What to Know When Treating Your High Risk Women Patients

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Cardiovascular disease in women

35%

of all deaths in women worldwide are caused by cardiovascular disease

275 million

women were diagnosed with cardiovascular disease in 2019

8·9 million

women died from cardiovascular disease in 2019

Cardiovascular disease among women is

understudied,
under-recognised,
underdiagnosed,
undertreated,
and women are
under-represented in
clinical trials.

Read more:

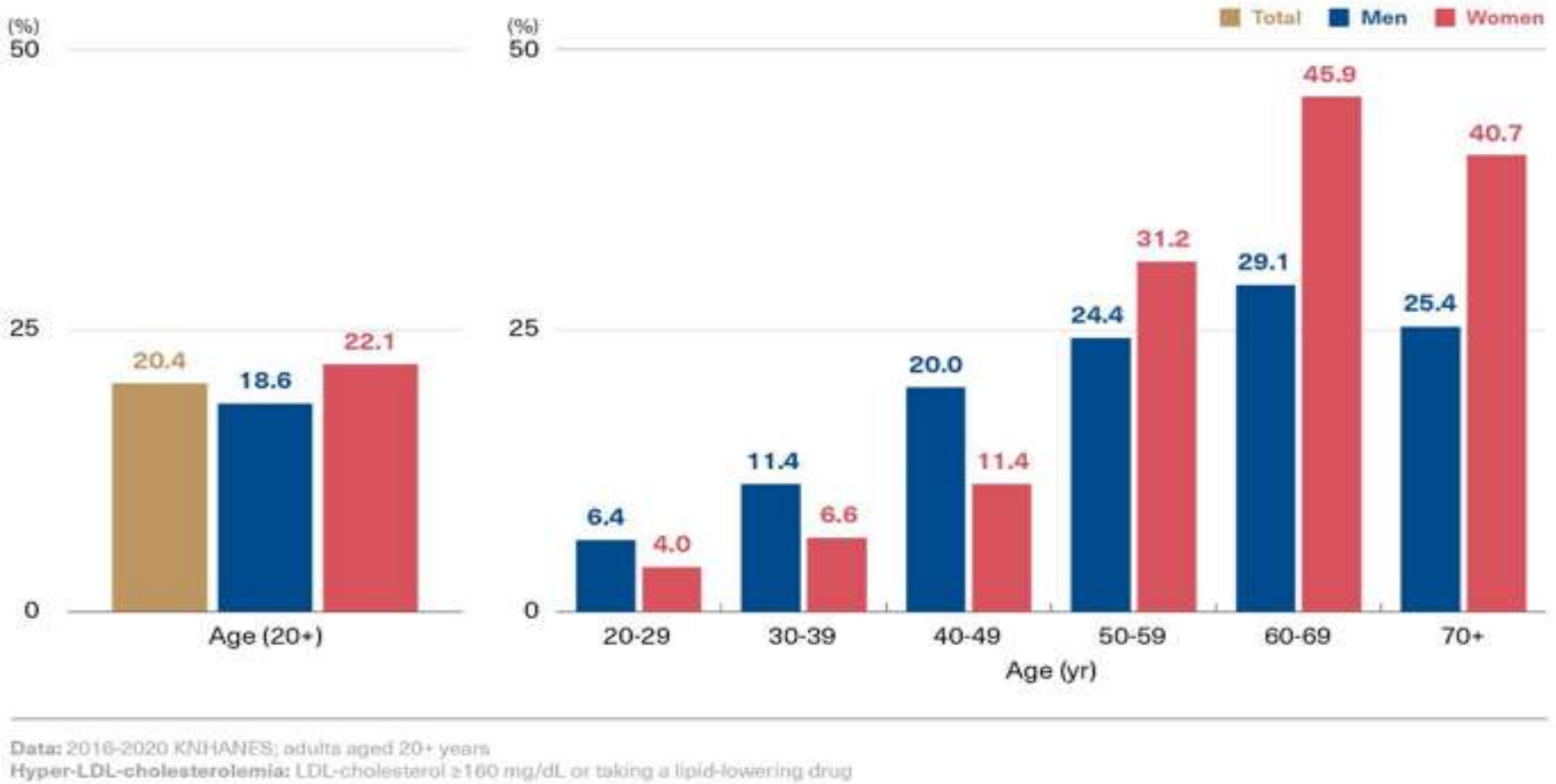
The *Lancet* women and cardiovascular disease Commission: reducing the global burden by 2030

THE LANCET

The best science for better lives

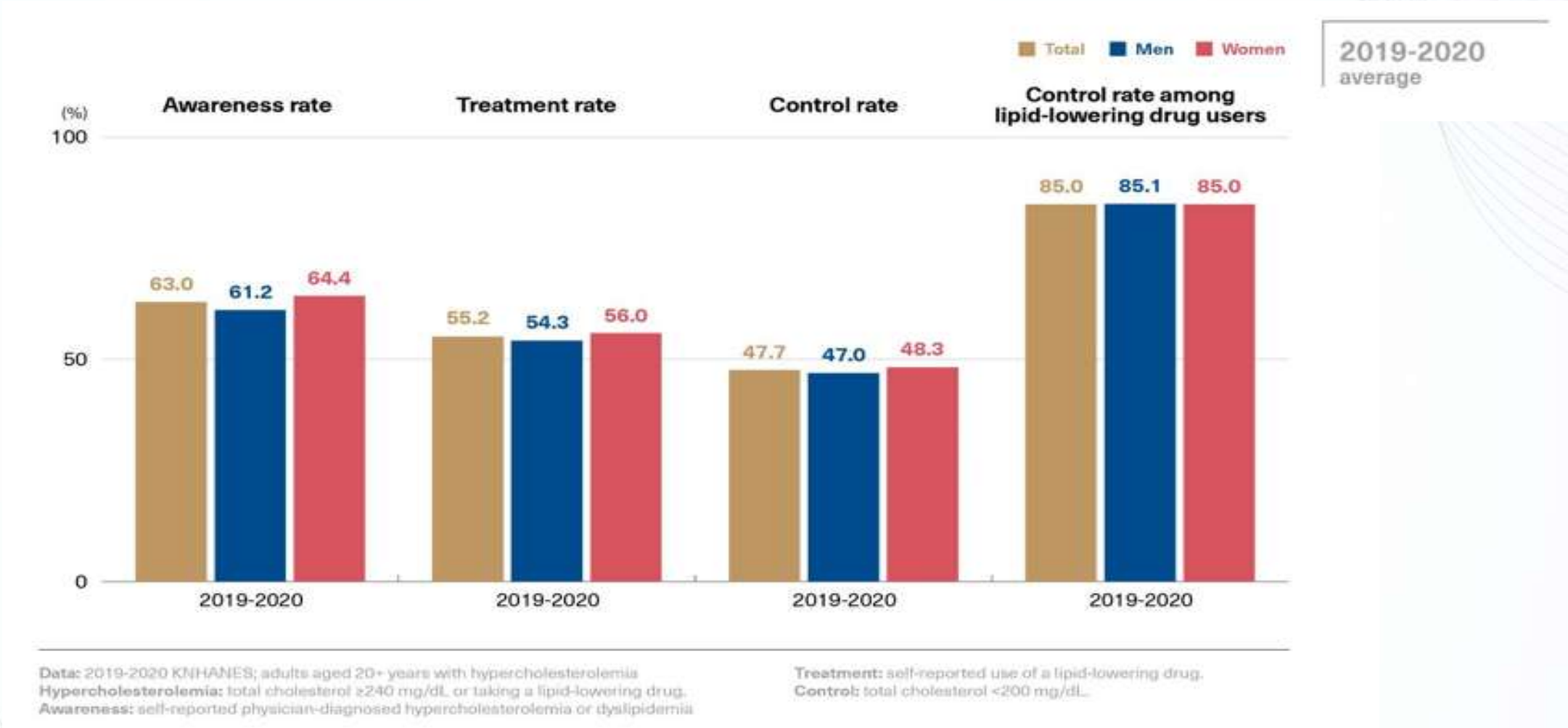
1. The Lancet, Vol. 397, No. 10292

Crude Prevalence of Hyper-LDL-Cholesterolemia by Sex and Age



DYSLIPIDEMIA FACT SHEET IN KOREA, 2022

Summary of Management of Hypercholesterolemia



DYSLIPIDEMIA FACT SHEET IN KOREA, 2022

Risk Factors for Coronary Heart Disease

For both men and women

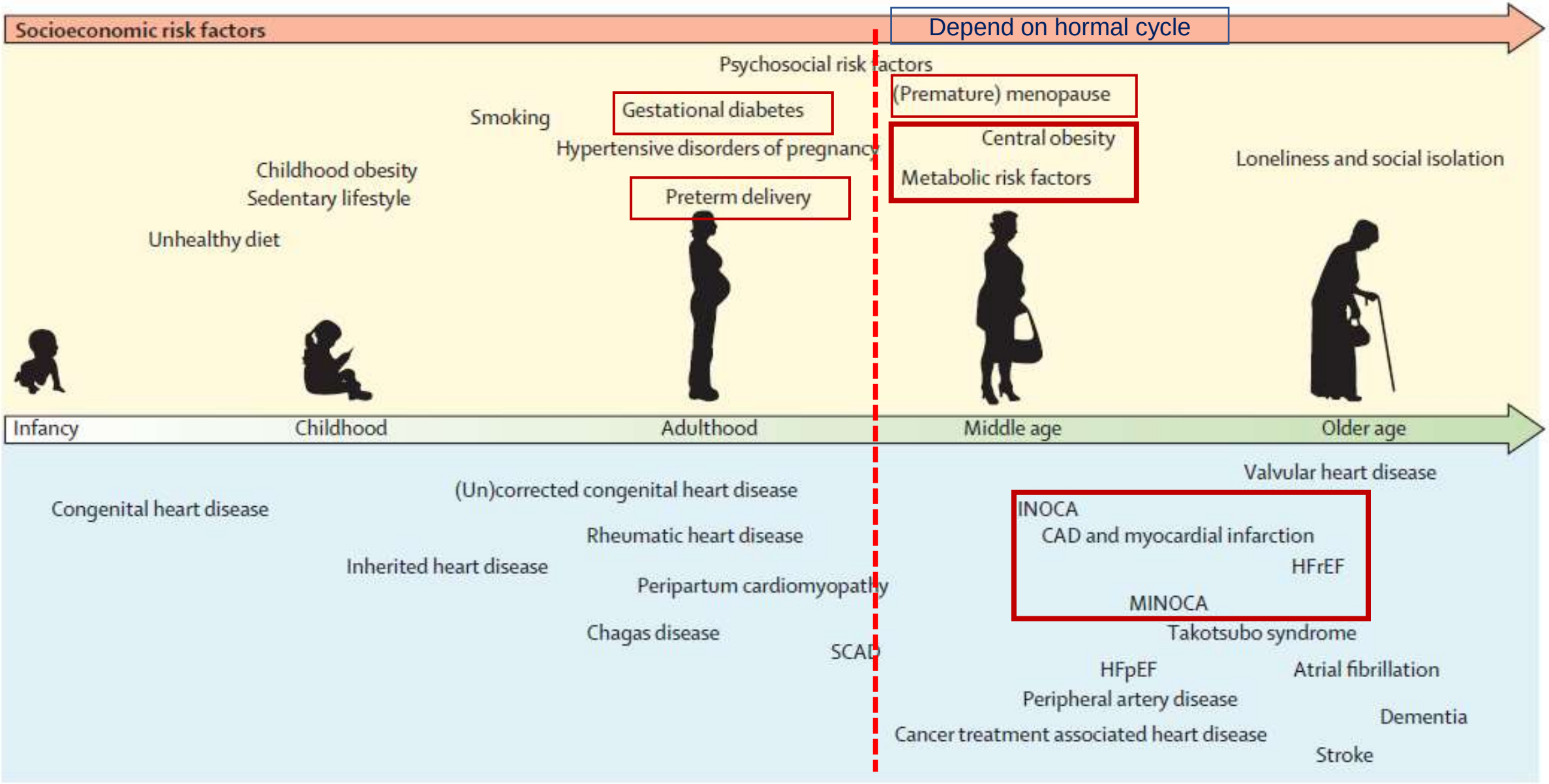
- Smoking
- Diabetes
- High Cholesterol (in particular high LDL and/or low HDL)
- High Blood Pressure
- Obesity
- Sedentary Lifestyle

For women only

- Menopause (Pre-menopause, pre-eclampsia)
- Birth Control Pills in Combination with Smoking

Characteristic of Cardiovascular Disease in Women's Lifetime

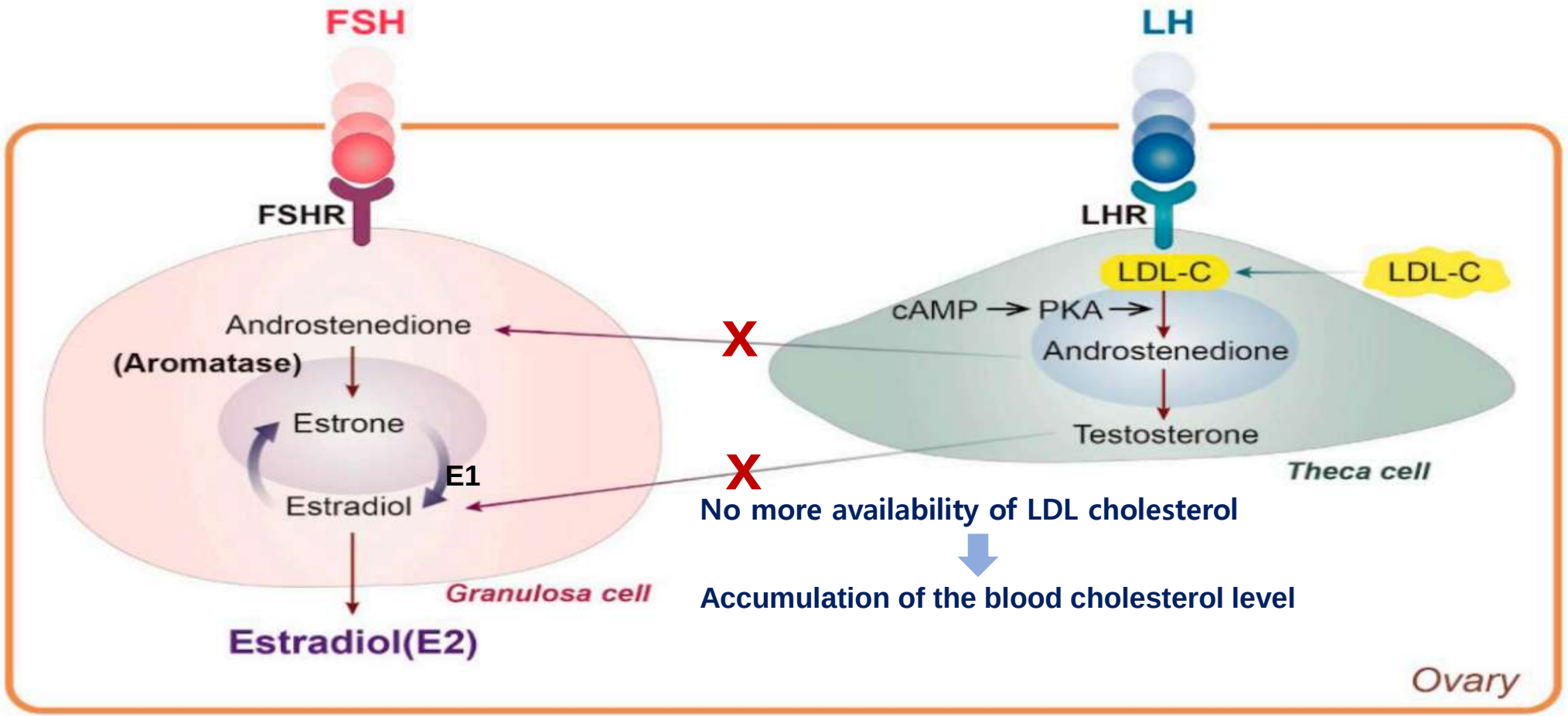
CV ds & Risk Factors During the Lifecycle of a Women



Ref) Birgit et al. Lancet 2021 Jun 19;397(10292):2385-2438

LDL cholesterol is used for E2 synthesis

Circulating E2 levels drop sharply to 10 pg/mL in postmenopausal women



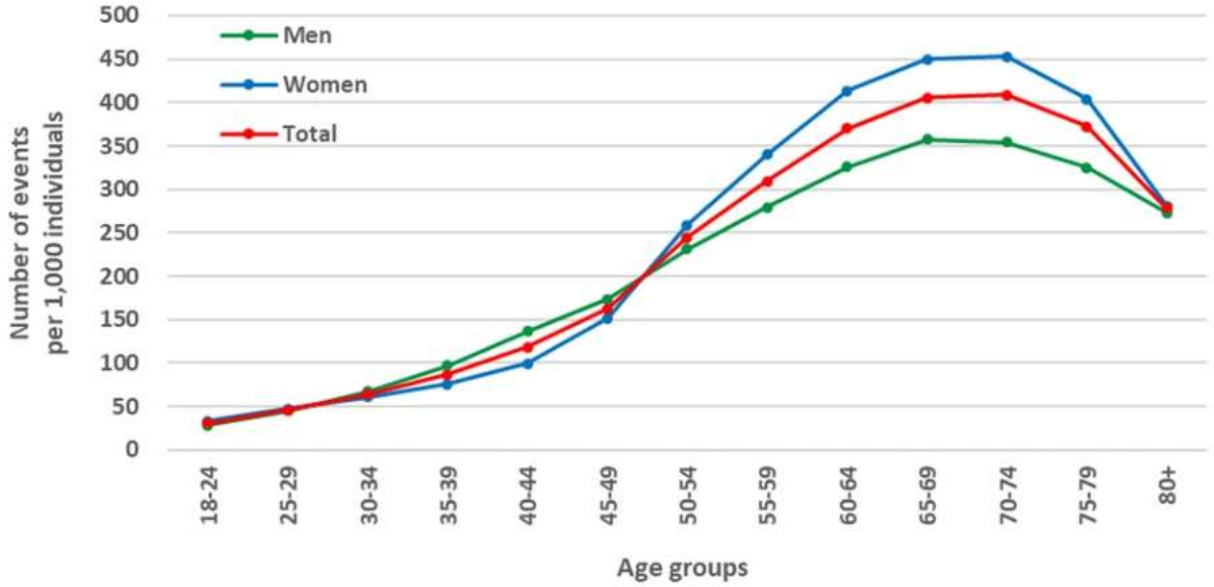
cAMP: cyclic adenosine monophosphate, E2:estradiol, FSH: follicle-stimulating hormone, FSHR: follicle-stimulating hormone receptor, LDL-C:low-density lipoprotein cholesterol, LH: luteinizing hormone

Nutrients 2021, 13, 4556

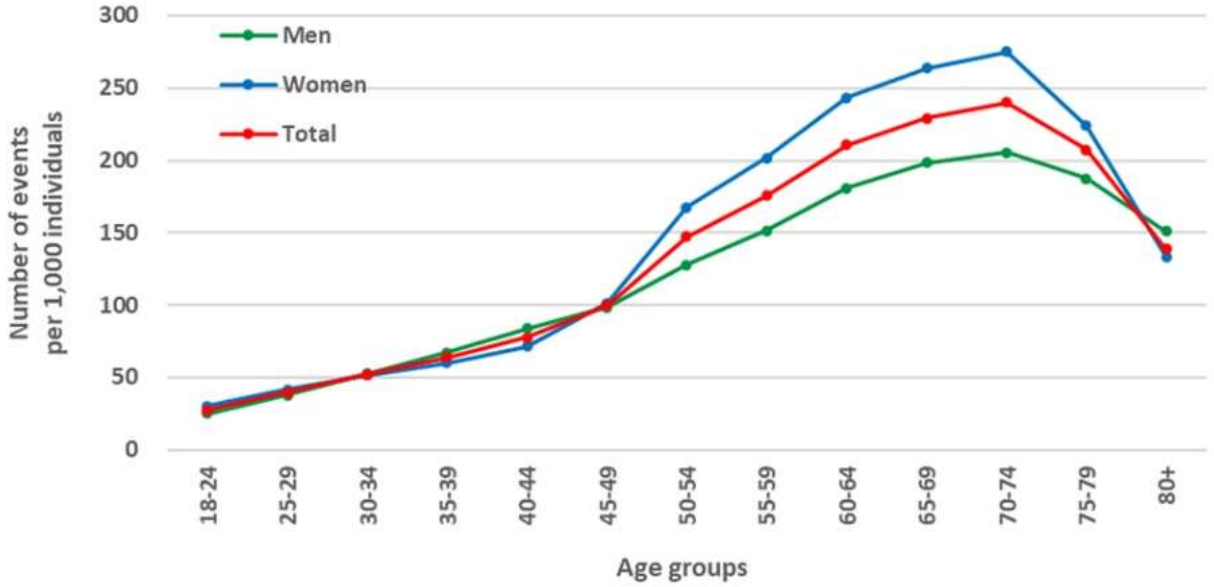
Prevalence and incidence of atherosclerotic cardiovascular disease and its risk factors in Korea: a nationwide population-based study

Hyungtae Kim, Siin Kim, Sola Han, Pratik P. Rane, Kathleen M. Fox, Yi Qian & Hae Sun Suh

BMC Public Health **19**, Article number: 1112 (2019) | Cite this article



(e) Prevalence per 1,000 persons of dyslipidemia



(f) Cumulative incidence per 1,000 persons of dyslipidemia

Overall prevalence and cumulative incidence of the risk factors for ASCVD by age group. ASCVD, atherosclerotic cardiovascular disease

BMC Public Health **volume 19, Article number: 1112 (2019)**

Gender differences in LDL particles and levels in the different phases of life

Artery

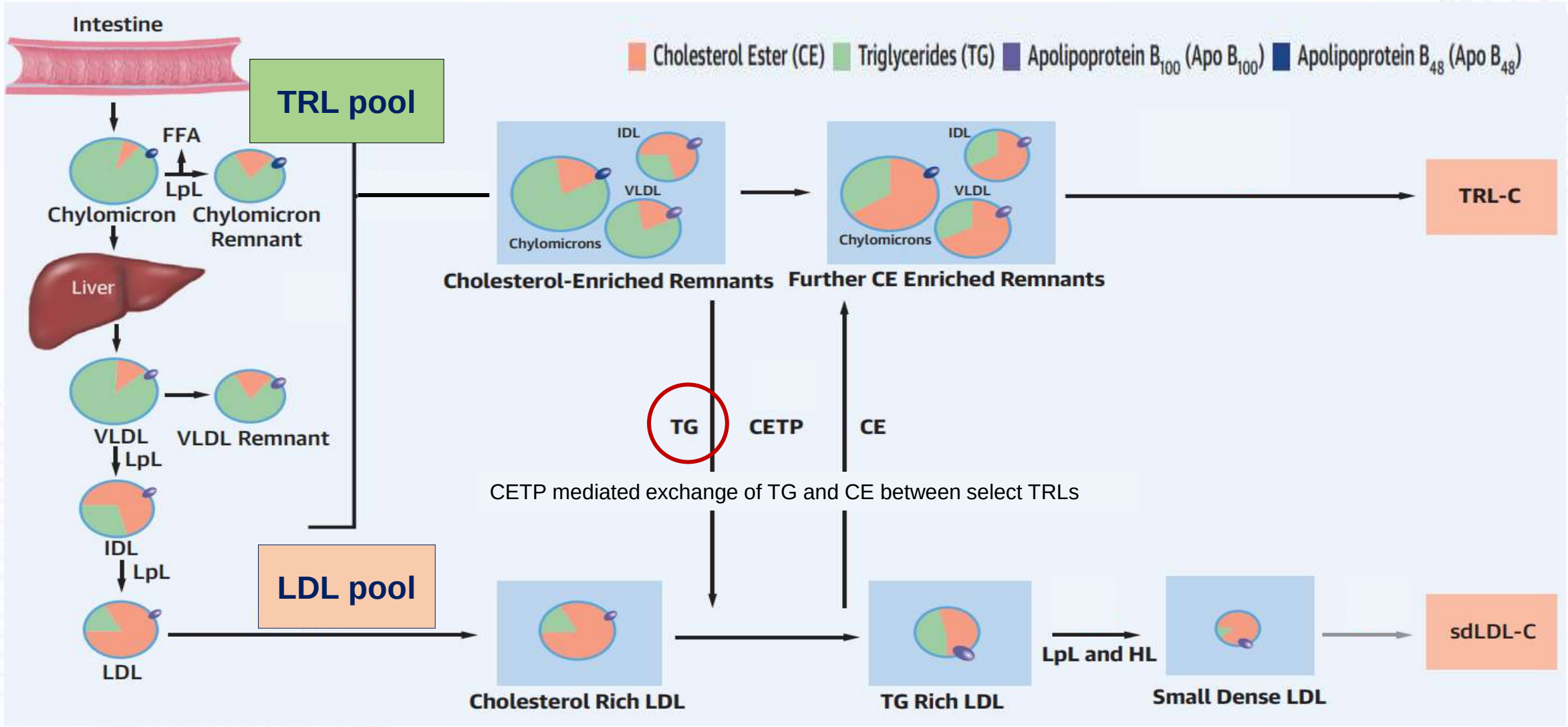
In men during their life, the size of the LDL become slowly small. In females it remains stable until menopause. After this period, LDL particles become smaller and CV risk is similar to men.

In males, LDL-C levels increase more rapidly.
In female it accerlated after 40 years and achieve peaks more than males

After menopause, Small dense LDLs increase and is similar to men

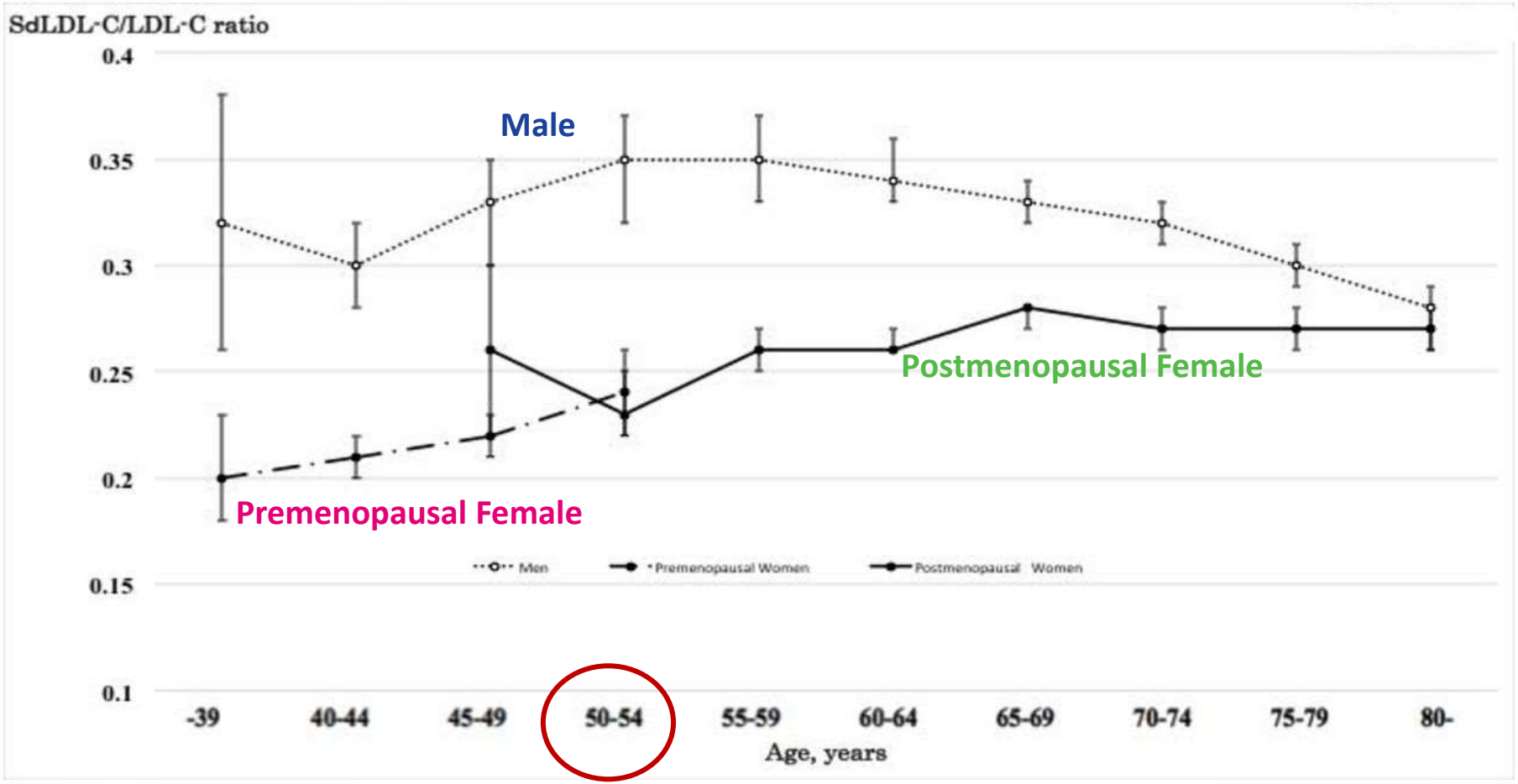
Clinical Lipidology. (2015) 10(6), 499–512

Triglyceride-Rich Lipoproteins and Small-Dense Low-Density Lipoprotein



Edward K. Duran et.al. J Am Coll Cardiol 2020;75:2122–35

(sdLDL-C) / (LDL-C) ratio for age, gender and menopausal status.

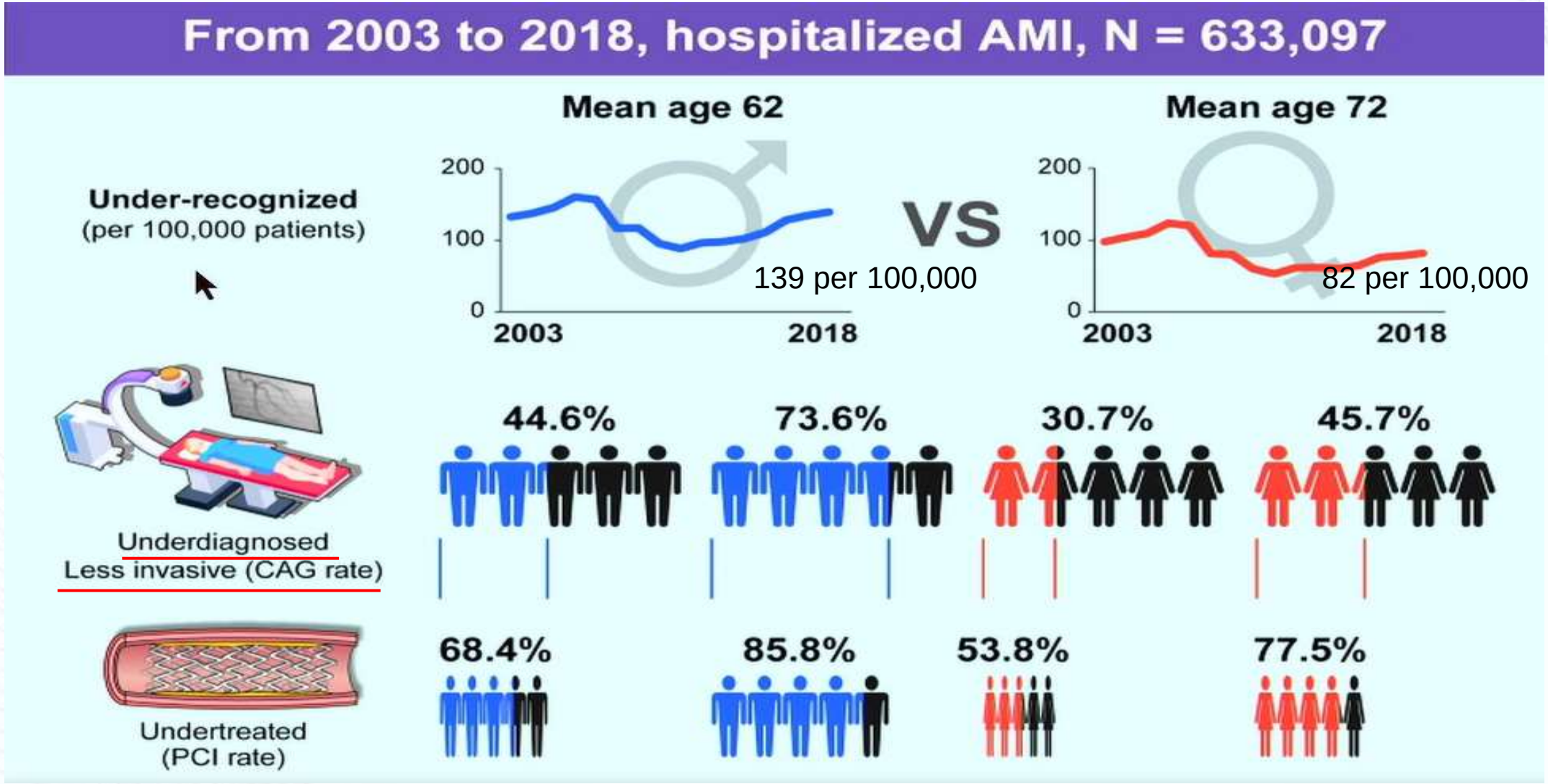


Small dense LDL / LDL cholesterol ratio is reflecting how much LDL cholesterol can be switched into small dense LDL particle

Toshihide Izumida et al. BMJ Open 2021;11:e041613

Sexual Disparity of Real Diagnosis &Treatment

Korean national insurance database



Scientifc Reports | (2023) 13:4120

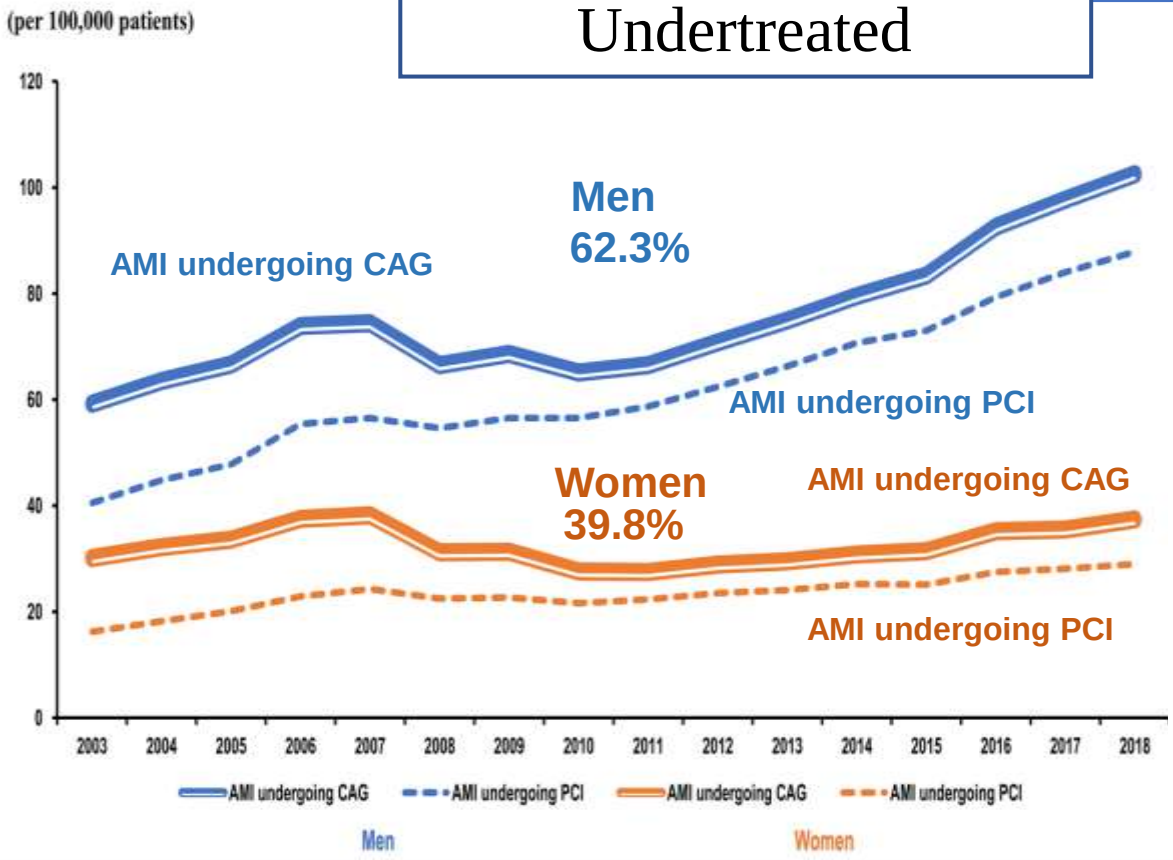
Underdiagnosed, and undertreated AMI in Women

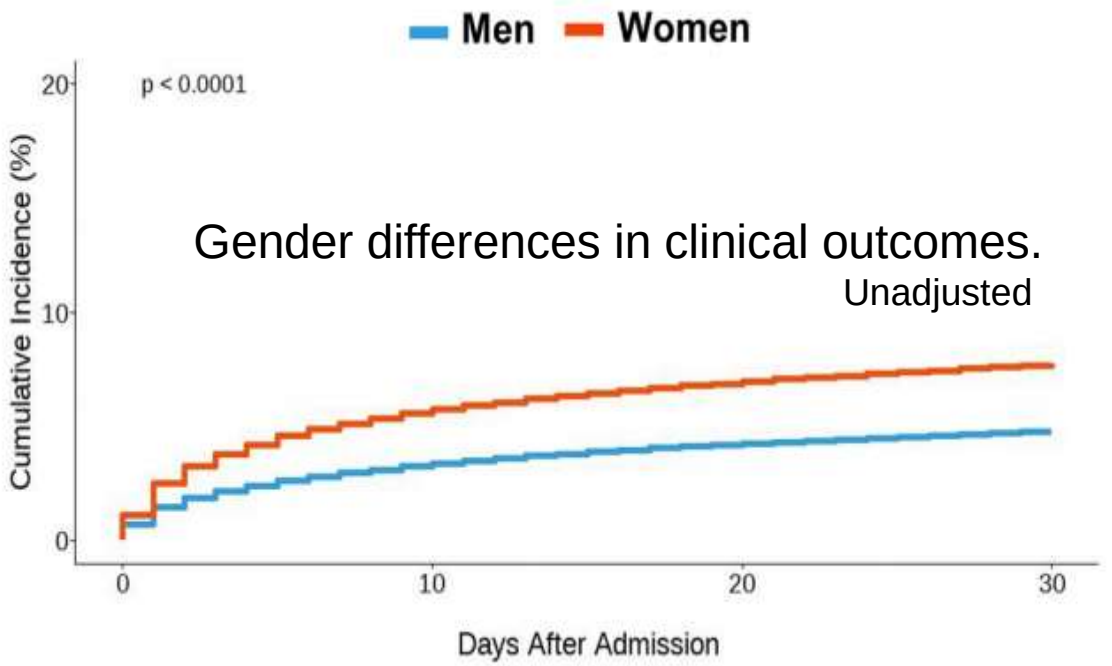
Korean National Health Insurance Claims Database

Underdiagnosed
Undertreated

→

1-month mortality





Gender differences in clinical outcomes.
Unadjusted

S.R Kim et.al. Scientifc Reports | (2023) 13:4120

Presumed Explanations for this Gender Gap

For under-recognized

- More atypical symptoms (Shortness of breathing rather than chest pain)

For underdiagnosed

- More late comer
- Older age
- More comorbidity

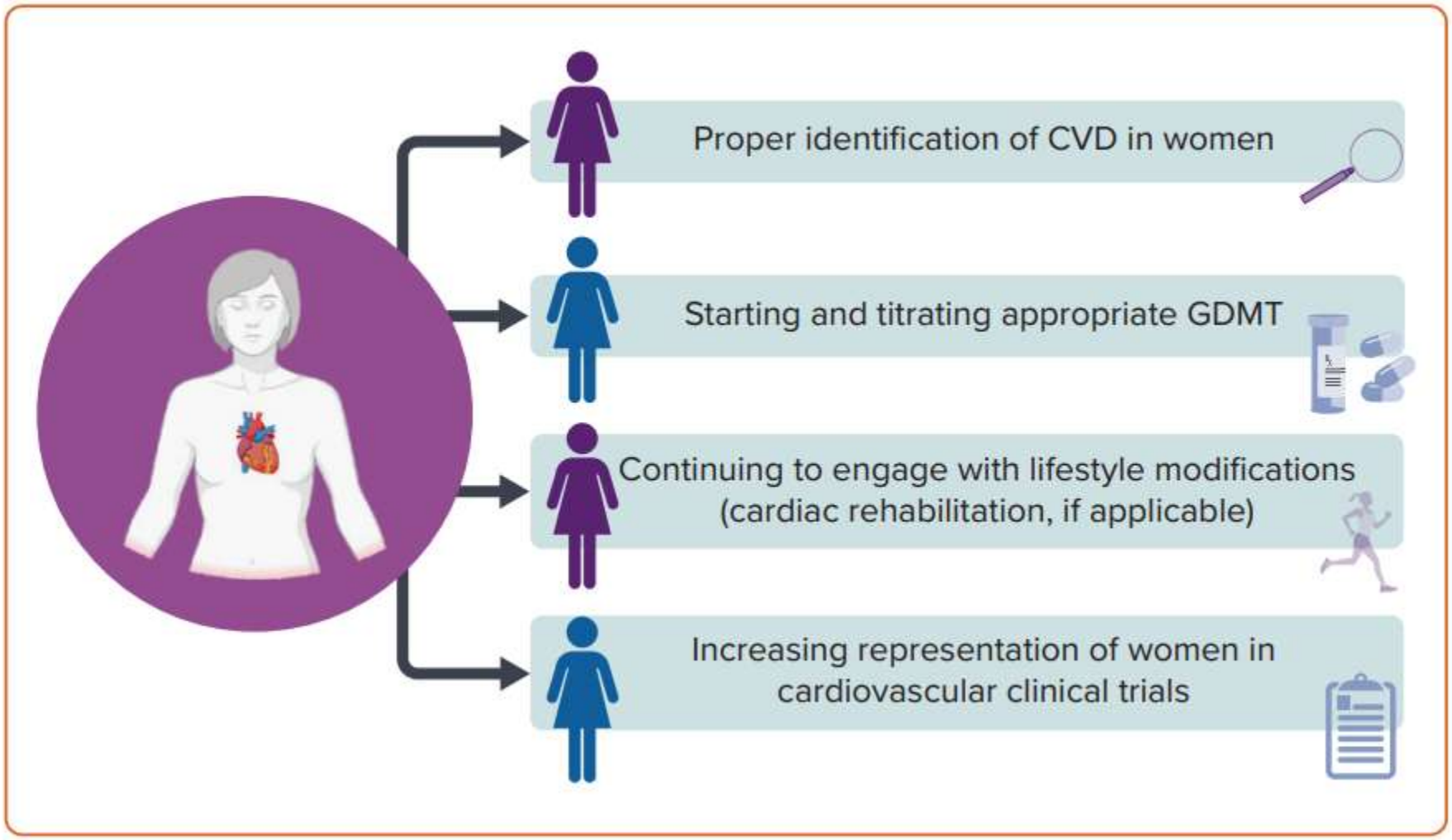
For undertreatment

- Less likely to perform CAG
- cardiovascular medications preferred to procedures
- more likely to be adverse events, less optimal medication

ESC
European Society of Cardiology

Closing the gaps in the cardiovascular care of women

ESC Statement on 'The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030' report.



Sex-specific Clinical Conditions (adulthood)

1. Pre-eclampsia **(defined as pregnancy-related hypertension accompanied by proteinuria)**

; an increase in CVD risk by a factor of 1.5 - 2.7 compared with all women, HTN (RR 3), DM (RR 2)

2. Pregnancy-related HTN

; affects 10 -15% of all pregnancies. HTN (RR 2.0~7.2)

3. Preterm & still birth

; Preterm (CV risk: RR 1.6) , stillbirth (CV risk: RR 1.5)

4. Gestational DM

; upto 50% of affected women developing DM within 5 yrs after pregnancy, CV risk(RR 4)

5. Polycystic ovary syndrome, Premature menopause

; 5% in fertile women, DM (RR 2~4)

Ref) 2021 ESC Guidelines on CV ds prevention. EHJ (2021) 42, 3227-3337

Effect of treatment on Statin or Statin/Ezetimibe combination

Therapeutic approach in several conditions specific to women

- **Several conditions specific to women**
  (gestational HTN, preeclampsia, gestation Dm, preterm or stillbirth)

1) Interventions should include aggressive lifestyle counseling to reduce ASCVD risk

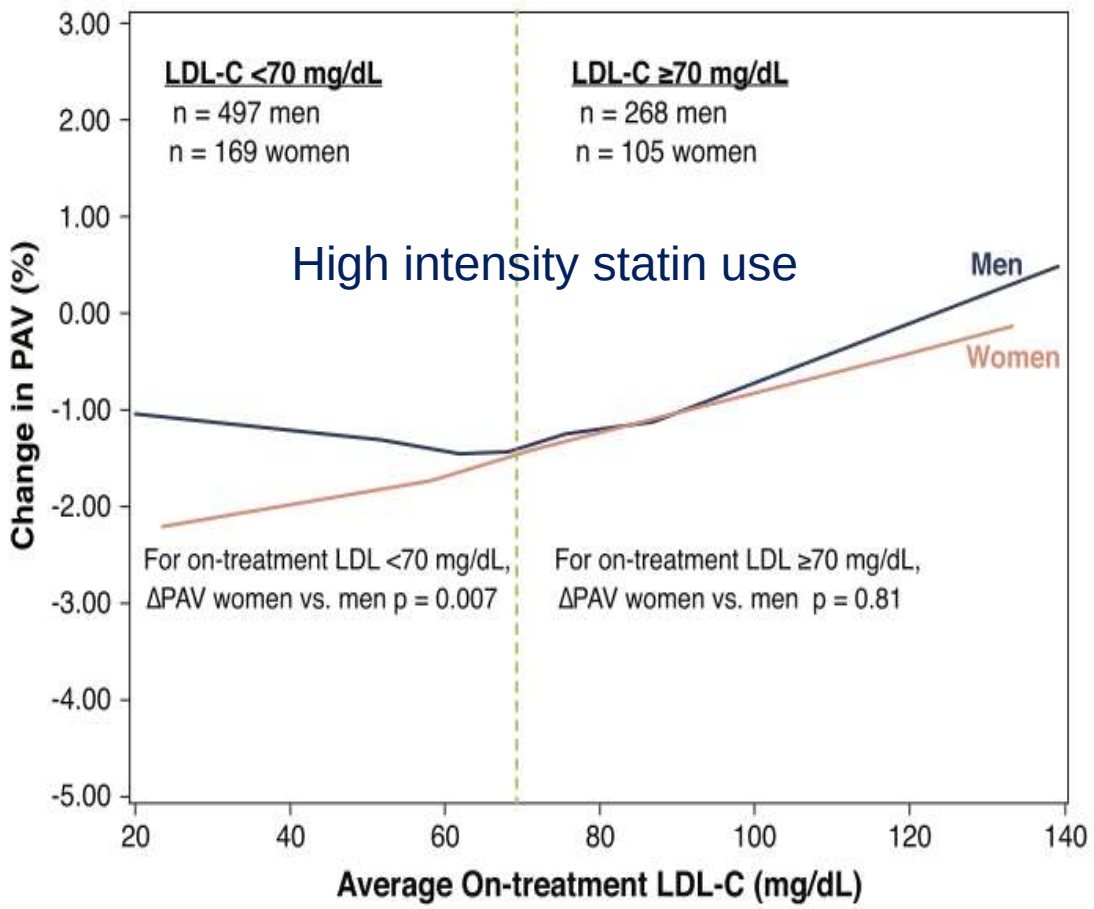
2) when appropriate, statin therapy, if ASCVD risk estimation indicates that the potential for benefit from statin therapy outweighs the potential for adverse effects.

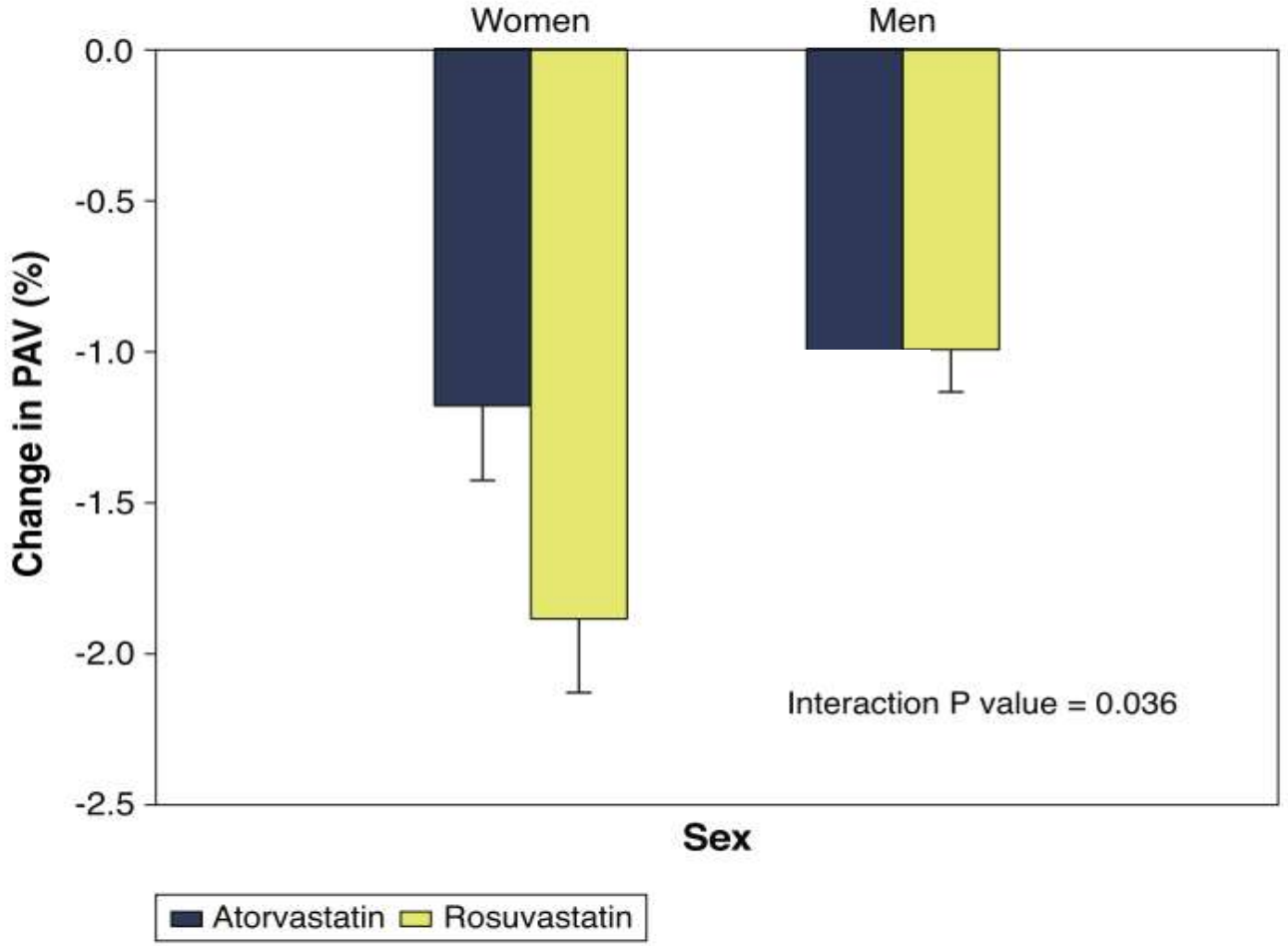
Decisions should be made in the context of a risk discussion and should take into consideration an informed patient preference.

Ref) Scott et al. 2018 AHA/ACC Guideline on the management of blood cholesterol

Sex-Related Differences of Coronary Atherosclerosis Regression

Insights From SATURN





Rishi Puri et.al. J Am Coll Cardiol Img 2014;7:1013–22

CV Reductions for Women in Only 3 Constituent Trials

Trial	Median duration follow up (survivor years)*	Treatment comparison (mg/day)	Number of patients	Women		History of vascular disease‡	
				n	%	n	%
Statin vs. Control							
4S	5·4	S20–40 vs placebo	4444	827	19%	4444	100%
WOSCOPS	4·8	P40 vs placebo	6595	0	0%	499	8%
CARE (Secondary)	5.0	P40 vs placebo	4159	576	14%	4159	100%
Post-CABG	4·3	L40–80 vs L2·5–5	1351	102	8%	1351	100%
AFCAPS/ TexCAPS	5·2	L20–40 vs placebo	6605	997	15%	19	<1%
LIPID	6.0	P40 vs placebo	9014	1516	17%	9014	100%
GISSI Prevention	2.0	P20 vs no treatment	4271	587	14%	4271	100%
LIPS	3·9	F80 vs placebo	1677	271	16%	1677	100%
HPS (Secondary)	5·4	S40 vs placebo	20536	5082	25%	17375	85%
PROSPER	3·3	P40 vs placebo	5804	3000	52%	2550	44%
ALLHAT–LLT	4·9	P40 vs usual care	10355	5051	49%	2318	22%
ASCOT–LLA	3·3	A10 vs placebo	10305	1942	19%	1445	14%
ALERT	5·5	F40 vs placebo	2102	715	34%	400	19%
CARDS	4.1	A10 vs placebo	2838	909	32%	100	4%
ALLIANCE	4.7	A10-80 vs usual care	2442	434	18%	2442	100%
4D	4.0	A20 vs placebo	1255	578	46%	911	73%
ASPEN	4.0	A10 vs placebo	2410	811	34%	747	31%
MEGA‡‡	5.0	P10-20 vs usual care	8214	5547	68%	95	1%
JUPITER (Primary)	2.0	R20 vs placebo	17802	6801	38%	0	0%
GISSI-HF	4.2	R10 vs placebo	4574	1032	23%	4574	100%
AURORA	4.6	R10 vs placebo	2773	1050	38%	1110	40%
CORONA	3.0	R10 vs placebo	5011	1180	24%	5011	100%
SUBTOTAL: 22 trials	**4.8†**		**134537**	**39008**	**29%**	**64512**	**48%**

CTT meta-analysis , The Lancet, Volume 385, Issue 9976, 11–17 April 2015, Pages 1368-1369

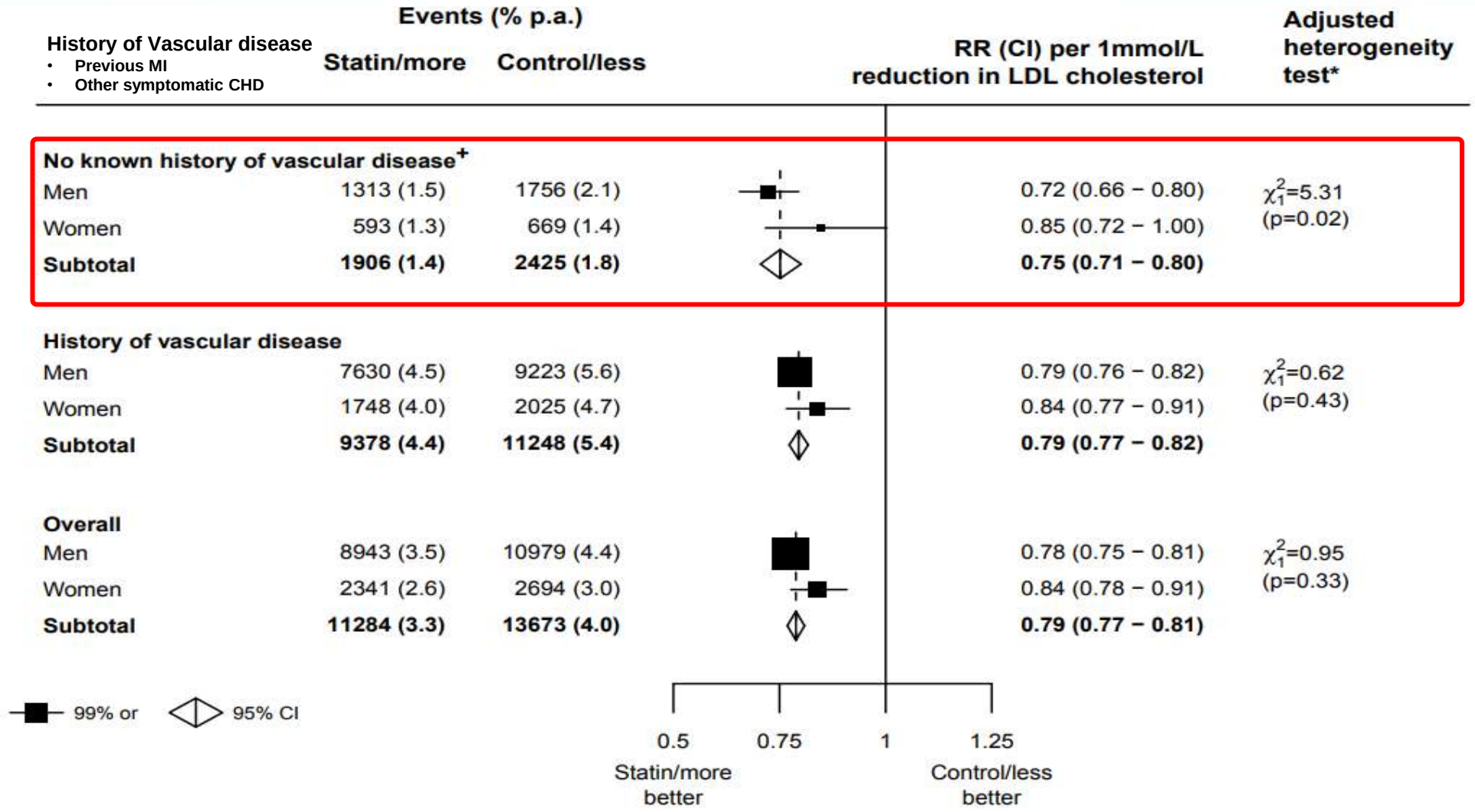
Primary & Secondary Prevention Trials & Proportion of Women

Table 1. Clinical trials with women.

Trial	Statin	Women n (%)	Total population	Mean follow-up (years)
Primary prevention:				
– AFCAPS/TexCAPS	Lovastatin	997 (15)	6605	5.2
– HPS	Simvastatin	1816 (30)	5963	5.4
– ALLHAT-LLT	Pravastatin	5051 (49)	10355	4.9
– ASCOT-LLA	Atorvastatin	1942 (19)	10305	3.3
– MEGA	Pravastatin	5547 (68)	8214	5.0
– JUPITER	Rosuvastatin	6801 (38)	17802	2.0
Secondary prevention:				
– 4S	Simvastatin	827 (19)	4444	5.4
– CARE	Pravastatin	576 (14)	4159	5.0
– LIPID	Pravastatin	1516 (17)	9014	6.0
– HPS	Simvastatin	3266 (22)	14573	5.4
– TNT	Atorvastatin	1902 (19)	10001	5.0
– SEARCH	Simvastatin	2052 (17)	12064	7.0

Clinical Lipidology. (2015) 10(6), 499–512

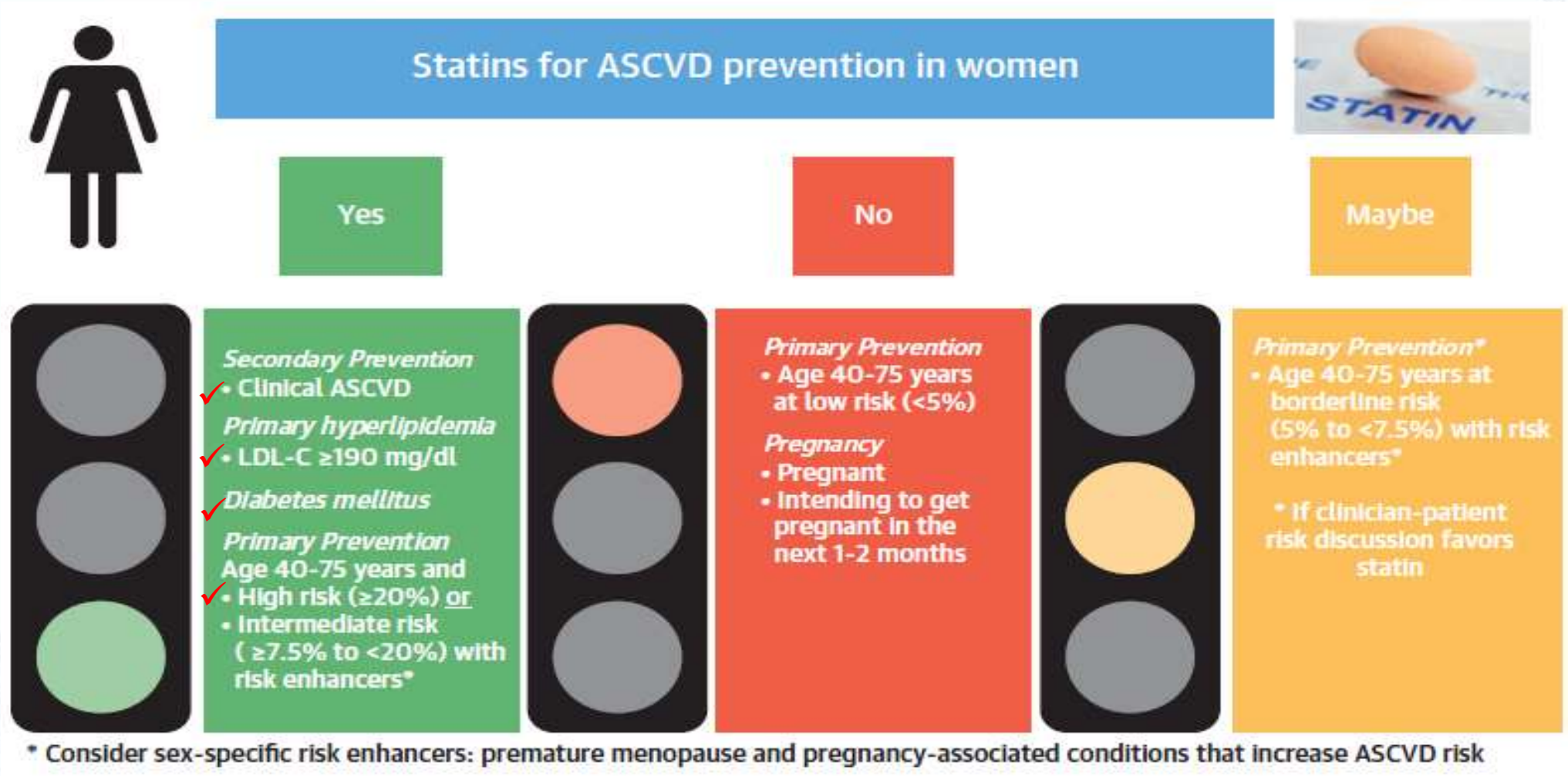
Proportional Reduction in Major Vascular Events (per 1.0 mmol/L) with 22 trials



Fulcher J et.al. Lancet. 2015;385:1397–1405.

No-Specific Guidelines of Statin for Primary Prevention in Women

: *2020 JACC State-of-the-Art Review ：*



Cho Leslie et al., Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women, J Am Coll Cardiol 2020;75:2602-18

Statin Utilization in Female vs Male Patients

Sex differences in statin treatment using the PALM, the US national registry,

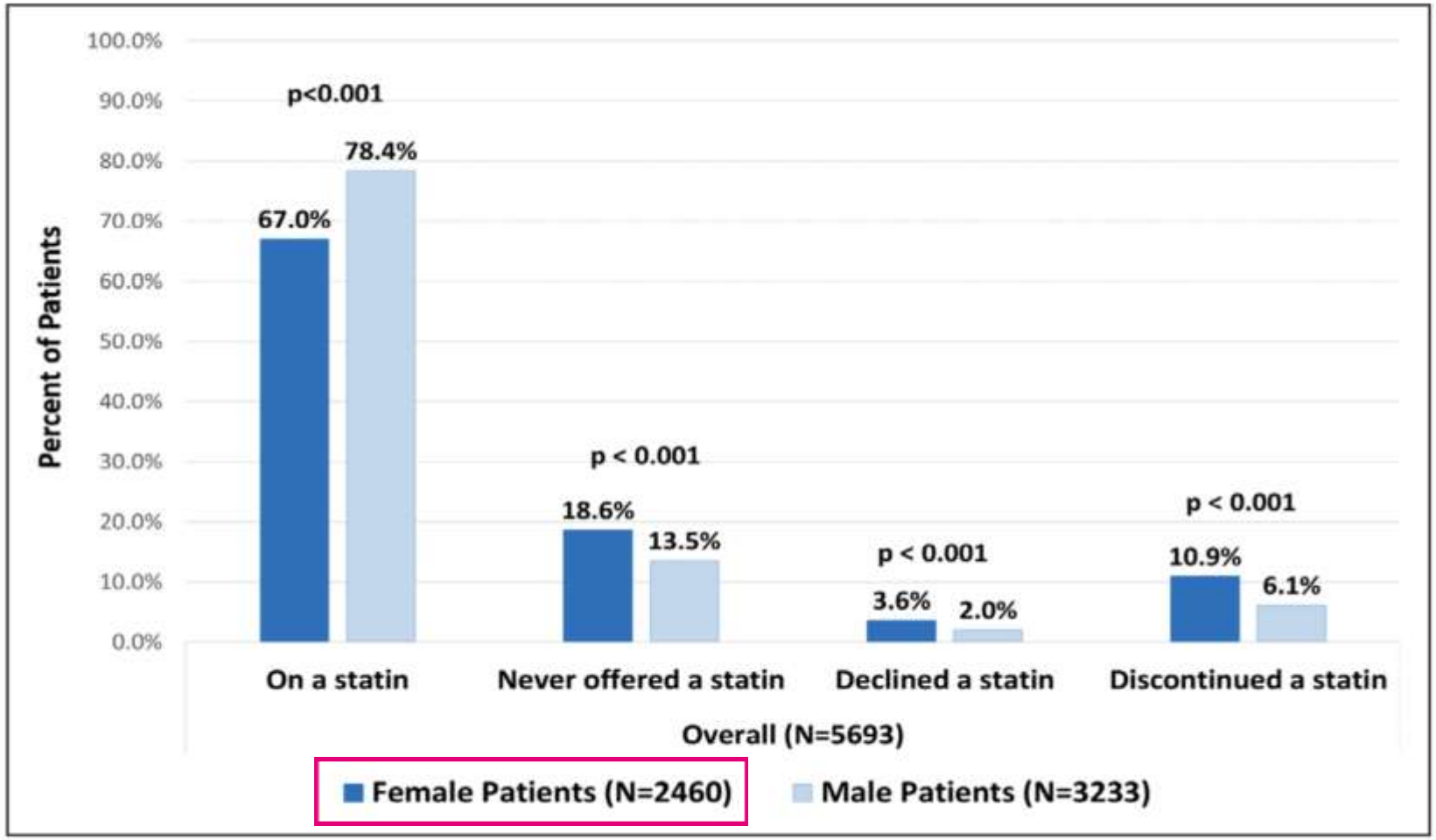


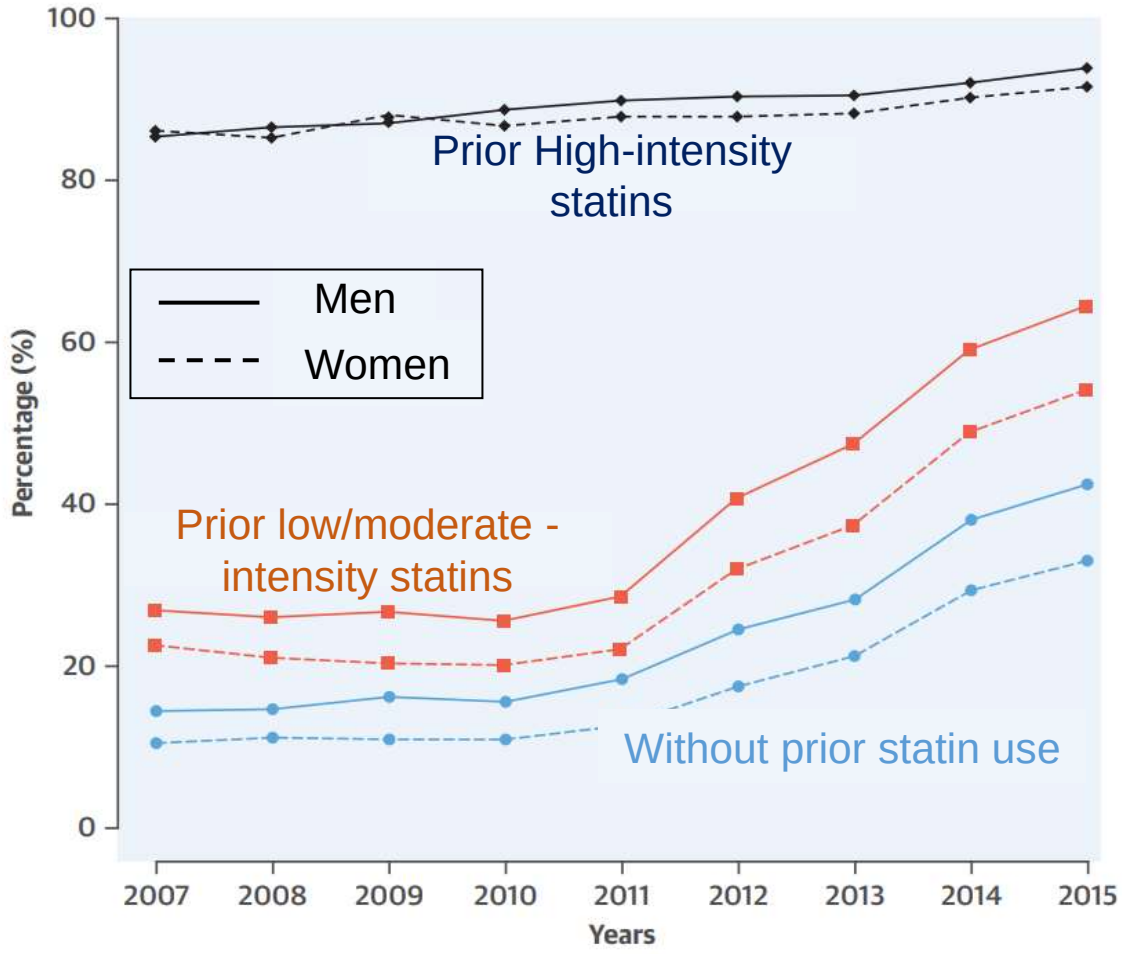
Figure 1. Statin utilization in female vs male patients.
This figure displays statin utilization in male and female patients according to percentages on a statin, never offered a statin, declined a statin, and discontinued a statin.

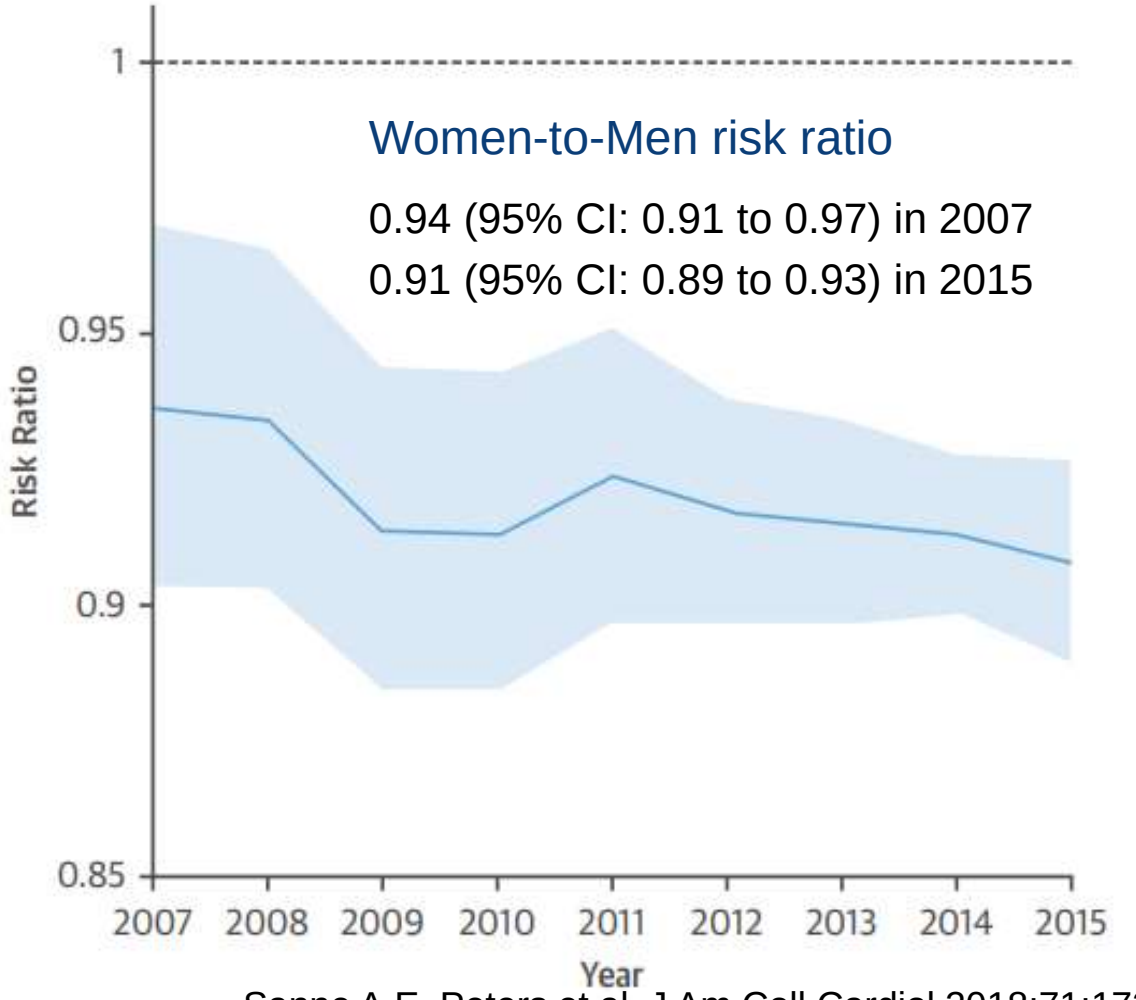
Circ Cardiovasc Qual Outcomes. 2019;12:e005562

Guideline-Recommended Therapy following MI

Still less likely than men

Women continue to fill a less prescription for high-intensity statins following hospitalization for MI





Sanne A.E. Peters et.al. J Am Coll Cardiol 2018;71:1729–37

Secondary prevention of CVD in Women : Closing the Gap

Atypical Presentations and Obstacles to Treatment

- As a result of these different presentations and overall lower perceived risk of CVD, women often have delayed diagnoses and are less likely to get urgent revascularisation of their MI
- *For example, women are less likely to be treated with statin or aspirin therapy and have controlled hypertension, and, overall, are less likely to be linked to appropriate cardiac rehabilitation (CR) programmes..*
- *Disparities in access to care for women extend throughout all ages and stages of CVD. Previous reviews have demonstrated that minimising modifiable risk factors at every aspect of care from diagnosis to treatment can help close the gap and improve outcomes.*

Sex Differences in Medication Side-effects

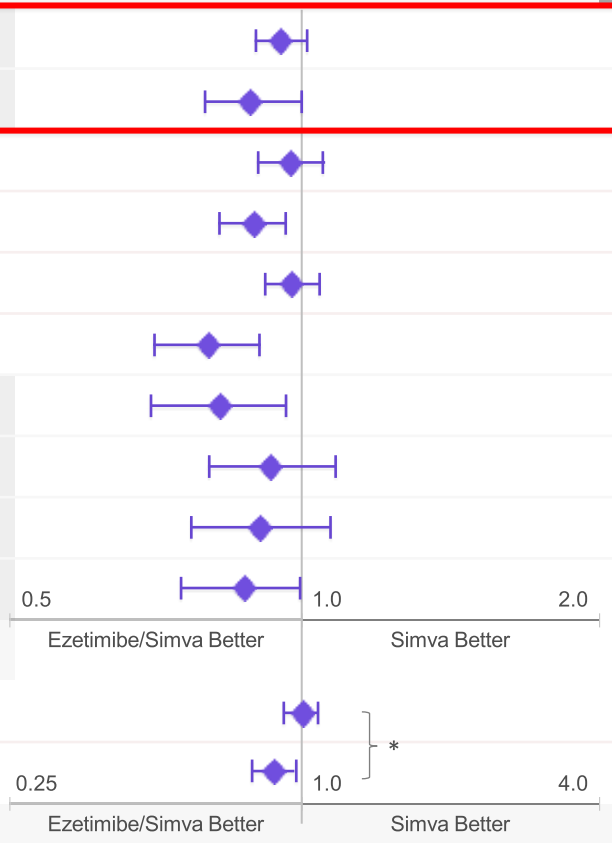
- ***28%* more likely to have new or worsening muscle symptoms with statin therapy** *(adjusted OR 1.28; 95% CI [1.16, 1.42]) and* ***48%* more likely to discontinue their statin therapy due to muscle symptoms** *(adjusted OR 1.48; 95% CI [1.25.1.75]) than men*

1. Eur Cardiol 2021 Nov 8;16:e41. doi: 10.15420

Different Results of Women's Statin Management in a Trial

IMPROVE-IT sub-analysis

Major Prespecified Subgroups[2]



	Simva†	EZ/Simva†
Male	34.9	33.3
Female	34.0	31.0
Age <65 years	**30.8**	**29.9**
Age ≥65 years	**39.9**	**36.4**
Age <75 years	**32.46**	**31.67**
Age ≥75 years	**47.60**	**38.95**
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
Baseline LDL-C >95 mg/dL	31.2	29.6
Baseline LDL-C ≤95 mg/dL	38.4	36.0
No diabetes	**30.8**	**30.2**
Diabetes	**45.5**	**40.0**

Adapted from Cannon CP, *et al.*[2]

† 7-year event rates * *p*-interaction =0.023, otherwise >0.05

IMPROVE-IT : Improved Reduction of Outcomes: Vytorin Efficacy International Trial, **CV** : Cardiovascular, **LLT** : Lipid lowering treatment, **LDL-C** : Low density lipoprotein cholesterol, **EZ/Simva** : Ezetimibe/Simvastatin

1. Cannon CP, Blazing MA, Giugliano RP, *et al*; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397. **2.** Cannon CP, *et al.* Ezetimibe added to statin therapy after acute coronary syndromes. Supplementary Appendix. *N Engl J Med.* 2015;372:2387-97.

ORIGINAL RESEARCH

Efficacy and Safety of Adding Ezetimibe to Statin Therapy Among Women and Men: Insight From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)

Eri Toda Kato, MD, PhD; Christopher P. Cannon, MD; Michael A. Blazing, MD; Erin Bohula, MD, DPhil; Sema Guneri, MD; Jennifer A. White, MS; Sabina A. Murphy, MPH; Jeong-Gun Park, PhD; Eugene Braunwald, MD; Robert P. Giugliano, MD, SM

Background—IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) showed that adding the nonstatin ezetimibe to statin therapy further reduced cardiovascular events in patients after an acute coronary syndrome. In a prespecified analysis, we explore results stratified by sex.

Methods and Results—In IMPROVE-IT, patients with acute coronary syndrome and low-density lipoprotein cholesterol of 50 to 125 mg/dL were randomized to placebo/simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg. They were followed up for a median of 6 years for the primary composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization ≥30 days, and stroke. Among 18 144 patients in IMPROVE-IT, 4416 (24%) were women. At 12 months, the addition of ezetimibe to simvastatin significantly reduced low-density lipoprotein cholesterol from baseline compared with simvastatin monotherapy in men and women equally (absolute reduction, 16.7 mg/dL in men and 16.4 mg/dL in women). Women receiving ezetimibe/simvastatin had a 12% risk reduction over those receiving placebo/simvastatin for the primary composite end point (hazard ratio, 0.88; 95% confidence interval, 0.79–0.99) compared with a 5% reduction for men (hazard ratio, 0.95; 95% confidence interval, 0.90–1.01; P=0.26 for interaction). When the total number of primary events was considered, women had an 18% reduction with the addition of ezetimibe (relative risk, 95% confidence interval, 0.81; 0.71–0.94) and men had a 6% reduction (relative risk, 0.94; 95% confidence interval, 0.87–1.02; P=0.08 for interaction). The addition of ezetimibe did not increase the rates of safety events in either women or men.

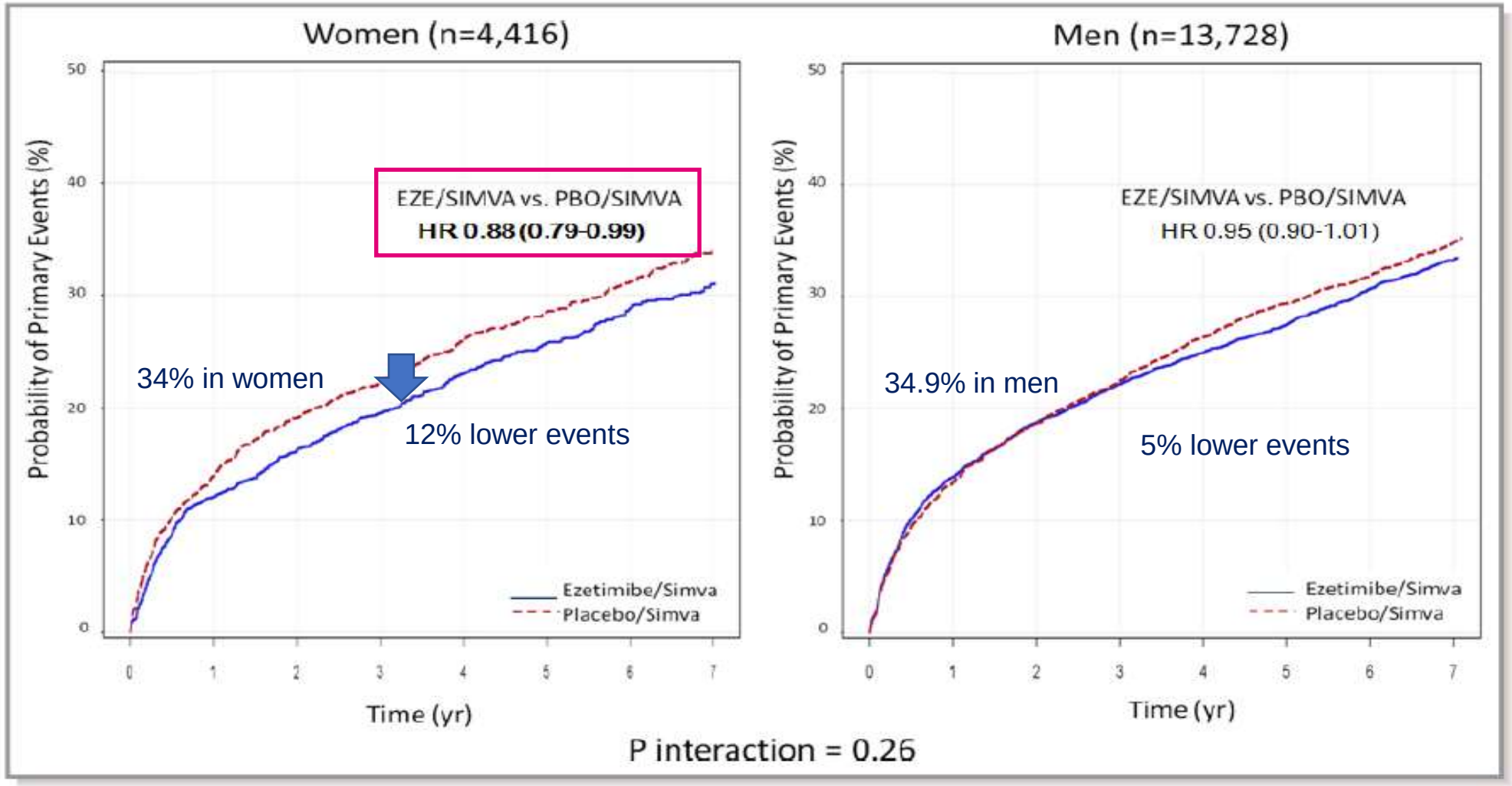
Conclusions—IMPROVE-IT demonstrated that the benefit of adding ezetimibe to statin is present in both women and men, with a good safety profile supporting the use of intensive, combination, lipid-lowering therapy to optimize cardiovascular outcomes.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00202878. (***J Am Heart Assoc.*** **2017;6: e006901. DOI: 10.1161/JAHA.117.006901.)**

Key Words: cholesterol • chronic ischemic heart disease • coronary artery disease • ezetimibe • lipids and lipoprotein metabolism • secondary prevention • sex • women

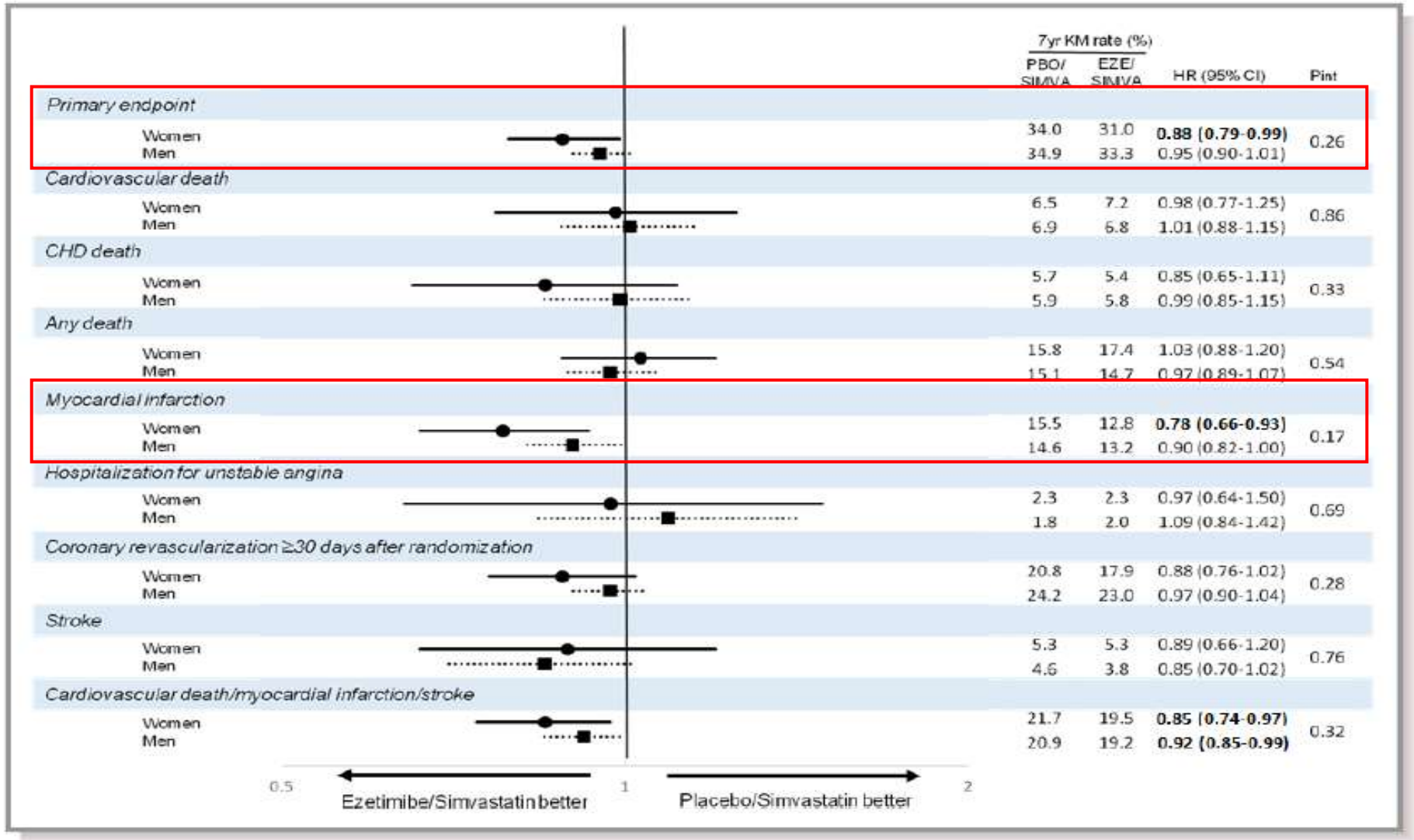
1. J Am Heart Assoc. 2017;6: e006901. DOI: 10.1161/JAHA.117.006901.

Seven Year Kaplan-Meier Curves of Primary End Point by Sex



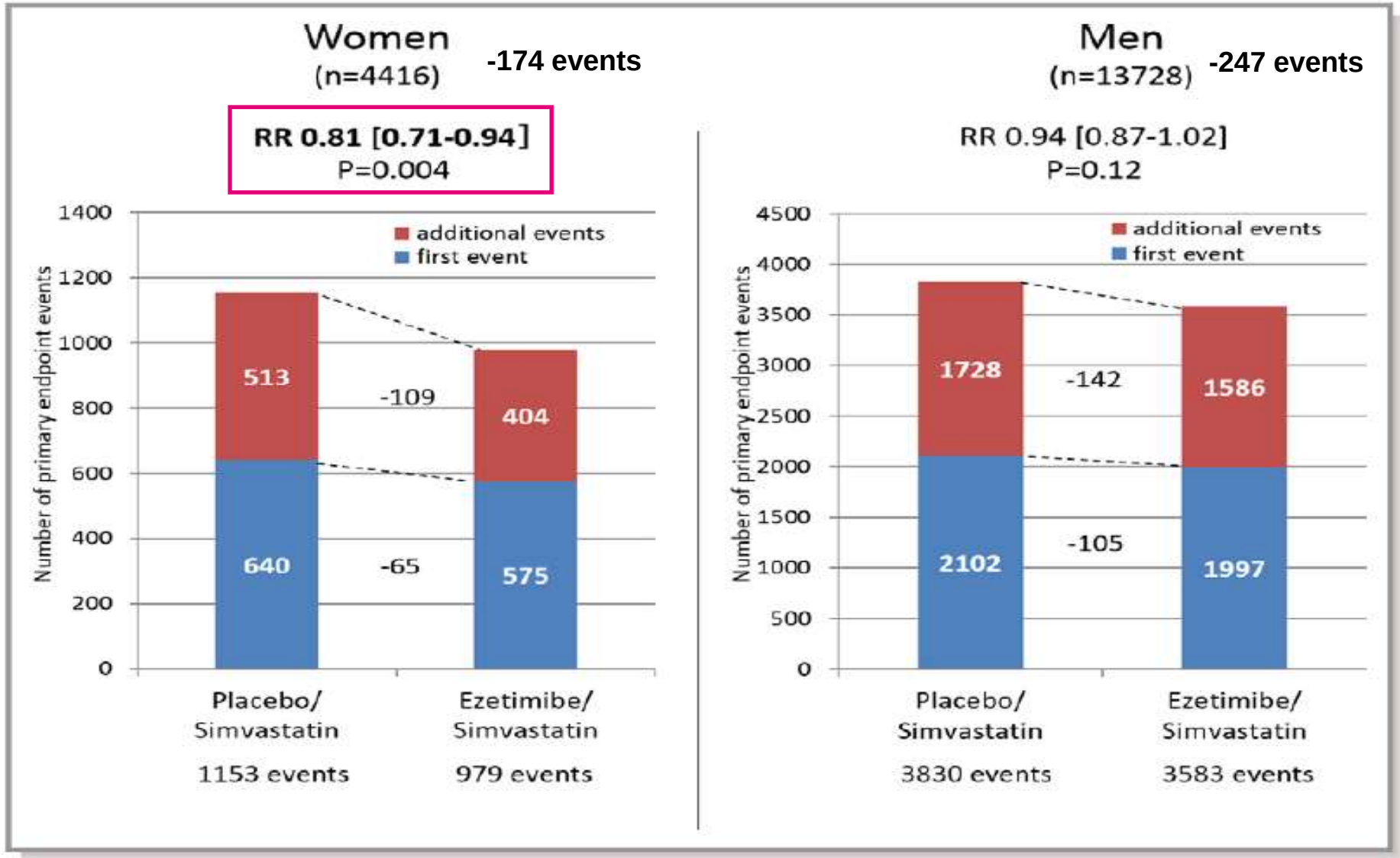
1. J Am Heart Assoc. 2017;6: e006901. DOI: 10.1161/JAHA.117.006901.

Different Efficacy Outcomes by Sex



1. J Am Heart Assoc. 2017;6: e006901. DOI: 10.1161/JAHA.117.006901.

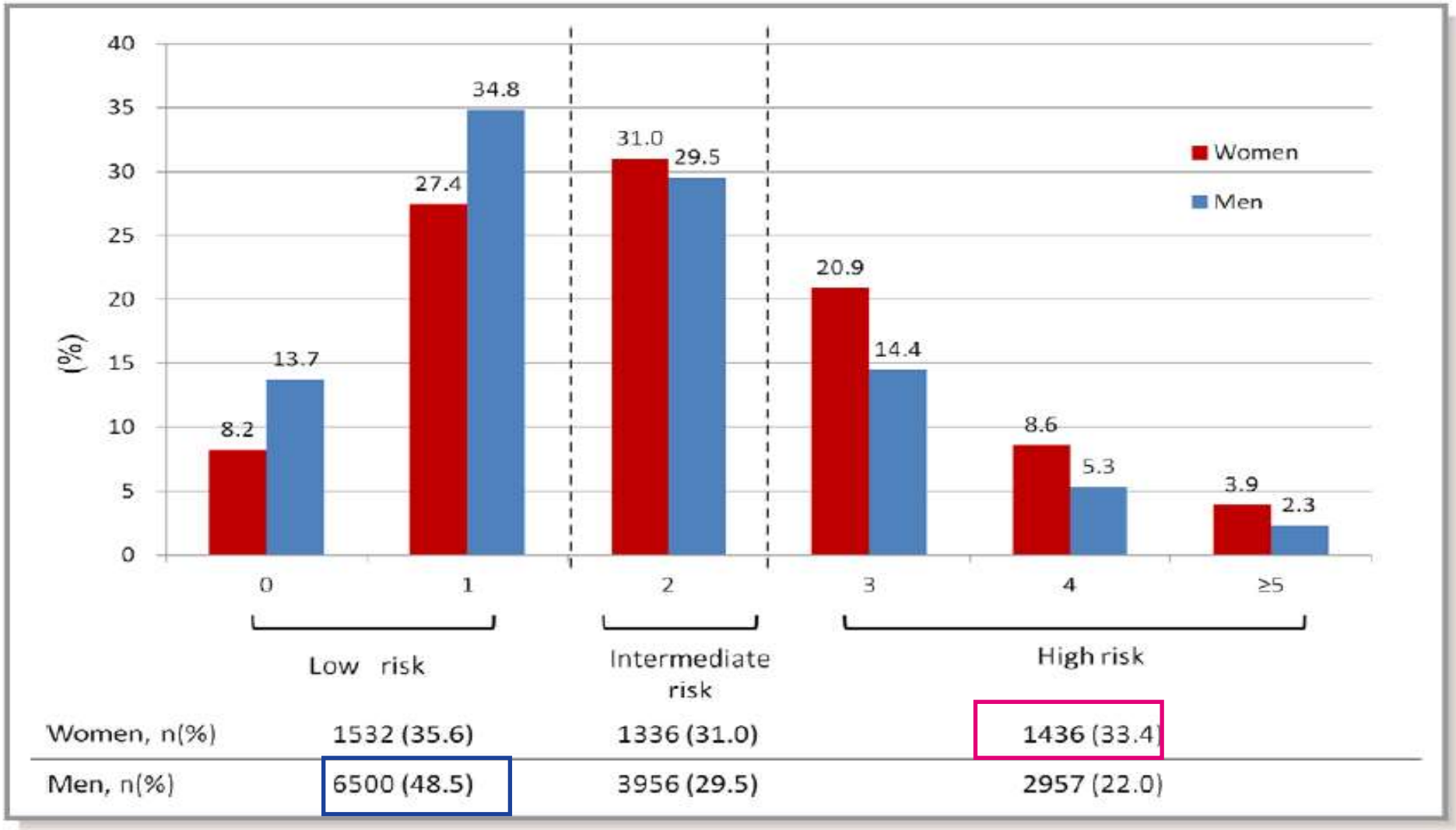
Cumulative Events by Sex



1. J Am Heart Assoc. 2017;6: e006901. DOI: 10.1161/JAHA.117.006901.

Risk stratification by sex

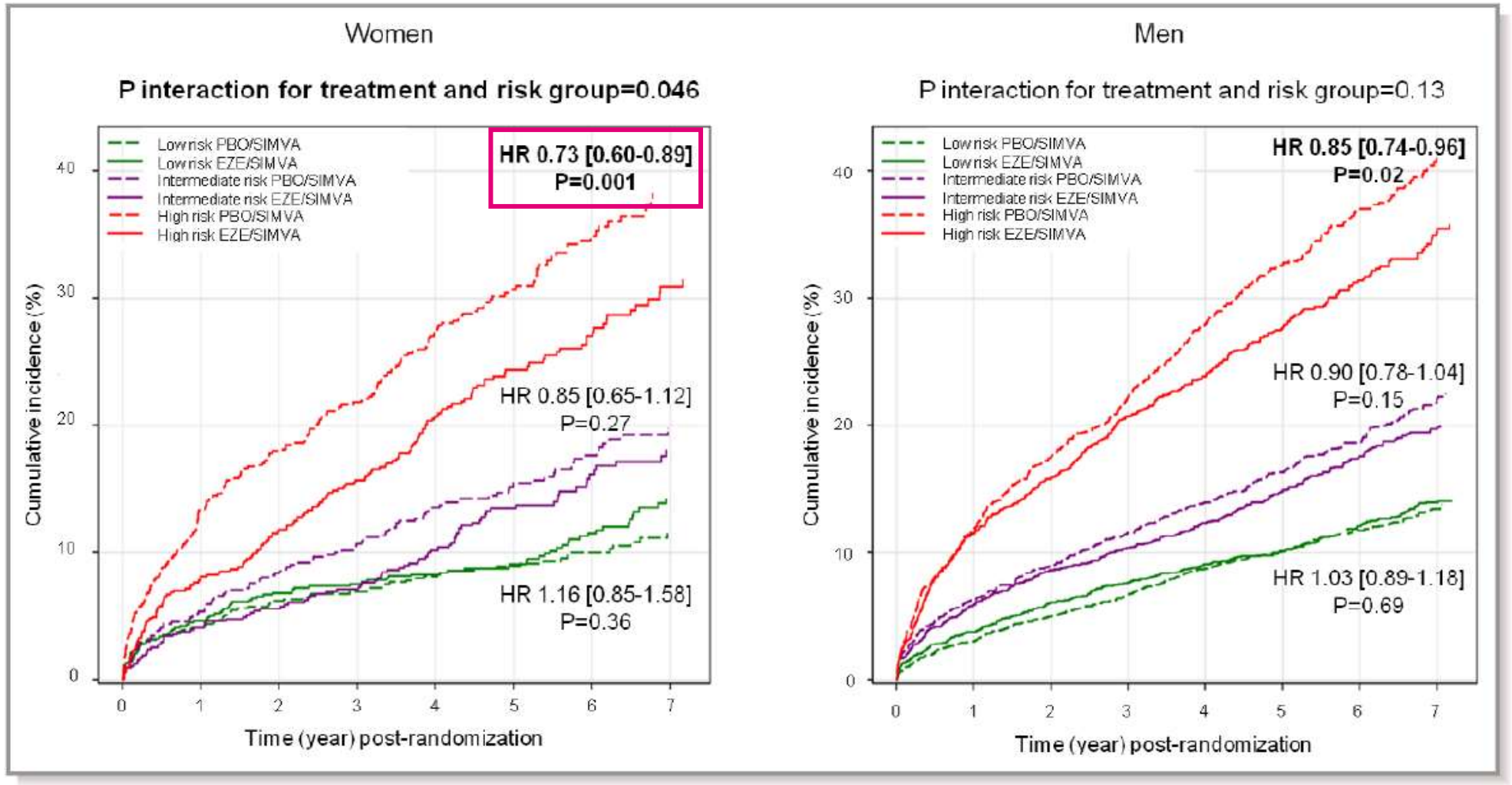
TIMI (Thrombolysis in Myocardial Infarction) Risk Score for Secondary Prevention



	Low risk	Intermediate risk	High risk
Women, n(%)	1532 (35.6)	1336 (31.0)	1436 (33.4)
Men, n(%)	6500 (48.5)	3956 (29.5)	2957 (22.0)

1. J Am Heart Assoc. 2017;6: e006901. DOI: 10.1161/JAHA.117.006901.

Cumulative Incidence of CV Events by Risk Stratification and Treatment Group in Women and Men

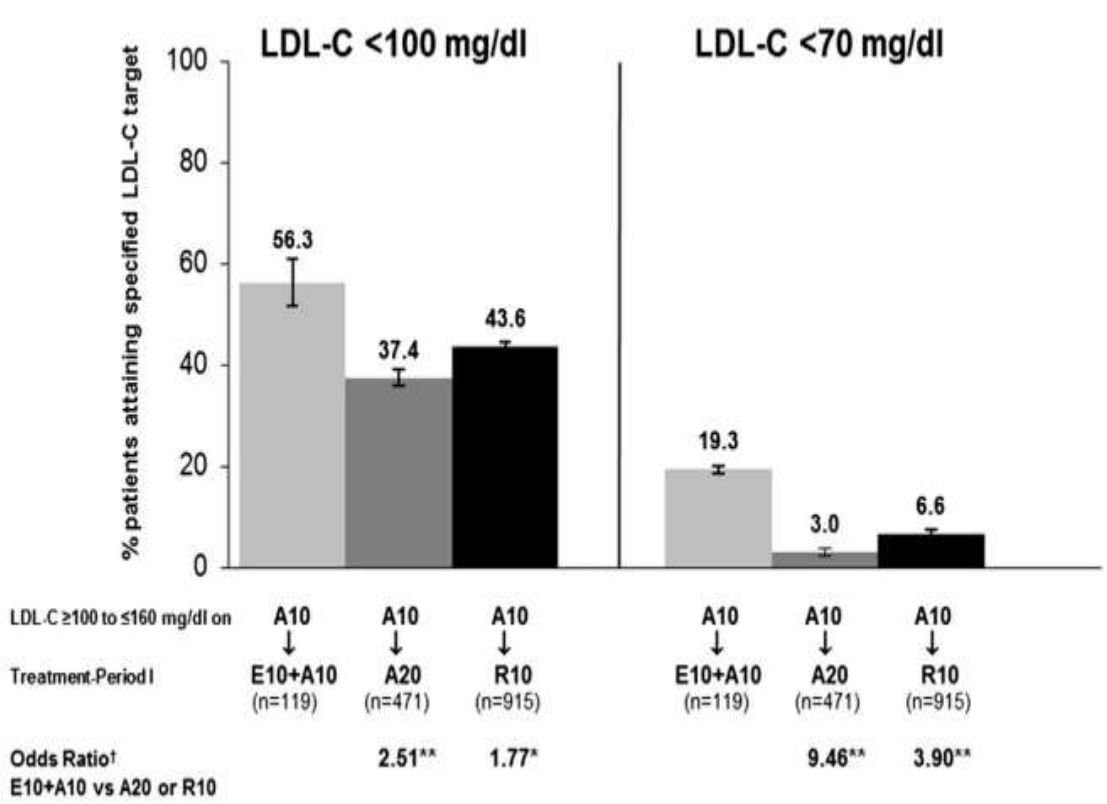


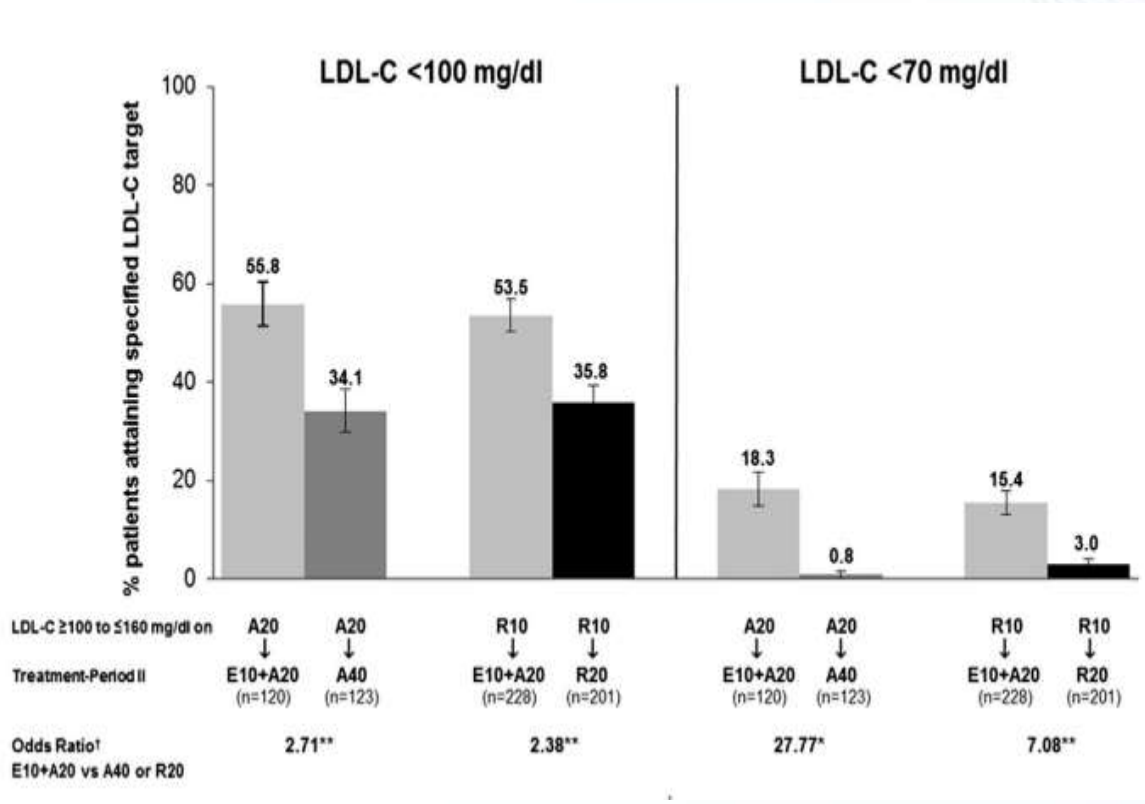
1. J Am Heart Assoc. 2017;6: e006901. DOI: 10.1161/JAHA.117.006901.

Efficacy of Ezetimibe added on Atorvastatin 10mg or 20mg

High risk patients with Atorvastatin 10 or 20 mg

+ (adding ezetimibe 10mg vs Uptitration vs Switching to Rosuvastatin 10 or 20mg)





Harold E. Bays et.al. Am J Cardiol 2013;112:1885e1895

Summary

1. Lipid profile varies before and after menopause in female patients, and it's important to understand dyslipidemia. There is an increase in prevalence and a gap for heart disease depending on gender. (gender specific risk)

2. There are tricky aspects in diagnosis and treatment of female heart disease for subjective judgments such as symptoms and fatigue of statin-related side effects, including SAMS, and women are more resistant to drug use than men.

3. Excellent benefits through Ezetimibe add-on in high-risk female patients were confirmed in IMPROVE IT sub-analysis.

4. **The Ezetimibe combination can better effective for reducing CV events in the higher risk group, especially in female for secondary prevention.**