Lipids in Women Across the Lifespan

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#WCIRDC2022

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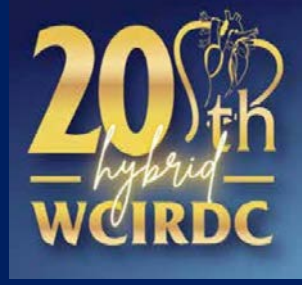
Disclosures

- Dr. Michos reports Advisory Boards with Amgen, AstraZeneca, Amarin, Bayer, Esperion, Novartis, Novo Nordisk, and Pfizer



Sex Differences in lipids: Epidemiology

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Epidemiology of Cholesterol in Women

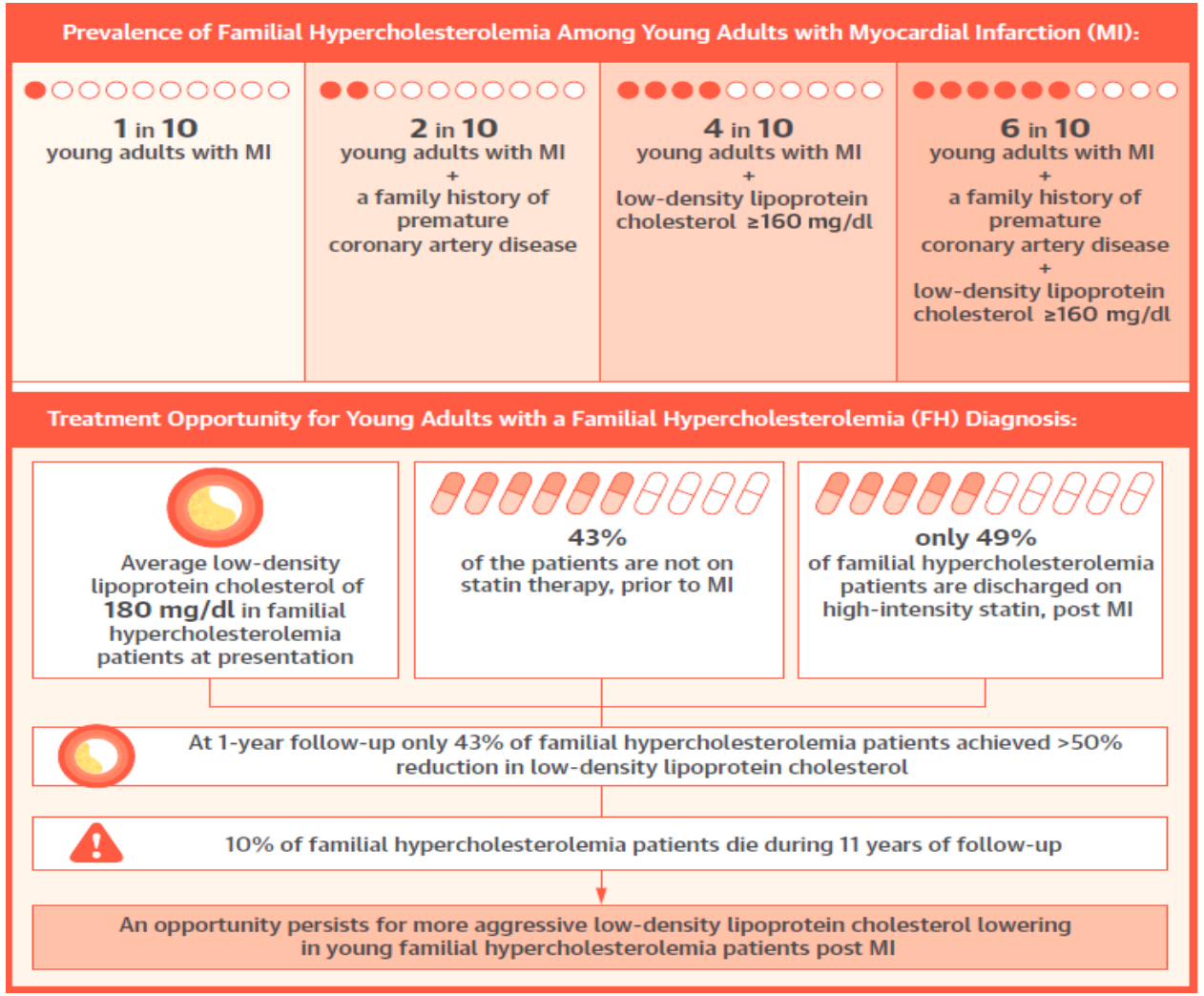
- Based NHANES data representing the U.S. population from 2015-2018:
  - 52.3 million women (40.4%) have a total cholesterol ≥200 mg/dL
  - 15.8 million women (12.1%) have a total cholesterol ≥240 mg/dL
  - 10.3 million women (8.5%) have a HDL-C <40 mg/dL

- From NHANES data 2013-2016:
  - 34.8 million (27.6%) of women had an LDL-C ≥130 mg/dL

- Total cholesterol levels are similar for women and men <35 years; however, subsequently there are sex-specific differences by age.
  - Compared to men, total cholesterol is lower in women for ages 35 to 49 years
  - Then higher in women compared to men after age 50

Familial Hypercholesterolemia (FH)

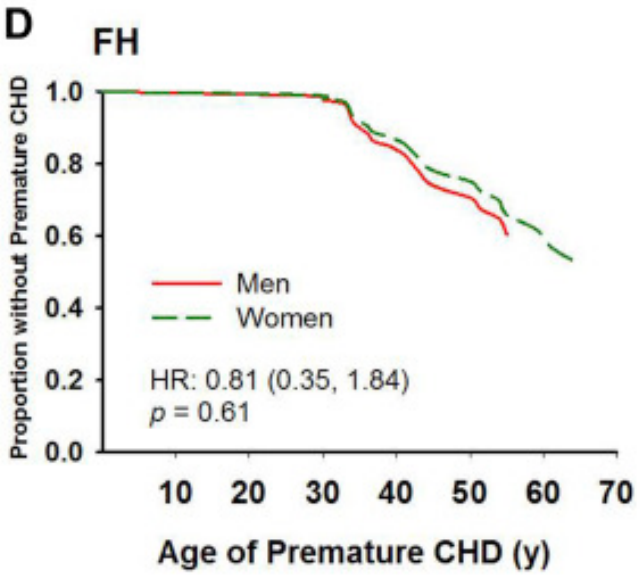
- Approximately 1 in 250 people has definite/probable FH
- Autosomal dominant
- 20-fold increased CVD risk
- FH phenotype (LDL-C >190 mg/dL) has acceleration in CHD risk
  - 10 to 20 years in males
  - 20 to 30 years in females
- ~30% of untreated women with FH will have a MI before age 60
- Continues to be undertreated



Singh A et al. *J Am Coll Cardiol*. 2019;73(19):2439-2450.
Virani SS, et al. *Circulation.* 2020;141(9):139-596.

FH and women – long term CVD risk

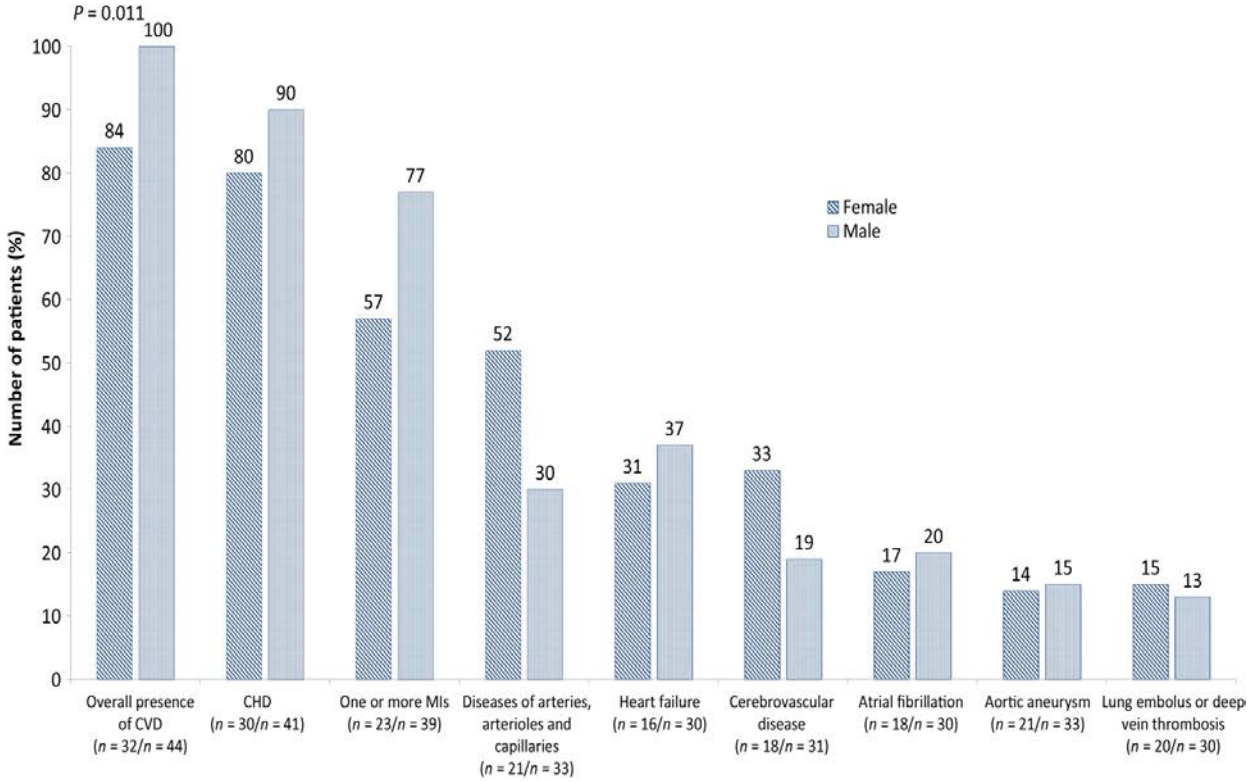
- Women with FH lose their female protection against CVD
  - Same age of onset of CVD as men
- ?Possible role – loss years of statin therapy due to concerns of pregnancy



FH adjusted for LDL-C and HDL-C as well as diabetes, hypertension, and smoking status.

Ahmad Z et al. Premature coronary heart disease and autosomal dominant hypercholesterolemia: Increased risk in women with LDLR mutations. *Journal of clinical lipidology*. 2016;10:101-8 e1-3.

No sex differences in age at the first CVD event or age at the time of death.



Presence of CVDs in FH patients at time of death by sex

Krogh HW et al Eur Heart J; 2016: Volume 37, Issue 17, Pages 1398–1405,

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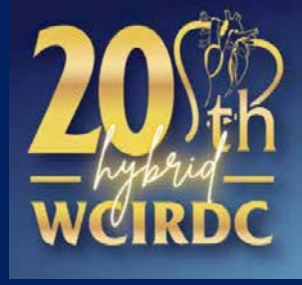

Lipid Levels in Women: Menses, PCOS, & Menopause

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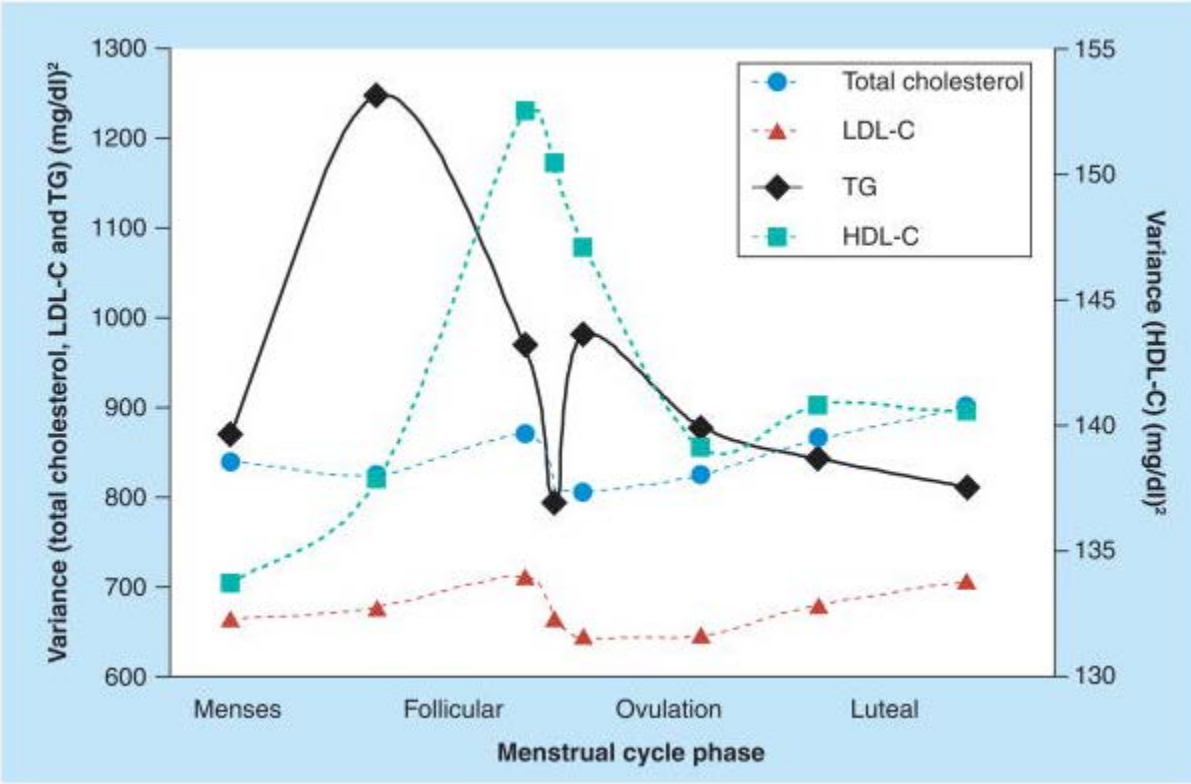
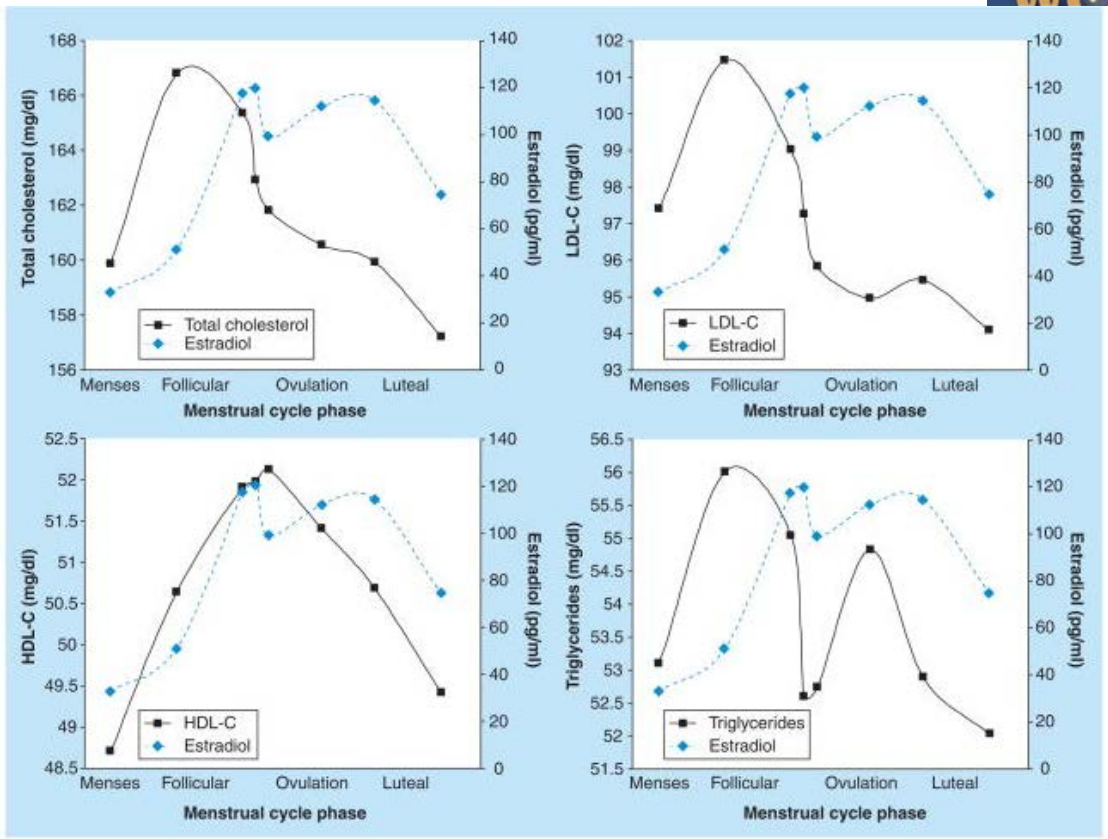
Change in lipid profile during menstrual cycle



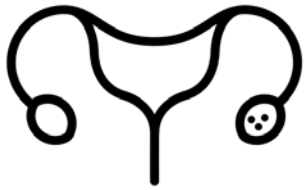
Significant reductions in total cholesterol, HDL cholesterol, and triglyceride concentrations in the luteal phase relative to the follicular phase



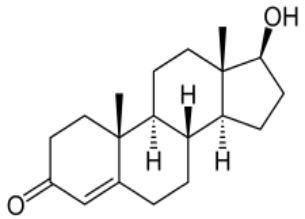
- TC and LDL-C levels increase rapidly after menses, peaking during the follicular phase and then declining throughout the luteal phase.
- Peak levels of TC and LDL-C were observed during the follicular phase prior to the rise and peak of estrogen, with TC and LDL-C levels declining during the luteal phase, corresponding to rising and peak concentrations of estrogen and progesterone.
- HDL-C levels were highest around ovulation, corresponding to high levels of estrogen, whereas triglyceride levels varied without a consistent pattern across the cycle.

Mumford, Sunni L et al. “Variations in lipid levels according to menstrual cycle phase: clinical implications.” Clinical lipidology vol. 6,2 (2011): 225-234.

Cardiovascular Risk in PCOS



Polycystic Ovary Syndrome



Hyperandrogenism

Cardiometabolic Risk Factors

Insulin resistance/Prediabetes/Diabetes
Elevated Blood Pressure/Hypertension
Dyslipidemia
Obesity
[and complications in pregnancy]

Atherosclerosis

Coronary Calcium
Carotid plaque

Cardiovascular Disease

Coronary Heart Disease
Stroke

Guan C…..**Michos ED**. *Fertility & Sterility 2022*

3 fold increased risk for T2D

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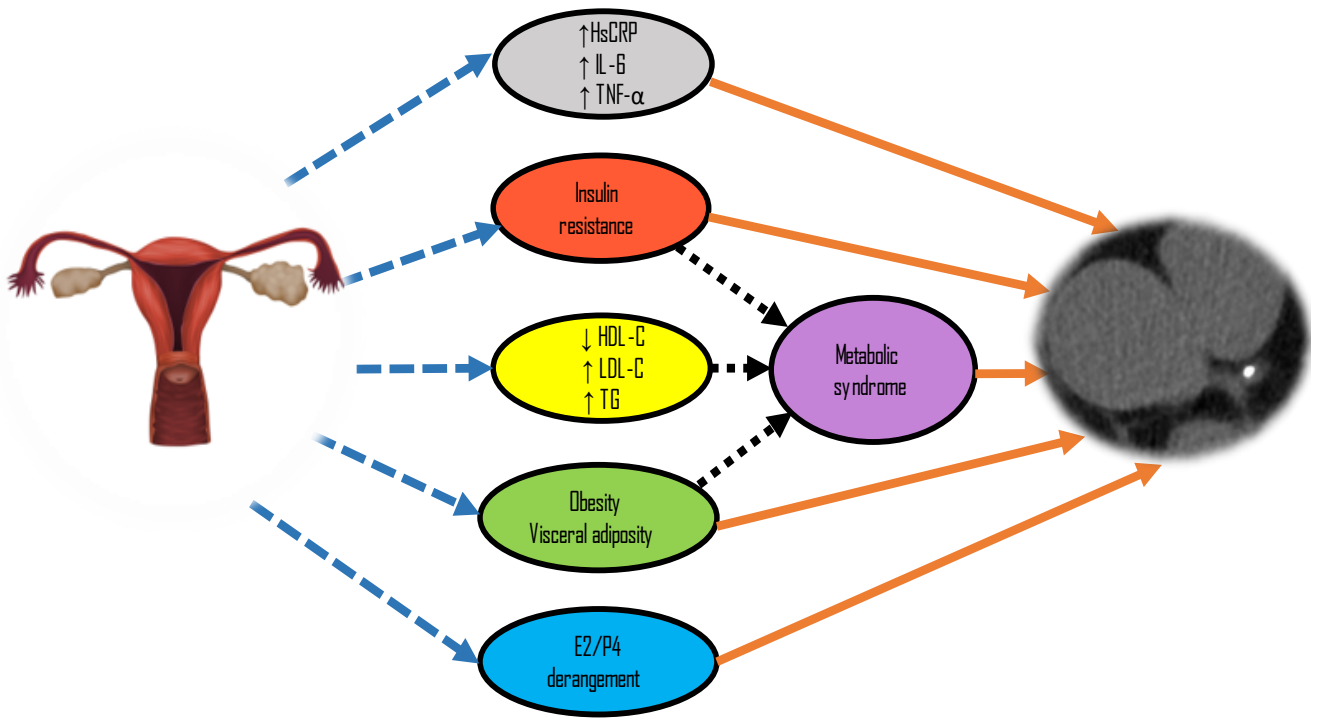
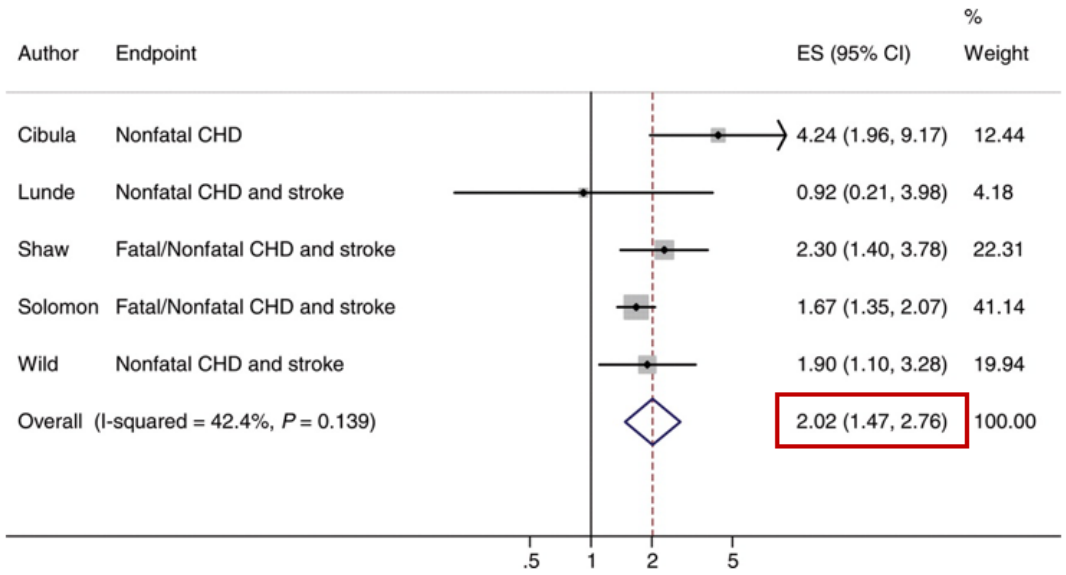
Cardio-Metabolic Risk in PCOS



Polycystic ovarian syndrome – 2 fold CVD risk

Meta-analysis of five cohort studies on the risk of CHD and stroke in PCOS.



de Groot P et al. Hum. Reprod. Update 2011;17:495-500

Osibogun O…..**Michos ED**. *Trends in CV Medicine* 2019

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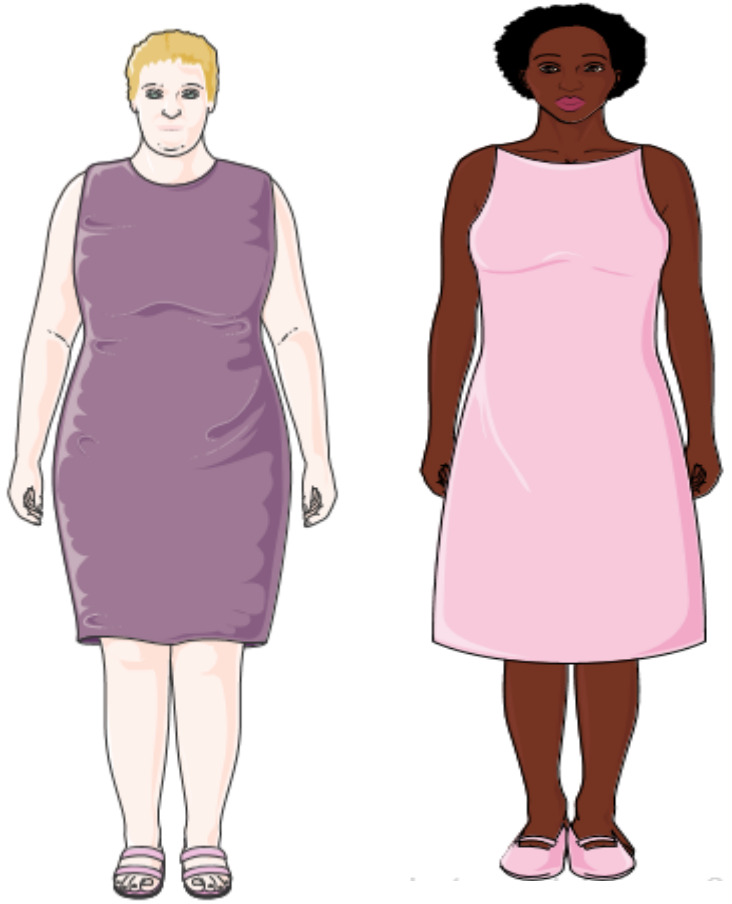
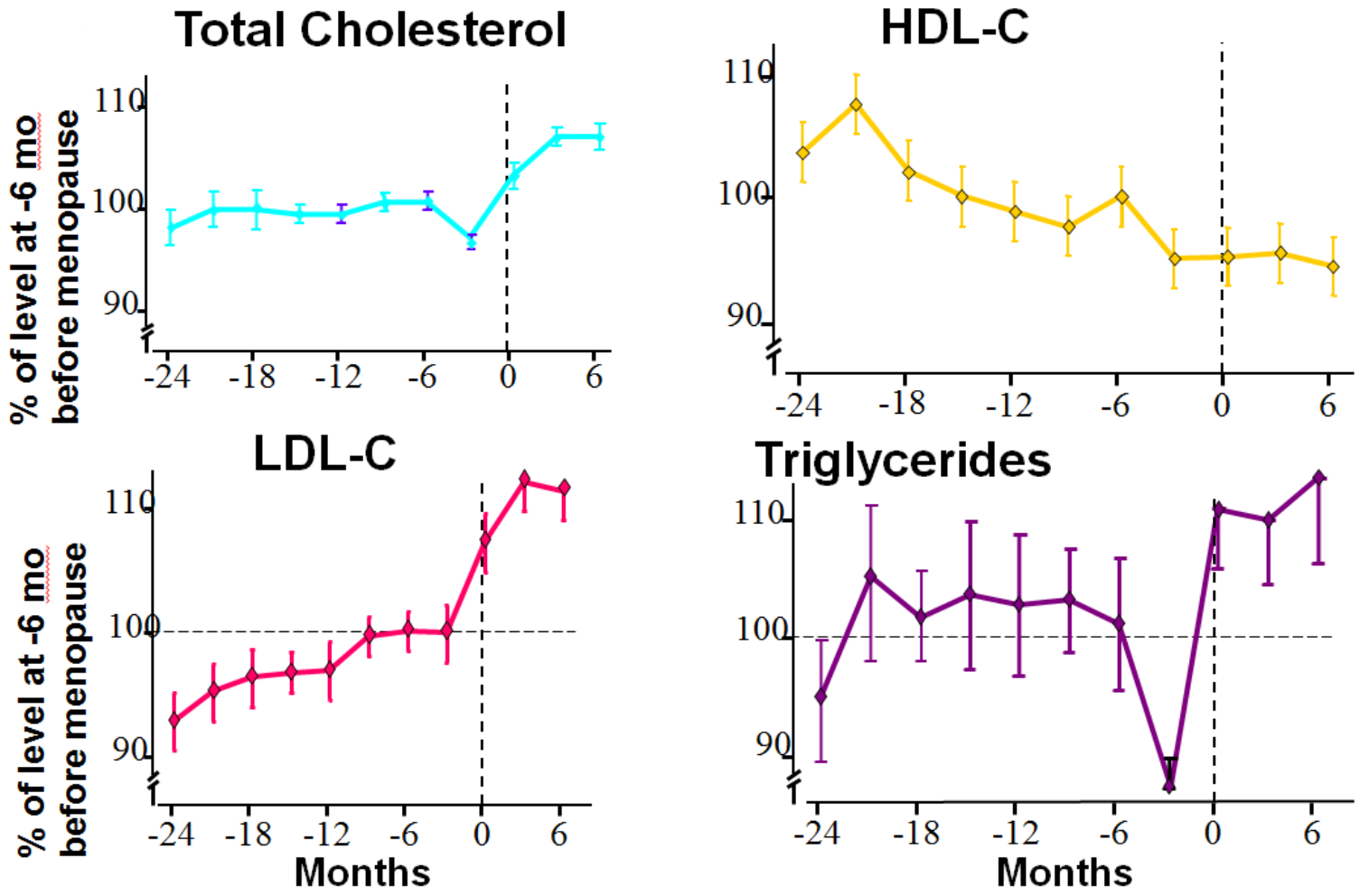
Metabolic Changes at Menopause

- Visceral fat: ↑ adipose deposition in abdomen and abdominal cavity
- Dyslipidemia: ↑ TG, ↑ LDL-C, ↓ HDL-C
- ↑ Lp(a) at menopause
- Insulin dysregulation: ↑ Insulin resistance, ↓ insulin secretion
- Endothelial dysfunction
- ↑ Blood pressure
- ↑ Sympathetic tone



Change in Lipids After Menopause



Jensen J et al. Maturitas 1990;12:321-31.

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Lipid Levels in Women: Pregnancy

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Cardiovascular Health among US Pregnant Women

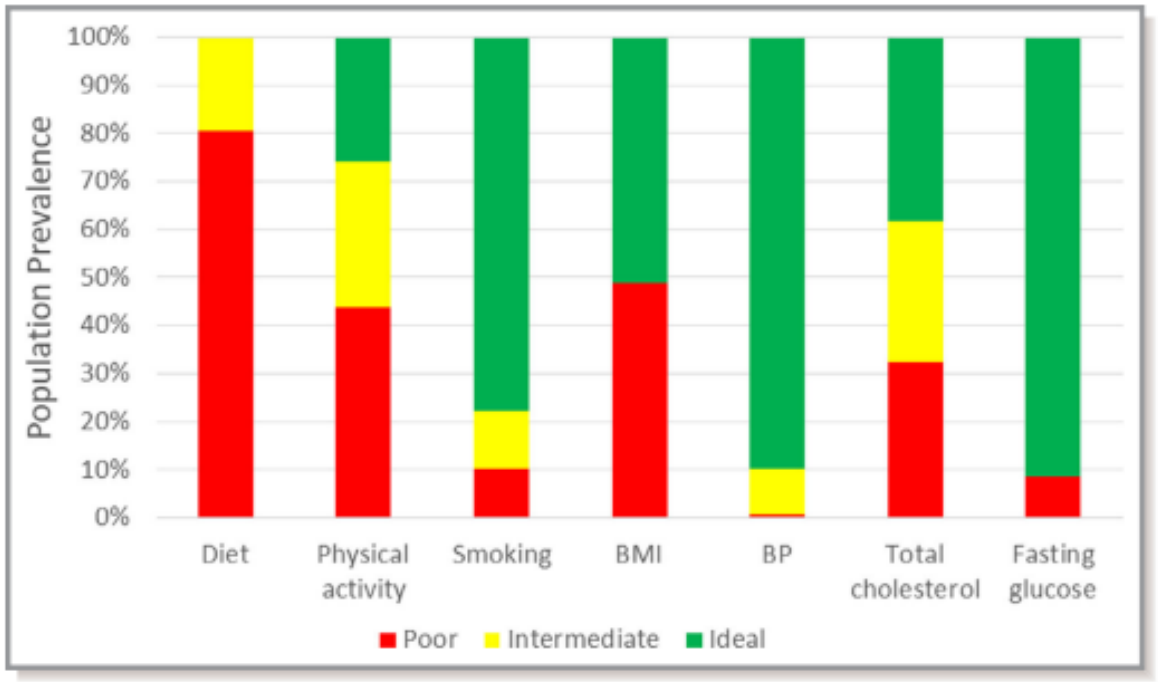

Figure 1. Status of individual cardiovascular health metrics among pregnant women, aged 20 to 44 years, in the United States, 1999 to 2014*. All estimates are based on population-weighted data from the National Health and Nutrition Examination Survey. *Body mass index (BMI) and fasting plasma glucose data are for 1999 to 2012, as month of pregnancy information was not available in 2013 to 2014. BP indicates blood pressure.

- From 1999 to 2014: <1 in 10 US pregnant women, aged 20 to 44 years, had high CVH.
- Among pregnant women, the prevalence of ideal levels of CVH metrics were 0.1% for diet, 27.3% for physical activity, **38.9% for total cholesterol**, 51.1% for body mass index, 77.7% for smoking, 90.4% for blood pressure, and 91.6% for fasting glucose.
- The mean total CVH score was 8.3 of 14
- High CVH in 4.6%, moderate CVH in 60.6%, low CVH in 34.8%.

Perak AM et al. J Am Heart Assoc. 2020;9(4):e015123.

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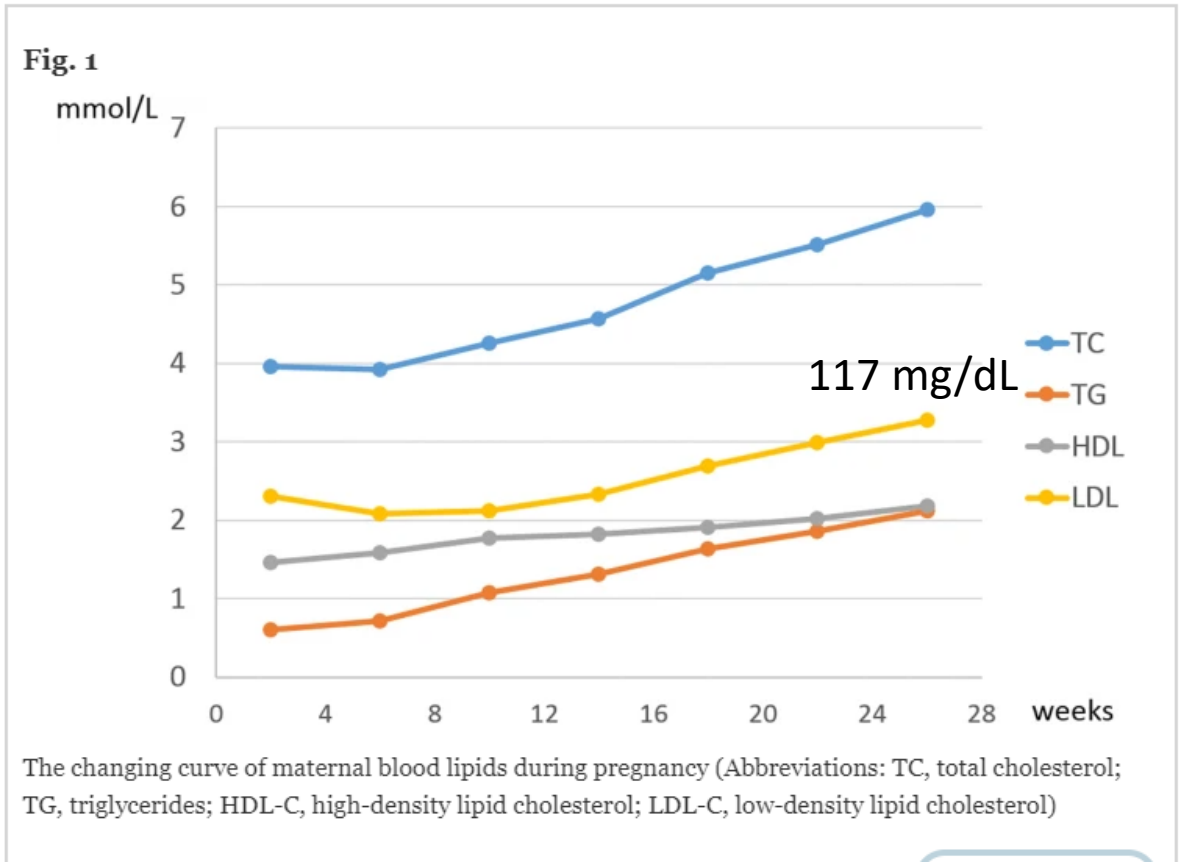
Cholesterol in Pregnancy

- Total cholesterol and TG levels rise during pregnancy, so women with known lipid disorders are recommended to have consultation with a lipid specialist prior to pregnancy.



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Statins in Pregnancy

- Early uncontrolled case series reported congenital anomalies associated with statins
- More recent observational studies showed no increased risk of congenital anomalies
- Karalis et al performed systematic review of 16 clinical studies

Karalis DG et al. J Clin Lipidol 2016; 10: 1081-1090

- "Our findings show no clear relationship of congenital anomalies with statin use in pregnancy, and our study supports the findings that statins are probably not teratogenic. However, until more information is available, statins should still be avoided in pregnancy."

- July 2021: FDA removes strongest label warning regarding statins in pregnancy
- Most women may stop statin prior to pregnancy but allows flexible options for women at highest CV risk

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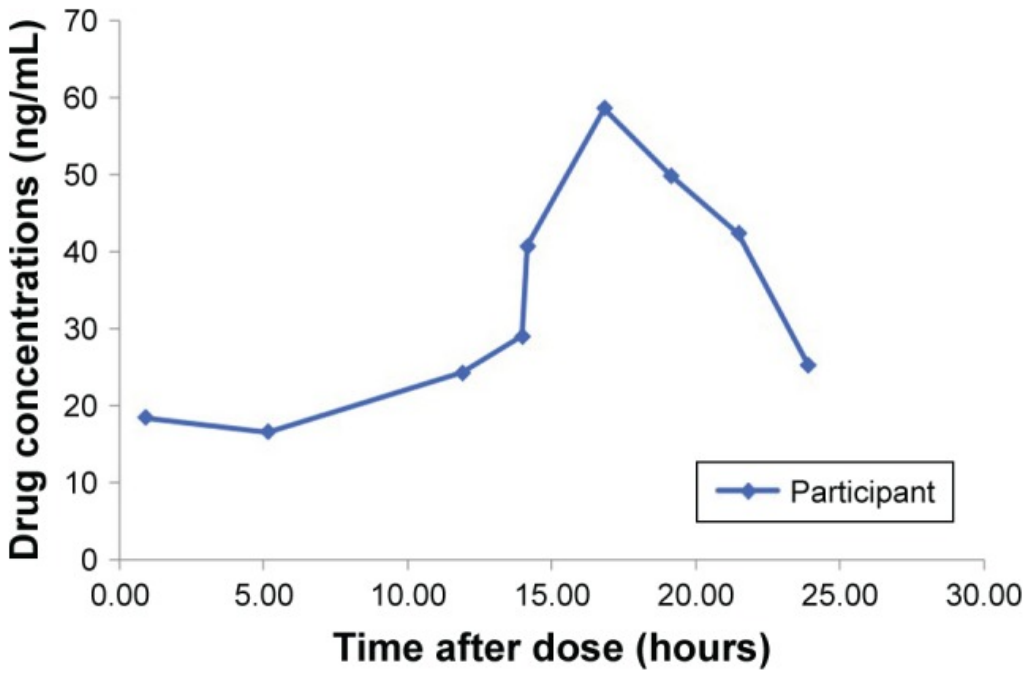
Statins and Breast Feeding

A 38-year-old breastfeeding mother was commenced on rosuvastatin 20 mg daily for secondary prevention after an ACS. Eight maternal breast milk samples and a single plasma sample were collected over a 24-hour period. The samples were quantified using a sensitive LC-MS/MS method.



Concentration–time curve of rosuvastatin in breast milk

- Very limited data on infant exposure via breast milk, but estimated exposure is low.
- The average concentration of rosuvastatin in breast milk was 30.84 ng/mL, and a peak concentration of 58.59 ng/mL occurred at 17 hours after oral administration. Although the milk-to-plasma (M/P) ratio was 16.49 at 14 hours, the theoretical infant dosage (TID) and relative infant dose (RID) were 0.005 mg/kg/day and 1.50%, respectively.
- The findings suggest that only small amounts of rosuvastatin pass into breast milk. Should the maternal condition necessitate treatment, consideration could be given to the use of rosuvastatin during breastfeeding provided the infant is monitored.

Lwin EMP, Leggett C, Ritchie U, Gerber C, Song Y, Hague W, Turner S, Upton R and Garg S. Transfer of rosuvastatin into breast milk: liquid chromatography-mass spectrometry methodology and clinical recommendations. *Drug Des Devel Ther*. 2018;12:3645-3651

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Lipid Lowering Therapies in Pregnancy

- Diet/Lifestyle
- Statins
  - Removal of strongest warning label
  - Most pregnant patients should still stop
- Ezetimibe
  - Pregnancy category C
- Bile Acid Sequestrants
  - Pregnancy category B (colesevelam) or C (cholestyramine) or not assigned (colestipol)
- Omega 3 supplementation
  - Pregnancy category not assigned
- Apheresis
  - Lipoprotein apheresis is also approved during pregnancy and considered safe for very high risk women with known significant atherosclerotic disease or HoFH

- Bile Acid Sequestrants
  - PRO
    - Not systemically absorbed, Felt safe in pregnancy
    - Lower LDL-C by ~15-20%
  - CON
    - GI side effects (constipation, heartburn, bloating, stomach pain)
    - Can elevate TGs (don't use for TG above 300 mg/dL)
    - Reduce absorption of certain meds

FDA Pregnancy Categories

Category	Description
A	Controlled studies of pregnant women show no risk in first trimester
B	Animal studies show no risk, or animals show risk unconfirmed in humans
C	Animal studies show risk, caution is advised, benefits may outweigh risks
D	Evidence of risk to human fetus, benefits may outweigh risks in serious conditions
X	Risk outweighs benefit

Adapted from Dwosh E, et al. Int MS J. 2003;10:52-59.

MedscapeCME

- Other LDL-C lowering agents – no safety data in pregnancy
  - PCSK9 inhibitor mABs
  - Inclisiran
  - Bempedoic acid

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Pre-pregnancy Lipid Levels and Risk of Pre-eclampsia

3494 women who gave birth after participating in the Nord-Trøndelag health study at baseline; of whom 133 (3.8%) delivered after a pre-eclamptic pregnancy

Pre-pregnancy Lipid Levels	aOR* of pre-eclampsia	Pre-pregnancy Lipid Levels	aOR* of pre-eclampsia
Triglycerides (mg/dL)		**HDL-C (mg/dL)**	
<60	REF	<46	1.3 (0.8, 2.4)
60-80	1.1 (0.6, 2.0)	46-54	1.3 (0.8, 2.2)
80-100	1.0 (0.6, 1.9)	54-58	1.3 (0.7, 2.5)
100-135	1.0 (0.5, 1.8)	58-65	1.1 (0.6, 1.8)
>=136	1.6 (0.9, 2.9)	>=65	REF
Total Chol (mg/dL)		**LDL-C (mg/dL)**	
<158	REF	<95	REF
158-174	1.3 (0.7, 2.4)	95-112	1.4 (0.8, 2.6)
174-190	1.0 (0.5, 2.0)	112-128	1.4 (0.7, 2.5)
190-216	1.2 (0.6, 2.3)	128-147	1.1 (0.6, 2.1)
>=216	**2.1 (1.2, 3.8)**	>= 147	**2.4 (1.3, 4.3)**

†Adjusted for maternal age at birth, duration between the baseline study and index delivery, education, parity, previous pre-eclampsia, smoking, receiving social security benefits, and time since last meal.

Magnussen EB et al. BMJ 2007;335(7627):978.

Medical Birth Registry of Norway. Analyses included 13 217 singleton pregnancies (average of 1.59 births to 8321 women) without preexisting hypertension

Pre-pregnancy Lipid Levels	aOR* of pre-eclampsia	aOR* of pre-eclampsia with pre-term delivery	aOR* of pre-eclampsia with term delivery
TG (mg/dL)			
<150	REF	REF	REF
>=150	**2.4 (1.71–3.30)**	**2.3 (1.29–4.07)**	**2.4 (1.65–3.52)**
Chol/HDL ratio			
<5.0	REF	REF	REF
≥5.0	**1.8 (1.17–2.84)**	**2.4 (1.24–4.65)**	1.6 (0.94–2.85)

Multinomial logistic regression model included covariates: baseline age (years), daily smoking (yes vs no), parity (0, 1, ≥2), pregravid diabetes mellitus, pre-CONOR history of gestational hypertension or preeclampsia, marital status (married/common law partner vs other), region of survey (Oslo vs other), education (≤12, 13–16, ≥17 y), and time between CONOR and delivery (months); mother was entered as a cluster variable.

Grace M. Egeland GM et al. *Hypertension*. 2016;67:1173-1180

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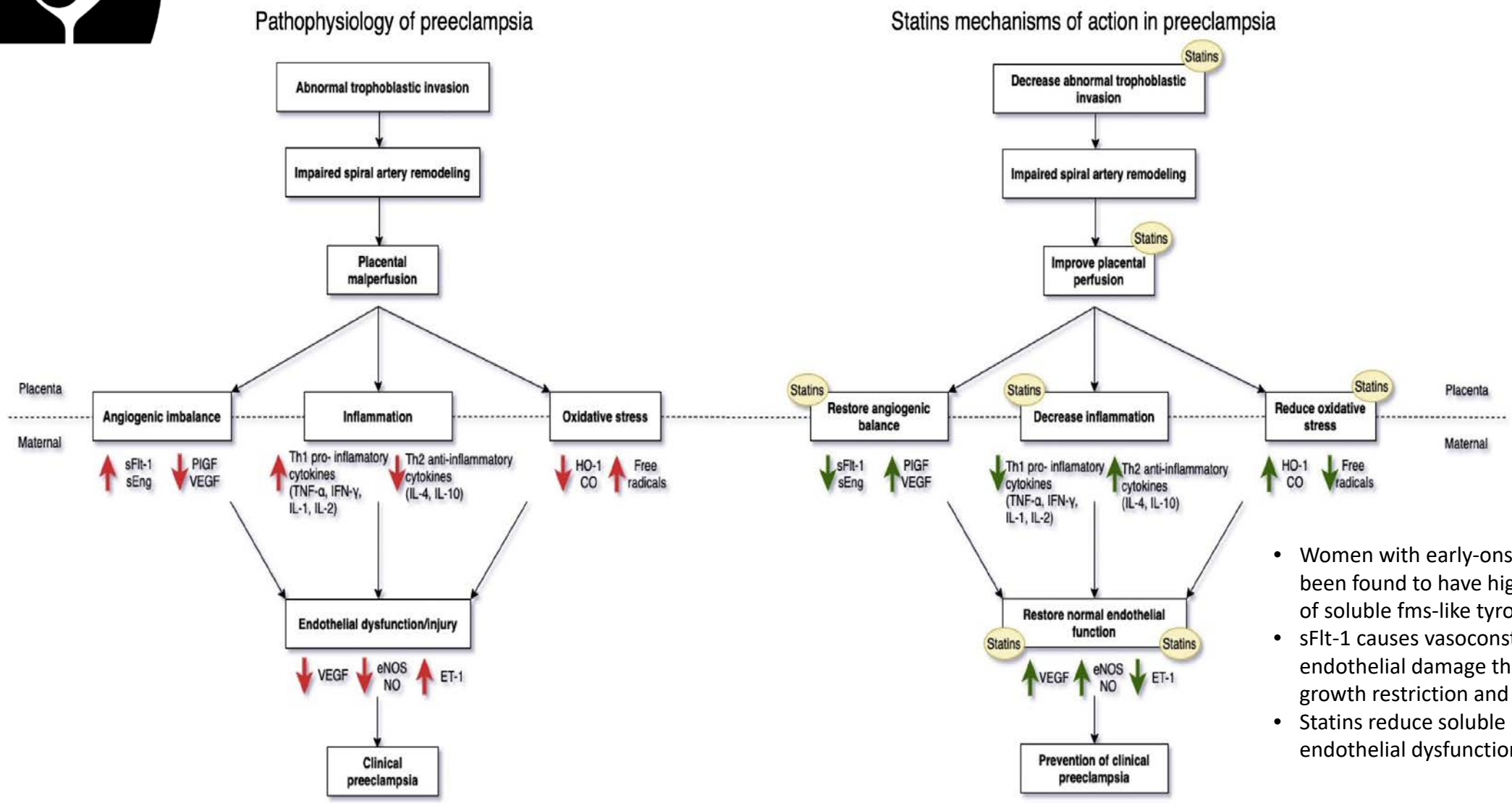
Statins for Prevention of Pre-eclampsia?



- Women with early-onset preeclampsia have been found to have higher circulating levels of soluble fms-like tyrosine kinase-1 (sFlt-1)
- sFlt-1 causes vasoconstriction and endothelial damage that may lead to fetal growth restriction and preeclampsia
- Statins reduce soluble Flt1, and quench endothelial dysfunction

Smith DD et al American Journal of Obstetrics & Gynecology 2020

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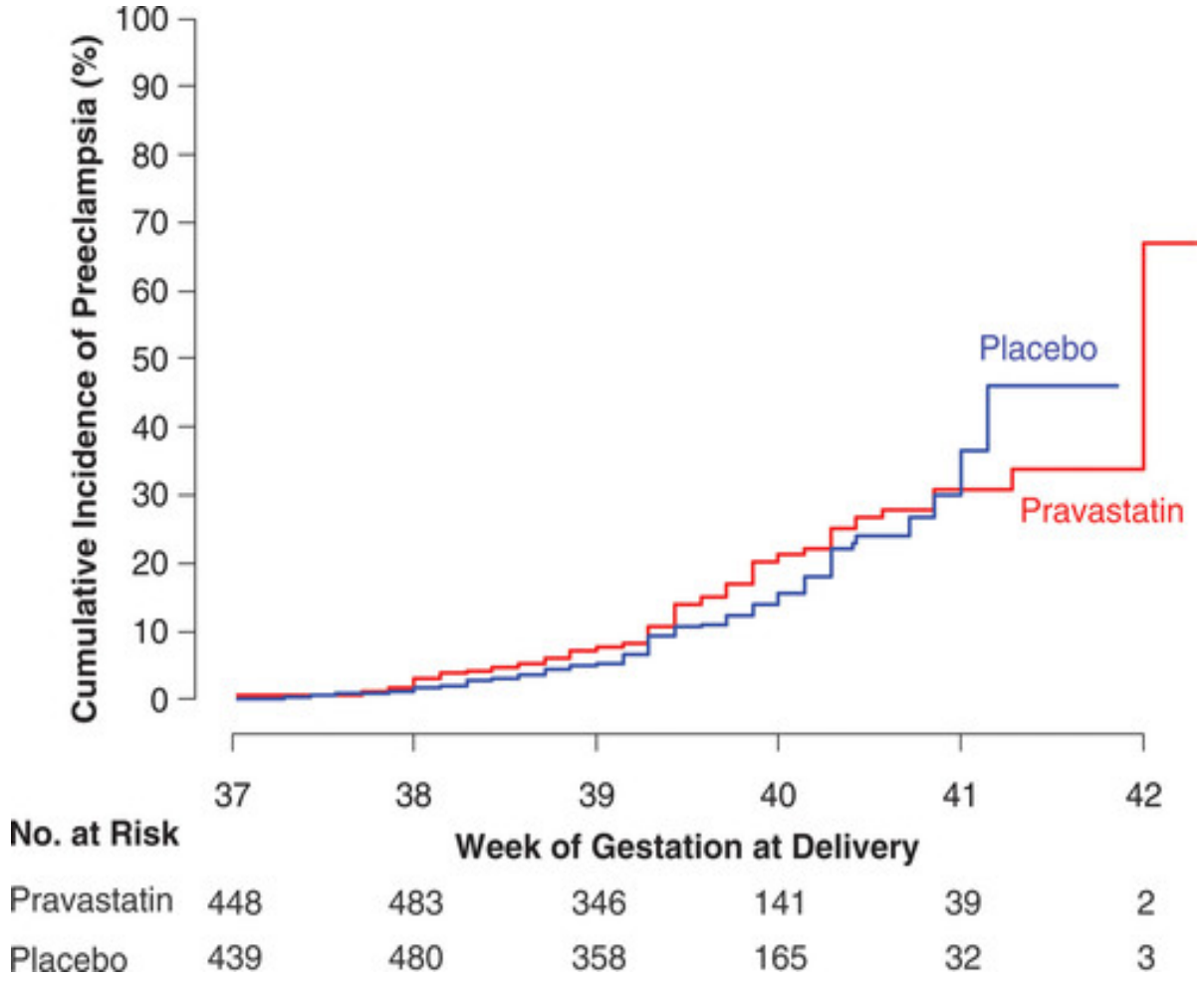
Pravastatin Versus Placebo in Pregnancies at High Risk of Term Preeclampsia



- 1120 women with singleton pregnancies at high risk of term preeclampsia to receive pravastatin 20 mg/d or placebo **from 35 to 37 weeks** of gestation until delivery or 41 weeks.
- The primary outcome was delivery with preeclampsia at any time after randomization.
- Cox regression showed no evidence of an effect of pravastatin (hazard ratio for statin/placebo, 1.08 [95% CI, 0.78–1.49]; *P*=0.65).

Döbert. M et al. Pravastatin Versus Placebo in Pregnancies at High Risk of Term Preeclampsia, Circulation 2021; 144(9),: 670-679,

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Pravastatin to Prevent Preeclampsia – an RCT

- Randomized controlled multi-center clinical trial
- 1,550 women with a prior history of preeclampsia that required delivery at less than or equal to 34 weeks
- Current gestational age at randomization between **12-17 weeks** days based on clinical information and evaluation of the earliest ultrasound
- Randomized to 1:1 to one of two arms
  - 20 mg pravastatin daily
  - Identical appearing daily placebo
- Outcomes
  - Primary outcome: Proportion of participants with composite of preeclampsia, fetal loss and maternal death [Time Frame: 48 hours postpartum]
  - Secondary outcomes include preterm delivery, severe preeclampsia, any gestational hypertension, gestational diabetes

ClinicalTrials.gov Identifier: NCT03944512

Recruitment Status : Recruiting
First Posted : May 9, 2019
Last Update Posted : October 22, 2020

See **Contacts and Locations**

Maternal Fetal Medicine Units Network clinical centers

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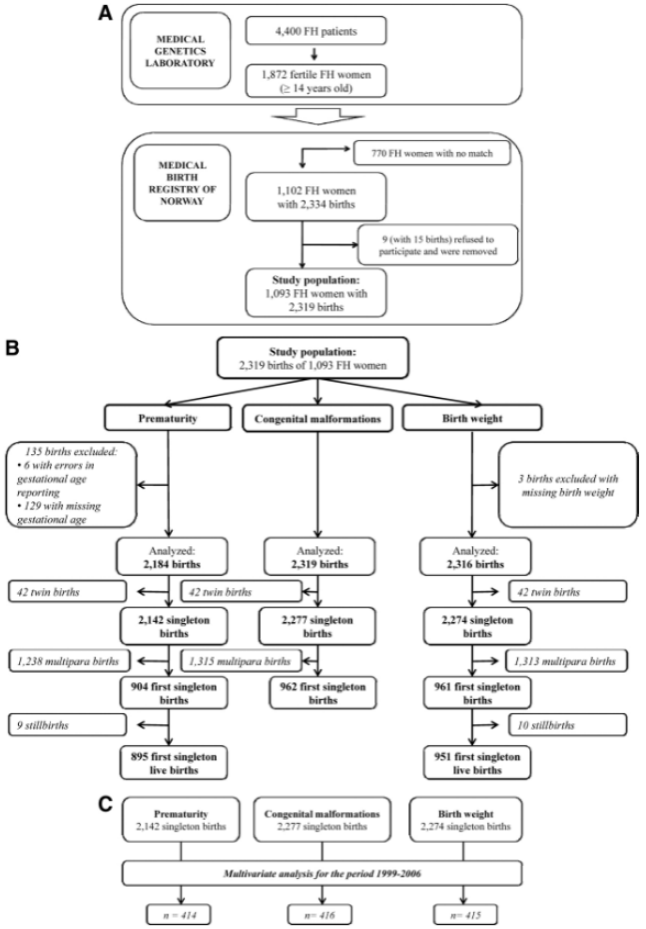
FH and Pregnancy



- Women with FH do not have an increased risk of
  - Premature Delivery
  - Low birth weight infant
  - Congenital malformations
  - Pre-eclampsia/HELLP
  - ?Myocardial infarction
- In some countries it is possible to test mutation in cord blood
- Lipid levels in children with FH and similar if inherited via mother/father

Toleikyte I et al. Pregnancy Outcomes in Familial Hypercholesterolemia, Circulation 2011 Volume: 124, Issue: 15, Pages: 1606-1614, DOI: (10.1161/CIRCULATIONAHA.110.990929)

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Step-wise approach of lipid management in pregnancy

YOUNG WOMEN OF CHILDBEARING AGE WITH HLD (BEFORE PREGNANCY)

- Clinician-guided discussion on pregnancy risks with lipid-lowering therapy, and pre-pregnancy counseling.
- Consider further risk stratification for residual risk with CAC, Lp(a), and hsCRP,
- Encourage guideline-recommended lifestyle modifications
- For high-risk patients (FH, premature CVD) ensure effective contraception with open communication of changes in pregnancy plans while on statin therapy
- Consider referral to a lipid-lowering specialist

1 TO 3 MONTHS PRIOR TO CONCEPTION

- In general, ensure all teratogenic medications are discontinued
- Ensure up to date lipid profile (within 1 year) is available for a baseline prior to pregnancy
- Aggressive lifestyle modifications

DURING PREGNANCY AND LACTATION PERIOD

- Avoid teratogenic lipid-lowering therapy
- Maintain or intensify lifestyle modifications if warranted
- If lipid-lowering medications are needed, consider referral to a lipid-lowering specialist
- Avoid statin use during breastfeeding periods
- Can resume statin if there are no plans for breastfeeding and if indicated

AFTER LACTATION PERIOD

- Discuss future pregnancy plans and methods of contraception if on lipid-lowering therapy
- Can resume pre-pregnancy lipid-lowering therapy or start new agents if clinically warranted after pregnancy counseling
- Routine cholesterol monitoring
- Consider adverse events (pre-eclampsia, eclampsia, gestational HTN, gestational DM) during pregnancy in CVD risk assessment Maintain heart-healthy lifestyle modifications

Grant JK et al. Current Cardiology Reports 2022

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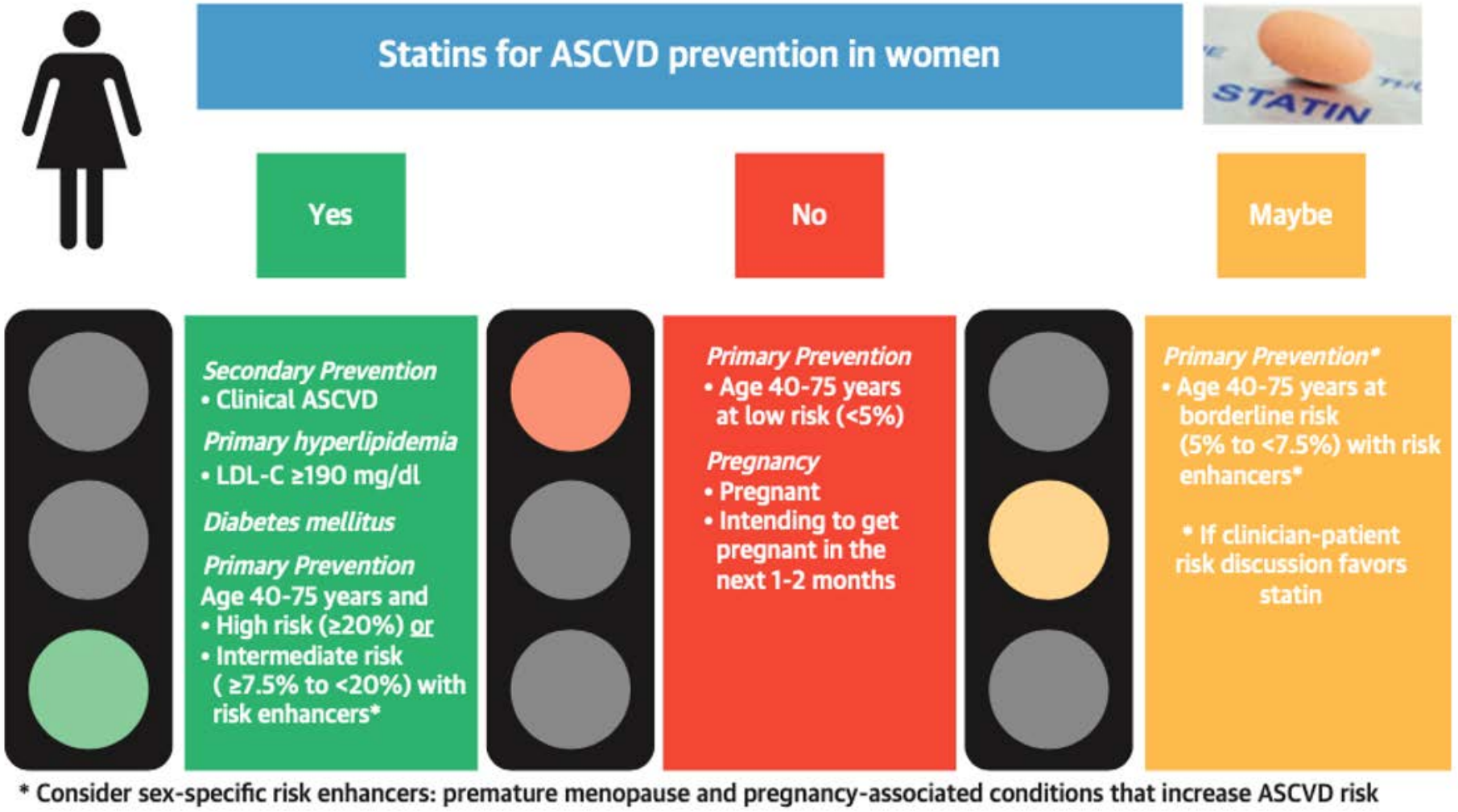
Efficacy by Sex

Statin Recommendations for Women



From Cho L, ……**Michos ED**….Volgman A. JACC 2020:75(20)2602-18

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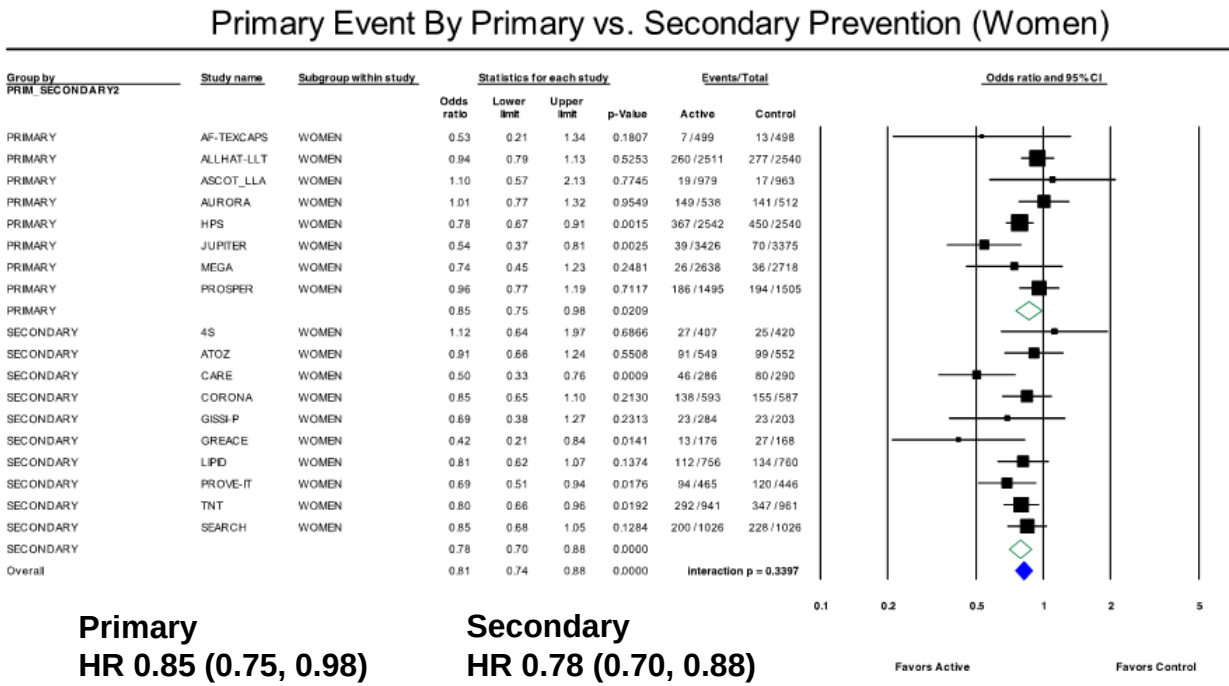
Statins: Similar Benefit for Women and Men

Meta-analysis of Statin Therapy

- 18 randomized clinical trials of statins with sex-specific outcomes
  - N = 141,235; 40,275 women; 21,468 cardiovascular events
- Overall 19% Reduction in CVD in Women
  - OR: 0.81, 95% CI: 0.75 to 0.89; p < 0.0001
- Benefit seen in both Primary and Secondary Prevention
- All-cause mortality also lower in both Women and Men with statin therapy
- No interaction of treatment effect by sex



Primary
HR 0.85 (0.75, 0.98)

Secondary
HR 0.78 (0.70, 0.88)

Implication: Statin therapy should be used in appropriate patients without regard to sex

Kostis et al. JACC 2012;59:572-82.

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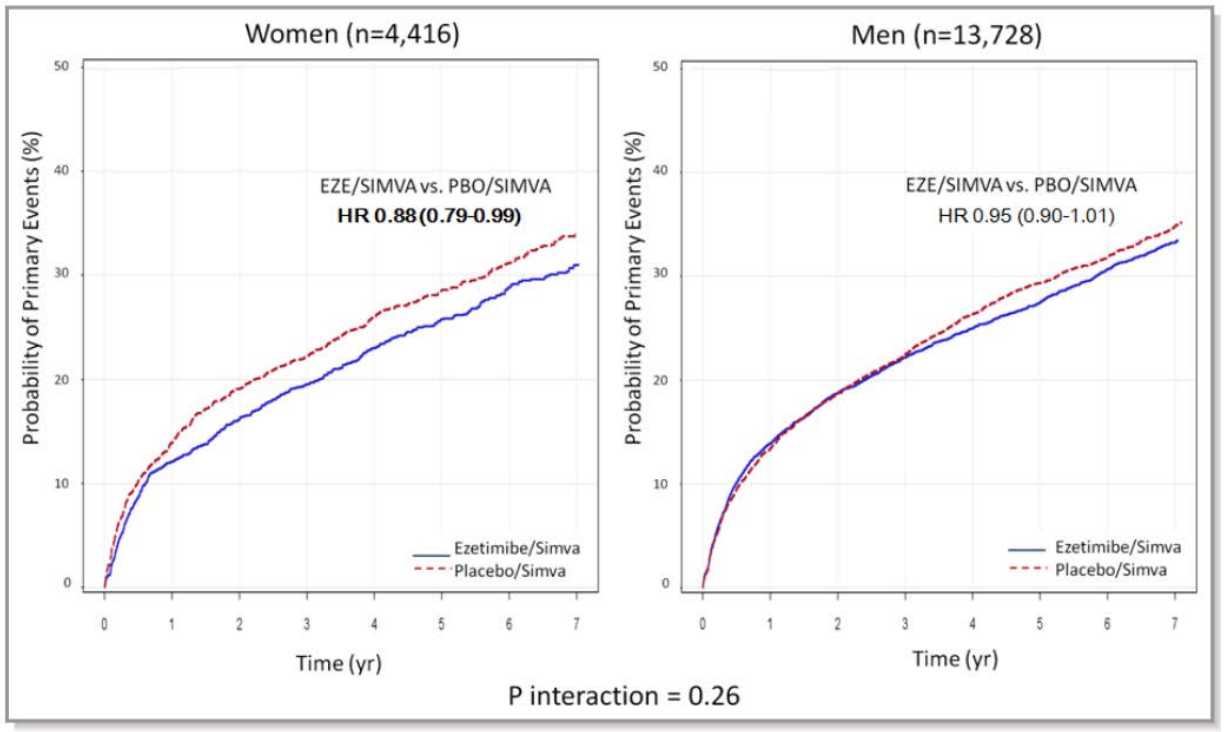
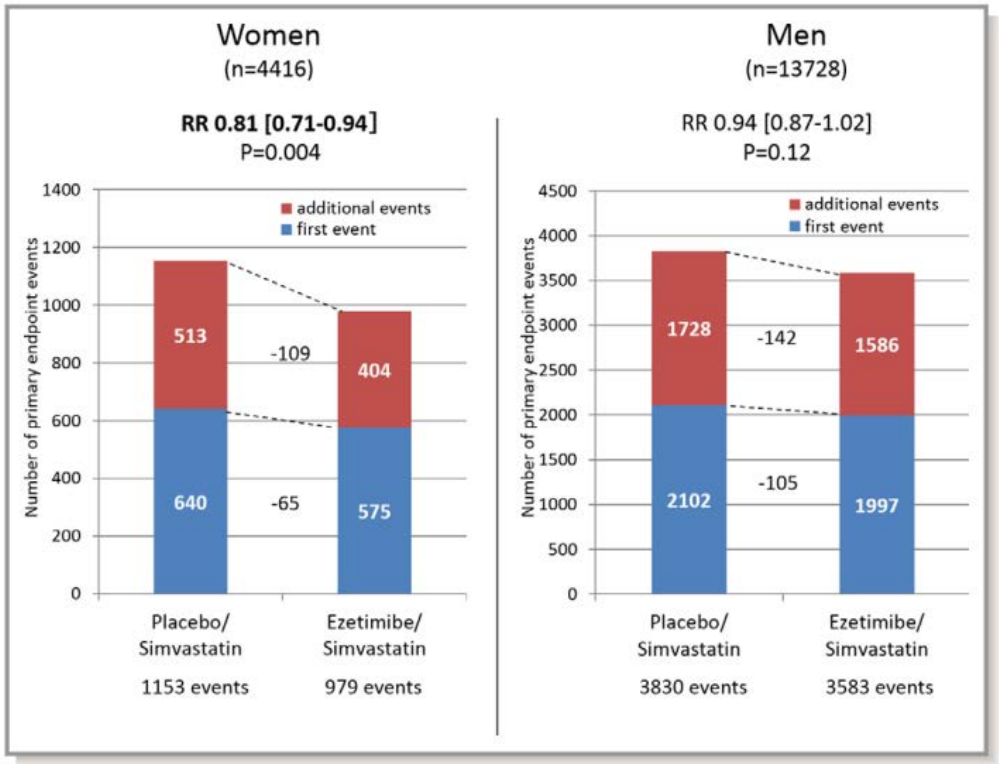
IMPROVE-IT: Benefit of Ezetimibe in Women

- 18,144 patients with ACS; 4416 (24%) trial participants were women.
- Ezetimibe vs placebo on background of simva 40 mg/day
- Ezetimibe conferred similar LDL-C lowering in women & men (~16 mg/dL lower for both).
- Ezetimibe reduced MACE by 12% in women
- No interaction of treatment effect by sex for primary outcome
- When total events considered, women had greater relative benefit
- The addition of ezetimibe did not increase rates of safety events in either women or men.





Kato ET et al. J Am Heart Assoc. 2017;6: e006901. DOI: 10.1161/JAHA.117.006901.

P=0.08 for interaction by sex

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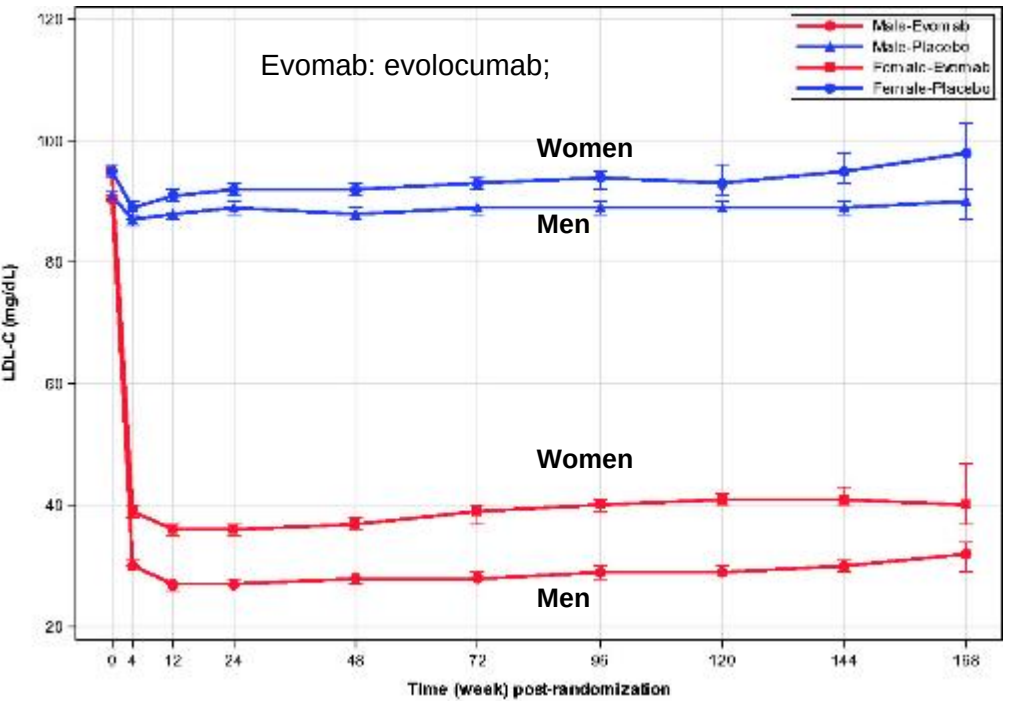
FOURIER: Benefit of PCSK9i in Women



Subgroup	Evolocumab Total N	Evolocumab Events N	Evolocumab 36-month KM (%)	placebo Total, N	placebo Events, N	placebo 36-month KM (%)	HR (95% CI)	Log rank P value	$P_{interaction}$
Primary endpoint									
Male	10,397	1068	13.50	10398	1229	15.32	0.86 (0.80–0.94)	<0.001	0.477
Female	3387	276	9.88	3382	334	12.54	0.81 (0.69–0.95)	0.008	
Secondary endpoint									
Male	10,397	643	8.39	10,398	785	10.17	0.81 (0.73–0.90)	<0.001	0.436
Female	3387	173	6.48	3382	228	9.17	0.74 (0.61–0.90)	0.003	

Evolocumab significantly and consistently reduced the primary endpoint of cardiovascular death, myocardial infarction, stroke, unstable angina requiring rehospitalisation, and coronary revascularisation, and the key secondary endpoint of cardiovascular death, myocardial infarction and stroke and in men and women. No statistical evidence of treatment effect modification by sex was observed ($P_{interaction}$ = 0.48 and 0.44 for the primary and key secondary endpoint, respectively).
KM: Kaplan–Meier; CI: confidence interval; HR: hazard ratio.

- FOURIER compared evolocumab with placebo in 27,564 patients with stable ASCVD receiving statin therapy
- 25% trial participants were women.
- Women had a slightly lower rate of MACE compared to men at 3 years (12.5% vs 15.3%)
- However, evolocumab reduced CV events to a similar degree in women; no interaction by sex.
- Women were more likely to have injection site reactions.
- Otherwise no significant differences in adverse events between in both sexes.

Sever P. Eur J Prev Cardiol 2020 Feb 4;2047487320902750

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Inclisiran: Safety and Efficacy by Sex Pooled Data from Orion 9, 10, 11

- Of a total 3660 patients, 32.5% were females and 67.5% were males.
- At baseline, females were less likely to receive statins [or high-intensity statins] (90% [70%] *vs* 93% [76%]), or have ASCVD (73.6% vs 90.3%)
- Females had higher LDL-C at baseline (122.9 mg/dL *vs* 105.8 mg/dL)
- Efficacy and safety of inclisiran *vs* placebo was similar in both sexes
- Reduction in LDL-C with inclisiran was greater in females than males
  - placebo-corrected **mean absolute reduction in LDL-C at day 510 (62.6 *vs* 54.0 mg/dL**, *P*<0.05)
- Most AEs were similar between inclisiran *vs* placebo for both sexes except for injection-site AEs that were higher in the inclisiran arm than placebo (females 9.4% *vs* 0.2%, males 2.8% *vs* 0.9%).

Wright RSS et al. Abstract 16311. Circulation. 2020;142:A16311

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Sex differences in LDL-C response with Bempedoic Acid

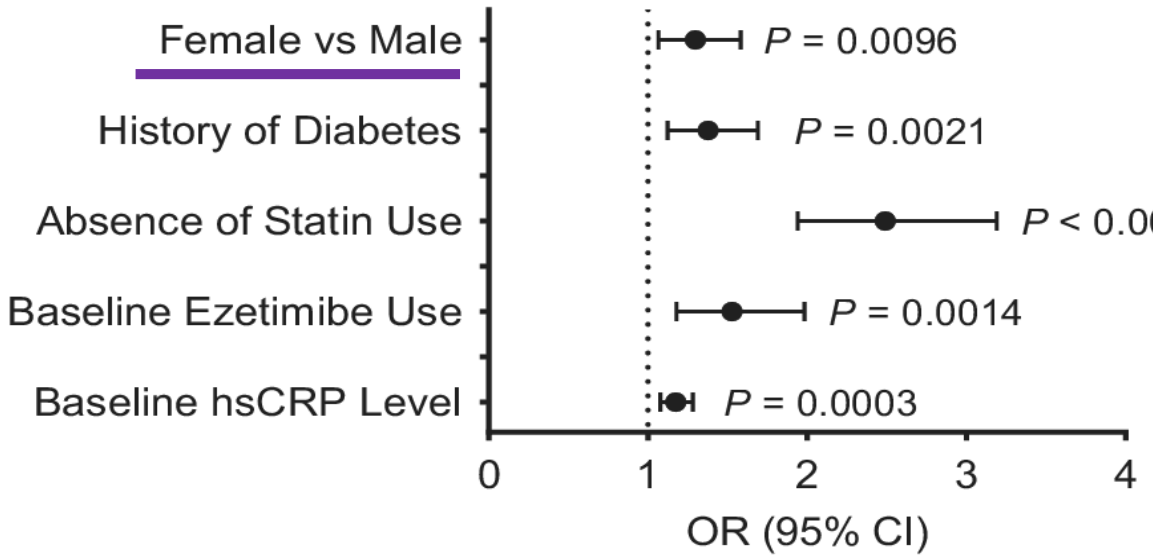
Table 1. LDL-C Levels From Baseline to Week 12 in Patients Who Received Bempedoic Acid or Placebo in 4 Phase 3 Studies, by Sex

	Women ♀		Men ♂	
	Bempedoic Acid	Placebo	Bempedoic Acid	Placebo
ASCVD/HeFH on statins pool, N	583	302	1427	697
Baseline LDL-C, mg/dL, mean (SD)	117.1 (38.8)	116.9 (40.2)	103.9 (28.5)	103.4 (29.3)
LS mean (SE) % change LDL-C	−18.9 (0.9) (n = 550)	2.3 (1.6) (n = 283)	−15.8 (0.5) (n = 1372)	1.5 (0.8) (n = 685)
LS mean difference (95% CI)	−21.2 (−24.8, −17.5)		−17.4 (−19.2, −15.5)	
P value	*P* < 0.001		*P* < 0.001	
P value for sex and treatment interaction	**-21%**	*P* = 0.044	**-17%**	
Statin intolerant pool, N	242	117	173	82
Baseline LDL-C, mg/dL, mean (SD)	148.7 (39.1)	143.5 (36.4)	142.2 (39.1)	137.9 (39.6)
Mean (SE) % change LDL-C	−26.3 (1.4) (n = 234)	1.3 (1.7) (n = 108)	−20.5 (1.7) (n = 165)	1.5 (1.7) (n = 81)
Mean difference (95% CI)	−27.7 (−32.1, −23.2)		−22.1 (−26.9, −17.2)	
P value	*P* < 0.001		*P* < 0.001	
P value for sex and treatment interaction	*P* = 0.079			

ANCOVA, analysis of covariance; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SD, standard deviation.
LS Means, 95% CIs and P-value are based on an ANCOVA with percent change from baseline as the dependent variable, study and treatment as fixed factors, and baseline as a covariate. Only observed data were included in the analysis.

Goldberg AC et al. Abstract 13130. Circulation 2020

Factors associated with increased rates of achieving ≥30% LDL-C reduction with BA



Ballantyne CM et al. J Am Heart Assoc. 2022;11:e024531

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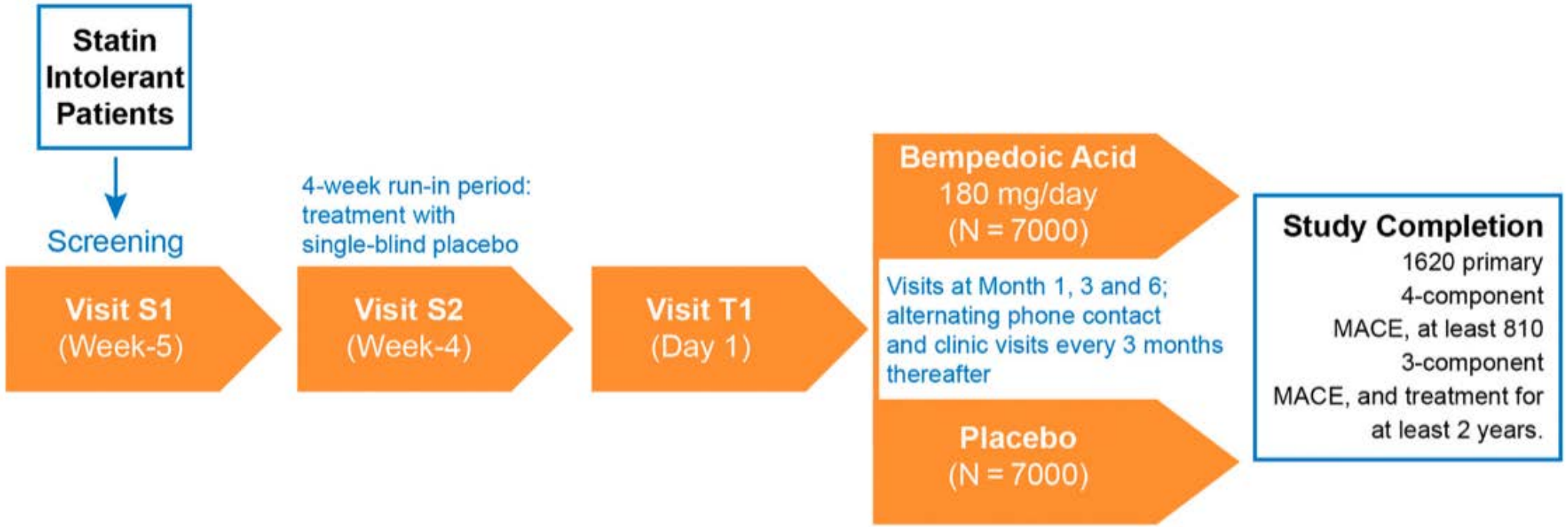
CLEAR OUTCOMES – CVOT for Bempedoic Acid to report out soon

14,014 randomized, 48.2% women



Study design of the CLEAR outcomes study.

NCT02993406 Nicholls SJ et al. Am Heart J 2021

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Intensive LDL-C lowering, does baseline LDL-C matter?

- Meta-analysis of 53 RCTs (329,897 patients) of LDL-C lowering therapies (statin, ezetimibe and PCSK9 inhibitors) and stratified according to the baseline LDL-C thresholds.
- Reduction in CV mortality only seen among those with LDL-C >100 mg/dL
- In contrast, the reduction in MACE was independent of baseline LDL-C levels.
- Findings consistent by sex

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/the-american-journal-of-preventive-cardiology

Short Report

Cardiovascular mortality after intensive LDL-Cholesterol lowering: Does baseline LDL-Cholesterol really matter?

Safi U. Khan [a], Erin D. Michos [b,*]

[a] Department of Medicine, West Virginia University, Morgantown, WV, USA
[b] The Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins School of Medicine, Baltimore, MD, USA

Khan SU, **Michos ED**. Am J Prev Cardiol 2020; 100013

Sex	MACE	P-interaction by sex
Men	0.81 [0.77, 0.86]	0.28
Women	0.85 [0.80, 0.90]	

Table 1. Subgroup analysis of outcomes per 38.7 mg/dL reduction in low density lipoprotein cholesterol in trials with baseline LDL-C >100 mg/dL.

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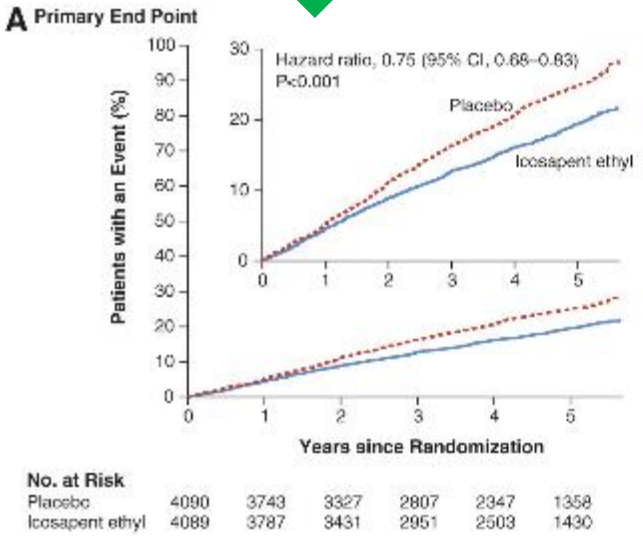
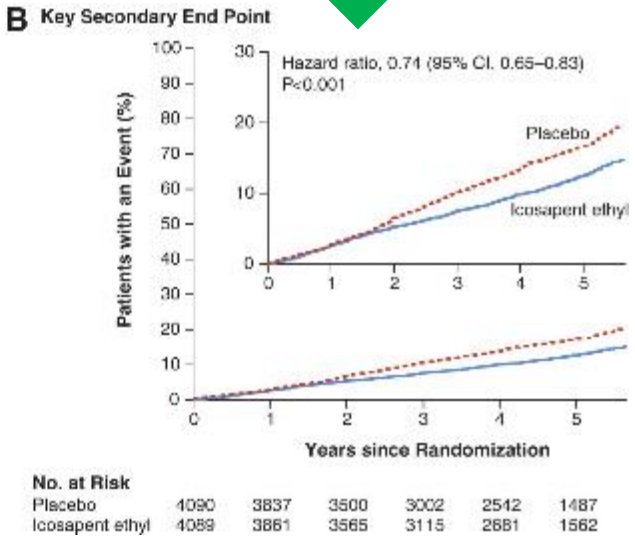
REDUCE IT: Icosapent Ethyl for Women

- REDUCE-IT trial (enrolled 8,170 patients (29% women) with established ASCVD or with diabetes and multiple risk factors who had moderate hypertriglyceridemia (135-500 mg/dL) despite statin treatment and LDL-C control.
- REDUCE-IT tested the benefit of a highly purified EPA preparation (icosapent ethyl) dosed at 4 grams/day compared to a control.
- No significant interaction by sex.

25%



29%



	HR (95% CI)	p-*Value for interaction*
Primary endpoint: composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina		
Male	0.73 (0.65–0.82)	0.33[a]
Female	0.82 (0.66–1.01)	
Key secondary endpoint: composite of cardiovascular death, nonfatal MI, or nonfatal stroke		
Male	0.72 (0.62–0.82)	0.44[a]
Female	0.80 (0.62–1.03)	

Bhatt DL, et al; REDUCE-IT Investigators. *N Engl J. Med.* 2019;380(1):11-22;

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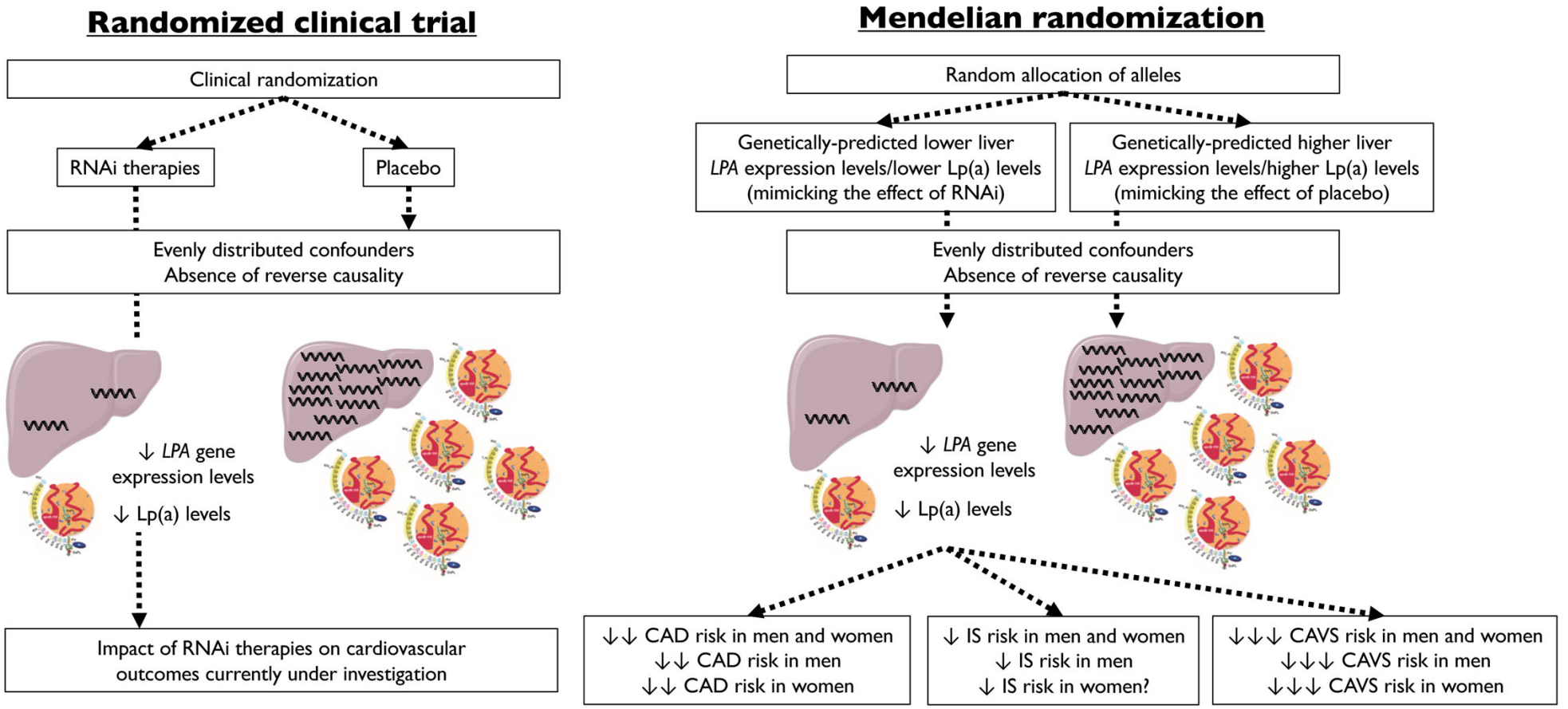
Lipoprotein (a) in women

Study objectives: Determine the sex-specific associations of genetically-predicted circulating Lp(a) and hepatic *LPA* gene expression levels with cardiovascular outcomes using Mendelian randomization



Study conclusions: Genetically-predicted circulating Lp(a) and hepatic *LPA* gene expression levels are associated with a lower risk of CAD, IS and CAVS in men and women included in the UK Biobank

Guertin J et al. Circulation: Genomic and Precision Medicine. 2021;14:e003271

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Differences in Lipid Management: Side Effects and Treatment Disparities

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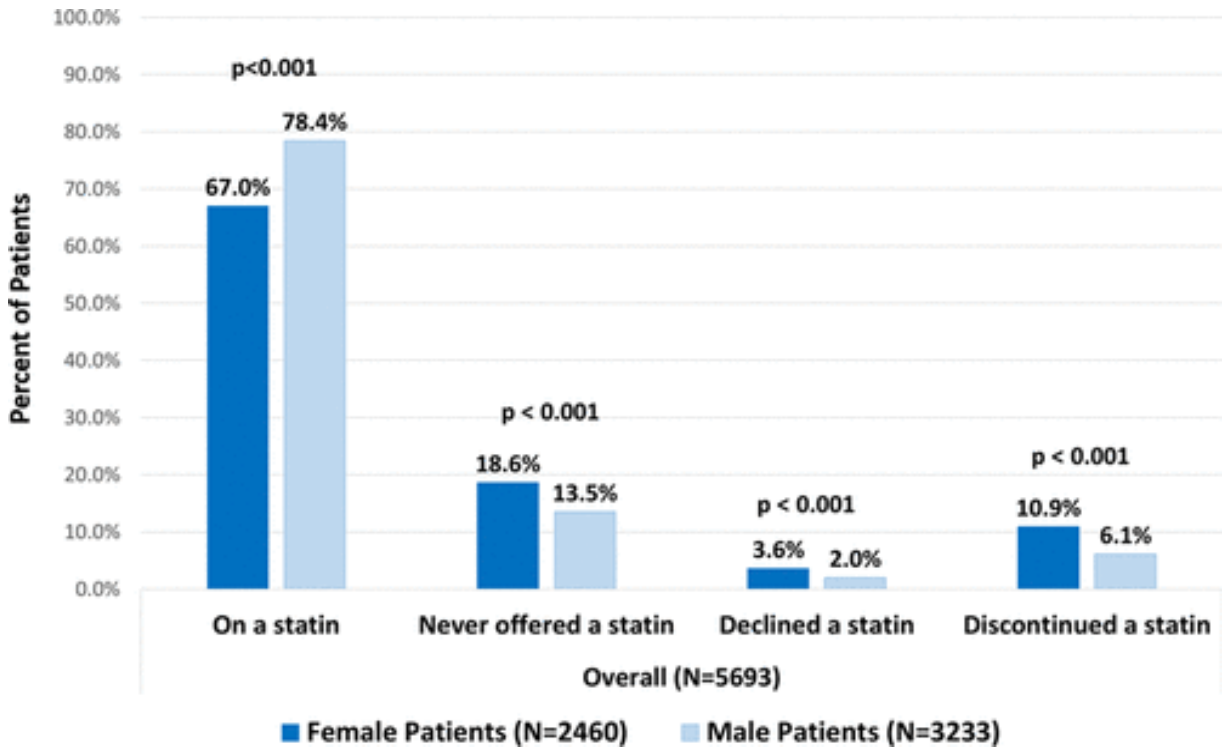
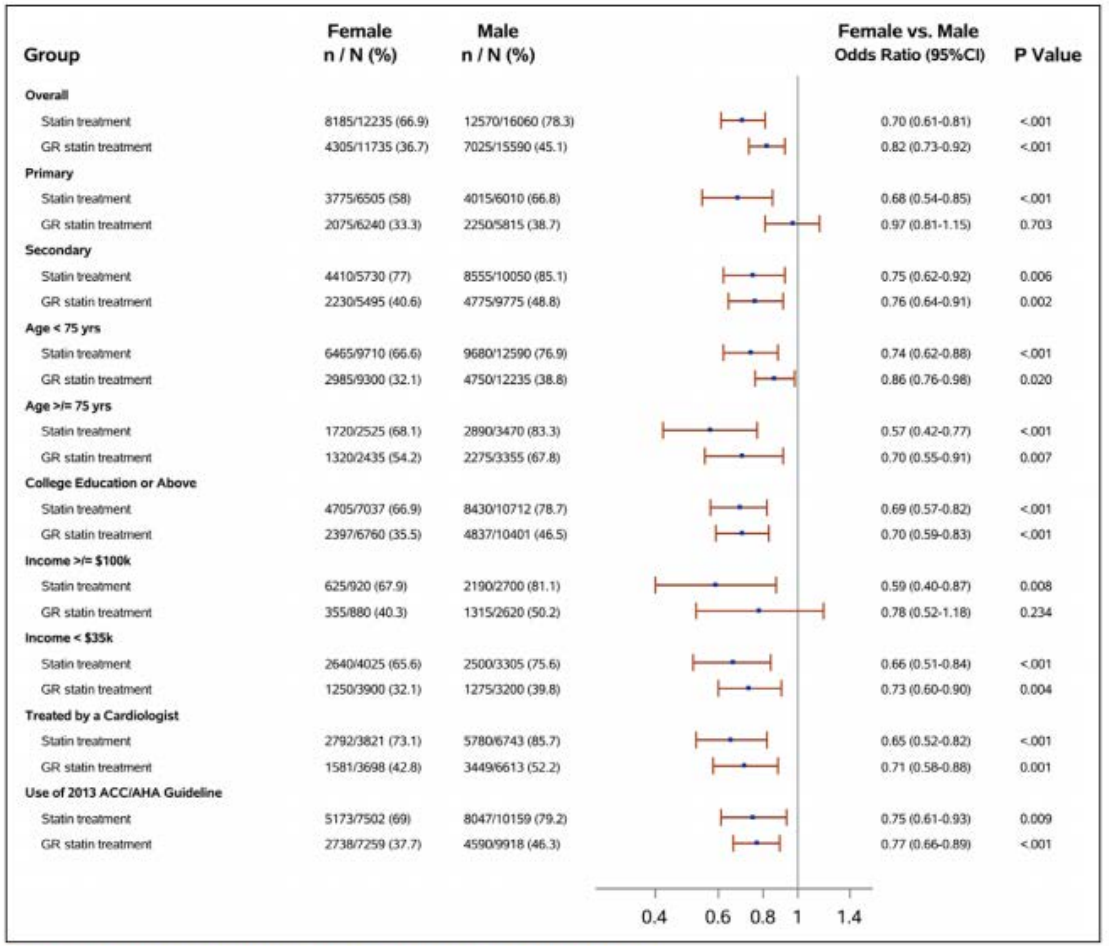
Women less likely be offered statin and more likely to decline

Patient and Provider Assessment of Lipid Management (PALM) Registry—a nationwide registry of outpatients with or at risk for ASCVD





Group	Female n / N (%)	Male n / N (%)	Female vs. Male Odds Ratio (95%CI)	P Value
Overall				
Statin treatment	8185/12235 (66.9)	12570/16060 (78.3)	0.70 (0.61-0.81)	<.001
GR statin treatment	4305/11735 (36.7)	7025/15590 (45.1)	0.82 (0.73-0.92)	<.001
Primary				
Statin treatment	3775/6505 (58)	4015/6010 (66.8)	0.68 (0.54-0.85)	<.001
GR statin treatment	2075/6240 (33.3)	2250/5815 (38.7)	0.97 (0.81-1.15)	0.703
Secondary				
Statin treatment	4410/5730 (77)	8555/10050 (85.1)	0.75 (0.62-0.92)	0.006
GR statin treatment	2230/5495 (40.6)	4775/9775 (48.8)	0.76 (0.64-0.91)	0.002
Age < 75 yrs				
Statin treatment	6465/9710 (66.6)	9680/12590 (76.9)	0.74 (0.62-0.88)	<.001
GR statin treatment	2985/9300 (32.1)	4750/12235 (38.8)	0.86 (0.76-0.98)	0.020
Age >/= 75 yrs				
Statin treatment	1720/2525 (68.1)	2890/3470 (83.3)	0.57 (0.42-0.77)	<.001
GR statin treatment	1320/2435 (54.2)	2275/3355 (67.8)	0.70 (0.55-0.91)	0.007
College Education or Above				
Statin treatment	4705/7037 (66.9)	8430/10712 (78.7)	0.69 (0.57-0.82)	<.001
GR statin treatment	2397/6760 (35.5)	4837/10401 (46.5)	0.70 (0.59-0.83)	<.001
Income >/= $100k				
Statin treatment	625/920 (67.9)	2190/2700 (81.1)	0.59 (0.40-0.87)	0.008
GR statin treatment	355/880 (40.3)	1315/2620 (50.2)	0.78 (0.52-1.18)	0.234
Income < $35k				
Statin treatment	2640/4025 (65.6)	2500/3305 (75.6)	0.66 (0.51-0.84)	<.001
GR statin treatment	1250/3900 (32.1)	1275/3200 (39.8)	0.73 (0.60-0.90)	0.004
Treated by a Cardiologist				
Statin treatment	2792/3821 (73.1)	5780/6743 (85.7)	0.65 (0.52-0.82)	<.001
GR statin treatment	1581/3698 (42.8)	3449/6613 (52.2)	0.71 (0.58-0.88)	0.001
Use of 2013 ACC/AHA Guideline				
Statin treatment	5173/7502 (69)	8047/10159 (79.2)	0.75 (0.61-0.93)	0.009
GR statin treatment	2738/7259 (37.7)	4590/9918 (46.3)	0.77 (0.66-0.89)	<.001

Figure 2. Multivariable modeling results for statin utilization in female vs male patients.
Based on results of a logistic regression model that included age, race, prior atherosclerotic cardiovascular disease (ASCVD) grouped into coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral vascular disease (PAD), diabetes mellitus, obesity, smoking, hypertension, heart failure, yearly income, insurance status, education level, patient numeracy, patient beliefs including worry about heart disease, physician trust, statin beliefs about safety, effectiveness, and the link between high cholesterol and heart attack risk, cardiologist vs noncardiologist, use of 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline, urban vs rural setting, and provider time in practice. In subgroup analyses, the variable that defined the subgroup was not adjusted for except in the secondary prevention group where type of ASCVD was included in the model (CAD vs CVD vs PAD). GR indicates guideline recommended.

Michael G. Nanna. Circulation: Cardiovascular Quality and Outcomes. Sex Differences in the Use of Statins in Community Practice, 2019 Volume: 12, Issue: 8, DOI: (10.1161/CIRCOUTCOMES.118.005562)

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Women are more likely to have SAMS and to stop therapy

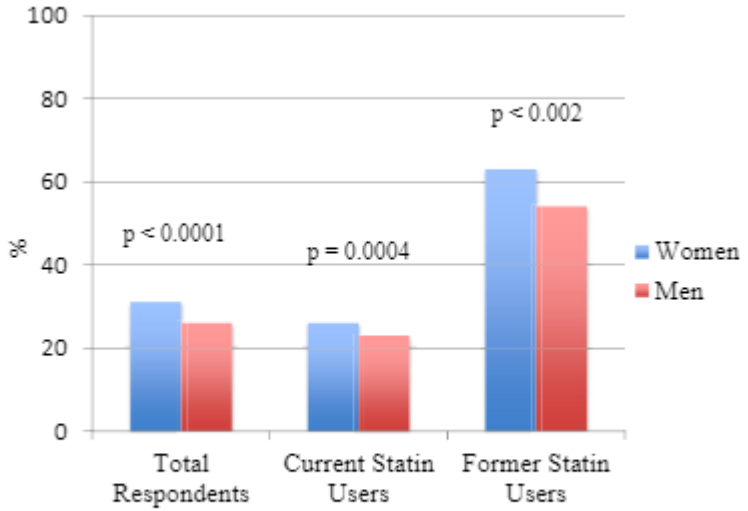

Figure 1 Prevalence of reported new and/or worsening muscle symptoms while taking a statin.

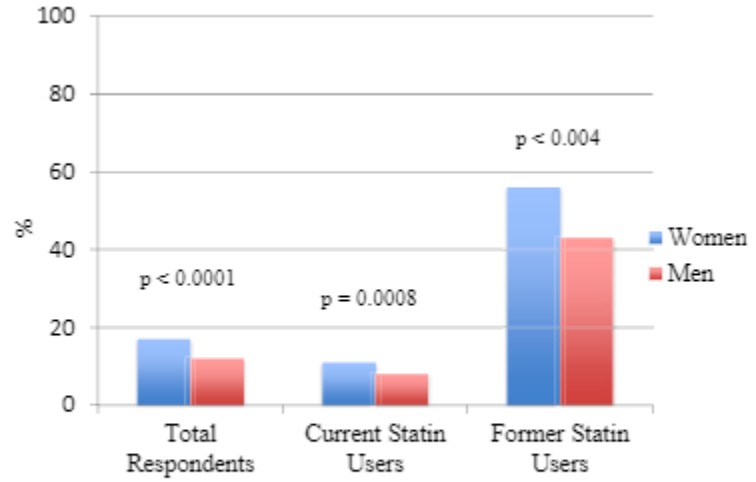

Figure 2 Prevalence of reporting of having stopped a statin due to muscle symptoms.

Understanding Statin Use in America and Gaps in Patient Education (USAGE) survey
10,138 adults surveyed in 2011

Table 4 Odds ratio of women reporting muscle symptoms or stopping a statin due to muscle symptoms

	Odds ratio (95% CI)	*P* value
New or worsening muscle symptoms		
Women	1.29 (1.18–1.41)	<.0001
Age adjusted	1.30 (1.19–1.42)	<.0001
Multivariate*	1.28 (1.16–1.42)	<.0001
Stopped a statin due to muscle symptoms		
Women	1.52 (1.31–1.77)	<.0001
Age adjusted	1.53 (1.32–1.79)	<.0001
Multivariate*	1.48 (1.25–1.75)	<.0001

CI, confidence interval.
*Adjusted for reported history of arthritis, cardiovascular disease, depression, diabetes, gastroesophageal reflux, hypertension, osteopenia/osteoporosis, and thyroid disorders.

Karalis DG. J Clin Lipidol 2016;10(4):833-841.

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Gender Disparities in Patient-Reported Outcomes in ASCVD

Medical Expenditure Panel Survey (MEPS) data 2006-2015
Represents ~11 million women in U.S with ASCVD.

	[Yes vs. No; OR* (95% CI)]
Surrogate Measures for Clinical Outcomes (in women compared to men)	
Statin usage	**0.55 (0.48-0.62)**
Aspirin usage	**0.65 (0.58-0.72)**
≥ 2 ED visits/yr	**1.28 (1.11-1.46)**
≥ 2 Hospitalizations visits/yr	1.05 (0.88-1.25)
*Odds ratios compare women to men and were adjusted for age, race/ethnicity, level of income, region, health insurance, educational status, modified charlson comorbidity index (without the cardiovascular component), and cardiovascular risk factors.	

Okunrintemi V…..**Michos ED**. J Am Heart Assoc 2018;7:e010498

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Younger women less likely to be adherent to statins

Younger men <55 were significantly more likely than younger women to initiate appropriate treatment post MI (adjusted OR, 1.38; 95% CI, 1.10–1.75)

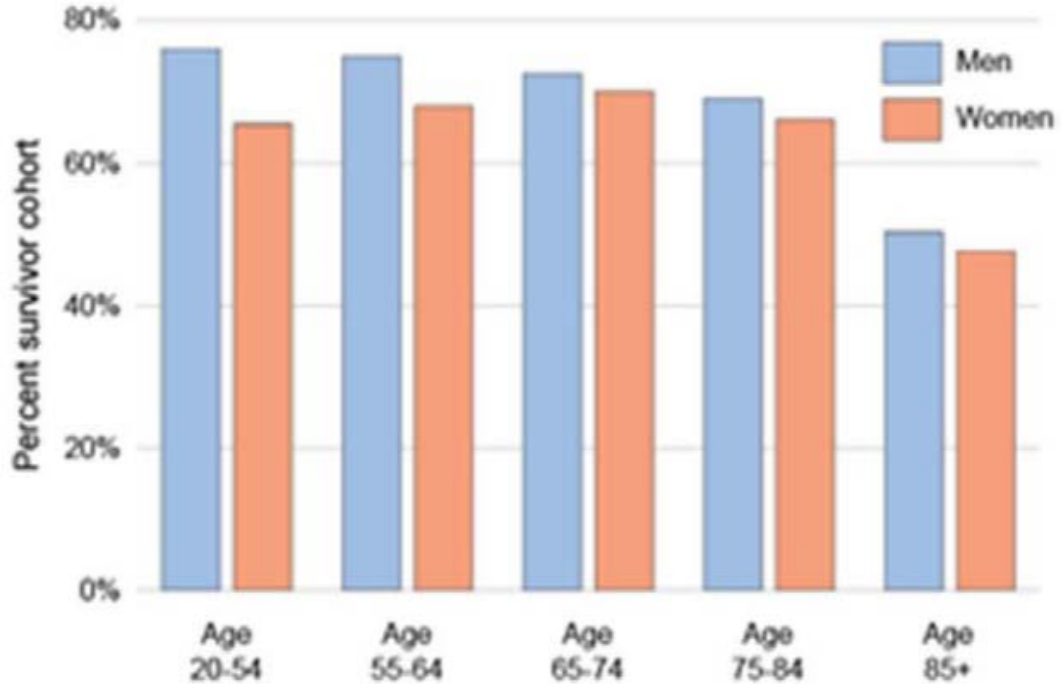

Figure 2. Initiation on appropriate therapy within 2 months of discharge, by sex and age group.

Smolina K et al. Circ Cardiovasc Qual Outcomes. 2015;8:586-592.
DOI: 10.1161/CIRCOUTCOMES.115.001987

Sex Differences in CVD: Enrollment of Women in Lipid Lowering Trials

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Enrollment of Women in Lipid Lowering RCTs 1990-2018

Figure: Proportion of women enrolled in clinical trials over time

- Overall representation of women was 29%

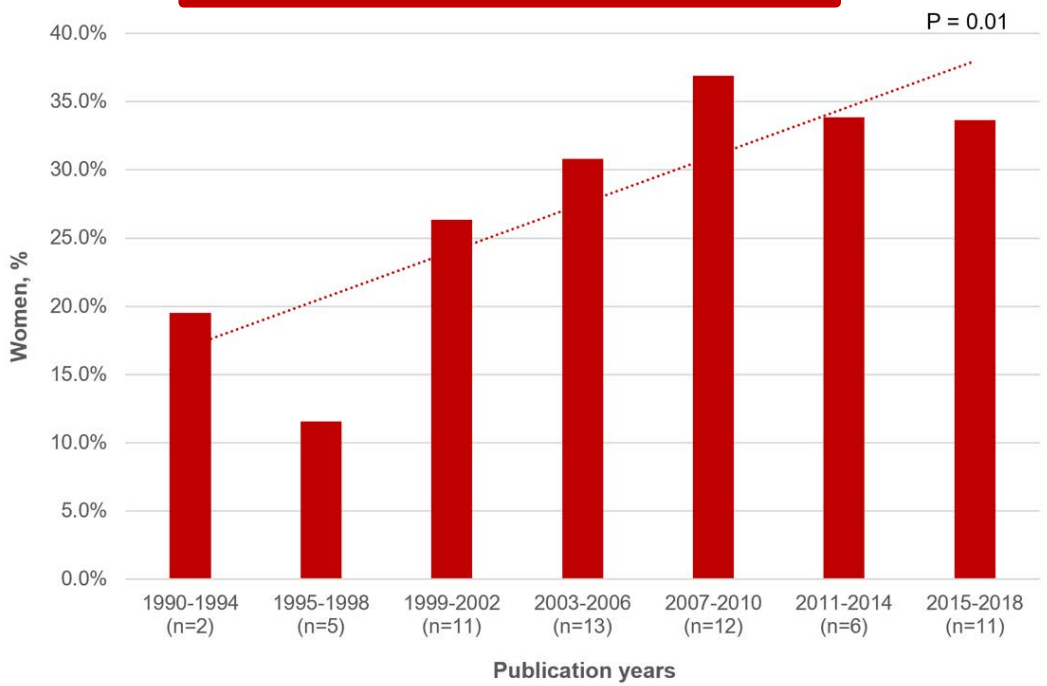
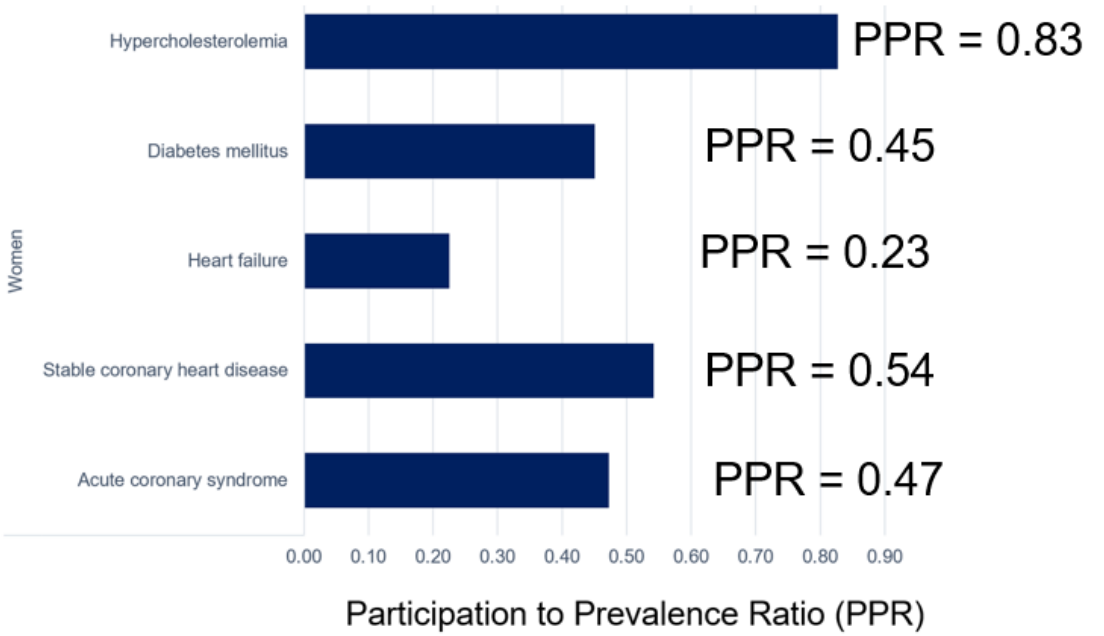


Figure: Participation of women in lipid lowering therapy trials: prevalence-corrected estimate



Women under-represented in trials relative to their disease prevalence

Khan SU…..Michos ED. JAMA Network Open 2020

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Representation of Women Authors in Trials of Lipid-Lowering Therapy 1994 - 2018

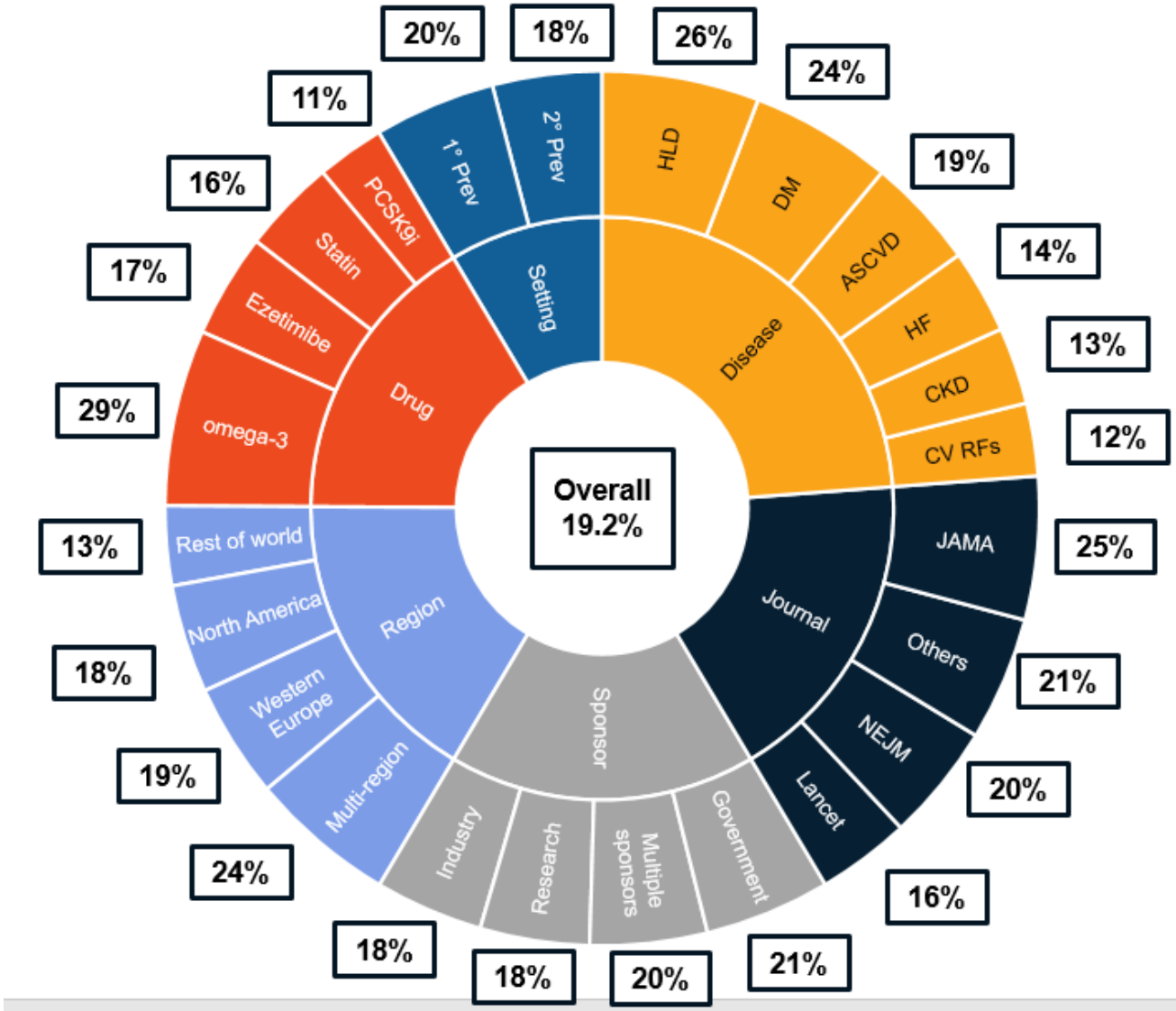

Figure: Percent women authors by LLT trial study characteristics

- 59 trials (485 409 participants) of LLT trials
- Median number of men and women authors were 10 (9–16) vs 2 (1–3)
- Overall, proportion of women as authors was 19.2% (95% CI, 15.3–23.8%).
- Proportions of women as first and senior authors were 17% each.
- Proportion of women authors did not significantly change over time and did not vary according to the journal, disease state, setting, sponsor, drug, or region (Figure).

Raghu Subramanian C… **Michos ED**. J Am Heart Assoc. 2021;10:e020663

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Take Home Points: Lipid Management in Women

- Women with dyslipidemia are special
  - Menstrual cycle affects lipid levels
  - Pregnancy involves timely counseling.
  - Delay in treatments in women of reproductive age affect long-term CVD risk
  - Menopause increases LDL-C levels
- Women benefit from statins and other lipid lowering therapies, but are undertreated
- Women under-represented in clinical trials and results often not reported by sex
  - Opportunities remain to improve representation of women in cardiology & cardiovascular trial leadership that may benefit women patients

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Lipids in Women across the Lifespan

Adolescent

Universally screen for familial hyperlipidemia

Estrogens in CHCs ⬆ TG & HDL, & ⬇LDL

Instill healthy lifestyle at an early age

Pregnancy

Preeclampsia, gestational diabetes, preterm delivery: ⬆ ASCVD risk

With pregnancy: ⬆ TG & ⬆ LDL

FDA recommends statin Rx in select pts

Perimenopause

Consider coronary calcium score, breast arterial calcifications, carotid atherosclerosis & rheumatologic disorders in ASCVD risk assessment

Menopause

Menopause ⬆ fat mass, ⬇ skeletal muscle mass & ⬆ visceral adiposity, assoc. with ⬆ ASCVD

Menopause results in ⬆ LDL, Lp(a) & TC

Premature and early menopause ⬆ ASCVD

Older Adult

Lipid lowering Rx recommended in all at risk or known ASCVD patients

Do not deescalate lipid lowering Rx in elderly who are tolerating meds

Sharma J.…**Michos ED**….Lindley KJ. Am J Prev Cardiol 2022; 100333

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