



**ICT 2023**

28th International  
Congress on Thrombosis

# Thrombosis in women: Gender differences

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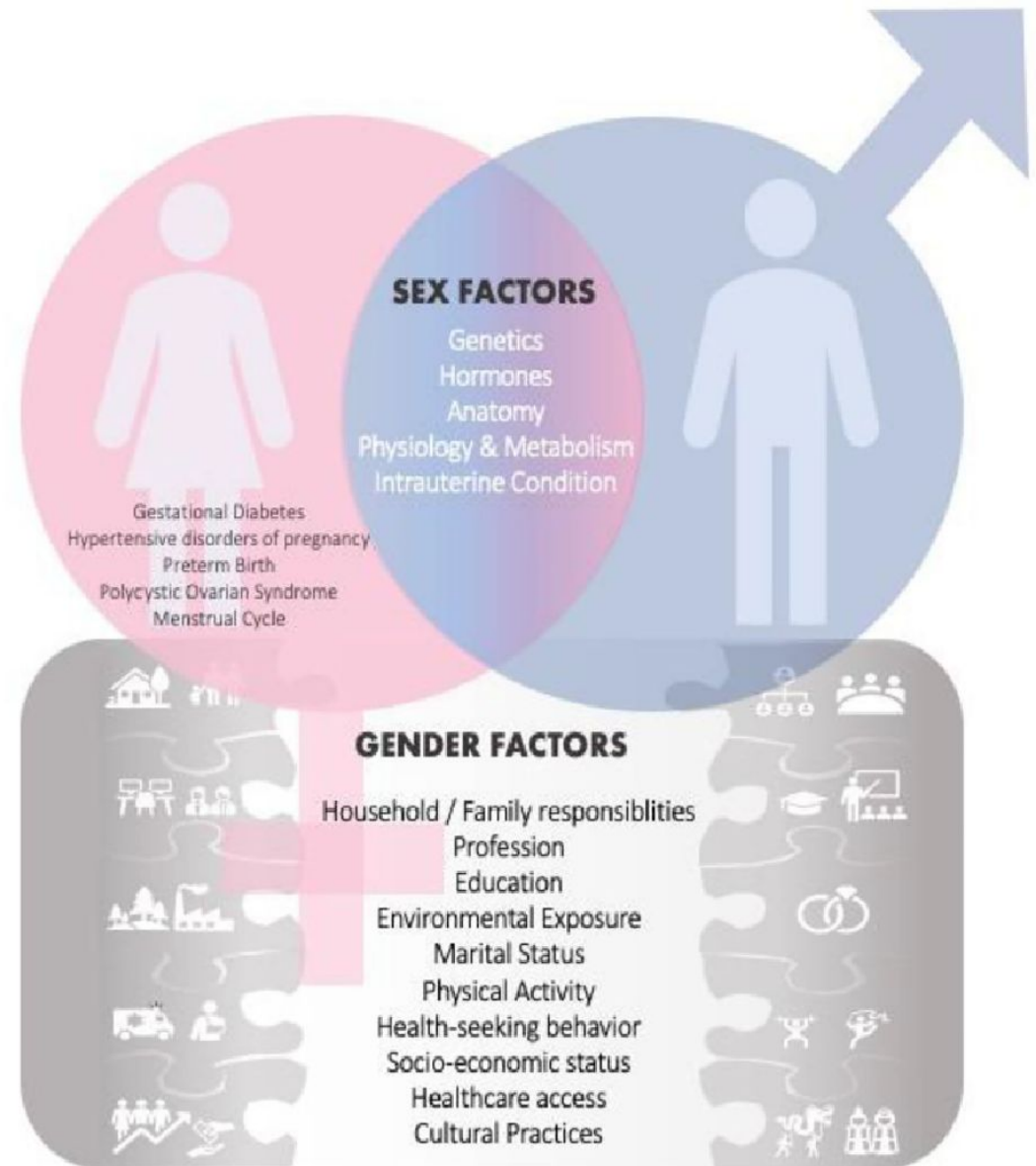
*Emeritus Professor of Biochemistry – Clinical Chemistry*



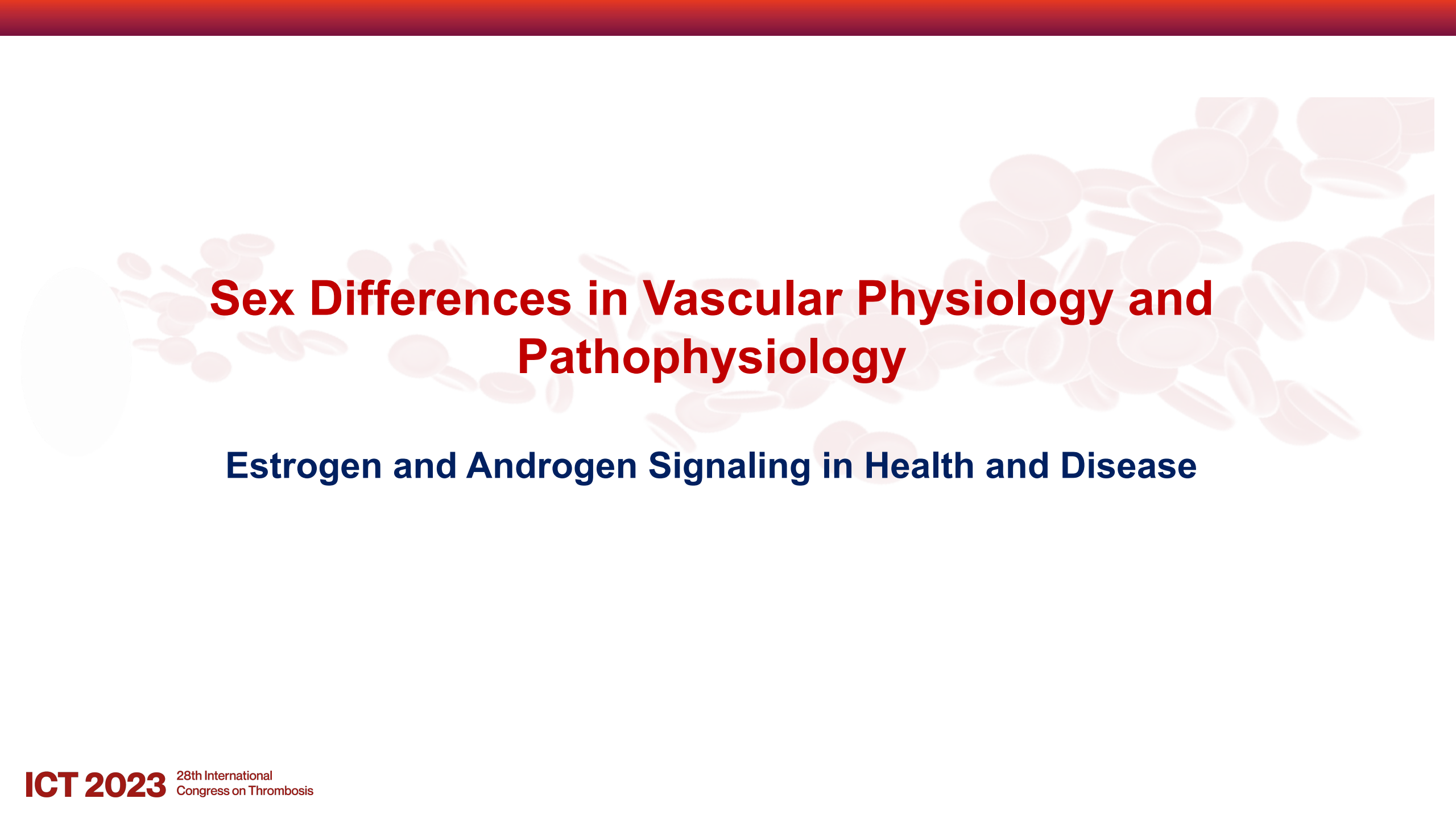
## Declaration of Conflict Of Interest

- I have no potential conflict of interest to report
- I have the following potential conflict(s) of interest to report

# Sex and Gender Factors influence health outcomes



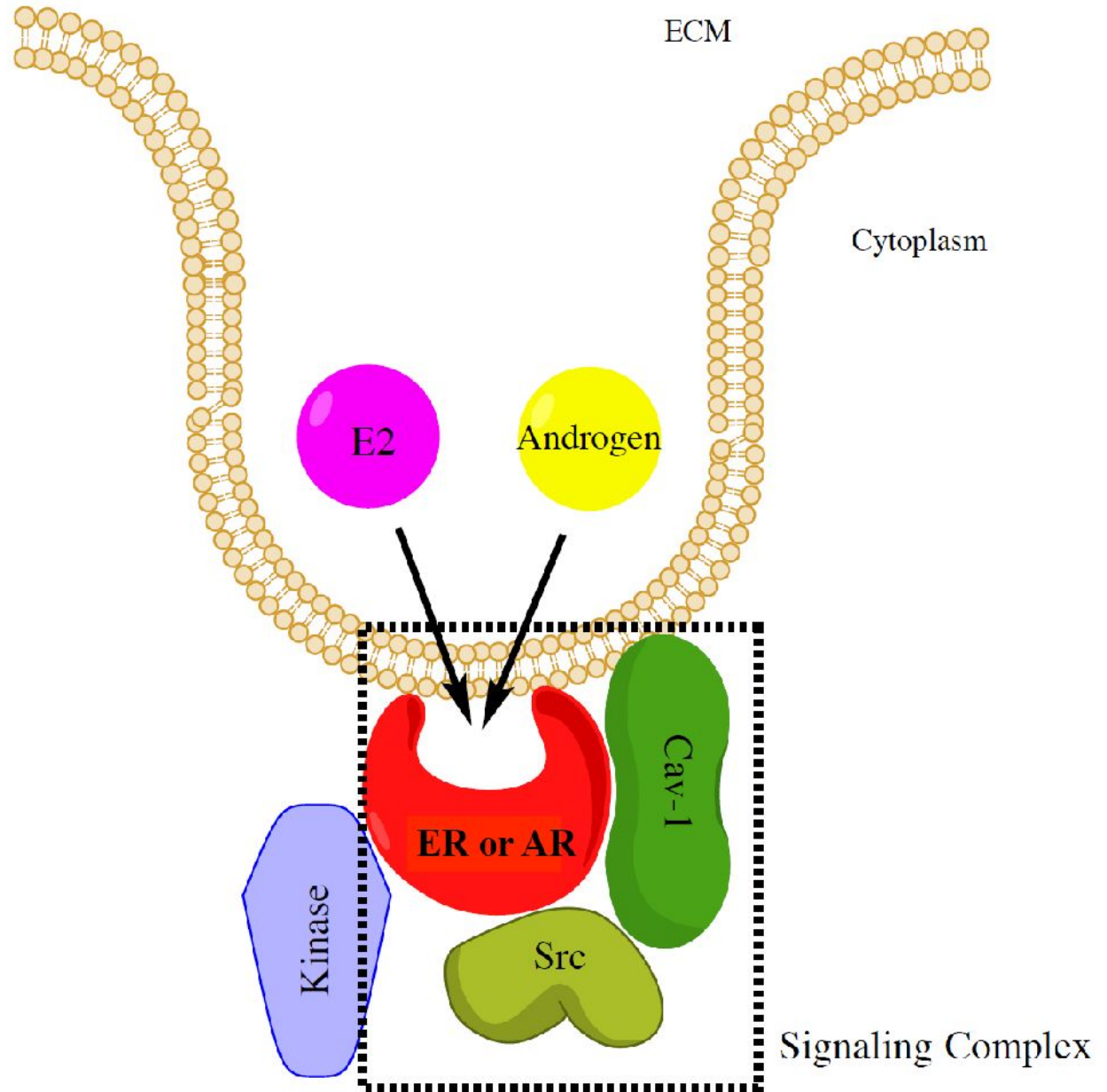
Hernandez L, et al. *Front. Cardiovasc. Med.* 9:916194.

The background features a light pinkish-red gradient with a pattern of semi-transparent red blood cells scattered across it. On the left side, there is a large, faint white oval shape.

# **Sex Differences in Vascular Physiology and Pathophysiology**

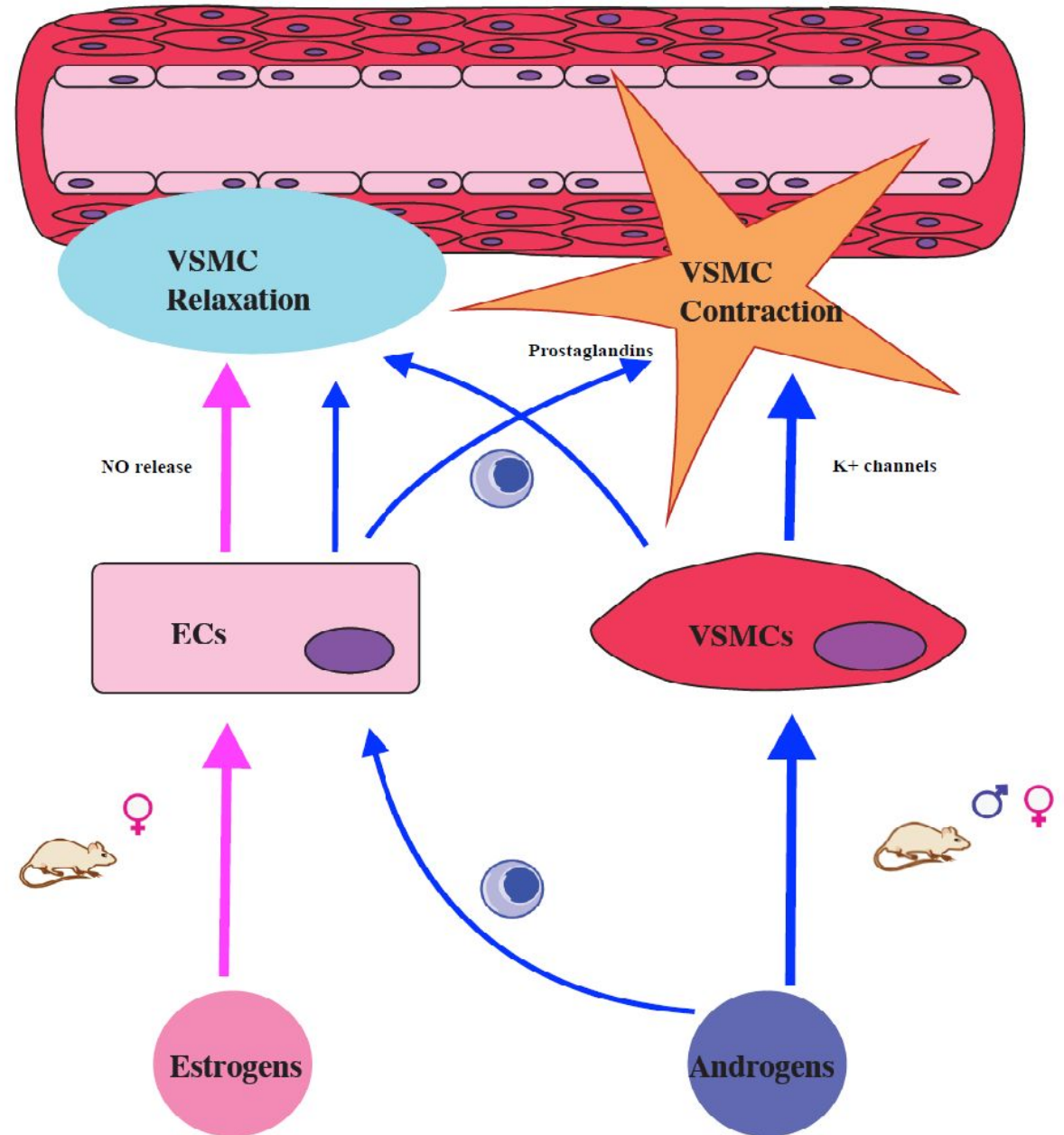
## **Estrogen and Androgen Signaling in Health and Disease**

# Rapid estrogen receptor (ER) and androgen receptor (AR) signaling pathways in vascular ECs and VSMCs



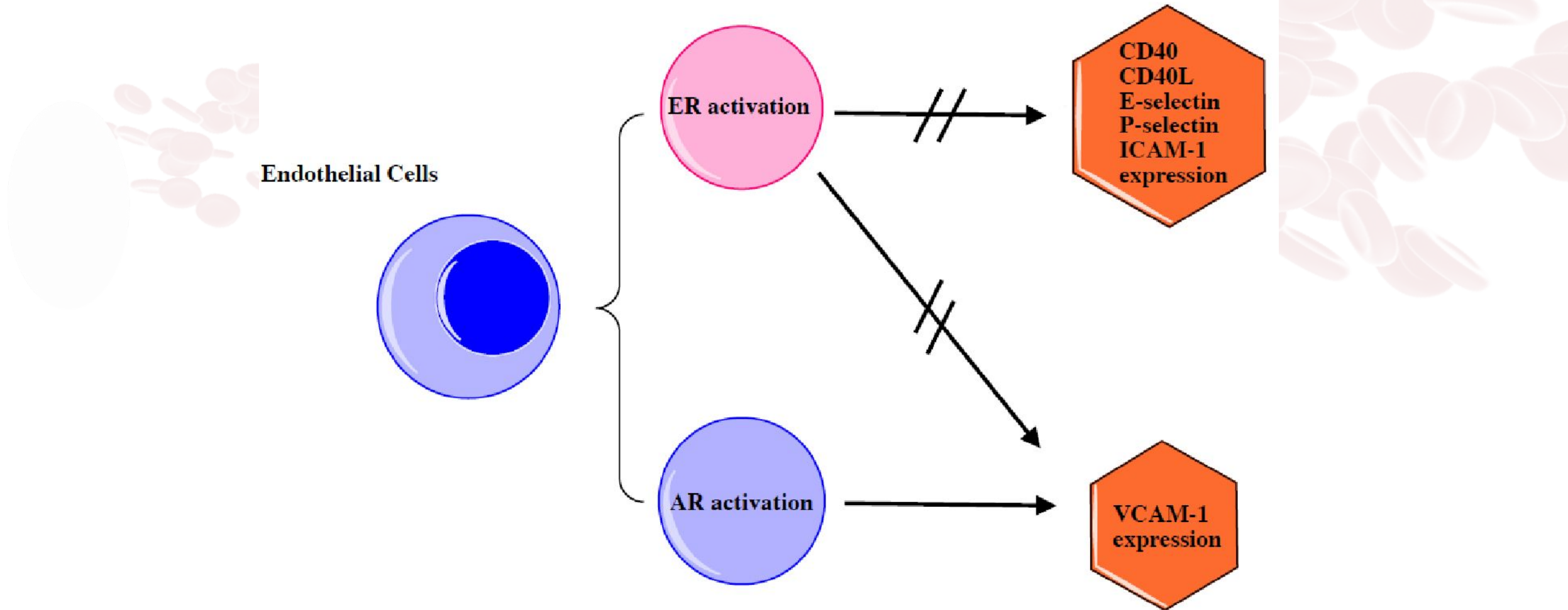
Boese AC, et al. Am J Physiol Heart Circ Physiol. 2017

# Estrogens and androgens influence vascular tone



Boese AC, et al. Am J Physiol Heart Circ Physiol. 2017

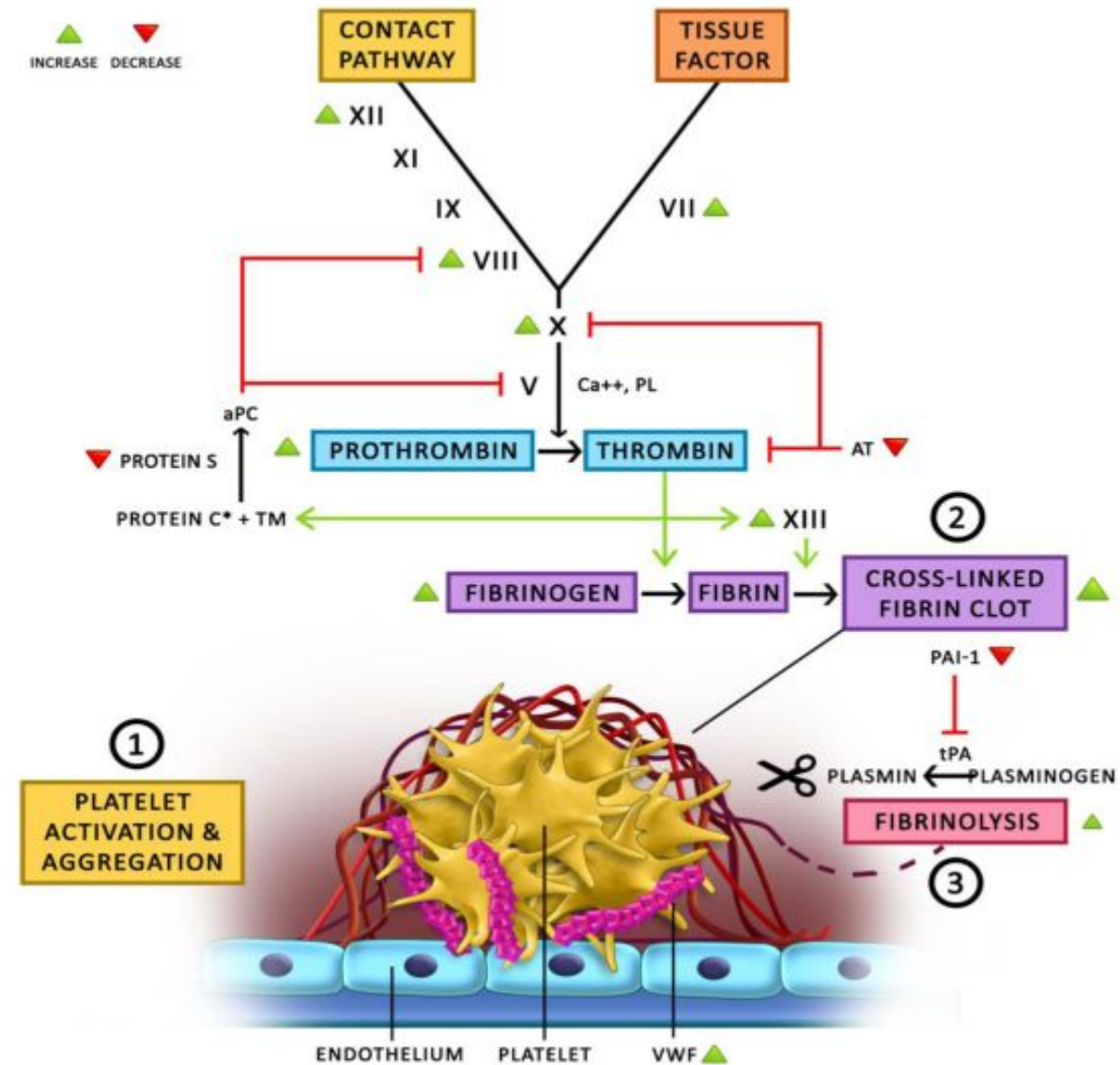
# Role of estrogen receptor (ER) and androgen receptor (AR) signaling on adhesion molecule expression in endothelial cells (ECs)



# The effects of estrogen on Hemostasis and Thrombosis

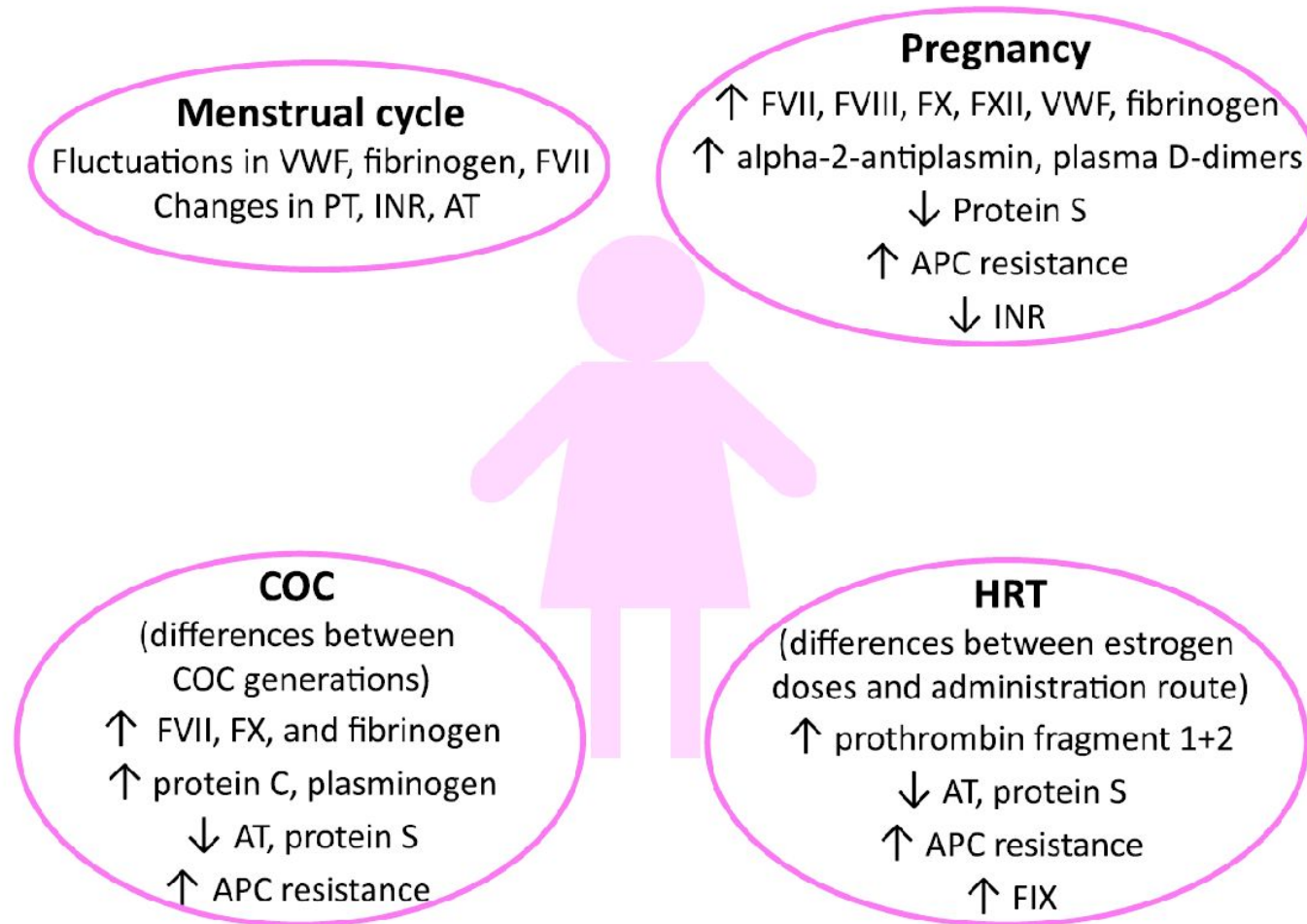
1. Estrogen increases VWF levels which plays a central role in platelet adhesion and activation
2. Estrogen leads to increased thrombin generation and fibrin clot formation by increasing the levels of variable coagulation proteins (green arrowheads) and decreasing the levels of anticoagulant proteins (red arrowheads)
3. Conversely, estrogen induces increased fibrinolysis due to decreased PAI-1 levels, which does not seem to balance out the increase in coagulation

**The net effect overall of estrogens is prothrombotic**



# Hemostasis in Women

Changes of coagulation factors and anticoagulant factors according to hormonal status are associated with **menstrual cycle, pregnancy, hormone-based contraceptives, and hormone replacement therapy**





# VTE in Women

# Classification of VTE

Venous Thromboembolism				
<i>Endothelial Alterations</i>		<i>Hypecoagulable State</i>		<i>Venous stasis</i>
<i>Damage</i>	<i>Dysfunction</i>	<i>Acquired</i>	<i>Hereditary</i>	<i>Acquired</i>
Venous cathehter	Smoking	Tumors	Mutation factor V Leiden	Immobility
Surgery	Hypertensions	Chemotherapy	Mutation prothrombin gene	Hemoconcentration
Trauma	Autoimmune infiltrate	Radiotherapy	Proteina C and S Deficiency	Polycytemia
Infusions	Chronic persistent inflammation	Pregnancy	Antithrombin III deficiency	Emolysis
	Cirrhosis	Obesity		
		Thrombocytosis		

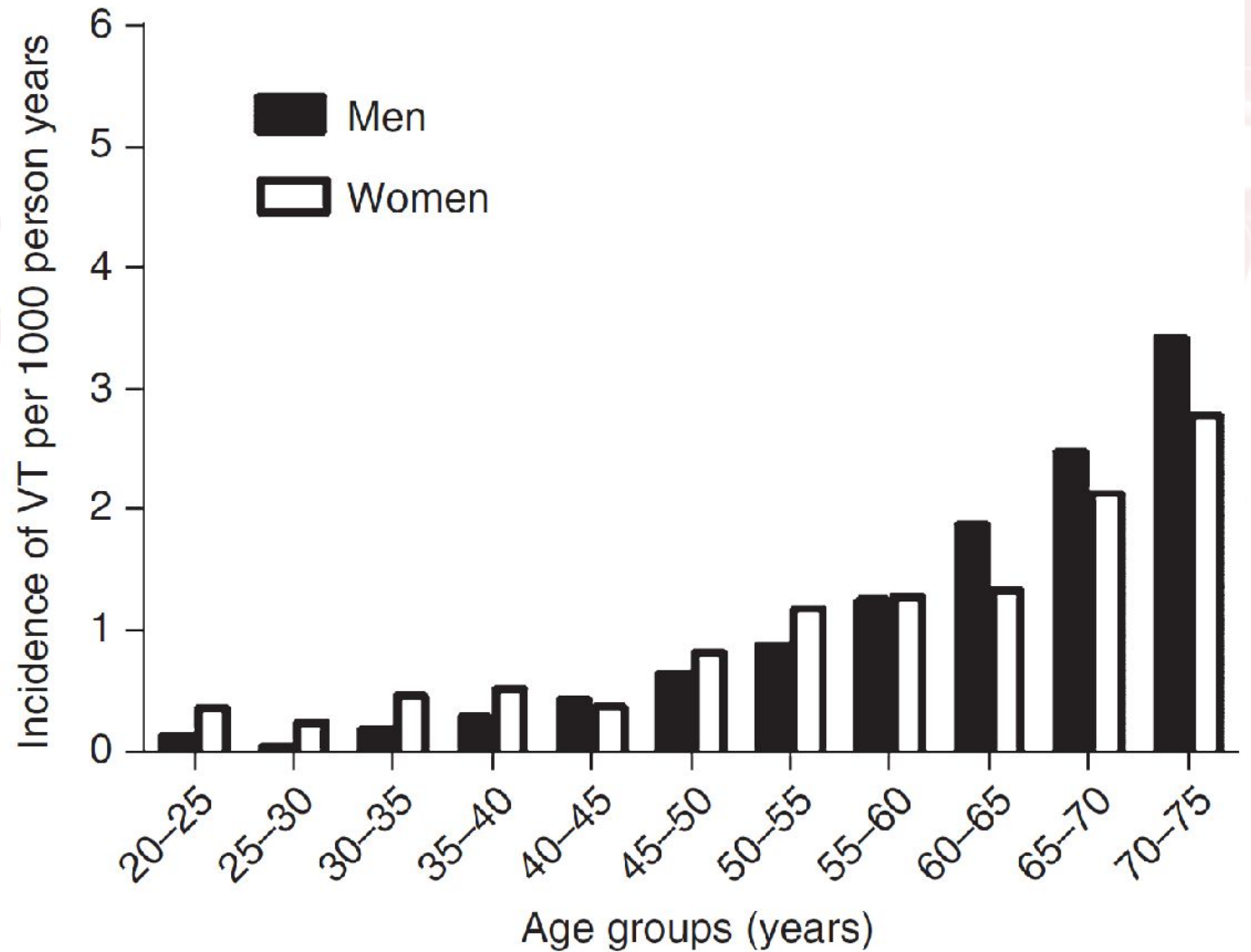
Ciarambino T, et al. *Stresses*. 2023;3:167-181

## Venous thrombosis risk factors in Males and Females

	Male controls, N (%)	Female controls, N (%)	OR in men	OR in women	PAR men	PAR women
<b><u>Genetic risk factors</u></b>						
Factor V Leiden	123 (4)	133 (4)	3.7 (3.0–4.6)	3.1 (2.4–3.8)	10%	8%
Prothrombin G20210A	37 (2)	57 (2)	3.2 (2.2–4.8)	2.6 (1.9–3.5)	4%	3%
Blood group non-O	1227 (54)	1397 (54)	2.2 (1.9–2.5)	2.0 (1.8–2.3)	39%	35%
<b><u>Acquired risk factors</u></b>						
Plaster cast use*	11 (0.4)	23 (0.7)	14.5 (7.7–27.2)	7.4 (4.7–11.6)	5%	4%
Hospitalization*	68 (2)	108 (3)	8.6 (6.6–11.2)	6.7 (5.4–8.4)	13%	15%
Surgery*	92 (3)	91 (3)	6.4 (5.0–8.1)	6.8 (5.4–8.6)	14%	15%
Malignancy†	51 (2)	65 (2)	5.3 (3.9–7.3)	5.0 (3.8–6.6)	8%	8%
Trauma*	83 (3)	102 (3)	5.5 (4.2–7.1)	4.0 (3.2–5.0)	12%	8%
<b><u>Thrombophilia</u></b>						
Hyperhomocysteinemia§	69 (5)	76 (5)	1.3 (0.9–1.8)	1.1 (0.8–1.6)	1.5%	0.5%
<b>Other</b>						
<u>Height &gt; 170 cm</u>	4282 (91)	1865 (39)	1.4 (1.1–1.7)	1.2 (1.0–1.3)	27%	7%
<b><u>Cardiovascular risk factors</u></b>						
Normal weight (BMI 18.5–25 kg m <sup>-2</sup> )	1648 (44)	1648 (54)	Reference	Reference		
Overweight/obesity (BMI > 25 kg m <sup>-2</sup> )	1491 (56)	1384 (46)	1.5 (1.3–1.6)	1.8 (1.6–2.0)	22%	27%
Never smoking	885 (33)	1448 (46)	Reference	Reference		
Ever smoking	1813 (67)	1709 (54)	1.2 (1.0–1.3)	1.3 (1.2–1.4)	12%	14%

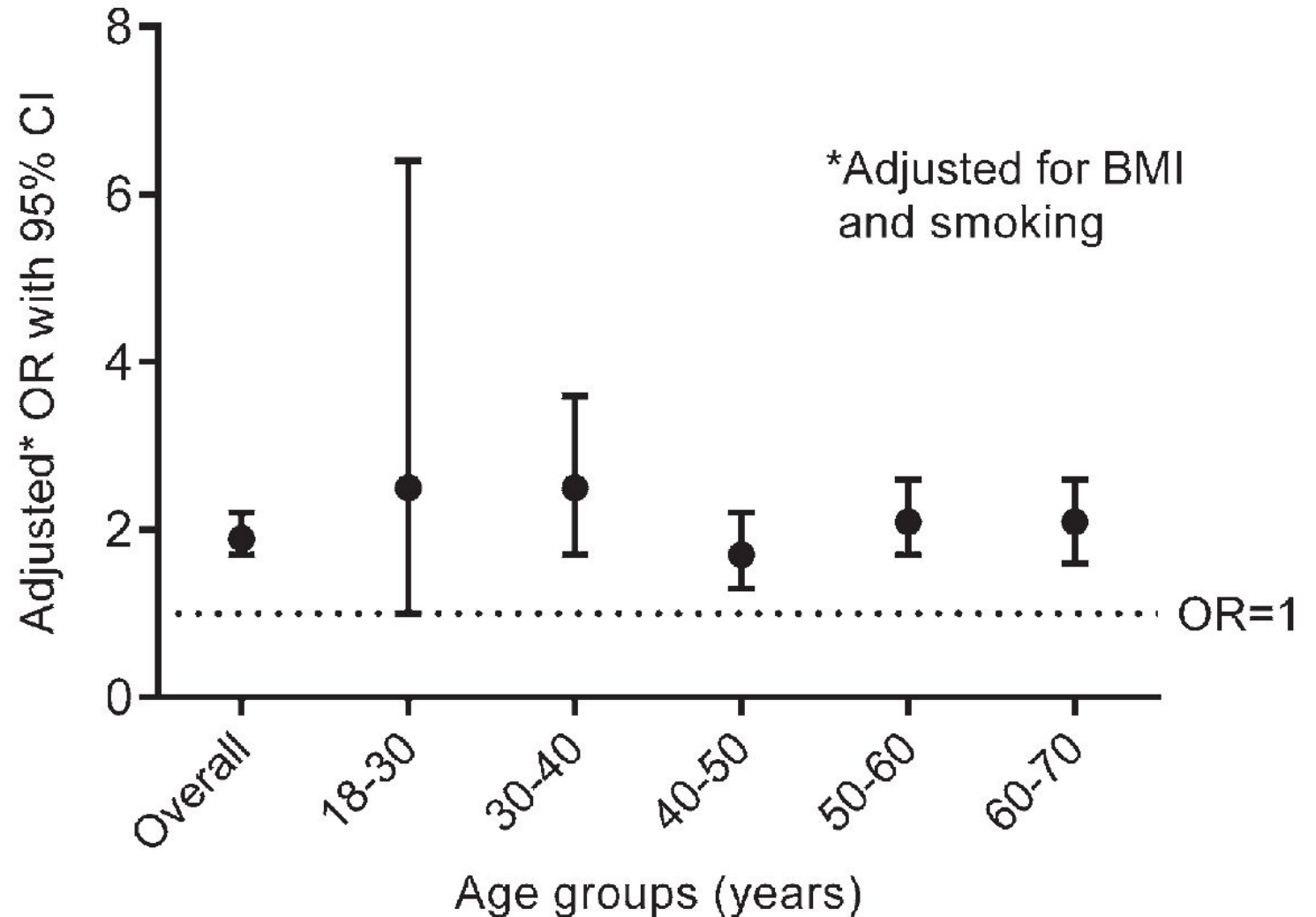
# The absolute risk of first Venous Thrombosis in Men and Women

- The incidence of first venous thrombosis is **higher among women of childbearing age** than among men of the same age group
- In the years thereafter, the incidence is **higher among men than among women**
- This variation may be due to changes in female endogenous hormone levels, female exposure to exogenous hormones, or pregnancy



# Adjusted risk of Venous Thrombosis in men compared with women taken into account reproductive risk factors

When female reproductive risk factors are taken into account, the risk of a first venous thrombosis is **twice as high in Men** as compared with Women



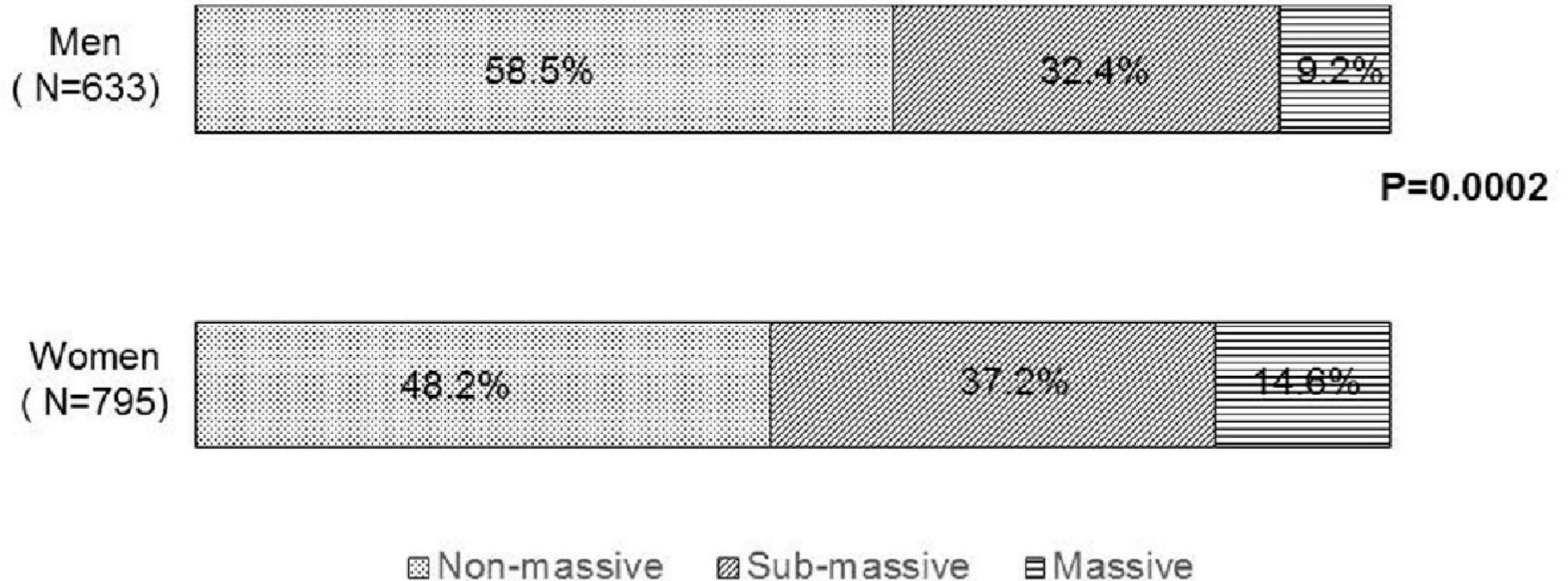
# Gender Differences Among Patients With Acute Pulmonary Embolism

## Patients' characteristics

Variable	Men n = 633	Women n = 795	p value
Age	60.9 ± 15.6	68.0 ± 16.1	p < 0.0001
Height (cm)	168.3 ± 8.1	153.3 ± 7.3	p < 0.0001
Body weight (kg)	70.6 ± 16.6	55.4 ± 12.1	p < 0.0001
Body mass index (kg/m <sup>2</sup> )	24.9 ± 4.7	23.5 ± 4.5	p < 0.0001
Nosocomial case	86 (13.6%)	160 (20.1%)	p = 0.0002
Hypertension	231 (36.5%)	317 (39.9%)	p = 0.21
Hyperlipidemia	109 (17.2%)	143 (18.0%)	p = 0.73
Diabetes mellitus	90 (14.2%)	90 (11.3%)	p = 0.11
Active cancer	30 (4.7%)	46 (5.8%)	p = 0.41
Ischemic heart disease	29 (4.6%)	31 (3.9%)	p = 0.60
Cerebrovascular disease	42 (6.6%)	51 (6.4%)	p = 0.91
Smoker	186 (29.4%)	70 (8.8%)	p < 0.0001
Vital signs at first contact			
Body temperature (°C)	36.3 ± 2.7	36.1 ± 3.1	p = 0.19
Systolic blood pressure (mm Hg)	130.6 ± 24.7	126.9 ± 27.8	p = 0.011
Diastolic blood pressure (mm Hg)	81.5 ± 15.8	77.1 ± 18.2	p < 0.0001
Heart rate(/min)	91.9 ± 21.8	93.1 ± 21.0	p = 0.31
Respiratory rate(/min)	20.6 ± 6.0	21.6 ± 5.9	p = 0.011
SpO <sub>2</sub> (%) room air oxygen administration	91.5 ± 8.0, 95.3 ± 4.6	91.3 ± 8.4, 94.9 ± 5.6	p = 0.79, p = 0.20

## The gender difference in APE severity

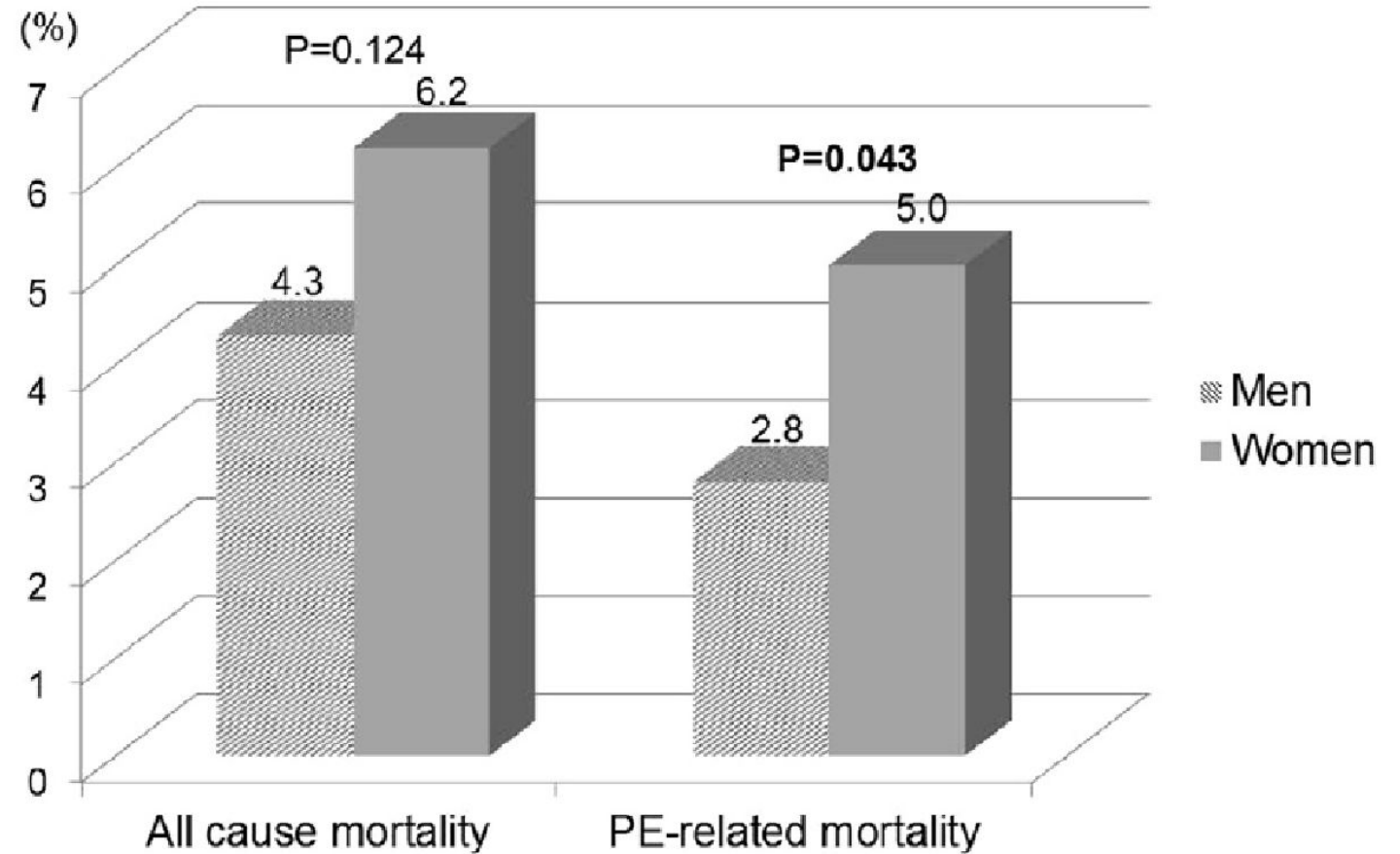
The female patients had more disease severity than the male patients did





## 30-day prognosis

All cause 30-day mortality in women (6.2%) was higher than that in men (4.3%) although it was not significant

PE-related 30-day mortality in women was significantly higher than that in men

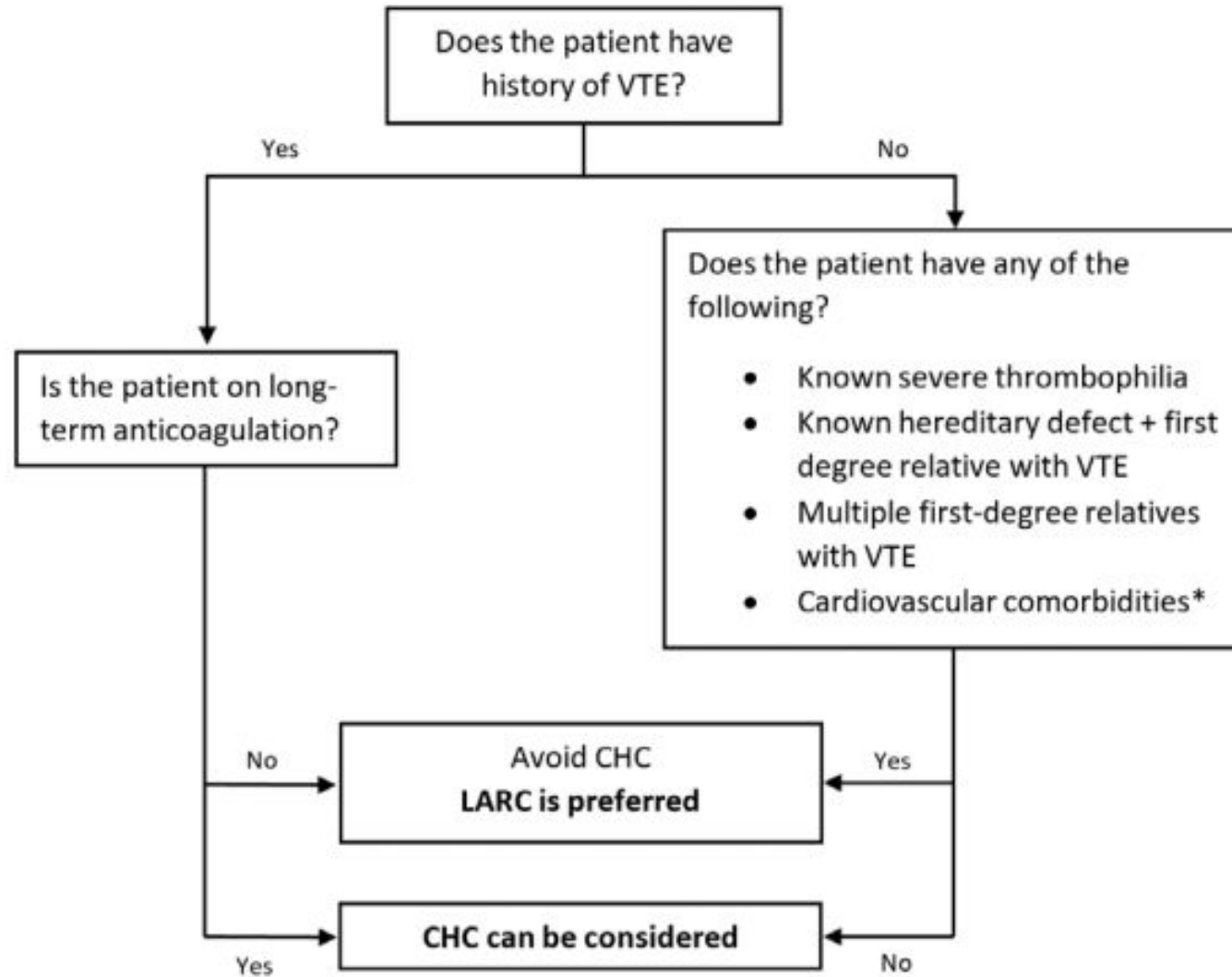


# The CHA<sub>2</sub>DS<sub>2</sub>-VASc Score calculates stroke risk for patients with AF



	<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factor</b>	<b>Points</b>
<b>C</b>	Congestive heart failure	+1
<b>H</b>	Hypertension	+1
<b>A<sub>2</sub></b>	Age 75 years or older	+2
<b>D</b>	Diabetes mellitus	+1
<b>S<sub>2</sub></b>	Previous stroke, transient ischaemic attack or thromboembolism	+2
<b>V</b>	Vascular disease	+1
<b>A</b>	Age 65–74 years	+1
<b>Sc</b>	<u>Sex category (female)</u>	+1

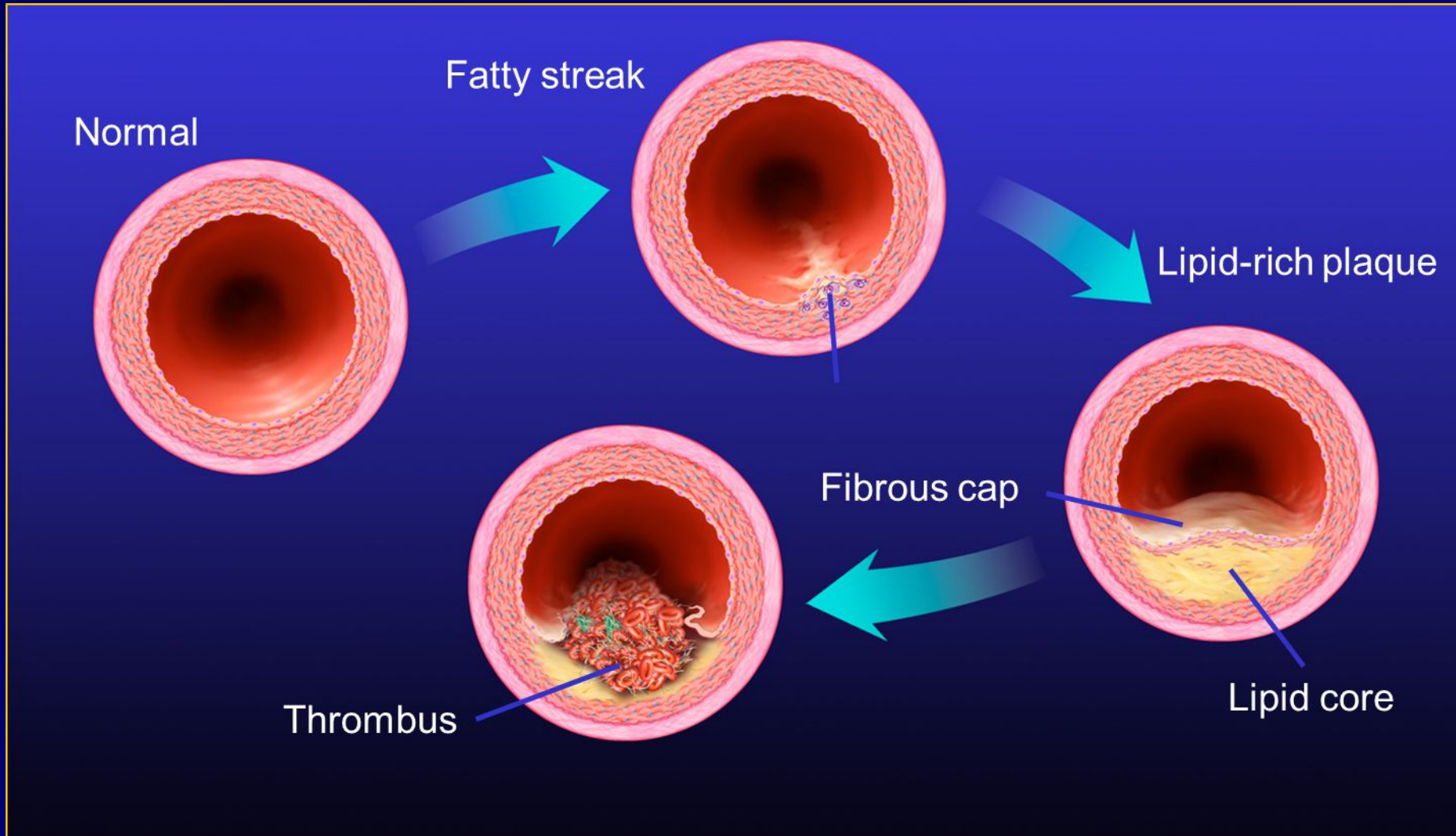
# Proposed algorithm to guide contraceptive management for women at high risk of VTE



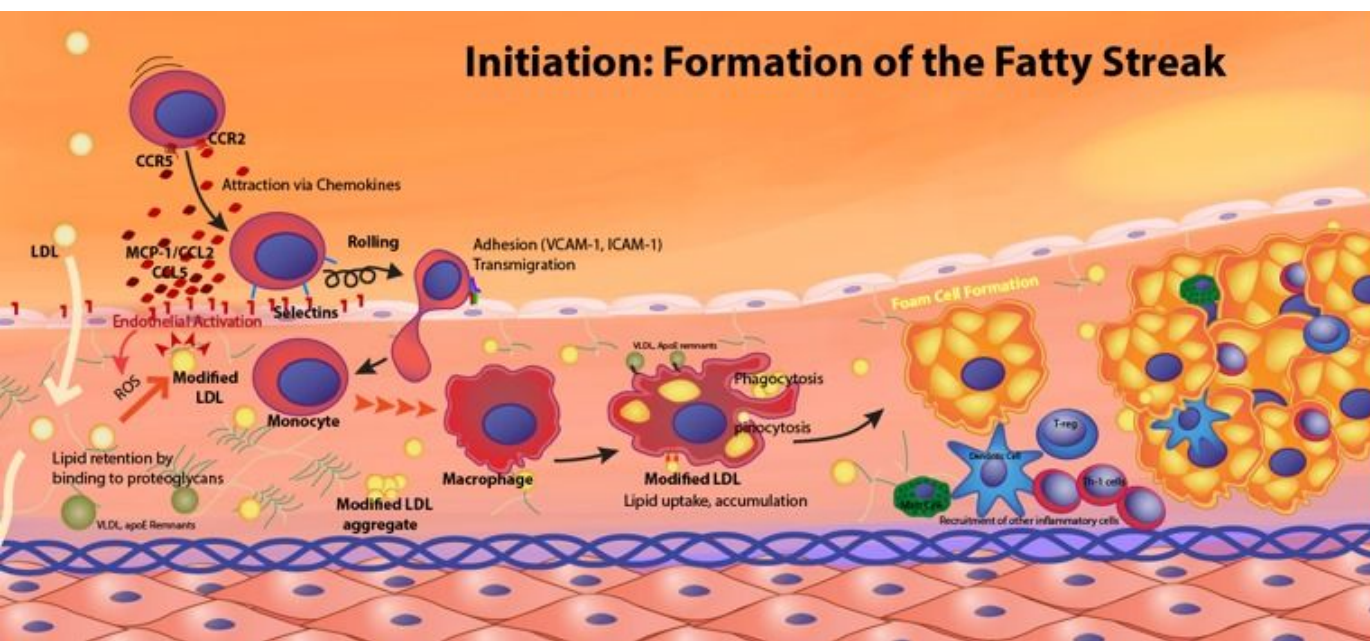
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# Atherothrombosis in Women

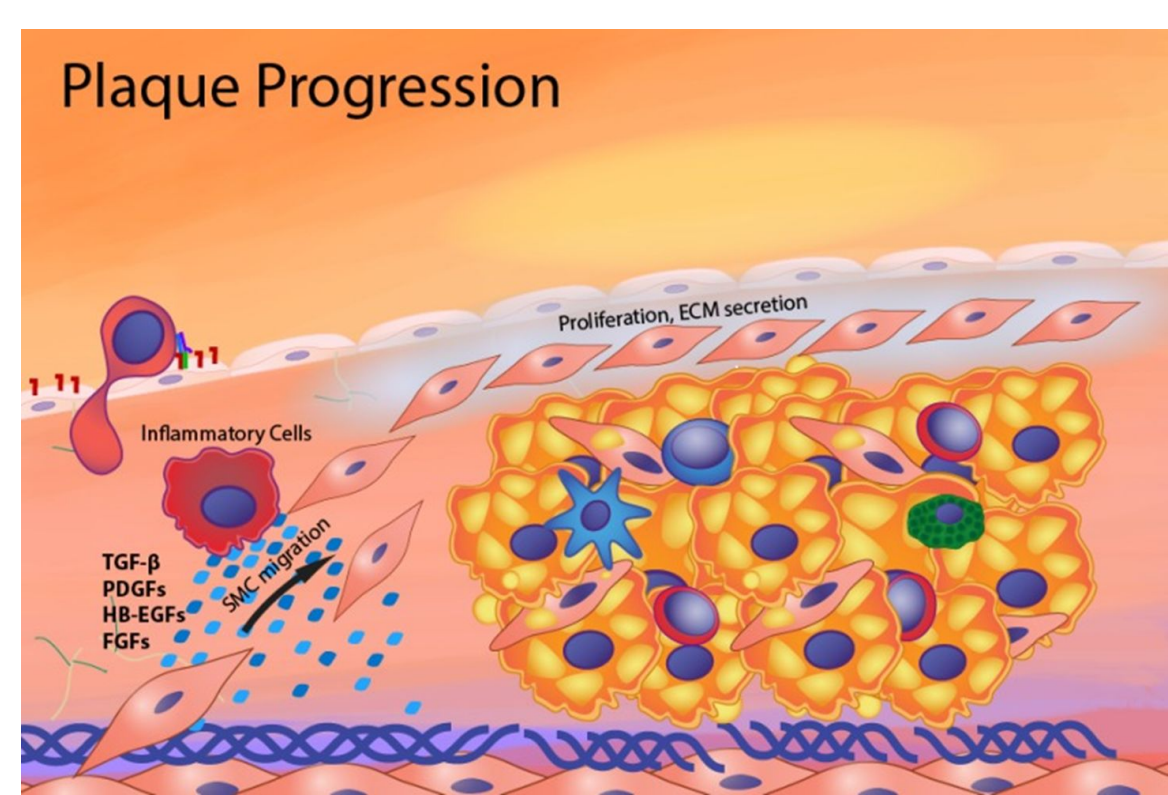
# Development of the Atherosclerotic plaque



## Initiation: Formation of the Fatty Streak

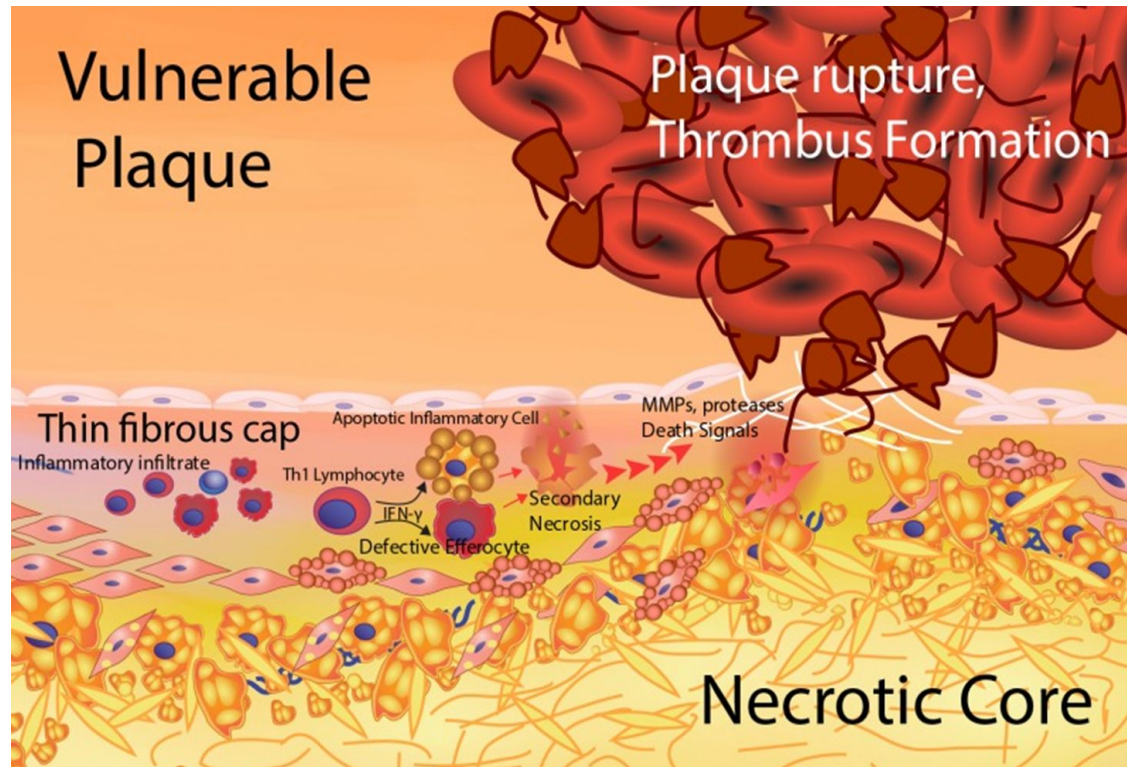


## Plaque Progression

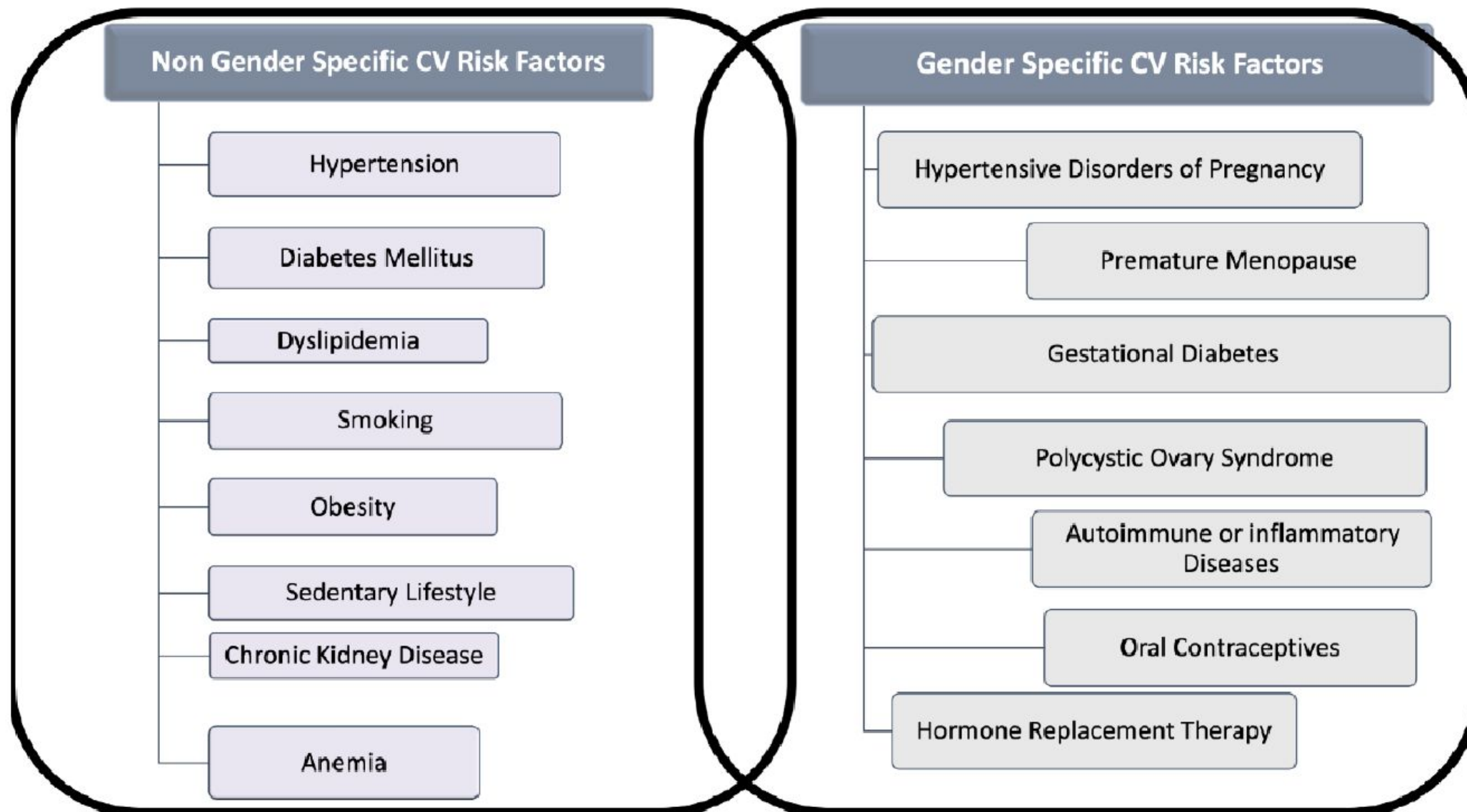


## Vulnerable Plaque

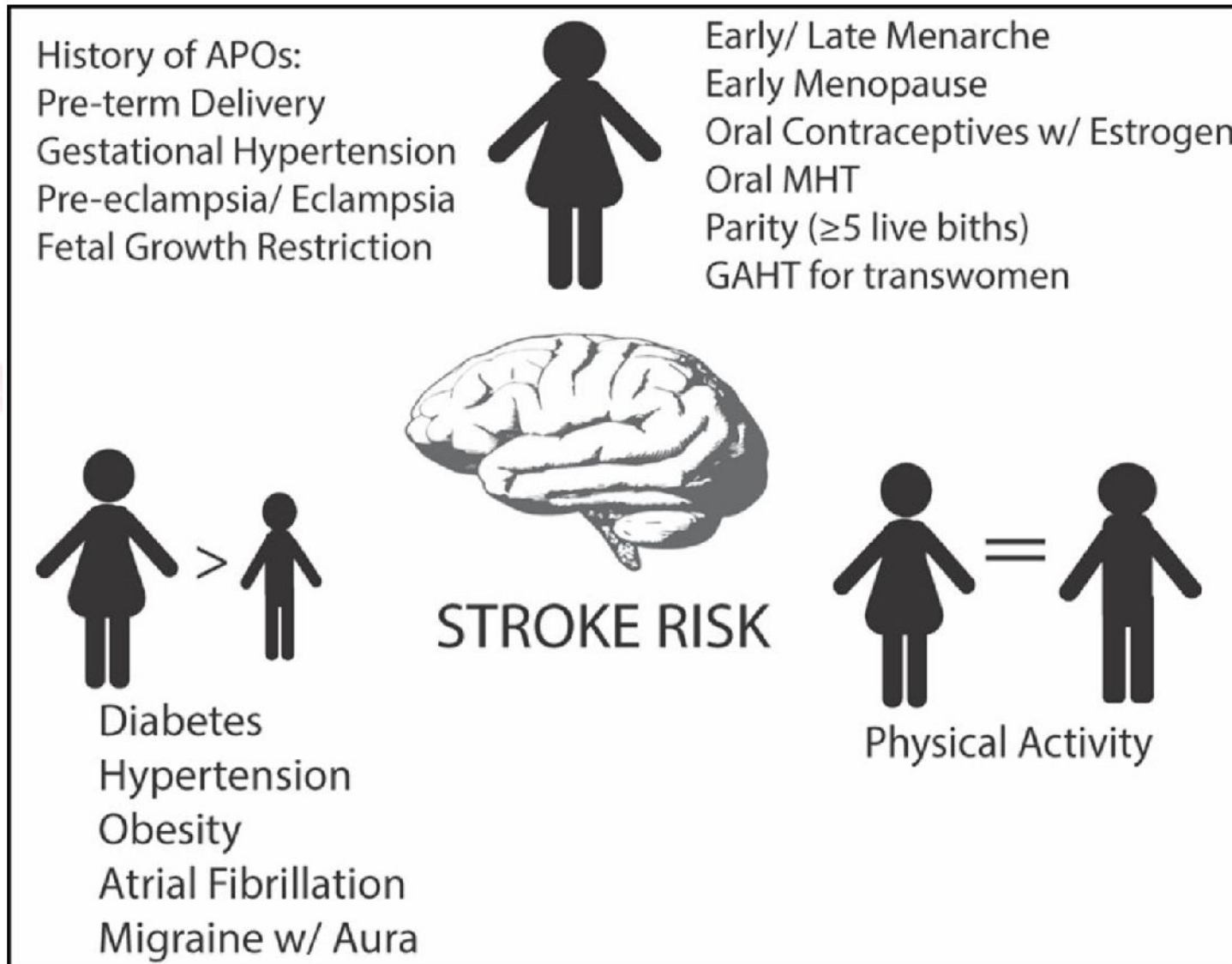
## Plaque rupture, Thrombus Formation



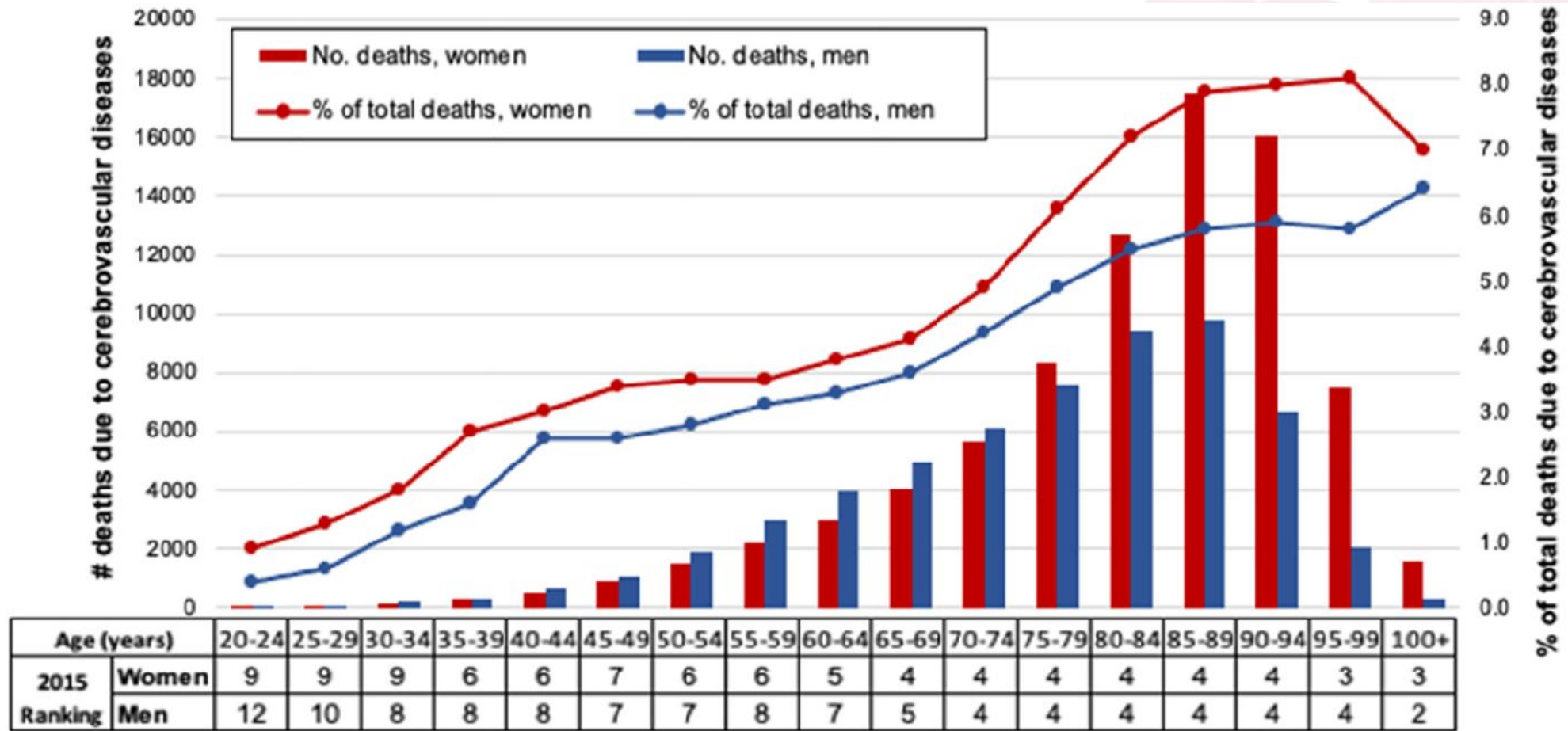
# Gender and Non-Gender CV Risk factors for CVD in women



# Sex differences in Stroke Risk Factors



# Sex- and age-specific ranking, percentage, and total number of deaths attributed to cerebrovascular diseases



Sex- and age-specific ranking of cerebrovascular diseases as leading cause of death in the U.S., 2015

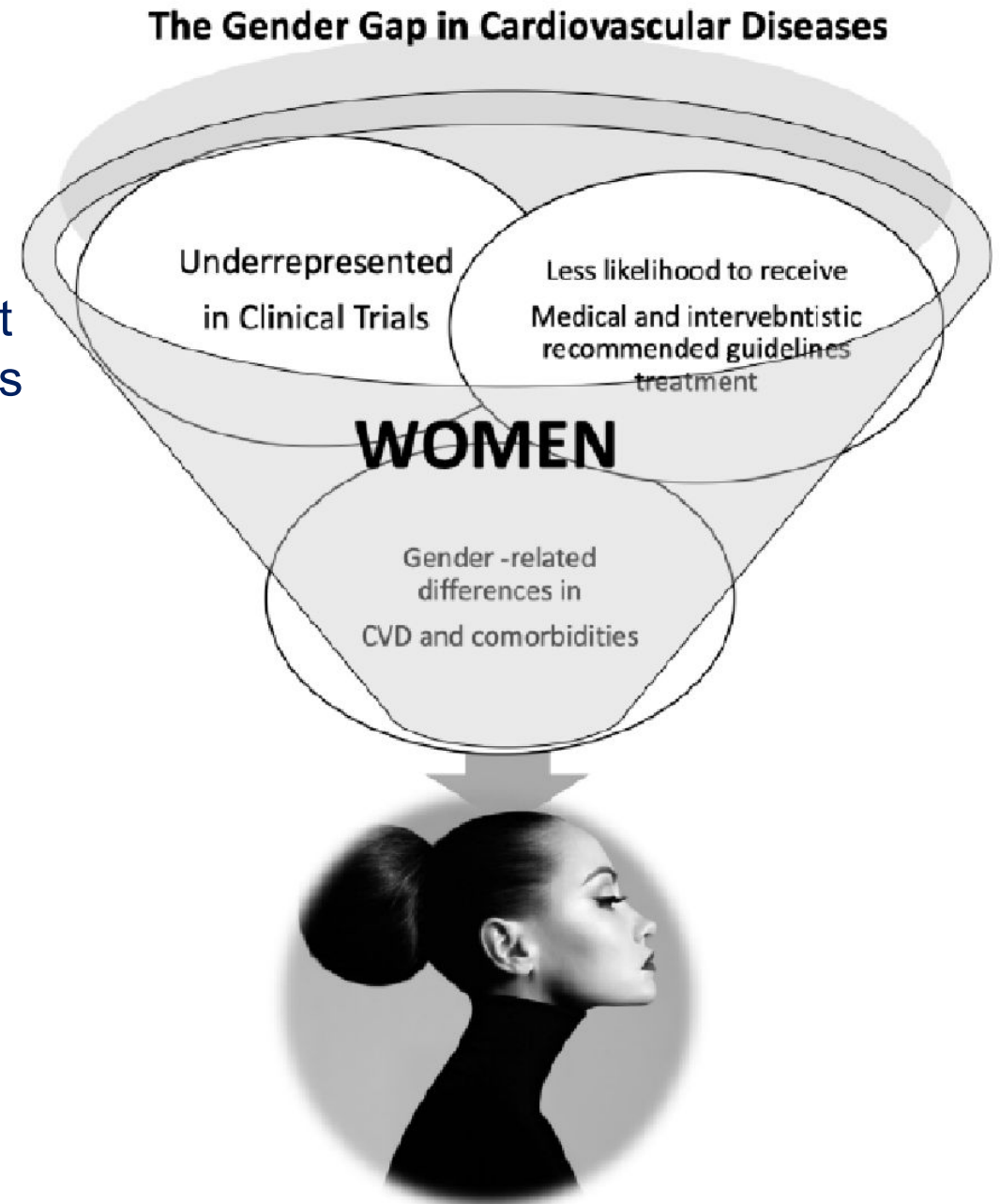
## DISCUSSION

- **Women face a disproportionate burden of stroke mortality and disability**
- **Biologic sex and sociocultural gender both contribute to differences in stroke risk factors, assessment, treatment and outcomes**
- **There are substantial differences in the strength of association of stroke risk factors as well as female-specific risk factors. Moreover, there are differences in presentation, response to treatment and stroke outcomes in women**

# The gender GAP in CVD

- In spite of the high incidence of CVD, more significant difficulties to healthcare access and gender disparities in treatment are commonly experienced by women
- There are many observational reports of under-treatment of women for stable CAD and suspected or diagnosed ACS.
- They receive less cholesterol screening, less evidence-based treatment, and less counseling.

Lucà F, et al. *J. Clin. Med.* 2022;11:1176



# Antithrombotic Treatment in Women

- The VTE risk or VTE-related death in the absence of oral anticoagulation seems significantly higher in male than in female patients, while it appeared non-significantly different in male and female patients treated with DOACs
- Some indications are available about the use of anticoagulants in **pregnancy**, although clinical data are scarce in this setting, as pregnant women are usually excluded from randomized trials, and the safety profile of drugs is here a crucial and largely unresolved concern
- **LMWHs are safe drugs during pregnancy**. Potential advantages of LMWH versus UFH are less bleeding, a more predictable and stable effect and reduced risk of heparin-induced thrombocytopenia

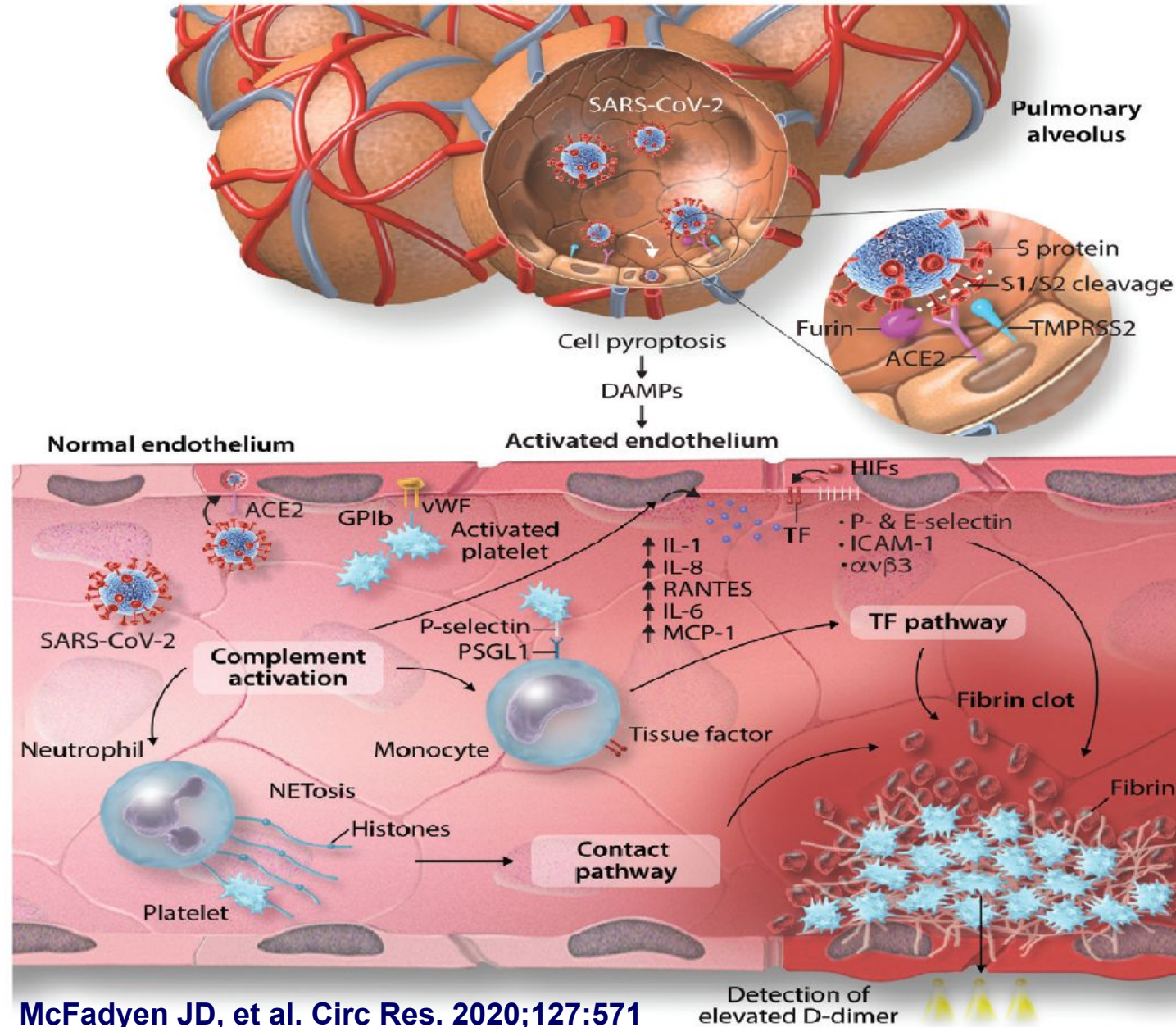
# Antithrombotic Treatment in Women

- In primary CV prevention, the benefit of aspirin seems to be related to a significant decrease of major coronary events in men, but not in women
- For secondary CV prevention, no significant gender-related difference in the efficacy of antiplatelet agents has emerged
- The lower benefit of anticoagulant treatment with vitamin K antagonists on stroke prevention in women with AF, relative to men, is not fully understood, but suggests that women may be less well anticoagulated



# COVID-19 and Thrombosis in Women

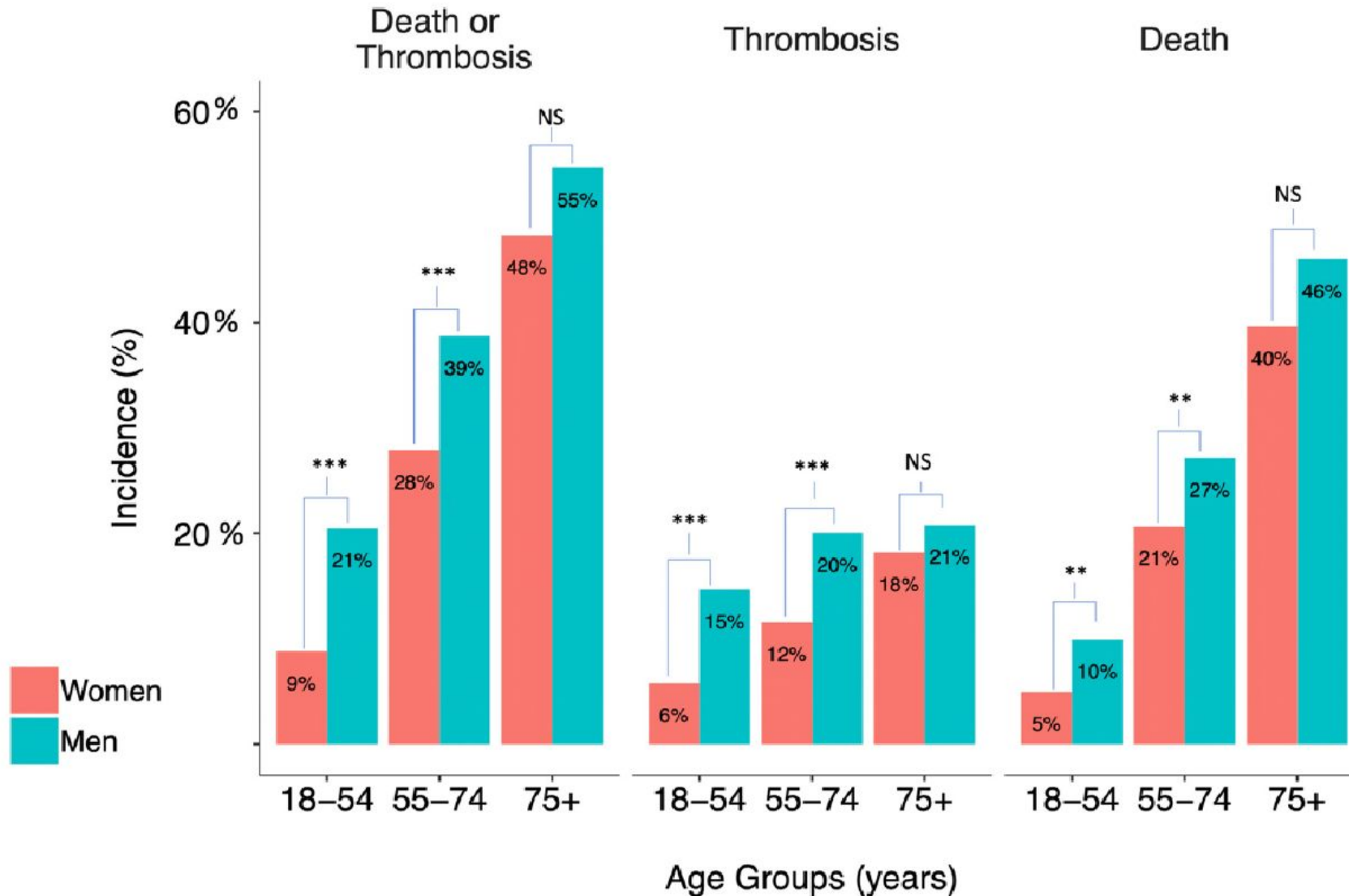
# Proposed mechanisms of SARS-CoV-2 transmission and COVID-19-associated thrombosis



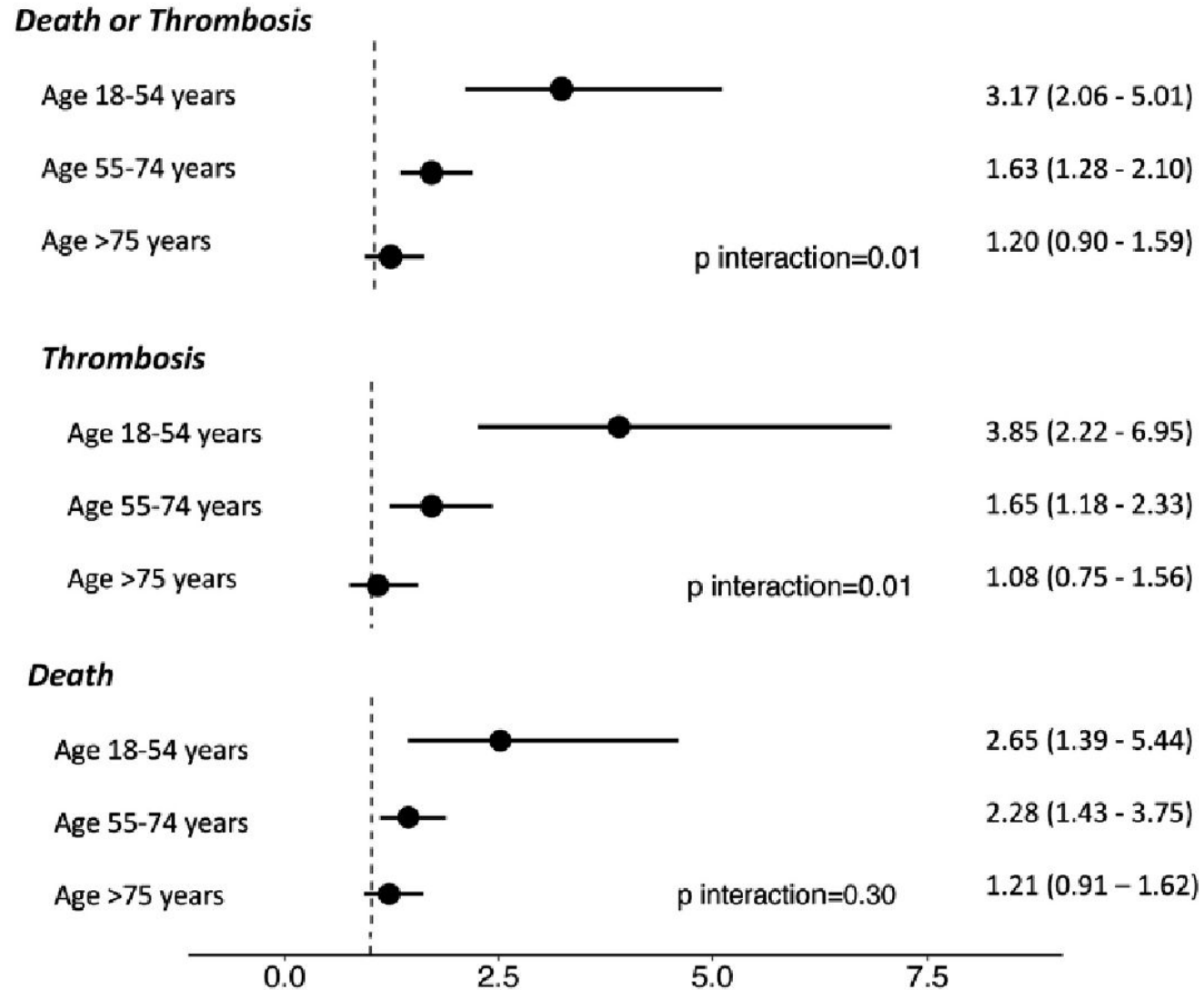
# Sex Differences in Thrombosis and Mortality in Patients Hospitalized for COVID-19

- Consecutive 3,334 adult patients aged  $\geq 18$  years (61% men) hospitalized with COVID-19 at a large New York health system from March 1, 2020, to April 17, 2020, were included in the study.
- Thrombotic events of interest included those occurring in both the venous and arterial circulation. VTE was defined as DVT or PE, and arterial thrombosis was defined as ischemic stroke, MI, or other systemic thromboembolism.
- In-hospital thrombosis and all-cause mortality were evaluated by gender and stratified by age group.

# Incidence of Events in men and women hospitalized with COVID-19 infection by age group



# Adjusted Odds of Events in Men Relative to Women Hospitalized with COVID-19 by Age Group



## Conclusion

- ❑ Men hospitalized with COVID-19 are at greater risk of thrombosis and death than women, and gender-specific differences are most pronounced in younger age groups
- ❑ Outcomes of men and women with COVID-19-associated thrombosis are poor
- ❑ Additional investigations of SARS-CoV-2 pathophysiology and host response are needed to explain the observed age and gender differences in thrombosis risk observed among hospitalized patients with COVID-19

Tanya Wilcox T, et al. Am J Cardiol. 2022;170:112–117



**Thank you for your attention**