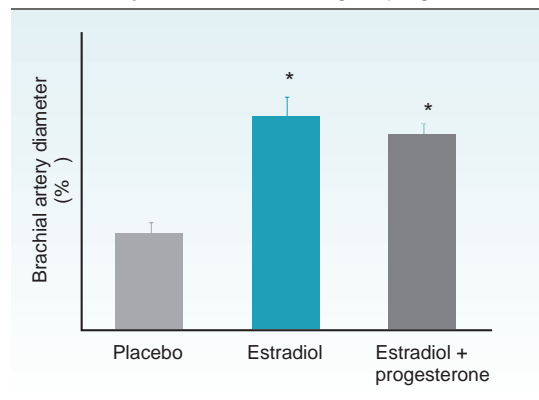
Inflammation may play a significant role in the pathogenesis of cardiovascular events, potentially by decreasing plaque stability. Indeed, increased levels of the inflammatory marker hs-CRP (high-sensitivity C-reactive protein) have been observed in women taking HRT in the Women's Health Study and in those randomly assigned to HRT in the Postmenopausal Estrogen Progestin Intervention (PEPI) trial.^{33,34} In healthy women participating in the Women's Health Study, hs-CRP was the only inflammatory or lipid marker measured that independently predicted cardiovascular risk over the traditional cardiovascular risk factors. Taken together, these findings raise concerns that HRT initiation may promote inflammation and plaque instability. Increased levels of CRP seen in women using HRT may represent hepatic induction with the oral estrogens or be representative of a generalized acute phase response.

Type and route of estrogen replacement therapy

The compounds and route of estrogen therapy selected in randomized trials may have contributed to the lack of observed benefit. Estrogen therapy in postmenopausal women is often referred to as estrogen "replacement." In fact, the therapy is not designed to restore premenopausal levels of estradiol and progesterone. Hormone therapy for women with intact uteri includes progesterone in order to reduce the increase in endometrial hyperplasia and endometrial cancer observed with unopposed estrogen therapy. Androgenic agents such as MPA may abrogate some of the beneficial effects of estrogen, in contrast to less androgenic progestins.³⁵⁻³⁷

Compounds are often administered orally and have additional effects that are attributable to first-pass hepatic metabolism. Compounds such as premarin contain many estrogenic compounds, in addition to low levels of estradiol. In contrast, transdermal estradiol contains a single compound and avoids first-pass metabolism. Differences in the hepatic production of oral and transdermal estradiol may affect hepatic production of compounds such as tissue type plasminogen activator levels.³⁸ Oral estrogen and progesterone administration may result in coagulation activation and increased fibrinolytic potential, whereas unopposed transdermal estradiol does not have any substantial effects on hemostasis.³⁹ In addition, while oral estrogen increases CRP levels, transdermal estradiol does not.⁴⁰

Figure 5: Transdermal route of estradiol administration improves endothelium-dependent flow-mediated vasodilation. The observed improved improvement is not attenuated by administration of vaginal progesterone.⁴¹



Transdermal estradiol administration results in improved endothelium-dependent vasodilation when administered to women with or without vaginal progesterone (Figure 5).⁴¹ This finding suggests that transdermal estradiol improves the bioavailability of the antiatherogenic compound nitric oxide, while avoiding the effects on thrombosis and inflammation secondary to first-pass metabolism. However, a cardioprotective benefit for transdermal estradiol has not been demonstrated in postmenopausal women and the risk for invasive breast cancer with this therapy is not clear.

Selective estrogen receptor modulation

If activation of estrogen receptors is essential for protection from CVD in premenopausal women, then selective activation of these receptors could confer further cardiovascular risk reduction in postmenopausal women and in men, and potentially avoid the observed risks of estrogen therapy.⁴⁷ Selective estrogen receptor modulators (SERMs) are nonsteroidal compounds (eg, tamoxifen and raloxifene) that can bind to estrogen receptors, and have intermediate properties between pure agonists and pure antagonists.⁴³ Efforts have focused on developing SERMs that have beneficial activity on bone and cardiovascular tissue, but none on reproductive tissue. Estrogen receptors act as transcription factors once they have been activated by binding and the conformation of the activated receptor depends on which compound is bound to the receptor. The conformation subsequently affects the binding of accessory proteins, co-repressors, and co-activators that will influence transcription. These accessory proteins are different in different tissues and may help explain the selective tissue effects among the different compounds.

Raloxifene is one of the first SERMs on the market because of its selective tissue effect profile.⁴⁴ Raloxifene has little effect on breast or endometrial tissue. It can lower LDL cholesterol, although to a smaller degree than estrogen, and has little effect on HDL cholesterol.⁴⁵ In contrast, it does not increase CRP to the same levels as oral estrogen.⁴⁶ In addition, raloxifene is approved for the prevention and treatment of osteoporosis.⁴⁷ Raloxifene is a less potent anti-resorptive agent than estrogen or alendronate. Raloxifene is also associated with an increased likelihood of

venous thromboembolic disease, similar to that seen with estrogen use.³⁰ There is a wide spectrum of tissue effects with current SERMs and a pure cardioselective estrogen receptor modulator has yet to be developed.

Raloxifene and cardiovascular events

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial enrolled 7,705 postmenopausal women with osteoporosis from 25 countries and followed them for an average of 3 years, excluding only women with malignancy or current estrogen use.³⁰ Women were randomized to 1 of 3 treatments: raloxifene 60 mg per day, raloxifene 120 mg per day, or placebo. At baseline, the average population characteristics were age 67 years, body mass index 25, total cholesterol 230 mg/dL, and LDL cholesterol 130 mg/dL. Only 2% of participants had known heart disease and 17% were cigarette smokers. Potential cardiovascular events were determined by a review of serious adverse event reports submitted to the sponsor. There was no significant difference in the cardiovascular event rate between active and placebo treatment. It is noteworthy that the MORE population was very different from the HERS population in that the total number of cardiovascular events was half that seen in the HERS population, while the number of subjects was twice as large. These small numbers markedly limit the ability to retrospectively observe a significant difference in cardiovascular events. A reduction of cardiovascular risk would be better demonstrated in a population at increased risk for atherothrombosis.

The Raloxifene Use in the Heart (RUTH) trial has enrolled 10,010 postmenopausal women with increased cardiovascular risk and will likely provide a more definitive assessment of cardiovascular risk or benefit from this SERM.

Other potential cardioprotective aspects of ovarian function

It is important to evaluate whether other aspects of ovarian function may be responsible for the cardioprotection observed in premenopausal women. Ovarian compounds such as activin-A, a member of the transforming growth factor beta superfamily and follistatin may have a role in atherogenesis. Activin-A is present in the systemic circulation and inhibits foam cell formation by regulating scavenger receptor mRNA expression;⁴⁸ this effect is abrogated by the binding protein, follistatin. Pregnancy-associated plasma protein A is a metalloproteinase found in men and women that is a specific activator of insulin-like growth factor 1, a mediator of atherosclerosis. It is also present in unstable plaques and much less so in stable plaques.^{49,50} Its production at times other than during parturition is unknown. The impact of other steroid hormones for cardioprotection or harm remains to be explored. These are selective examples of the other potential aspects of ovarian function that may play a role in cardioprotection.

Conclusion

The observation remains that female gender confers significant protection from CVD. It appears that oral HRT, as currently tested, does not confer this cardiovascular benefit to postmenopausal women. Therefore, we have yet to successfully “distill” and administer the female advantage with regard to cardiovascular disease. Ideally, this avenue of research should lead to identifying a way to

Table 1: Established guidelines for cardiovascular risk reduction

Therapeutic lifestyle changes	
• Smoking cessation	• Exercise
• Low cholesterol diet	• Weight loss
Treatment of risk factors	
• Hypertension	• Hyperlipidemia
• Diabetes	
Pharmacologic therapy	
• Antiplatelet agents	• Beta-blockers
• Angiotensin-converting enzyme inhibitors	• HMG CoA reductase inhibitors

extend the cardiovascular protection observed in premenopausal women to the entire population. Meanwhile, as healthcare providers, we need to ensure that both female and male patients receive the full complement of established therapies to reduce CVD (Table 1).^{50,51} Women should not be denied the benefits of proven therapies. For example, only 10% of the women with documented CAD who were enrolled in the HERS trial, had baseline LDL-cholesterol levels below the target of 100 mg/dL. At this time, we may not be able to distill and administer the “female advantage,” but we can improve cardiovascular care using established guidelines.

When currently assessing the postmenopausal woman, I feel it is important to assess her cardiovascular risk and treat it in a gender-blind fashion. Currently, I do not prescribe any form of sex HRT for cardiovascular risk reduction.

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Editor's note: In the July/August issue of *Cardiology Rounds*, entitled: *Exercise Testing, Part 2: The Value of Heart Rate Recovery* by Dr. Michael Lauer, the references for the figures were incorrectly identified. The correct reference for Figure 1 is #31, the reference for Figure 2 is #7, and the reference for Figure 3 is #23. My apologies for any inconvenience.

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