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Challenging Statin Pleiotropy: Preeclampsia

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Statins are increasingly being re-purposed as immune modulatory agents for non-cardiac systemic inflammatory diseases, including autoimmune disorders, inflammatory bowel disease, cognitive function/dementia, asthma and inflammatory lung disease, including COVID 19[1]. Currently 1 in 10 pregnancies result in term preeclampsia, which is the most common form of preeclampsia, is currently neither predictable or preventable, increases morbidity and mortality risk to both the mother and baby, and elevates future premature cardiovascular disease (CVD) risk in women[2]. Endothelial dysfunction and inflammation have been hypothesized to be involved in preeclampsia, suggesting they may be treatment targets, however relatively little investigation has been conducted.

While statins are traditionally used for lowering low density lipoprotein (LDL)-cholesterol to reduce CVD risk, the relation between statin-related LDL-cholesterol lowering and systemic inflammatory diseases is not well characterized. In pregnancy, cholesterol is not routinely measured, in part due to the known rise in cholesterol levels due to elevated placental steroid hormones, lack of normal pregnancy reference values and limited treatment options in pregnancy. While elevated maternal hypercholesterolemia has been linked to the development of preeclampsia, LDL-cholesterol appears to be less associated compared to total cholesterol, non-HDL-cholesterol and triglyceride levels[3]. In addition, women with familial hypercholesterolemia have not been demonstrated to have a higher risk of eclampsia, preeclampsia, or pregnancy-induced hypertension[4].

Rather, statin benefit in preeclampsia is hypothesized to rely on its non-cholesterol "pleiotropic" effects. Statins are thought to improve endothelial function and reduce inflammatory cytokines by reducing C-reactive protein (CRP) concentrations, inhibiting pro-inflammatory transcription factors, and blunting the T helper cell immune response[1]. Many of the proposed pleiotropic vascular effects of statins appear to involve restoring or improving endothelial function through increasing the bioavailability of nitric oxide, promoting re-endothelialization, reducing oxidative stress, and inhibiting inflammatory responses[5]. Yet more recent results from non-statin therapy CVD trials, including PCSK9

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inhibitors, ezetimibe, and bempedoic acid, challenge the concept of statin pleiotropy, dominantly failing to show differential benefit above that of LDL-lowering[1].

Given the emerging stance of healthy moms = healthy babies rationale stimulating the testing of medication for health conditions that adversely impact the health of mothers and therefore babies during pregnancy, in this issue the work of Döbert et al[6] is a welcome addition. Preliminary data from animal studies provided a strong rational for the use of pravastatin in preeclampsia prevention, but human trials have been lacking. In their double-blind, placebo-controlled trial of 1,120 women with singleton pregnancies at high-risk of term preeclampsia, the authors evaluated the effects of pravastatin 20 mg daily vs placebo from 35–37 weeks of gestation until delivery. They found no benefit of pravastatin for reducing the incidence of preeclampsia, with no evidence of interaction between the effect of pravastatin, estimated risk of preeclampsia, prior history of preeclampsia, adherence, and aspirin intake in prespecified subgroup analyses. There was also no difference in the treatment effects on soluble fms-like tyrosine kinase-1 concentrations (sFlt-1) and serum placental growth factor (PlFG), biomarkers that tend to higher and lower in preeclamptic vs normal pregnancies, respectively.

What are some potential explanations for these negative trial results? Serum sFlt-1/PlGF levels may start to elevate as early as 24 weeks gestation in some women who later develop term preeclampsia[7], thus starting pravastatin 20 mg at 35 weeks of pregnancy to reduce the later term pre-eclampsia outcome within 4–6 weeks may be too little statin given too late in the disease process. Indeed, a prior small clinical trial of pravastatin 10 mg starting at 12–17 weeks gestation had demonstrated promising trends toward higher PlGF and lower sFlt-1 levels with the statin[7], contrary to this study. While cholesterol lowering was not measured in this trial, clinical CVD trials usually demonstrate outcome benefits following more than 4 months of statin therapy[8], while the shorter-term benefits are typically observed with more potent statins at higher doses[9]. Thus, the lower potency and dose of the pravastatin may have contributed to the lack of benefit, as the more potent and higher dose atorvastatin has a documented shorter onset of benefit compared to other lower intensity statins[8]. Interestingly, despite comparable LDL lowering effects between simvastatin 40 mg and simvastatin 10 mg/ezetimibe 10 mg, simvastatin 40 mg produced greater flow-mediated dilation (improved endothelial function) than simvastatin 10 mg/ezetimibe 10 mg[10]. The findings of this study support the notion of statin pleiotropy that is dose-dependent and is in addition to the benefits of LDL lowering. Finally, the use of a hydrophilic statin, pravastatin, which has less vascular wall permeability compared to that of lipophilic statins, may be far less effective in preventing the detrimental effects of pre-eclampsia pro-inflammatory cytokines. It is also possible that the cytokine-mediated sFlt-1 and PlGF levels measured in the study, which did not differ by group in the current study, are not affected in the short-term by the pleiotropic effects of a low dose statin (Figure[5]). The low use of aspirin in the current study compared to the common use with statins in CVD trials may have also been a factor.

Over the last decade, emerging data regarding statin safety in pregnancy has questioned the original classification of all statins as category X medication. Statins have not been shown to be independently associated with increased risk of congenital malformations when taken in the first-trimester[11], with no adverse perinatal effects observed when taken in the

second and third trimesters in two small double-blinded placebo-controlled randomized clinical trials[7, 12]. In these two trials, both daily pravastatin 10 mg and 40 mg initiated between 12–17 weeks or 24–32 weeks (respectively) resulted in drug concentrations in umbilical cord and maternal blood near or below the lowest level of quantification of the assay, supporting the limited transplacental transfer of the hydrophilic pravastatin. Although pravastatin reduced maternal cholesterol levels, umbilical cord blood cholesterol levels and infant birthweight did not differ[7]. As expected with an intermediate pravastatin dose with short duration at the end of the third trimester, Döbert and colleagues' study provides some additional reassurance for lack of signal for adverse fetal, neonatal or maternal adverse outcomes. Consideration of a second-trimester potent statin might be considered in future trials, although sample size may be prohibitive unless a preeclampsia risk predictive model can be developed for second trimester.

Attempts to improve the prediction of preeclampsia have increased in the past decade, with the inclusion of angiogenic markers sFlt-1 and PlGF and blood pressure thresholds. An important contribution of the current investigation[6] is the validation and demonstrated effectiveness of the Bayesian model that detects term preeclampsia 75% with a clinically relevant 10% screen positive. This Bayesian model includes maternal demographic characteristics and medical history, as well as late third trimester mean arterial pressure and maternal serum sFlt-1 and PlGF levels. Thus, new trials testing additional interventions can now be planned with appropriate power/sample size for this important and common condition in pregnant women.

In summary, while knowledge gaps remain regarding the pleiotropic effect of statins in CVD and non-cardiac systemic inflammatory diseases, the current study adds to the evidence that statins likely confer the majority of benefit through LDL lowering. Additionally, substantially more knowledge gaps remain in our understanding of the pathophysiology of preeclampsia, as well as the mechanistic links between preeclampsia and future CVD in women, in part due to the prior stance of excluding pregnant women in research studies. We and others have documented mechanistic links between adverse pregnancy outcomes including pre-eclampsia with subsequent premature hypertension[13], ischemic heart disease with coronary microvascular dysfunction[14], and left ventricular hypertrophy and myocardial fibrotic scar[15]. The NHLBI-sponsored NuMoM2b-HHS[14] is exploring these gaps, and future investigation, including well-designed and rigorous randomized controlled trials such as Döbert and colleagues should be conducted in women during pregnancy.

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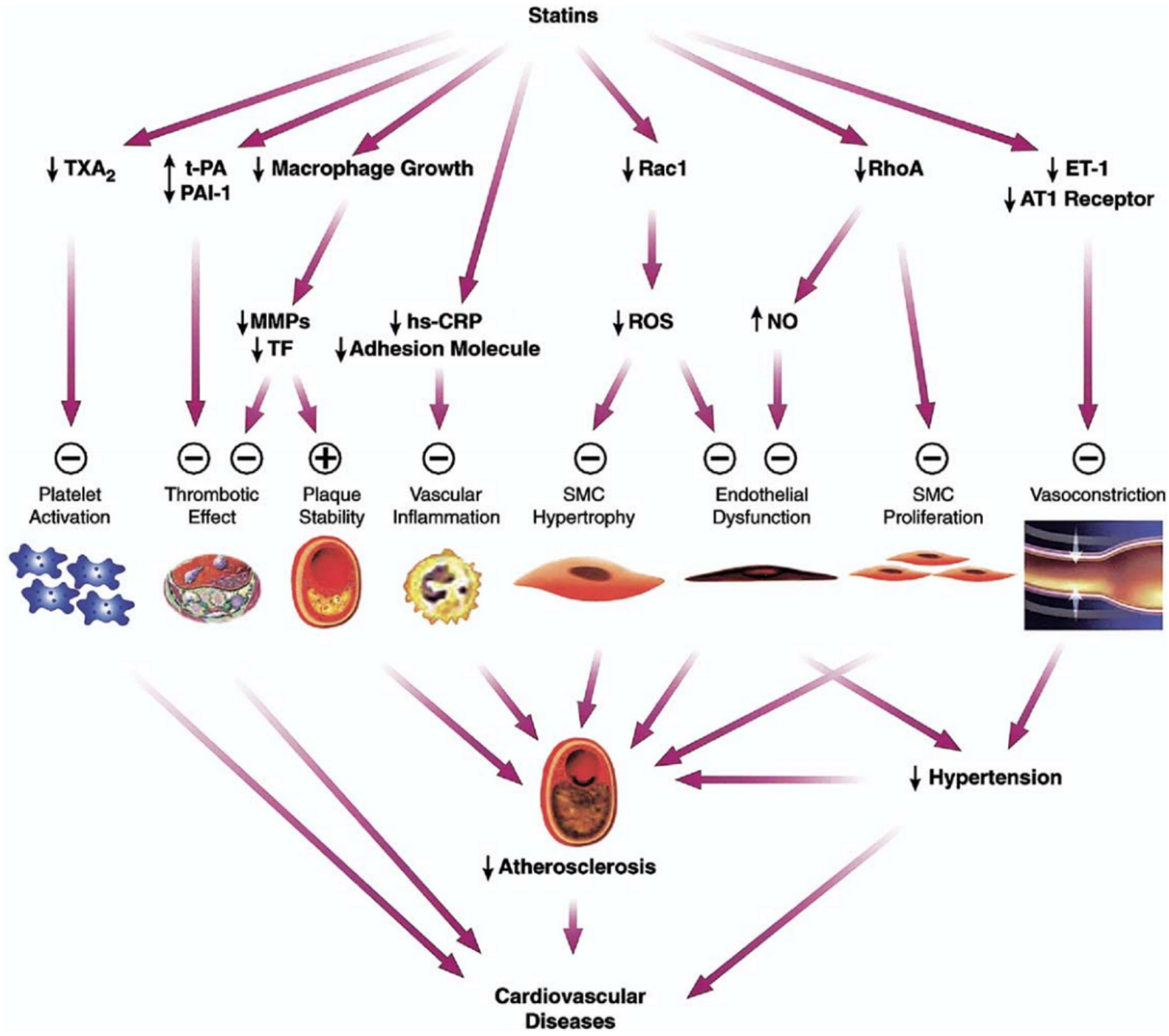

Figure : Pleiotropic effects of statins.

Plus sign = enhanced/activated; minus sign = inhibited; AT11 = angiotensin 1; ET-1 = endothelin 1; hs-CRP = high-sensitivity C-reactive protein; MMPs = matrix metalloproteinases; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1; ROS = reactive oxygen species; SMC = smooth muscle cell; TF = tissue factor; t-PA = tissue-type plasminogen activator; TXA2 = thromboxane A2. (Reprinted with permission[5])