La Medicina di Genere

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La medicina ufficiale, per un tempo infinito non si è posta il problema delle donne

Il primo ospedale a Torino è stato fondato nel 1575 (Ospedale Mauriziano)

...ma il primo reparto femminile solo quasi 300 anni dopo (1855)

Le donne delle classi abbienti erano curate a casa.....ma a causa del «pudore», e spesso del senso di possesso da parte del marito, essendo i medici tutti maschi non potevano accedere al corpo femminile, se non in modo indiretto

Dipinto del 1780 che mostra un medico mentre procede, con discrezione, all'esame del polso di una paziente.

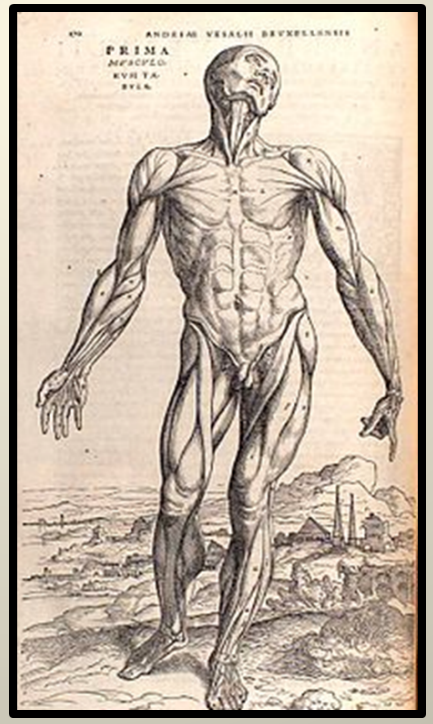
Le donne delle classi sociali più svantaggiate non ricevevano cure.

Era sempre uno svantaggio?

Mah…

Dato il livello medio della cultura medica, a volte no: l'esperienza empirica delle «donne sagge», delle anziane e delle levatrici, conosceva il corpo femminile molto meglio dei medici.

1543: Andrea Vesalio, il fondatore della moderna anatomia, nella sua opera «De humanis corporis fabrica» scrive: *"…è sufficiente studiare il corpo maschile, forma neutra universale, per capire anche il corpo femminile"*



Finalmente alla fine degli anni ’80 – inizio anni ‘90 del 1900 ci si pone un grande problema:

COSA SI CONOSCE DELLE DIFFERENZE TRA GLI ORGANISMI MASCHILI E FEMMINILI, AL DI LA’ DEI CARATTERI SESSUALI PRIMARI E SECONDARI?

Per dare una risposta, si sono analizzati migliaia di studi clinici pubblicati negli anni '80: con l'eccezione delle malattie dell'apparato riproduttivo, quasi nessuno arruolava donne. Il «modello» di riferimento era il maschio.

Sulla fisiologia delle donne nelle comuni malattie (cardiache polmonari endocrinologiche…) non si sapeva niente.

Non si erano fatti passi in avanti dall'epoca di Vesalio.

Sindrome del bikini

Fino al 1990 la medicina si costruisce sulla nozione che il corpo maschile sia il riferimento. Uniche differenze riconosciute riguardano **l'apparato riproduttivo/ginecologico**

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Nel 1991 Bernardine Healy, cardiologa e prima donna nella storia a dirigere l'Istituto Nazionale di Salute Pubblica (NIH) degli U.S.A. attacca duramente i cardiologi americani per le minori cure, le minori attenzioni, gli errori grossolani che gravavano sulle pazienti donne e non sugli uomini

...e in medicina si comincia a parlare di differenze di Genere

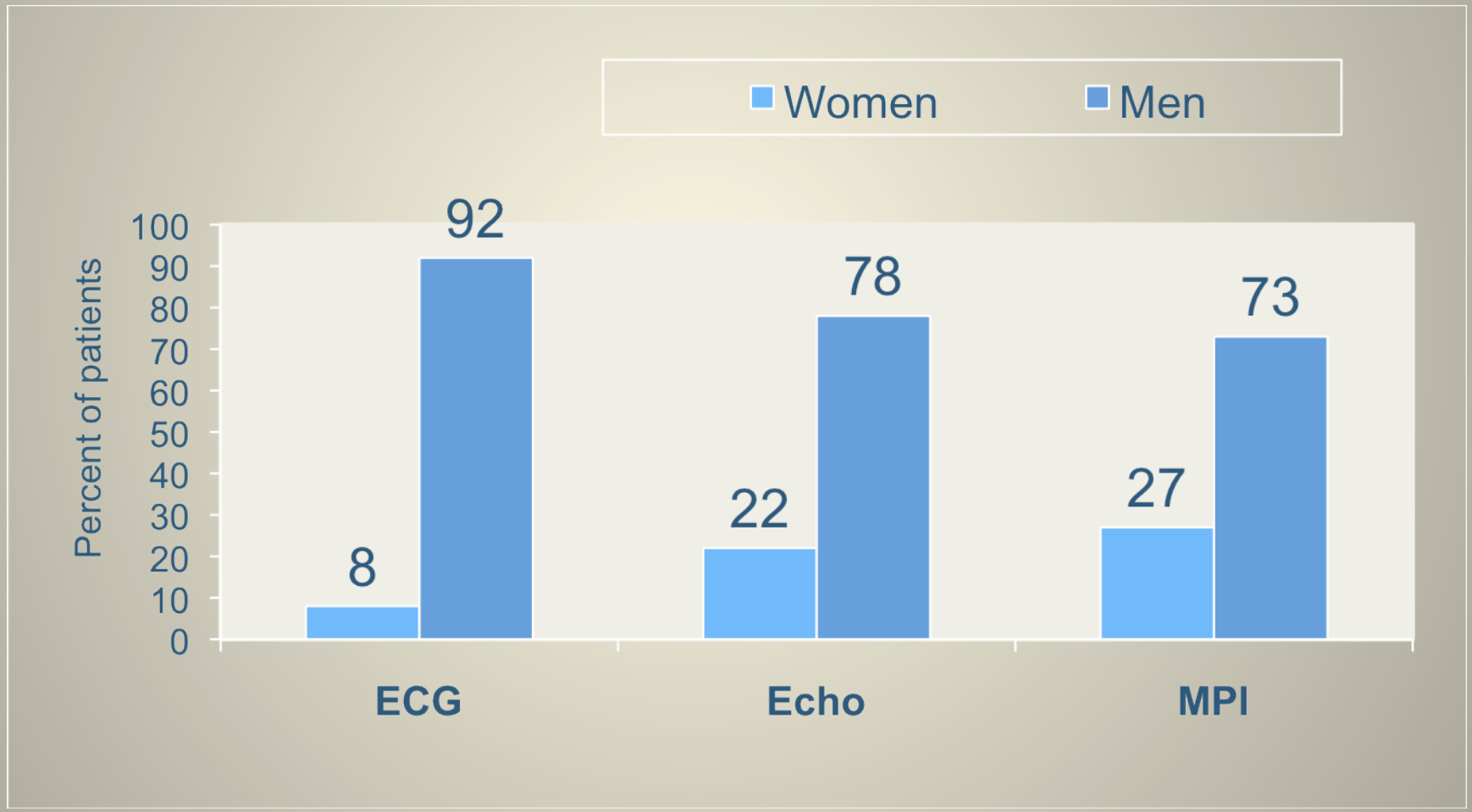
Bernardine Healy descrisse una malattia che chiamò "Sindrome di Yentl".

The New England Journal of Medicine

Yentl, l'eroina di una storia del Premio Nobel Isaac Bashevis Singer, dovette rasarsi i capelli e vestirsi da uomo per poter accedere alla scuola ebraica e studiare il Talmud, uno dei testi sacri dell'Ebraismo.
La Healy descrisse quindi sul New England Journal of Medicine, la ***discriminazione che aveva constatato nell'Istituto di Cardiologia che dirigeva***: le donne erano meno ospedalizzate, meno sottoposte a indagini diagnostiche (coronarografie) e terapeutiche (trombolisi, stent, bypass) rispetto agli uomini; le donne inoltre sottolineava erano per nulla o poco rappresentate nelle sperimentazioni per introdurre nuovi farmaci e nuove tecnologie diagnostiche e terapeutiche.

L'articolo suscitò molto scalpore in tutto il mondo, ma fu un buon punto di partenza per dare forza alla Medicina di genere.

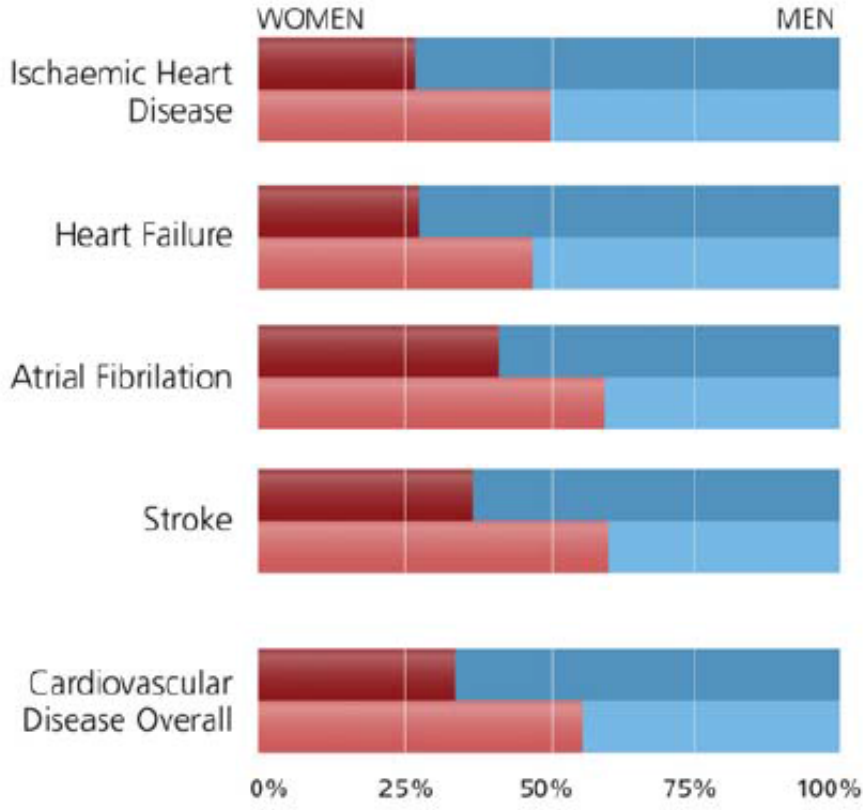
Limited Representation of Women in Studies of CAD Testing



Adapted from: Shaw LJ, et al. *Coronary Artery Disease in Women: What All Physicians Need to Know*. 1999

Percentage of Women in CVD Clinical Trials vs. Deaths

Women are underrepresented in CVD clinical trials



Data from European Union, 2006-2009

Stramba-Badiale, 2010
Allender et al., 2008
Müller-Nordhorn et al., 2008
Cleland et al., 2003

Cosa è cambiato?

Come mai, dopo migliaia di anni, finalmente ci si è posti il problema?

Tre sono i fattori principali che probabilmente hanno interagito

- La spinta culturale del femminismo americano
- L'aumento numerico delle donne medico (in Italia fino al 1876 alle donne era vietato iscriversi a medicina)
- Il fatto che, grazie alla «massa critica» raggiunta dalle donne in medicina, alcune raggiungono anche posti di alta responsabilità (come appunto Bernardine Healy)

Roberta Siliquini, prima donna nella storia italiana (2014) a diventare Presidente del Consiglio Superiore di Sanità

In Medicina, poco più di 20 anni non sono tantissimi, soprattutto quando ci si confronta con visioni e pregiudizi radicati a tutti i livelli: nei libri di testo

- nella formazione clinica e universitaria
- nelle linee guida
- nella pratica clinica quotidiana

E' necessario fare ricerche, molte ricerche, che richiedono investimenti.

E quando si ottengono certezze, ottenere che vengano applicate.

E questo è tutt'altro che scontato.

L’Italia non brilla.

Alcune tappe importanti:

1993. La FDA (l'ente governativo statunitense che si occupa della regolamentazione dei prodotti alimentari e farmaceutici) emette linee guida, perché entrambi i generi siano presi in considerazione durante le varie fasi di sviluppo dei farmaci e i risultati statistici siano valutati per genere .

2000. L’OMS (Organizzazione Mondiale della Sanità) ha inserito la medicina di genere nell’Equity Act. per promuovere cure appropriate per tutti e due i generi. Ma…

2014: Nuovo Codice di Deontologia Medica art. 48 Sperimentazione umana: «Il medico attua sull’UOMO le sperimentazioni…La sperimentazione sull’UOMO è subordinata al consenso informato….»

I pregiudizi di genere sono radicati nella classe medica ai massimi livelli, e vengono codificati anche in atti ufficiali.

Per ottenere certezze, che permettano di cambiare le impostazioni, sono necessarie come detto ricerche, investimenti, volontà politica.

Nonostante le difficoltà che incontra la medicina di genere, oggi e domani vi verranno fornite anche diverse certezze.

La Medicina di Genere non è la medicina delle donne: nella maggior parte delle malattie e delle cure, sono stati studiati solo gli uomini, ma i pregiudizi di genere possono agire a loro svantaggio: pensiamo all'osteoporosi, o alla depressione: sono considerate «malattie delle donne» e negli uomini diagnosticate e curate spesso tardi, e meno bene

La medicina di genere è la medicina della

Cerca la diagnosi e la cura giusta per donne e uomini, bambine e bambini, anziane e anziani

Ma non solo. E' la medicina del

cercare e riconoscere le differenze

…e RISPETTARE le differenze

Le donne sono oltre il 51% della popolazione italiana, gli uomini meno del 49%....

Sapete qual è la «quota rosa» nelle carceri italiane?

Le donne sono il 4.2%, gli uomini il 95.8%

Le donne delinquono enormemente di meno rispetto ai maschi: perché rispettano le regole, mentre gli uomini non rispettano le regole che loro stessi si sono dati.

E' ora che, nell'interesse della società tutta, cominciamo ad essere molto orgogliose e rivendicative delle nostre differenze .

La ***Medicina di genere*** non è quindi una nuova specialità, è una **necessaria** e **doverosa** dimensione interdisciplinare della medicina che vuole studiare l'influenza del sesso e del genere sulla fisiologia, fisiopatologia e patologia umana, vale a dire su come si instaurano, quali sono i sintomi, come si fa la prevenzione, come si curano le malattie negli uomini e **nelle donne**.

Uomini e donne pur essendo soggetti alle medesime patologie presentano significative differenze riguardo:

- Insorgenza
- Progressione
- Risposta ai trattamenti
- Prognosi di molte malattie

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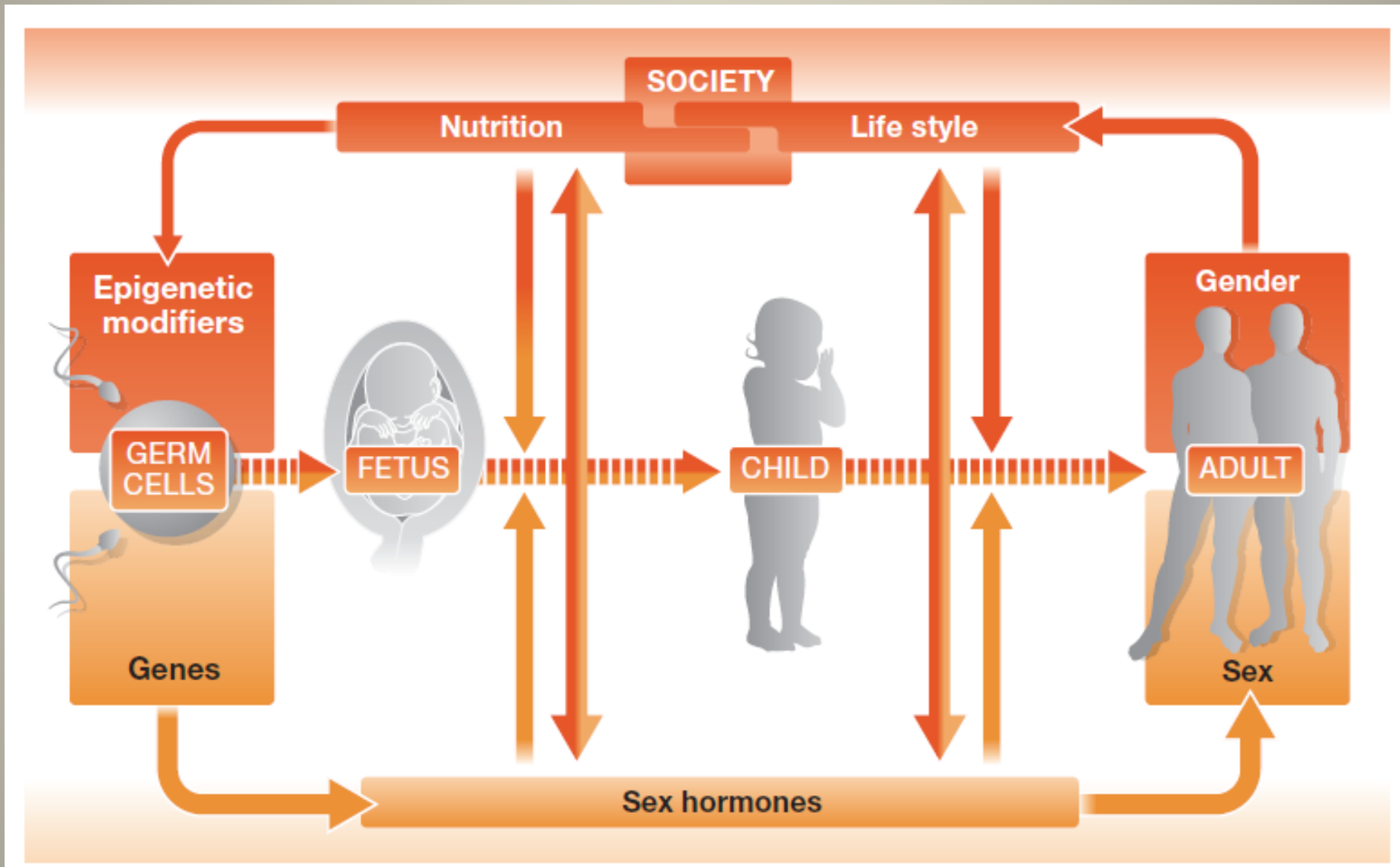
Non si tratta di studiare o approfondire solo le malattie che hanno una prevalenza di genere:
Malattie reumatologiche
Sclerosi multipla
Depressione

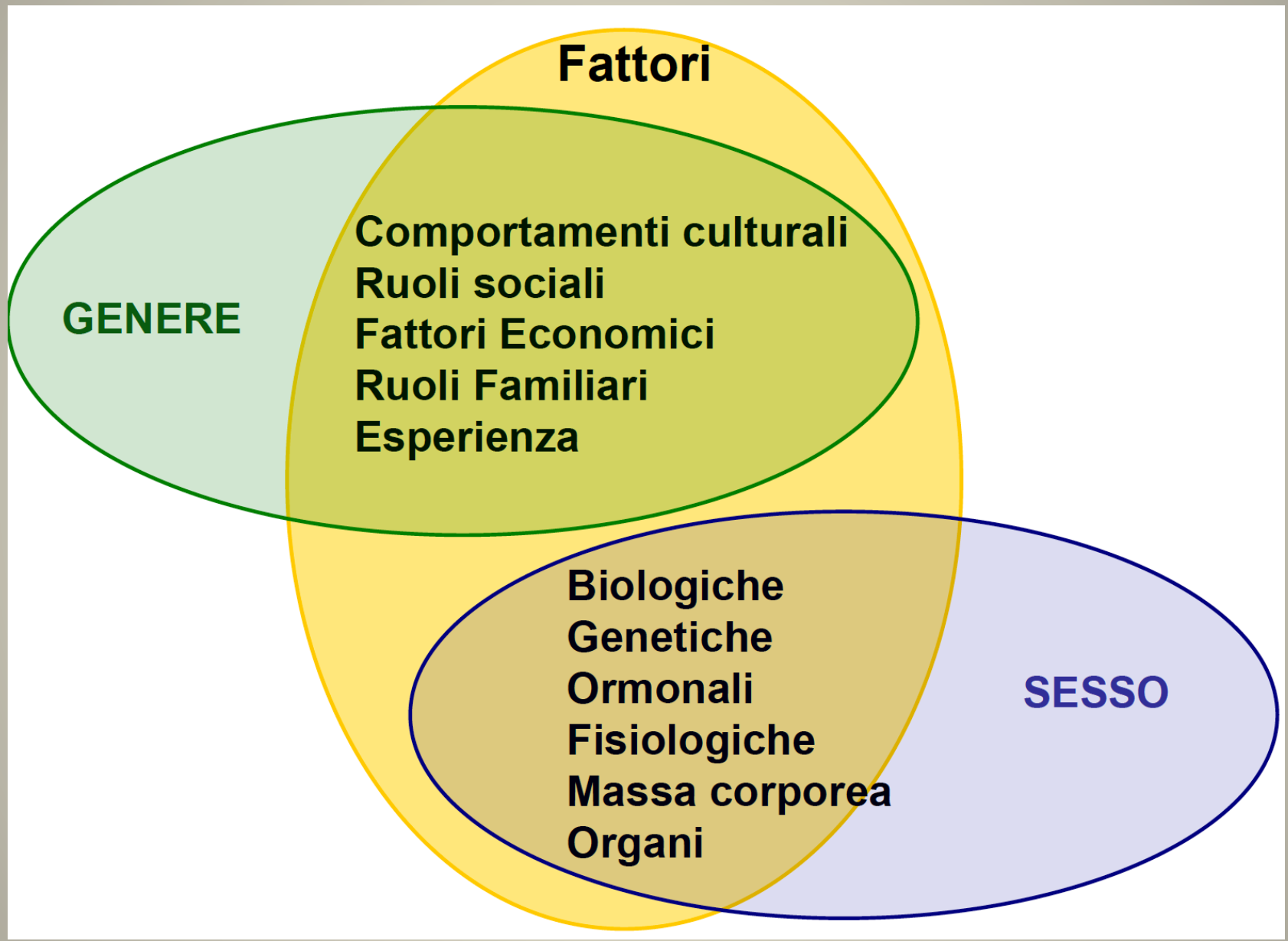
Non si tratta di aumentare la conoscenza delle patologie legate alle funzioni riproduttive dell'uomo e della donna.

E' necessario invece, studiare le patologie che affliggono uomini e donne nel quotidiano: malattie cardiovascolari, tumori, malattie metaboliche, neurologiche, infettive.

Perché differenza di genere?



Regitz-Zagrosek V - EMBO reports 2012


Fattori
GENERE
Comportamenti culturali
Ruoli sociali
Fattori Economici
Ruoli Familiari
Esperienza
Biologiche
Genetiche
Ormonali
Fisiologiche
Massa corporea
Organi
SESSO

Tab. 2 - DIFFERENZE BIOLOGICHE/SESSO (Signani 2012)

Genetiche	Nella trascrizione; nell'espressione, frequenza di mutazione e trasmissione dei geni
Epigenetiche	Metilazione, acetilazione, ecc
Nei recettori, enzimi e nelle proteine	Di livello tra uomo e donna, inter e intra-individuali; nei segnali di trascrizione; nella regolazione die recettori
Del livello di ormoni sessuali e loro effetti	Nell'espressione dei recettori, enzimi e nei legami di proteine; nella induzione degli enzimi
Nell'anatomia	Efficienza, funzione interna e di sistema e misura degli organi; suscettibilità al danno, all'invecchiamento, alla rigenerazione di ogni singolo organo
Nel metabolismo	Nella funzione e induzione metabolica; nell'espressione dei cofattori metabolici; nel metabolismo ai diversi stadi di età

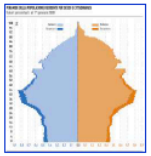
Tab. 3 - DIFFERENZE PSICOLOGICHE E CULTURALI/GENERE (Signani 2012)

Nella percezione personale e sociale di ruolo	Nella società, nel lavoro, nella famiglia e tra le mura domestiche; nello stress legato ai vari ruoli; come *caretaker* (custode della salute), *caregiver* (colui/lei che dà assistenza, *shock absorber* (colei/lui che si fa carico di ogni problema e preoccupazione, all'interno della famiglia)
Nella percezione personale e sociale e nelle strategie di adattamento alla salute/malattia	Comportamenti rischiosi e fattori di rischio; percezione e identificazione dei sintomi di malattia, capacità di descrivere i sintomi, le caratteristiche e la storia della malattia; tenersi in buona salute; nella disponibilità/possibilità ad accedere ai servizi sanitari; accettazione/rifiuto delle indicazioni mediche e farmacologiche; nell'accettare la malattia
Negli stereotipi personali e sociali e nella attribuzione prevalente	Attribuzione prevalente = attribuire certe patologia solo all'uno o all'altro sesso; attribuzione stereotipata di malattia, sia da parte dei pazienti, che da parte dei medici, differenze nella diagnosi e nella terapia, nella consapevolezza di malattia a causa di stereotipi di genere; nelle elaborazioni di rapporti di ricerca da parte delle agenzie di salute pubblica
Di fattori non medici che influenzano l'accesso alle cure	Nella Health Literacy (capacità di sapere la salute, di sapersi muovere nei servizi, capire l'opportunità e posologia delle medicine, etc); nella consapevolezza dei propri diritti; nel comportamento di contrattazione o meno con i medici (es. cercare più pareri diagnostici, da medici diversi, pretendere spiegazioni esaustive, etc.); tempo dedicato; possibilità economiche; sostegno famigliare e della società

Invecchiamento

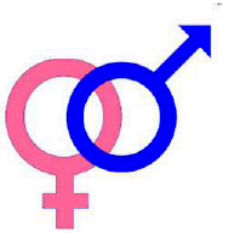
Nei paesi occidentali le donne hanno un vantaggio in numero di anni di vita rispetto agli uomini. Molte le teorie sul perché di questa differenza che spaziano dalla genetica alla cultura.

In Italia ad esempio la spettanza di vita alla nascita dell'uomo è 79,4 anni quella della donna è 84,5 (ISTAT 2011).

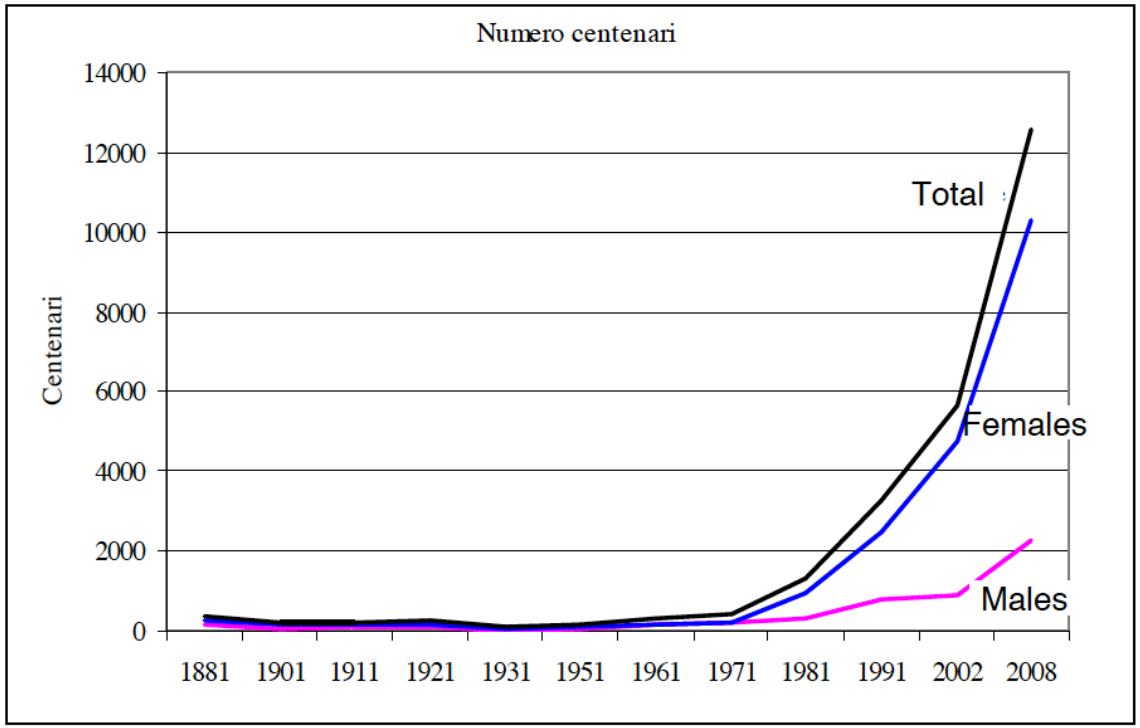


Spettanza di Vita alla nascita in Italia

	Maschi	Femmine
• 2006	78.4	84.0
• 2007	78.7	84.0
• 2008	78.6	84.0
• 2009	78.9	84.1
• 2010	79.1	84.3
• 2011	79.24	84.63



Number of Centenarians in Italy



Robine J-M, Caselli G. (2005). An unprecedented increase in the number of centenarians. Genus, Vol. LXI , n. 1, p. 57-82.

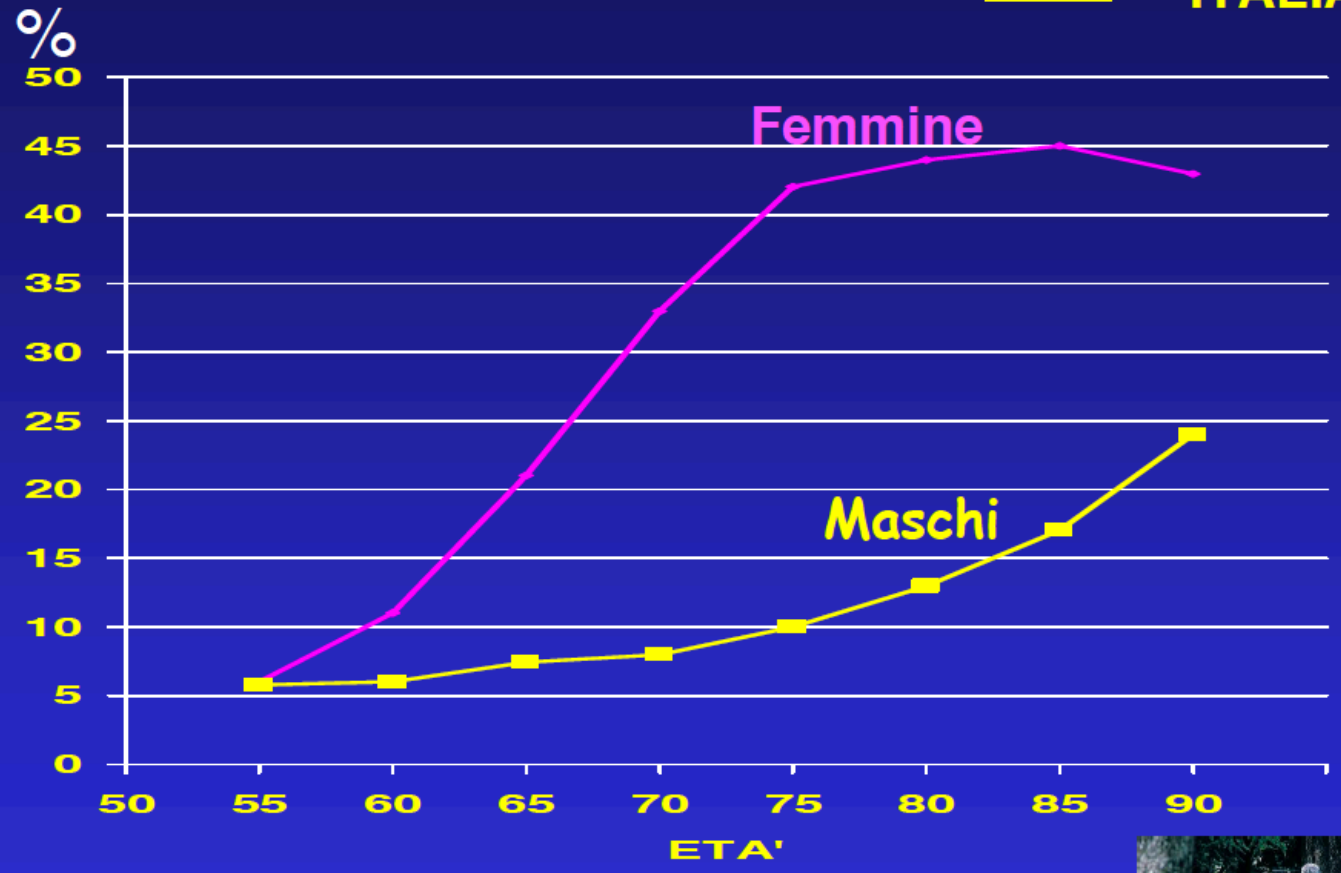
The oldest person in the world

IPF/STR REUTERS

Record holder: Jeanne Calment, who died in 1997, lived to be 122 years and 164 days old.

Anziani che vivono **soli**

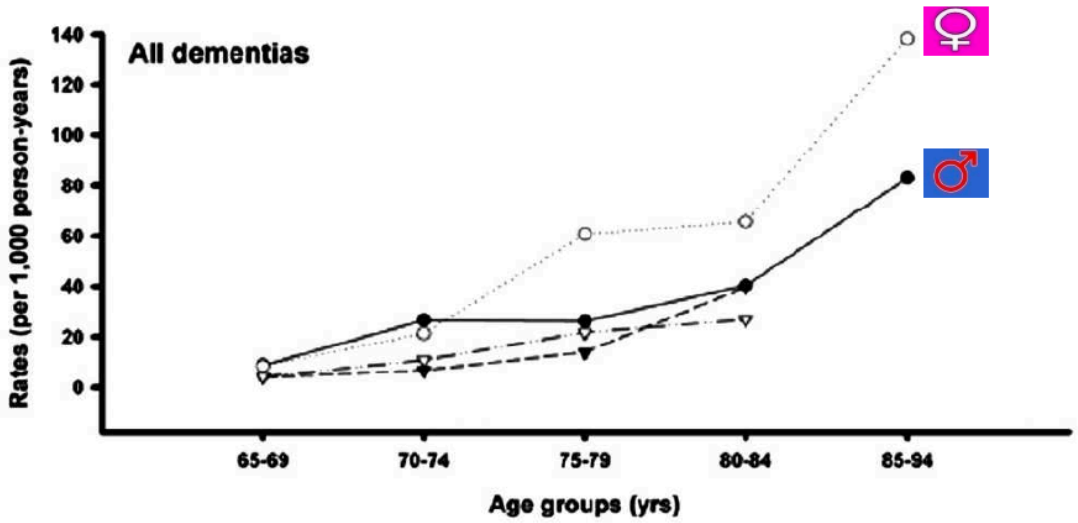
ITALIA



% : per 100 persone della stessa età

ISTAT, 1989

Conselice Study - Incidence of dementia



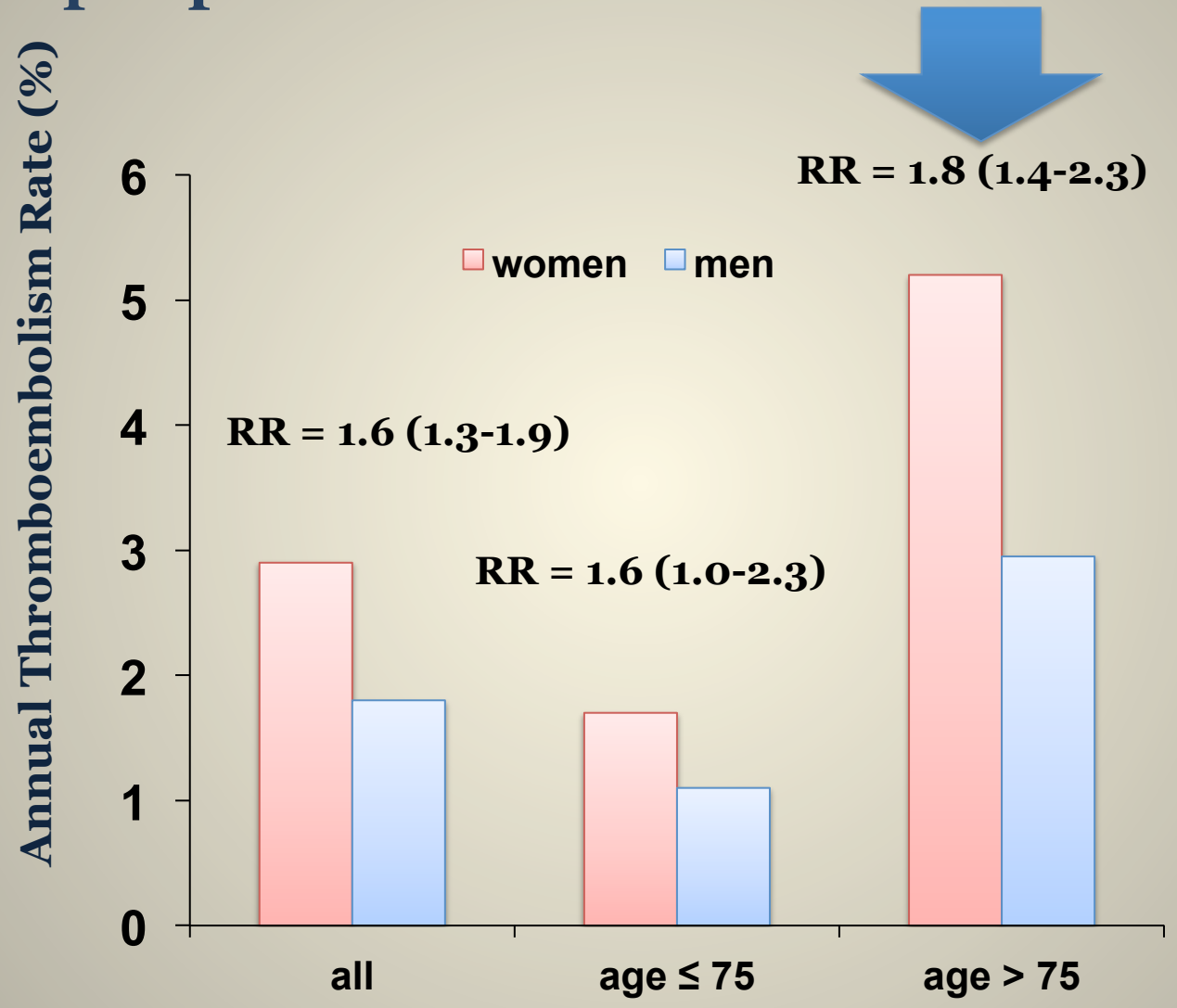
○ Conselice study Femmine

• Conselice study Maschi

▼ ILSA study

NEUROLOGY 2005;64:1525–1530

Gender differences in the risk of stroke and peripheral embolism in AF: the ATRIA study



Fang MC, et al. Circulation 2005;112:1687-91

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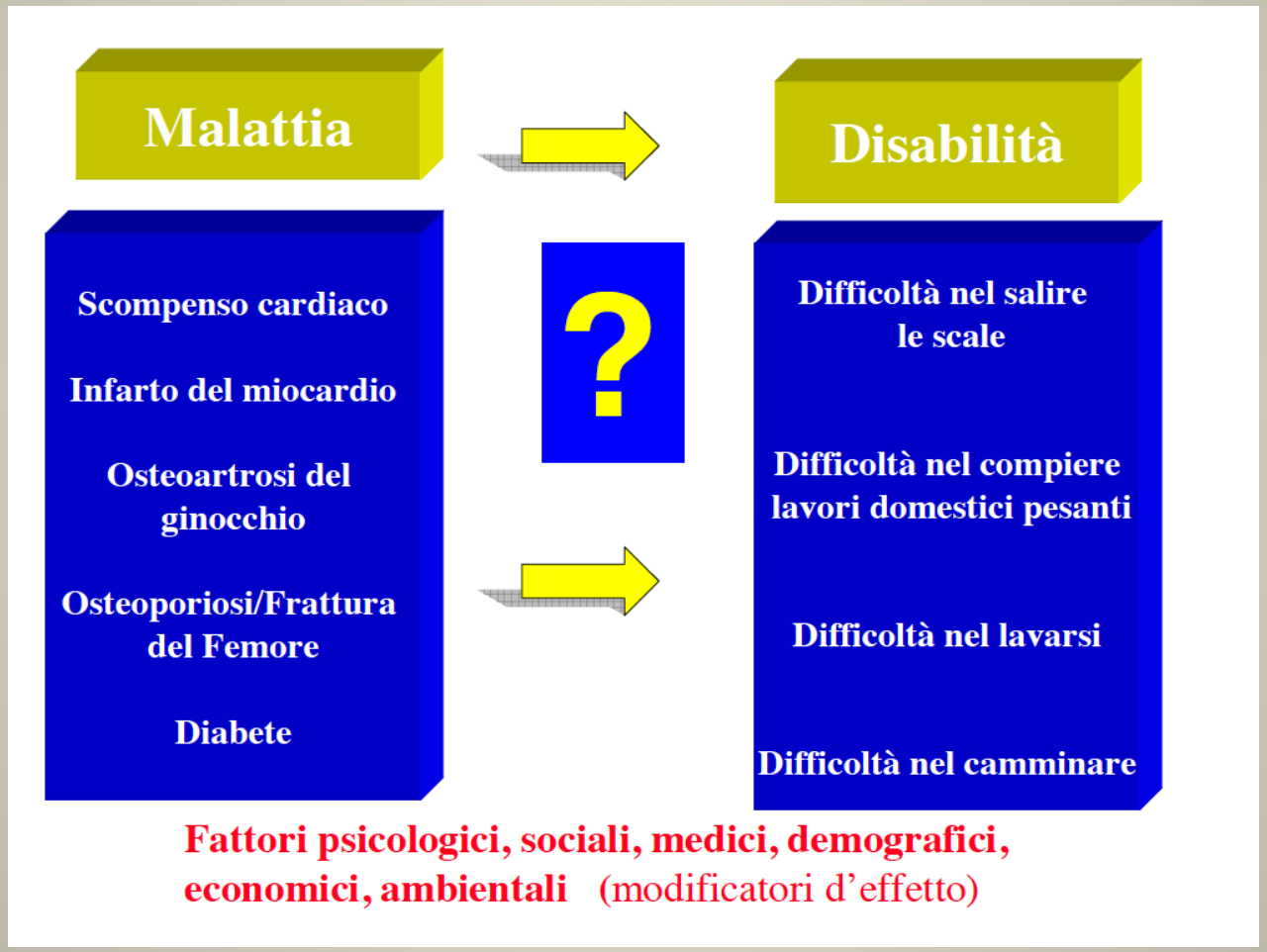

Malattia
Disabilità
Scompenso cardiaco
Infarto del miocardio
Osteoartrosi del ginocchio
Osteoporiosi/Frattura del Femore
Diabete
?
Difficoltà nel salire le scale
Difficoltà nel compiere lavori domestici pesanti
Difficoltà nel lavarsi
Difficoltà nel camminare
Fattori psicologici, sociali, medici, demografici, economici, ambientali (modificatori d'effetto)

Spettanza di Vita (SV) e Anni di Vita Sana (AVS) a 50 anni

	Uomini		Donne	
	SV	AVS	SV	AVS
AUSTRIA	29.08	**14.53**	33.70	**15.66**
FRANCIA	29.57	**18.01**	35.37	**19.74**
ITALIA	**30.37**	**20.63**	**35.31**	**20.86**
GERMANIA	28.96	**13.56**	33.41	**13.55**
OLANDA	29.14	**20.21**	33.28	**20.41**
PORTOGALLO	28.12	**14.90**	32.92	**12.67**
SPAGNA	28.48	**19.16**	35.02	**18.62**
SVEZIA	30.28	**20.22**	34.05	**20.31**
REGNO UNITO	29.46	**19.74**	32.69	**20.78**

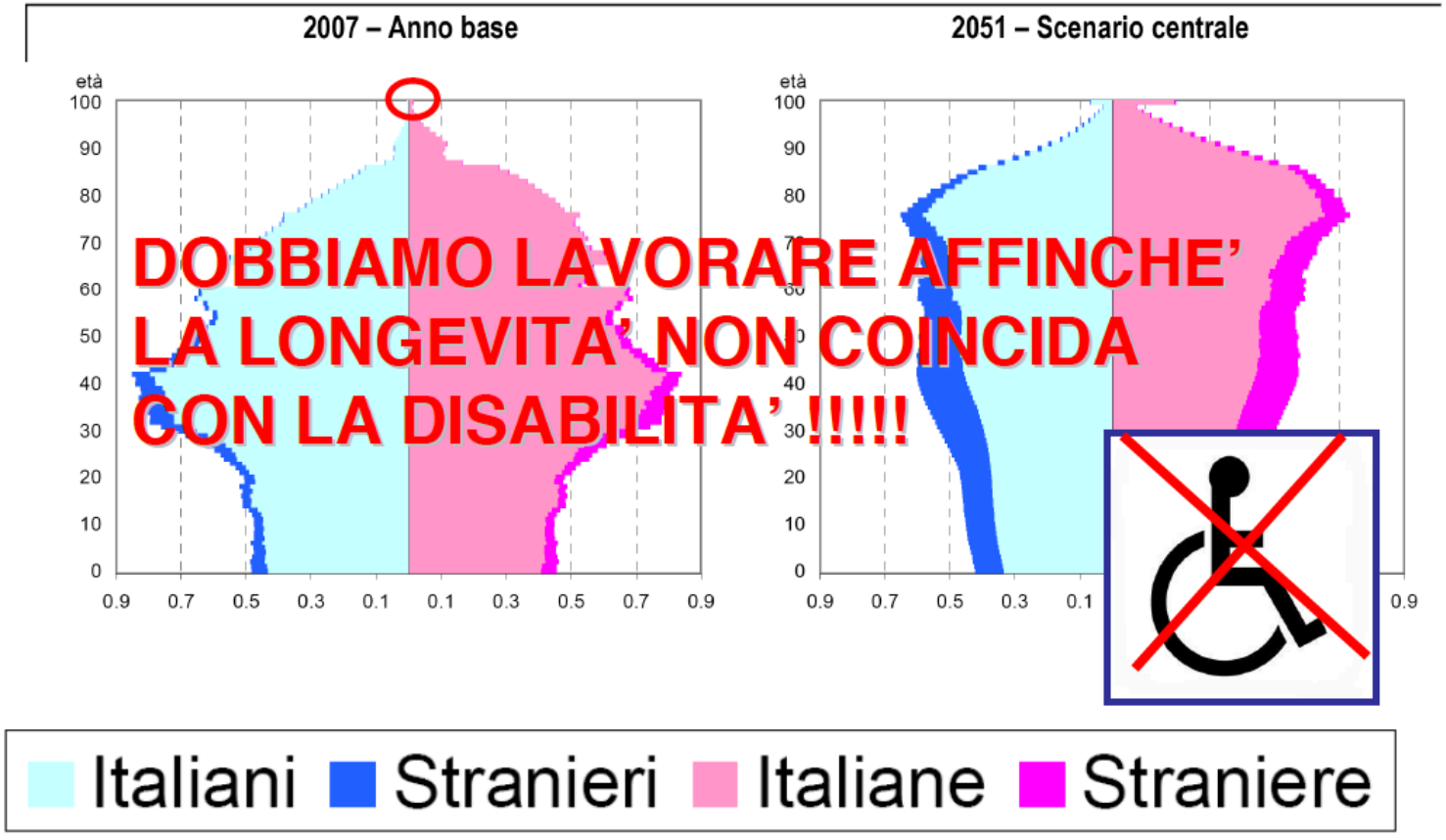
Jagger et al Lancet (2008) 372: 2124-2131

- Tuttavia la spettanza di vita sana è identica nei due generi, ***quindi i 5 anni di vantaggio della donna sono anni di vita ammalata e disabile principalmente per le conseguenze delle malattie cardiovascolari, osteoarticolari e neurologiche***. Questo ha una enorme influenza sulla qualità delle sua vita e sulla spesa sanitaria. La donna inoltre soprattutto con età superiore ai 65 anni è molto più sola dell'uomo, ha un livello culturale inferiore e un situazione economica molto più fragile.

Condizioni di salute	Differenze di genere			
	incidenza	decorso	sintomatologia	esempio
Malattie Cardiovascolari	Si, ritardate nella donna	Si	Si, puo' essere diversa	Infarto
Malattie Neurodegenerative	Si, piu' frequente nella donna	No	No	Alzheimer
Malattie autoimmuni	Si, piu' frequenti nella donna	No	No	Lupus
Malattie infettive	Si, specie in alcune infezioni virali	Si	No	Shock settico
Tumori	Si	Si, Aggessività localizzazione risposta alla terapia	No	Linfoma non-Hodgkin, Melanoma, Tumori tiroide, polmone, colon-retto, epatici
Malattie respiratorie	incerto	No	No	BPCO, Asma
Malattie Metaboliche	Si, piu' frequenti nella donna			Diabete

ITALIA

Figura 6 – Piramide della popolazione, Italia 2007 e 2051, dati al 1° gennaio, valori percentuali



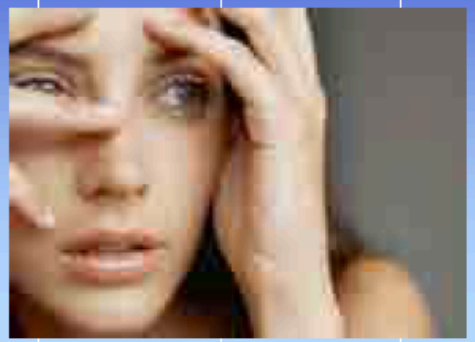
DOBBIAMO LAVORARE AFFINCHE' LA LONGEVITA' NON COINCIDA CON LA DISABILITA' !!!!!

Myths vs Facts

Myths	Facts
Men are more likely to have heart disease	**Heart disease is the #1 killer of men and women**; 50,000 more women than men die of heart disease every year
Cancer is a bigger **threat** than heart disease	Nearly twice as many US women die from heart disease and stroke than from all cancers combined
Doctors are **unaware of women's risk** for heart disease and act accordingly	**Under-treat**ment and **under-diagnosis of heart disease in women** contributes to excess mortality in women

Le donne e la conoscenza delle malattie

Dm1 Quali, tra le seguenti malattie, Le incutono maggiori timori?

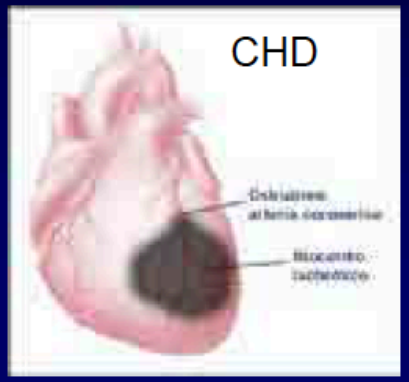


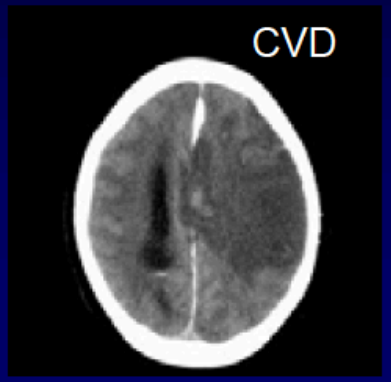
Base: 1000 donne over 50 anni

Datanalysis

Dipartimento Studi Socio Sanitari

Cause di morte della donna in Italia





Percentuale di morti in Italia (2001)
ISTAT - elaboratzione ISTISAN 95/34, modificata

La Trombosi e gli anti-trombotici in una prospettiva di genere.

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Thromboembolic Disease

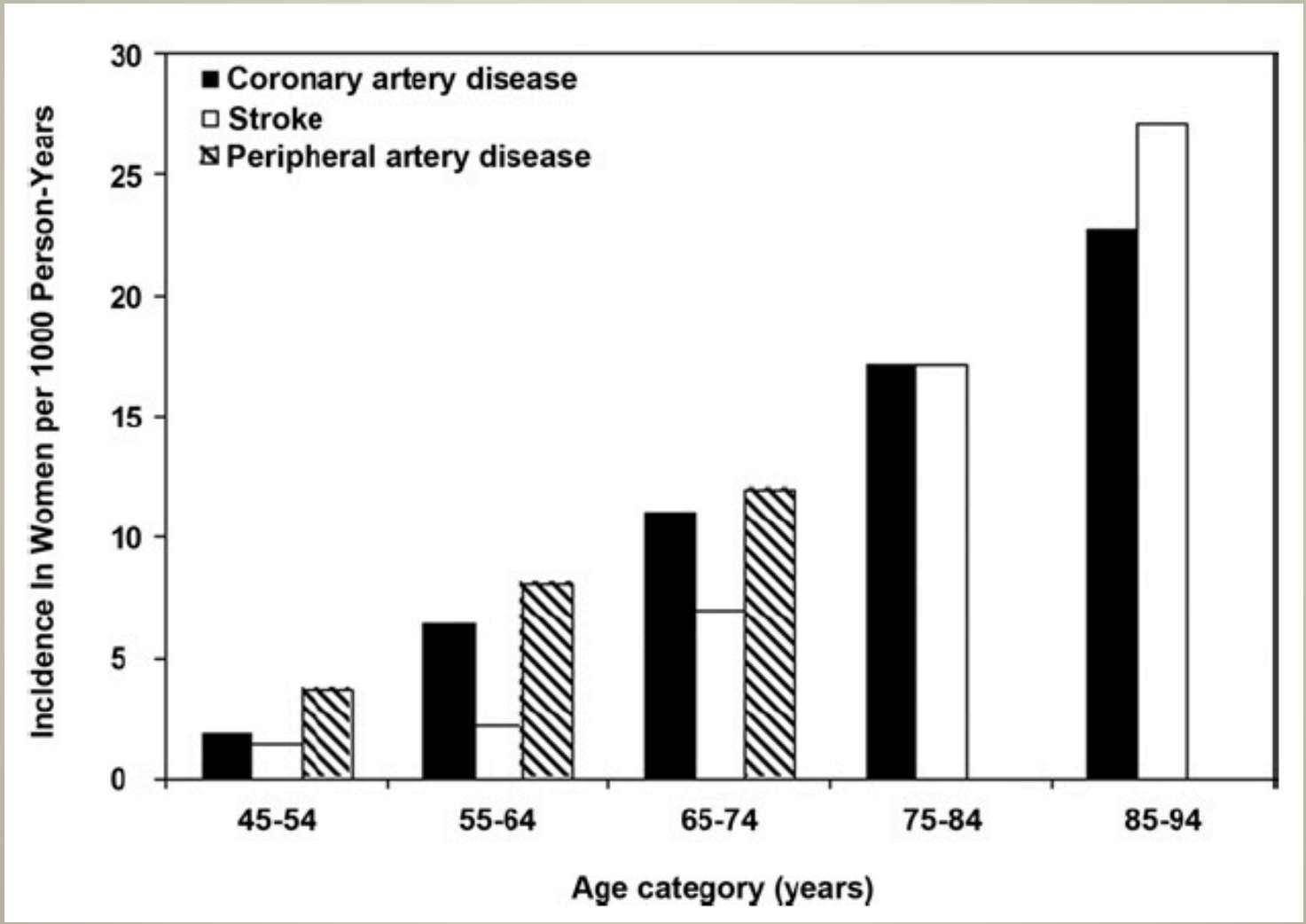
- **Arterial system**
  - Acute coronary syndrome
  - Stroke
- **Venous system**
  - Deep venous thrombosis
  - Pulmonary embolism

Arterial system

Acute coronary syndrome

Stroke

Incidence of Atherothrombotic Disease in Women by Age Category



JACC Vol. 59, No. 10, 2012

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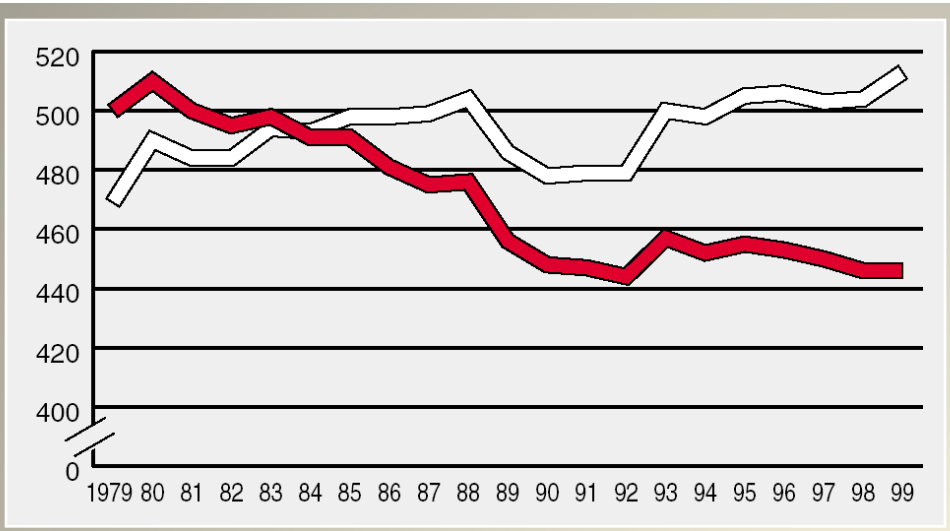
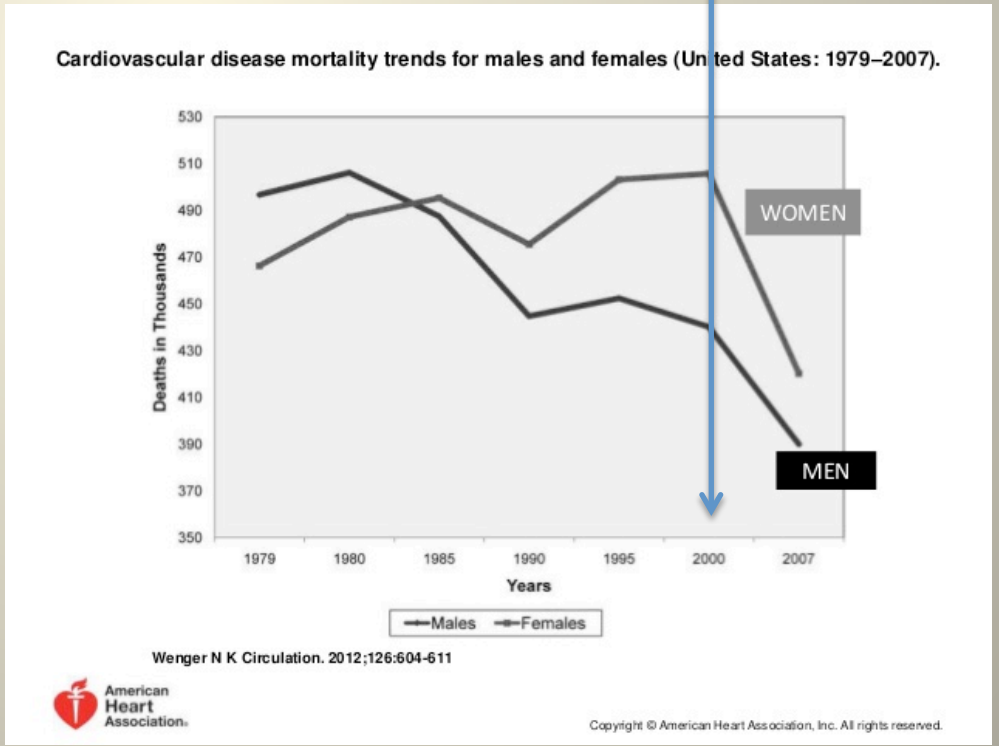


American Heart Association. *2002 Heart and Stroke Statistical Update*. 2001

Go Red for women



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Cardiovascular workgroup at the 2014 Academic Emergency Medicine (AEM) consensus conference to identify sex- and gender-specific gaps in the key themes and research questions related to emergency cardiac ischemia care.

Women in general are 10 to 15 years older than men when they develop CAD, but suffer worse post-infarction outcomes compared to age-matched men.

ACADEMIC EMERGENCY MEDICINE 2014;21:1350–1360

Risk Factors in Women >20 yrs

Risk Factor	%Women
■ High Blood Pressure	30-45%
■ Abnormal Lipids	40-55%
■ Overweight	60-75%
■ High Glucose	5-25%
■ Physical Inactivity	35-60%
■ Tobacco Use	~20%

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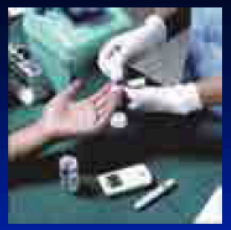
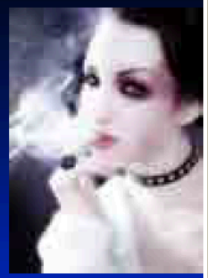
Lavori su fattori di rischio e prevenzione delle malattie cardiovascolari

- Baltomore's longitudinal study on aging (1958-1975): nessuna donna
- Physicians' health study of aspirin and CVD: 22.071 arruolati, nessuna donna
- MRFIT (1986): 355.222 uomini (nessuna donna)
- .....
- WOSCOPS (1995): 6600 arruolati, nessuna donna



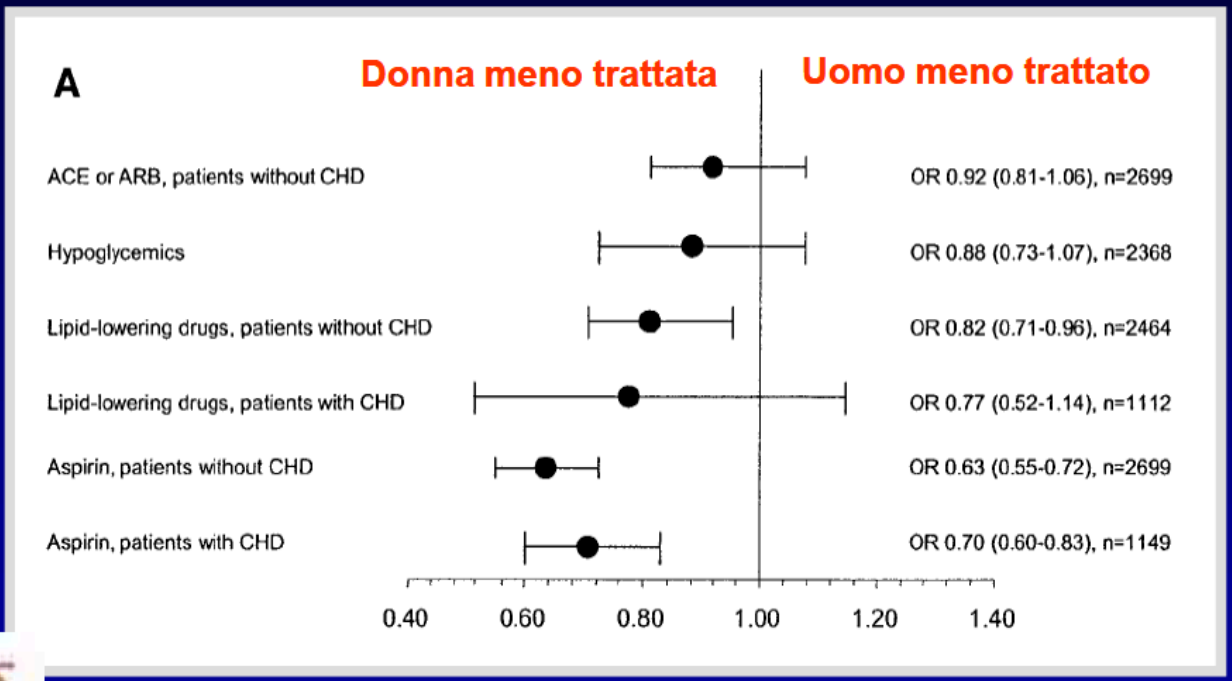
I FATTORI DI RISCHIO
hanno un impatto differente nella DONNA

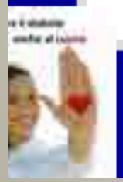


- **Diabete** molto più aggressivo sulle arterie delle donne
- **Colesterolo** totale meno importante del colesterolo **HDL**; **trigliceridi** molto importanti
- **Fumo** di sigaretta più dannoso
- **Ipertensione** pericolosa anche a valori più bassi
- **Sindrome metabolica** più frequente

Disparità nel trattamento dei Fattori di Rischio per CHD tra i sessi nei soggetti diabetici

(studio osservazionale, primary care, 3849 diabetici, 5 centri clinici)





Diabetes Care 2005;28:514-520

Cardiopatia Ischemica nella Donna

Età d'insorgenza più elevata

Sintomi atipici

Aterosclerosi "recente" → Placche più "giovani"

Patologia microvascolare

Deficit di cinetica ventricolare
Maggior compromissione emodinamica

Coronaropatia
più frequentemente
monovasale

Most female-specific risk factors are not included in the guidelines for CVD prevention in women (preeclampsia, polycystic ovary syndrome), as their causative impact on women's risk and their added predictive value to the current components of the guidelines are still not elucidated.

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Gender Differences in Heart Attack

Gender Differences in Heart Attack Symptoms - Milder symptoms (without chest pain).

Typical in both sexes

- Pain, pressure, squeezing, or stabbing pain in the chest
- Pain radiating to neck, shoulder, back, arm, or jaw
- Pounding heart, change in rhythm
- Difficulty breathing
- Heartburn, nausea, vomiting, abdominal pain
- Cold sweats or clammy skin
- Dizziness

Typical in women

- Milder symptoms (without chest pain)
- Sudden onset of weakness, shortness of breath, fatigue, body aches, or overall feeling of illness (without chest pain)
- Unusual feeling or mild discomfort in the back, chest, arm, neck, or jaw (without chest pain)

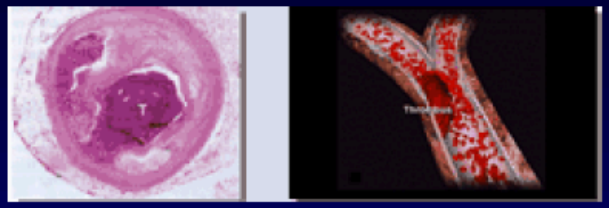
Review of 10 major studies found a higher percentage of women presenting with atypical symptoms (37.5% of women vs 27.4% of men)

Table 1. Acute Coronary Syndrome Presentation Without Chest Pain or Discomfort According to Sex—Summary of Studies From Large Cohorts

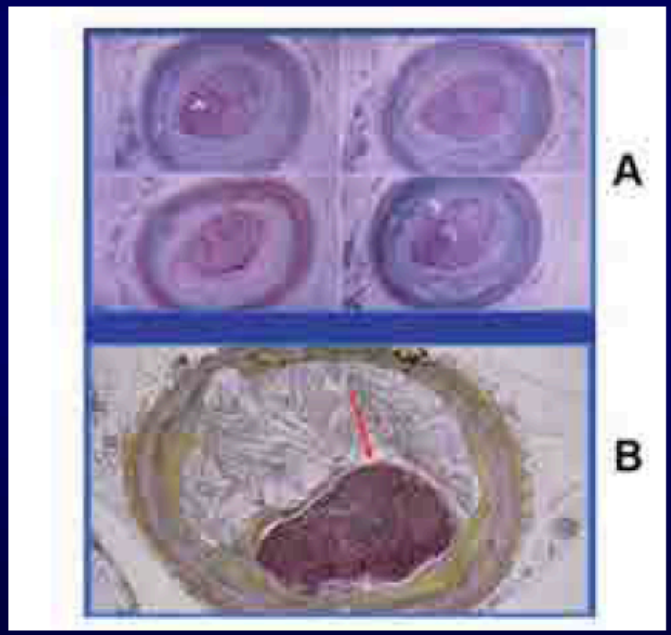
Source	Study Characteristic							Proportion Without Chest Pain, %		
	Study Description	Patient Population	Study Years	Sample Size	Mean Age, y	Age Adjusted	Race Adjusted	Men	Women	All
Brieger et al,[37] 2004	GRACE Registry	ACS	1999-2002	20 881	65.8	Yes	No	7.3	10.6	8.4
Canto et al,[8] 2000	National MI Registry	MI	1994-1998	434 877	69.3	Yes	Yes	28.6	38.6	32.7
Canto et al,[38] 2002	Alabama UA Registry	UA	1993-1999	4167	72.3	Yes	Yes	50.2	53.0	51.7
Culić et al,[39] 2002	CCUs Croatia	MI	1990-1995	1996	58.8	Yes	No	12.4	20.3	14.8
Dorsch et al,[7] 2001	United Kingdom	MI	1995	2096	70.6	Yes	No	17.6	24.6	20.1
Goldberg et al,[40] 1998	Worcester MI Study	MI	1986-1988	1360	67.7	Yes	No	18.0	23.0	20.0
Milner et al,[41] 2004	Worcester MI Study	MI	1997-1999	2073	70.2	Yes	No	30.9	45.8	37.3
Roger et al,[42] 2000	Olmsted County, Minnesota	UA	1985-1992	2271	63.0	Yes	No	25.0	19.0	22.0
Stern et al,[43] 2004	26 Hospitals, CCU, Israel	ACS	2000	2113	64.9	Yes	No	18.7	29.7	21.7
Cumulative	. . .	. . .	. . .	. . .	. . .	. . .	. . .	27.4 (76 036 of 276 933)	37.5 (73 003 of 194 797)	31.6 (149 039 of 471 730)

Arch Intern Med. 2007;167(22):2405-2413

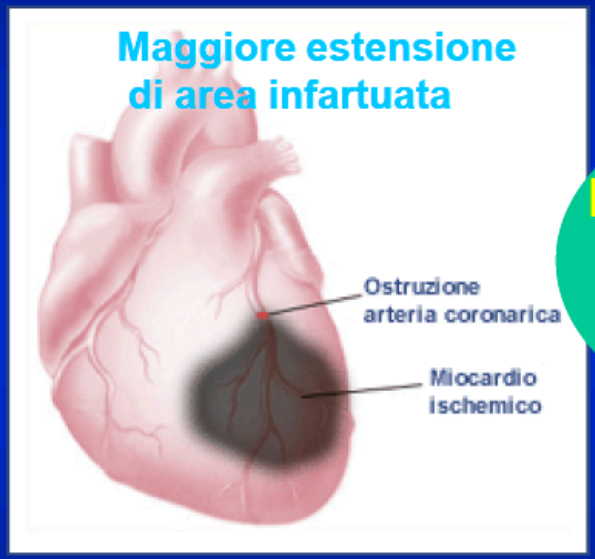
DIFFERENZE FISIOPATOLOGICHE



Nella donna giovane:
prevale l'**erosione** degli strati superficiali di placca con trombosi coronarica (anche in assenza di placca)

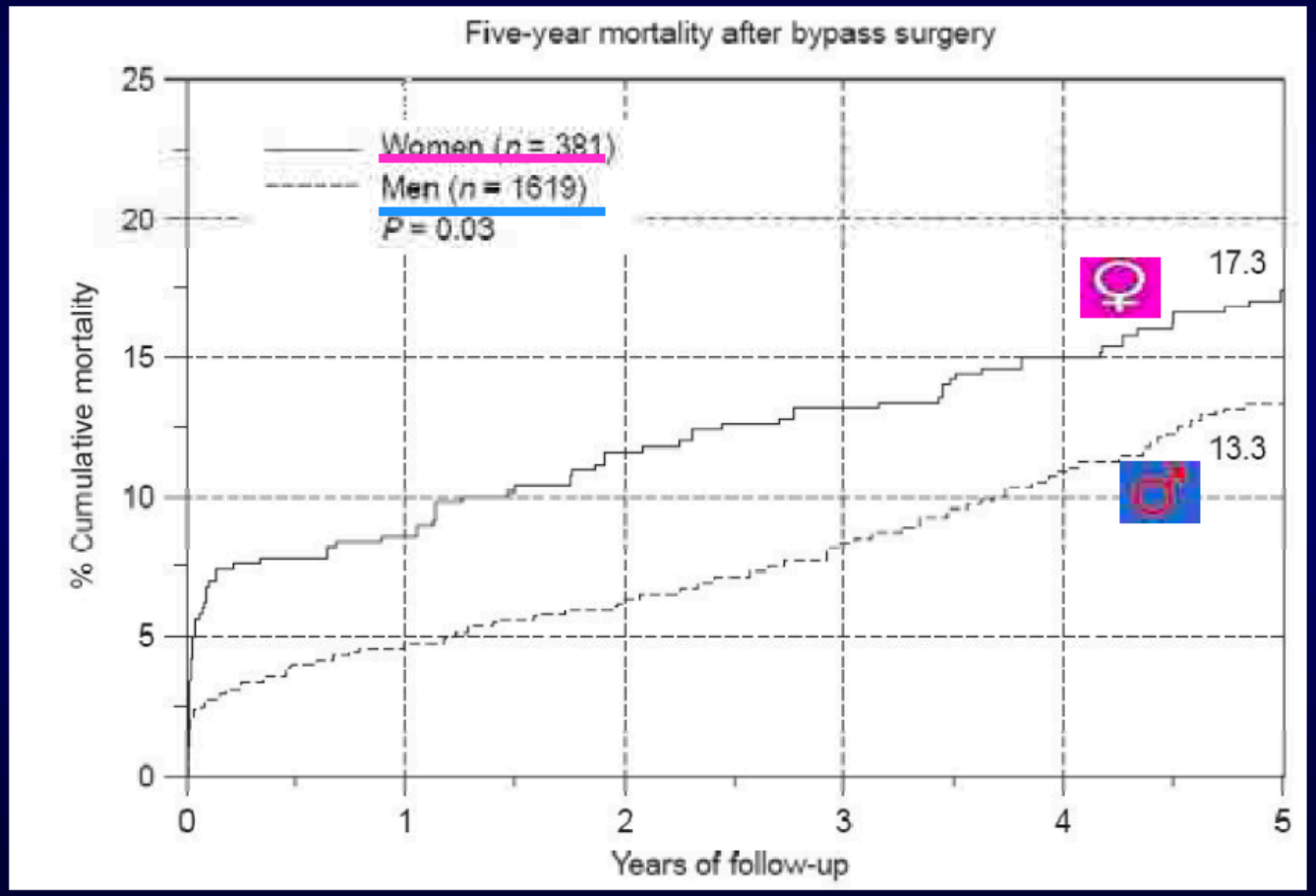


Nel sesso maschile e nella donna anziana:
prevale la **rottura** profonda di placca per riduzione di spessore del cappuccio



Nella donna sono più frequenti dopo infarto

MORTALITA' DOPO 5 ANNI DALL'INTERVENTO DI BYPASS



Herlitz et al, J Int Med 2000

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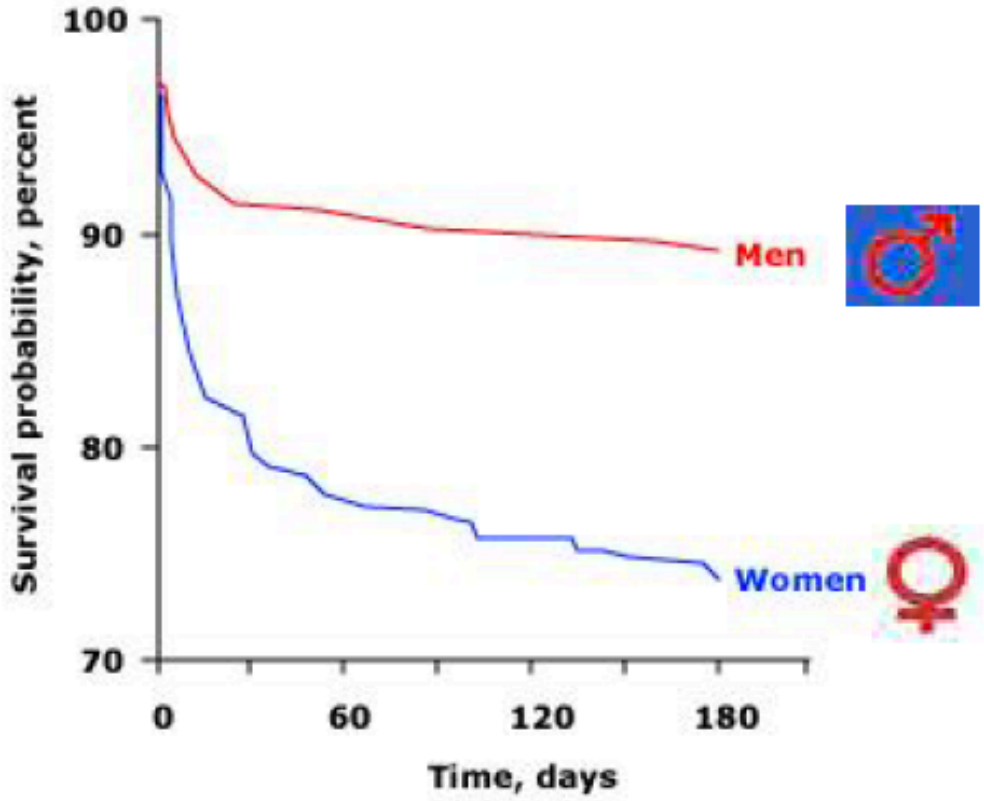
SOPRAVVIVENZA DOPO 6 MESI DA INFARTO



In the RESCATE study of 331 women and 1129 men, the six-month survival after a first myocardial infarction (MI) was lower in women than men (74 versus 89 percent, p<0.001).
Data from Marrugate, J, Sala, J, Massia, R, et al, for the RESCATE Investigators, JAMA 1998; 280:1405.

Il genere donna negli studi cardiologici europei

Trial	soggetti	donne %	riferimento
GISSI-1	11 711	25	Lancet 1986;1:397-402
ISIS-2	17 187	23	Lancet 1988;2:349-360
GISSI-2	12 490	20	Lancet 1990;336:65-71
GISSI-3	18 023	22	Lancet 1994;343:1115-22
4S	4 444	19	Lancet 1994;334:1383-89
ISIS-4	58 050	26	Lancet 1995;345:669-685
SMILE	1 556	27	NEJM 1995;332:80-85
EMIAT	1 486	16	Lancet 1997;349:667-674
GISSI-P	11 324	15	Lancet 1999;354:447-52
CIBIS-2	2 647	19	Lancet 1999;353:9-13

S. Priori, Policy Conference on CVD in Women

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Secondary prevention after AMI

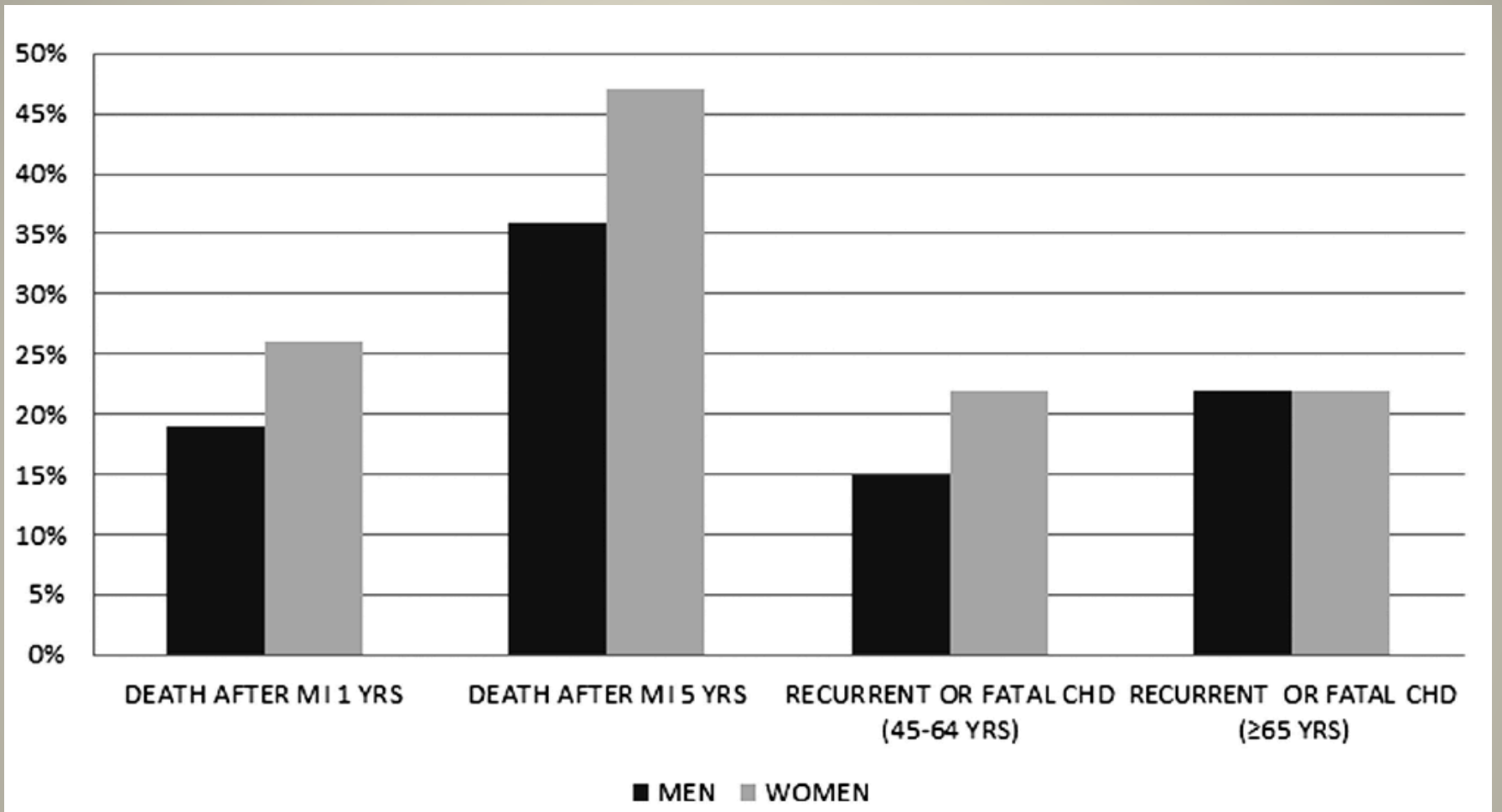


Fig. 3. Rates of cardiovascular events after myocardial infarction[6].

CHD: coronary heart disease; MI: myocardial infarction; YRS: years

J Atheroscler Thromb. 2015;22(2):109-25.

Cardiovascular workgroup at the 2014 Academic Emergency Medicine (AEM) consensus conference to identify sex- and gender-specific gaps in the key themes and research questions related to emergency cardiac ischemia care.

- the full spectrum of sex-specific risk as well as **presentation** of cardiac ischemia may not be captured by our standard definition of CAD and needs to incorporate other forms of ischemic heart disease (IHD);
- **diagnosis is further challenged** by sex/gender differences in presentation and variable sensitivity of **cardiac biomarkers**, **imaging**, and risk scores;

ACADEMIC EMERGENCY MEDICINE 2014;21:1350–1360

Cardiovascular workgroup at the 2014 Academic Emergency Medicine (AEM) consensus conference to identify sex- and gender-specific gaps in the key themes and research questions related to emergency cardiac ischemia care.

- sex-specific pathophysiology of cardiac ischemia extends beyond conventional obstructive CAD to include other causes such as **microvascular dysfunction, takotsubo, and coronary artery dissection**, better recognized as IHD;
- treatment and prognosis are influenced by sex-specific **variations in biology**, as well **as patient–provider communication**.

ACADEMIC EMERGENCY MEDICINE 2014;21:1350–1360

Women exhibit Acute Coronary Syndrome with open coronary arteries more frequently than men.

Sex-Specific Factors in Microvascular Angina

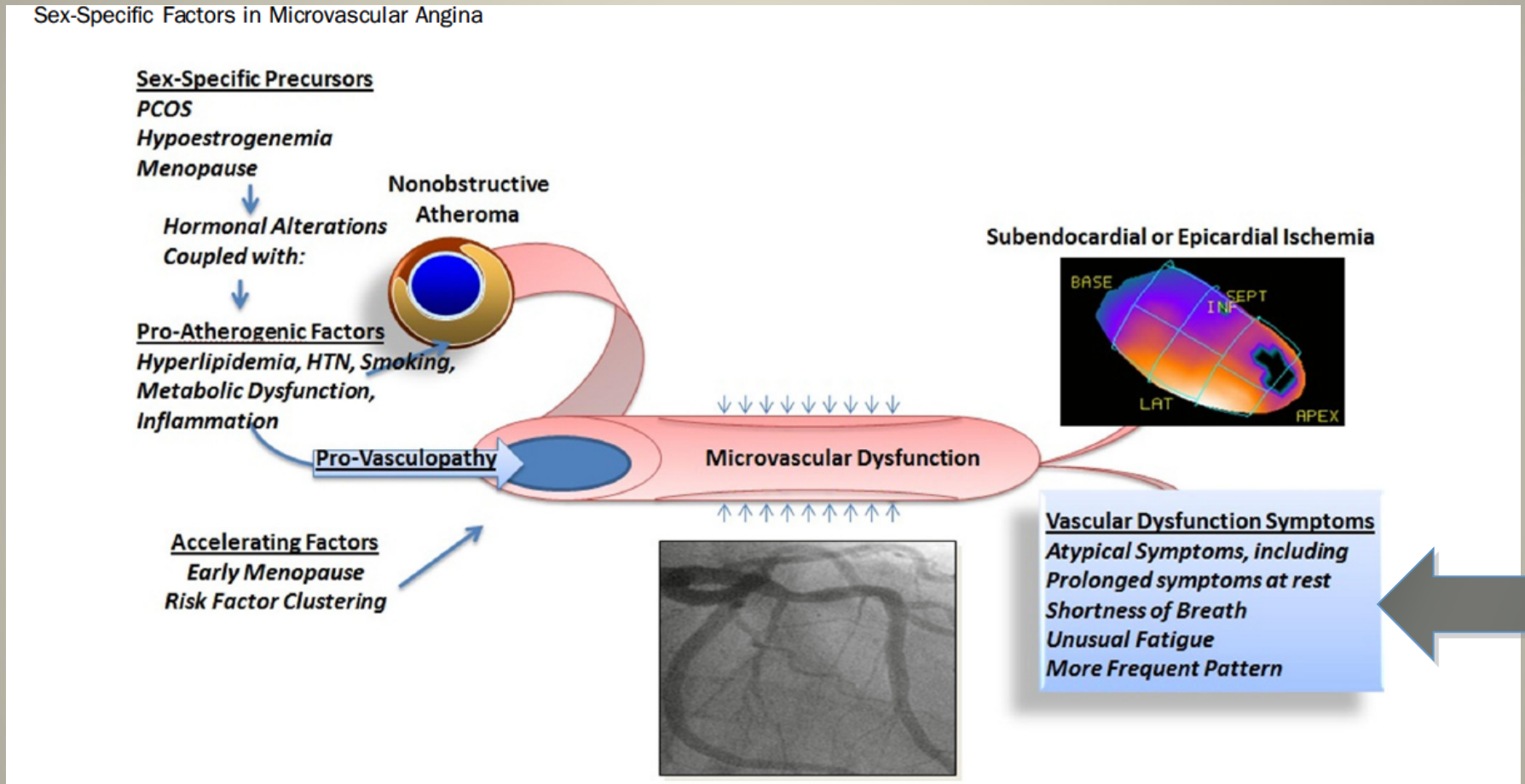


Figure 1. Model of microvascular angina in women. HTN, hypertension; PCOS, polycystic ovary syndrome. Reproduced from Shaw et al.[12] with permission from Elsevier.

Can J Cardiol. 2014; 30: 747-55.

Women and Stroke

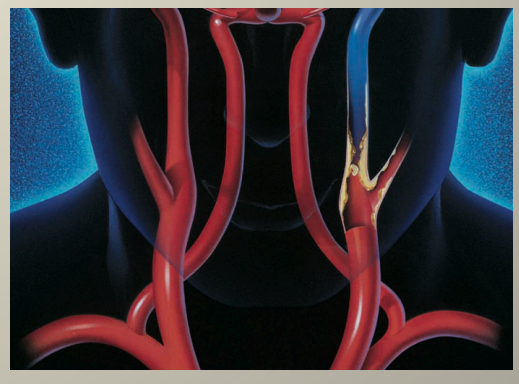
Stroke is the **third leading cause of death for women** (in comparison, stroke is the fifth leading cause of death for men).

Each year 55,000 more women have a stroke than men.

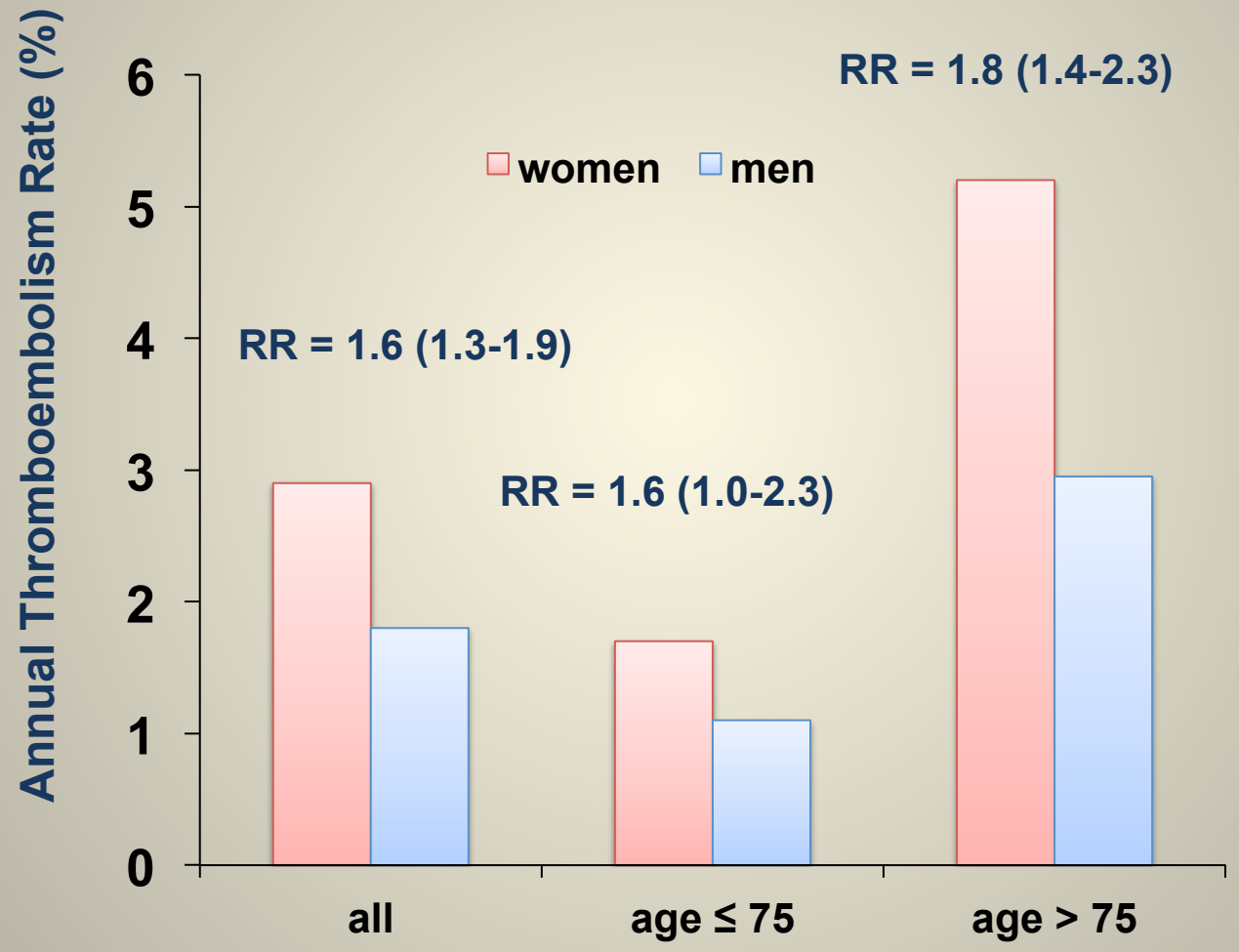
Because in general women live longer than men, stroke will have a more negative impact on their lives.

More women will:

- Live alone when they have a stroke
- Be more likely to live in a long term health care facility after a stroke
- **Have a worse recovery after stroke**



Gender differences in the risk of *stroke* and peripheral embolism in AF: the ATRIA study



Circulation 2005;112:1687-91

Stroke Risk in Atrial Fibrillation

The 2009 Birmingham schema expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc

	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age≥75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque]	1
Age 65-74	1
Sex **c**ategory [ie Female gender]	1

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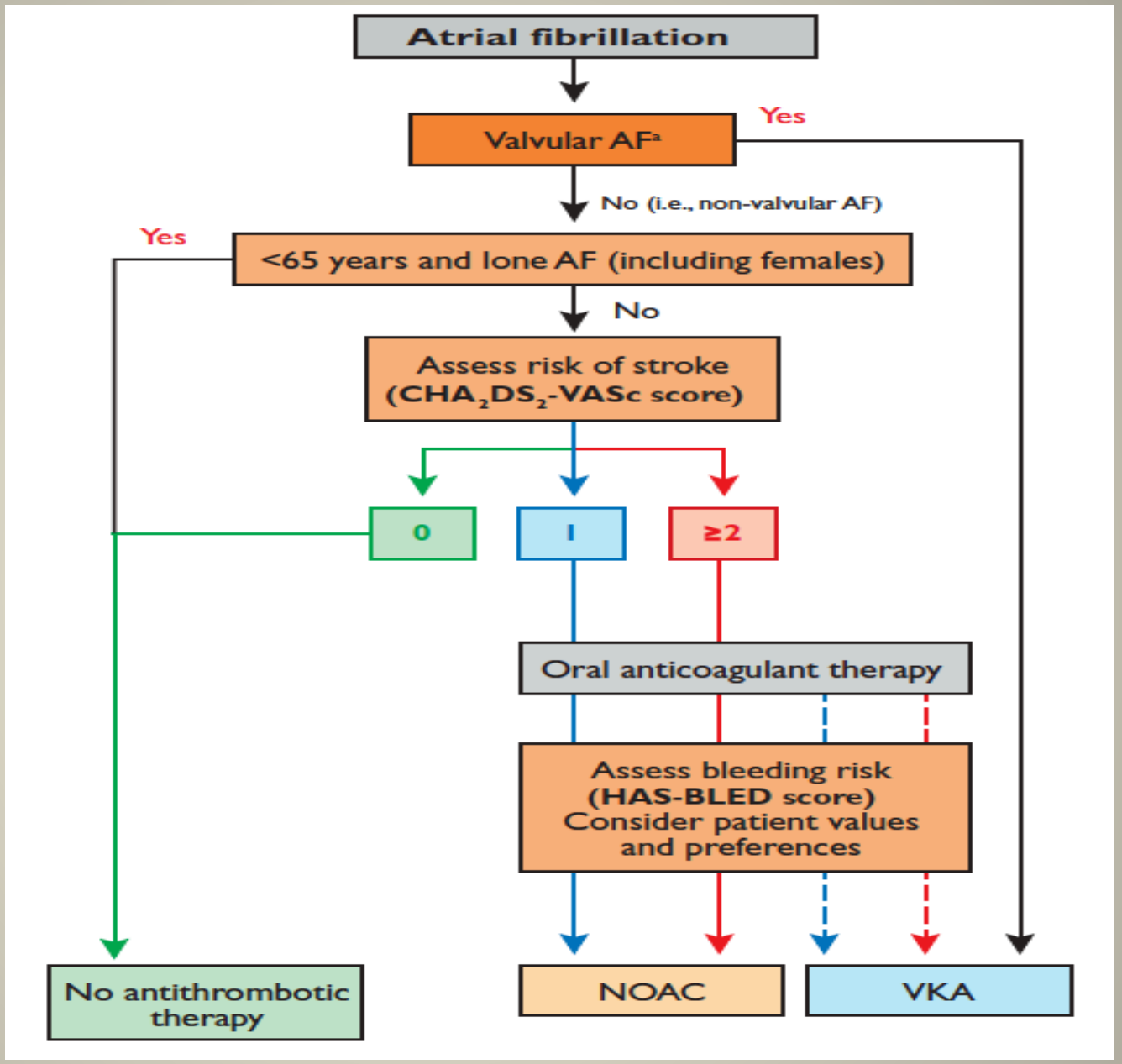
Authors/Task Force Members et al. Eur Heart J 2012;eurheartj.ehs253



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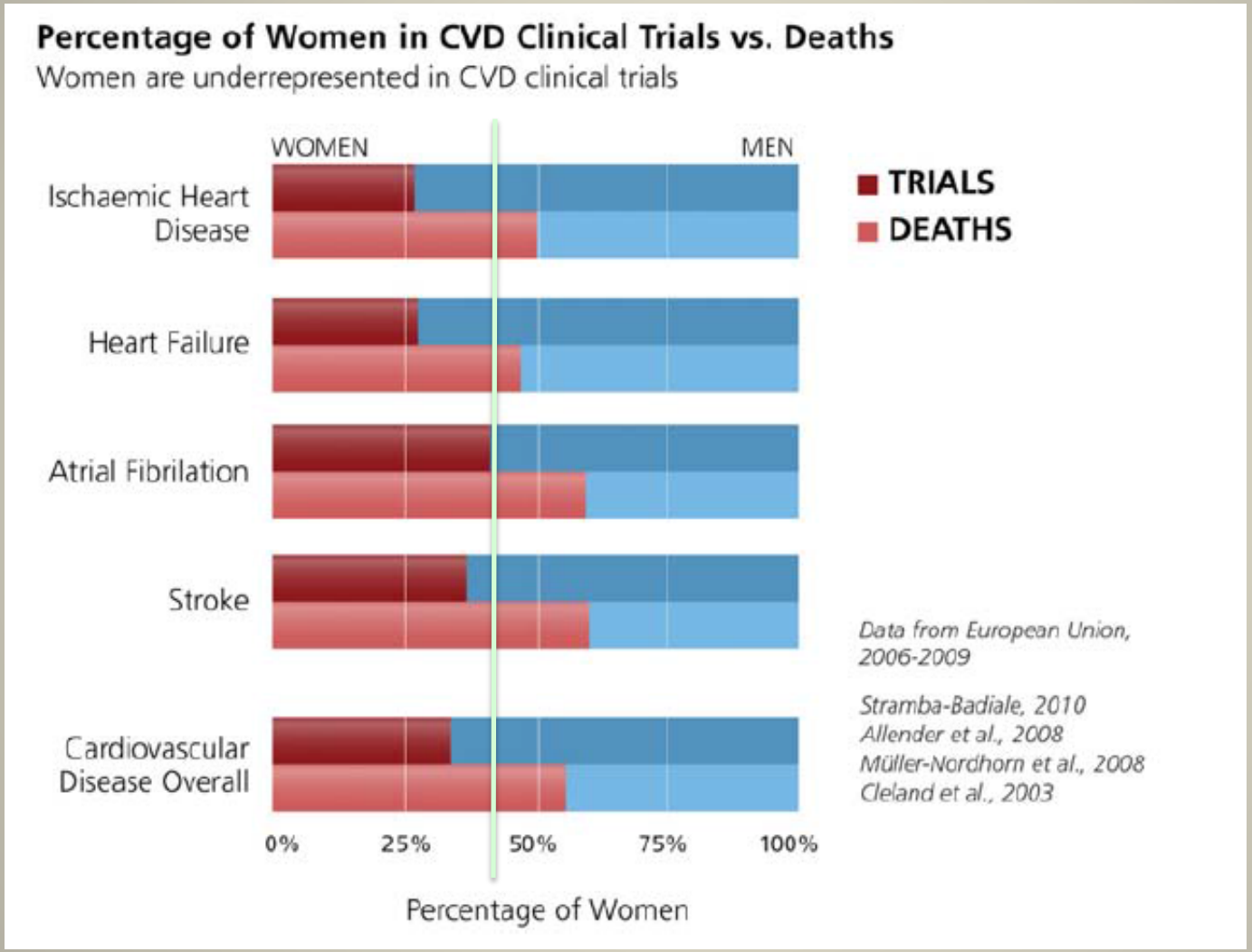
..... number of women included in CV studies **has often bee low**



DATI EUROPEI 2006-2010

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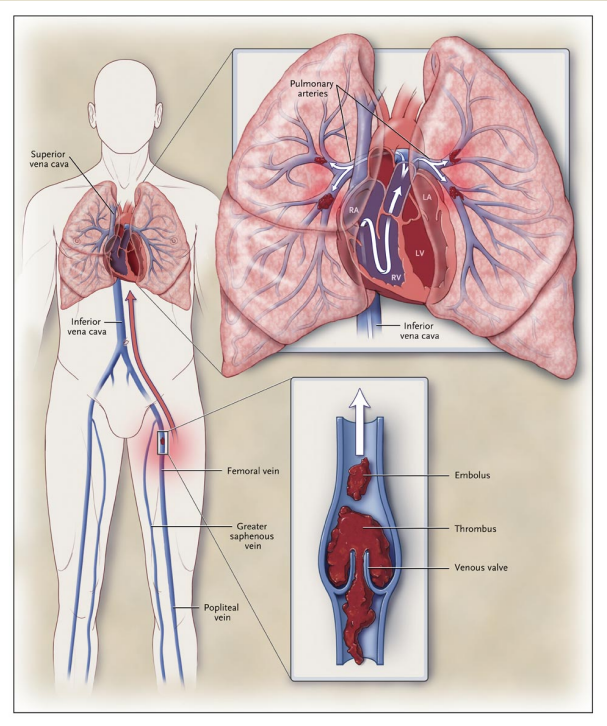
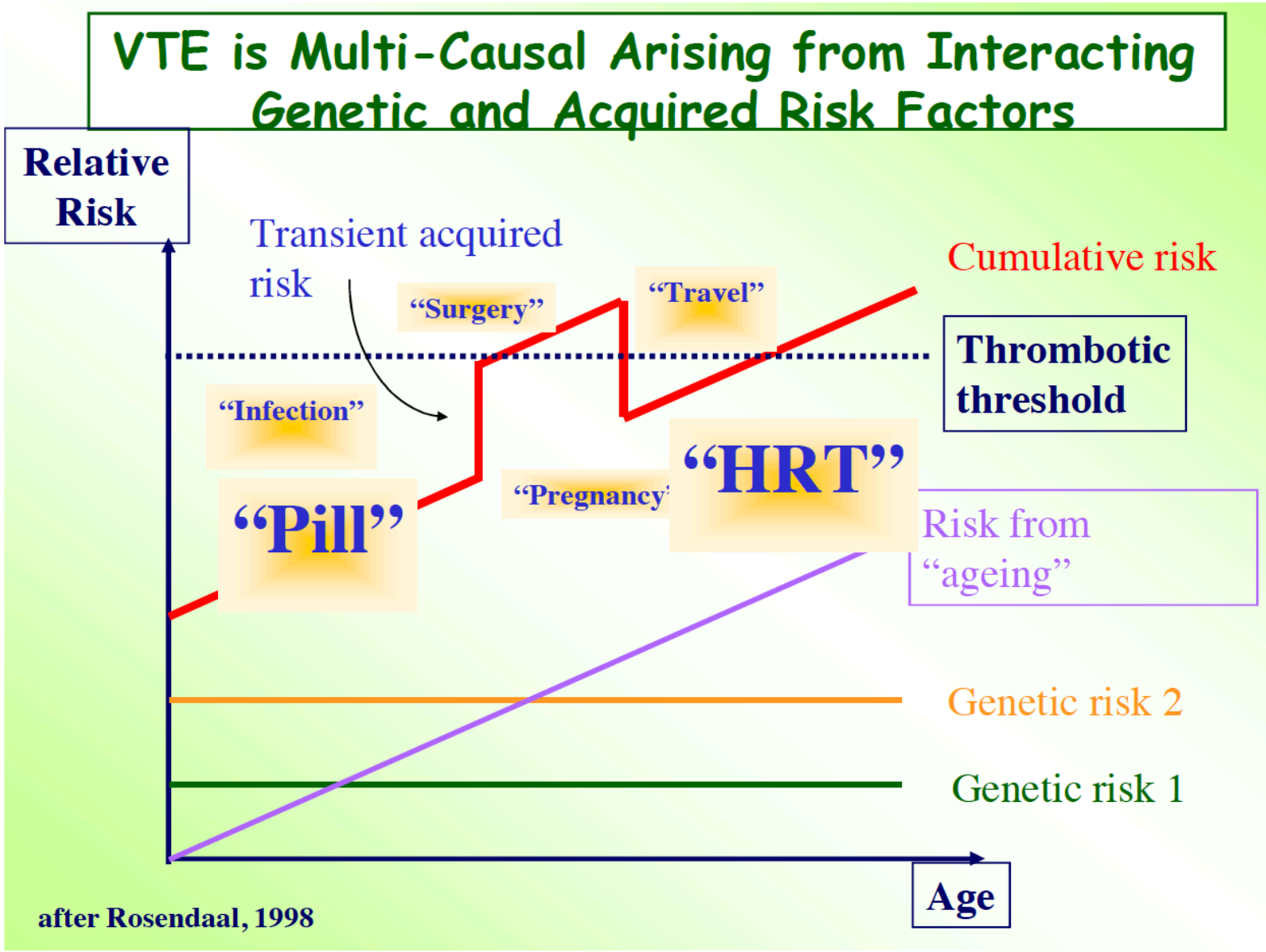
Venous Thromboembolism





Riprodotta da Abbate R.

A che punto è la Medicina di Genere in Italia?

Ci sono molte iniziative e ricerche scientifiche che hanno sensibilizzato molte realtà politiche regionali e il Parlamento Italiano .

La promozione dell'inserimento della Medicina di Genere nei programmi dei Corsi di Laurea in Medicina e Chirurgia è obiettivo della Conferenza dei Presidenti di Corso di Laurea Magistrale in Medicina e Chirurgia (Presidente Prof. A. Lenzi).

La creazione di centri Universitari di Medicina di Genere?

Le iniziative in Italia cominciano dunque ad essere molteplici.

E' assolutamente necessario che siano coordinate e che si formi una rete a supporto di questo campo della medicina rimasto così arretrato allo scopo di non disperdere energie.

Ma la cosa più importante sarebbe per ogni donna: **MAKE A CHANGE.**

American Heart Association. life is why™ | Go Red for women

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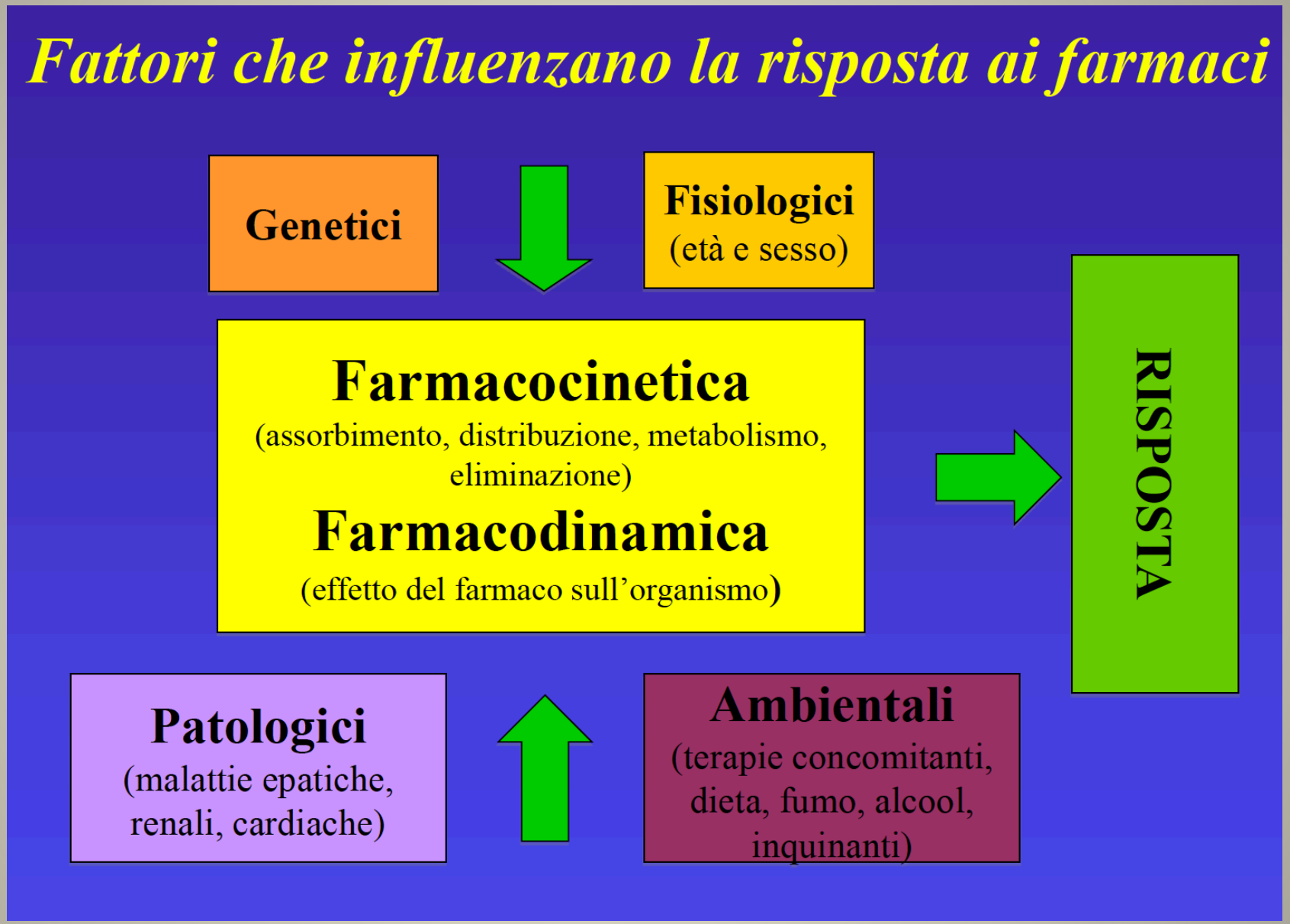
Perché differenza di genere nell'inclusione negli studi sperimentali con i farmaci?

Perché differenza di genere nella risposta al farmaco?

Fattori che influenzano la risposta ai farmaci



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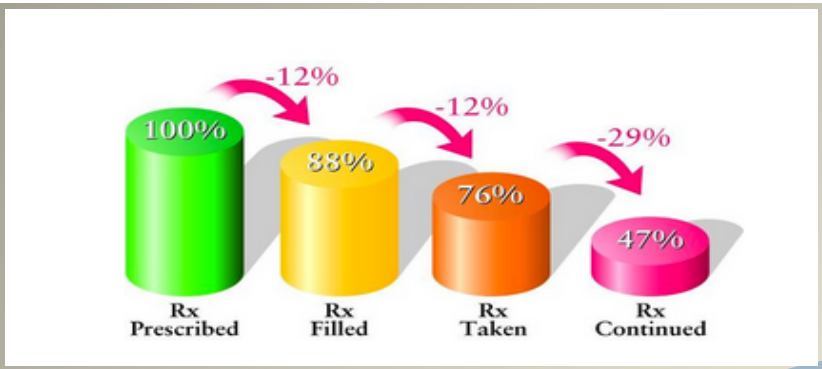


Adherence
taken as instructed for the prescribed period of time

Efficacy

Treatment goal

Safety/tolerability

Convenience
easy to take and to administer i.e. number of doses

5 dimensioni della aderenza

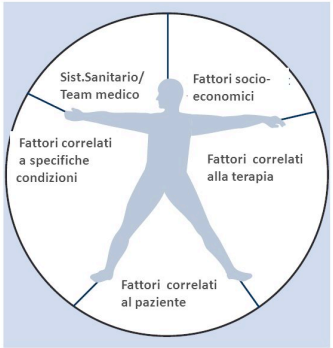
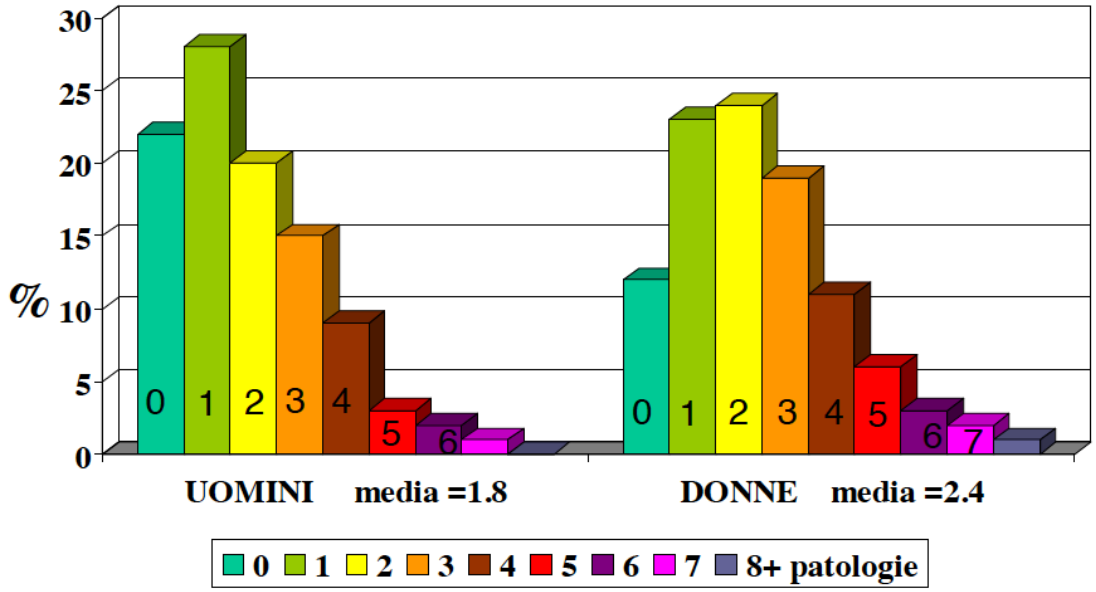


Table: Clinical Characteristics of Patients with Atherosclerotic Disease at Admission and According to Gender

	Overall	Male	Female	p
	n= 1673	n= 966	n= 707	
Age, *years* (median [IQR])	80 [74-85]	79 [73-84]	82 [76-87]	<0.001
Work Classes, n (%) *1577*				<0.001
Low Class	1223 (77.5)	633 (70.1)	590 (87.5)	
Middle Class	228 (14.5)	161 (17.8)	67 (9.9)	
High Class	126 (8.0)	109 (12.1)	17 (2.5)	
Caregiver, n (%) *1262*	710 (56.3)	207 (39.1)	323 (60.9)	0.004
Hypertension, n (%)	1350 (80.7)	768 (79.5)	582 (82.3)	0.149
Hypercholesterolemia, n (%)	161 (9.6)	91 (9,4)	70 (9,9)	0.742
Heart Failure, n (%)	302 (18.1)	181 (18.7)	121 (17.1)	0.394
Coronary Artery Disease, n (%)	**1154 (69.0)**	**689 (71.3)**	**465 (65.8)**	**0.015**
Myocardial Infarction, n (%)	173 (10.3)	108 (11.2)	65 (9,2)	0.187
Peripheral Arterial Disease, n (%)	196 (11.7)	131 (13.6)	65 (9.2)	0.006
Cerebrovascular Disease, n (%)	533 (31.9)	294 (30.4)	239 (33.8)	0.144
Polypharmacy, n (%) *1670*	1287 (77.1)	751 (77.8)	536 (76.0)	0.389

In press

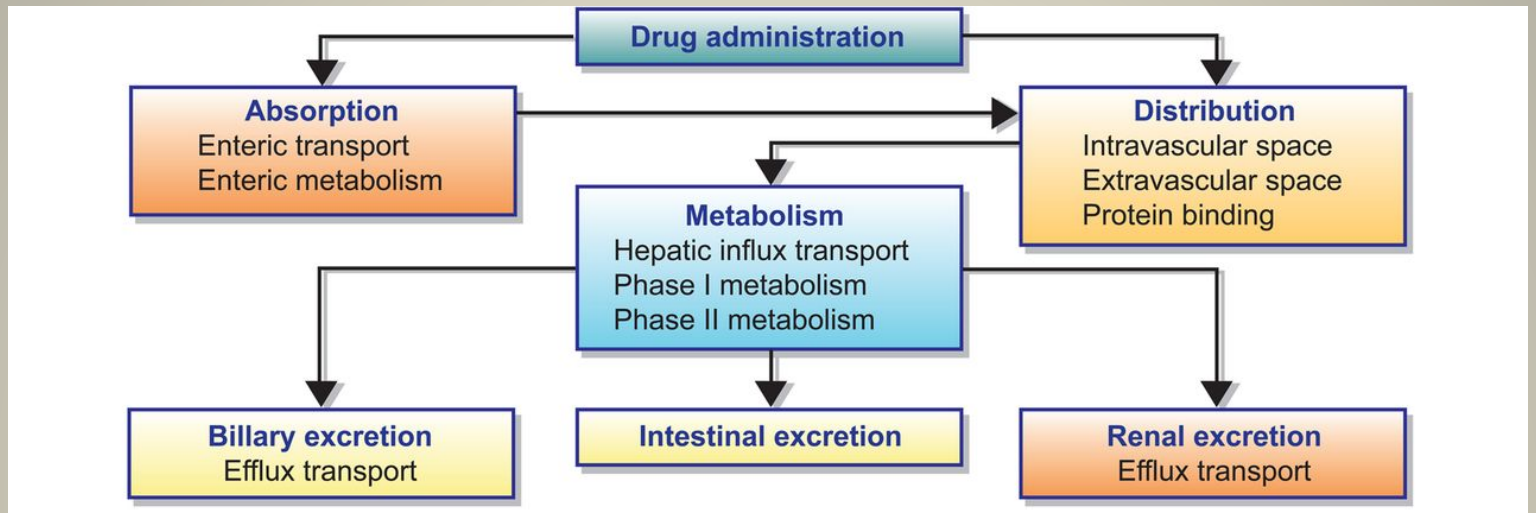
Distribuzione in percentuale del numero di patologie* in uomini e donne > 65 aa a casa: Studio PRO.V.A



* Patologie: Cardiovascolari, osteoarticolari, diabete, BPCO, cancro, Parkinson, frattura di femore, deficit visivo, deficit cognitivo, depressione.

Corti et al., JAGS, 2002

Gender differences in absorption and distribution and excretion of drugs responsible for gender differences in pharmacokinetic actions.



Absorption:
- Slower GI motility and transit time
- Lower gastric acid secretion
- Less drug enzymes and transporters
- Lower absorption rates

Body composition:
- Lower BW, organ size and blood flow

Distribution:
- Greater body fat and lower body water content (Higher Vd for lipophilic drugs, Lower Vd for water-soluble drugs)
- Less α1-acid glycoprotein
- Lower cardiac output

Excretion:
- Lower renal blood flow, glomerular filtration rate (GFR), tubular secretion and reabsorption
- Slower clearance of renally excreted drugs
- Longer elimination half-life

Other Factors:
- Differences in BW, cardiac output, plasma volume and regional blood flow

CYP Enzyme	Enzyme Activity
1A2	M > W
2A6	W > M
2B6	W > M
2C9	M = W
2C19	M = W
2D6	Mostly W > M
3A4	Mostly W > M
UDP-glucuronosyltransferases (UGTs)	M > W
Sulfotransferases	M > W
N-acetyltransferases	M < W
Methyltransferases	M > W

Eur Heart J 2015;eurheartj.ehv161

European Heart Journal

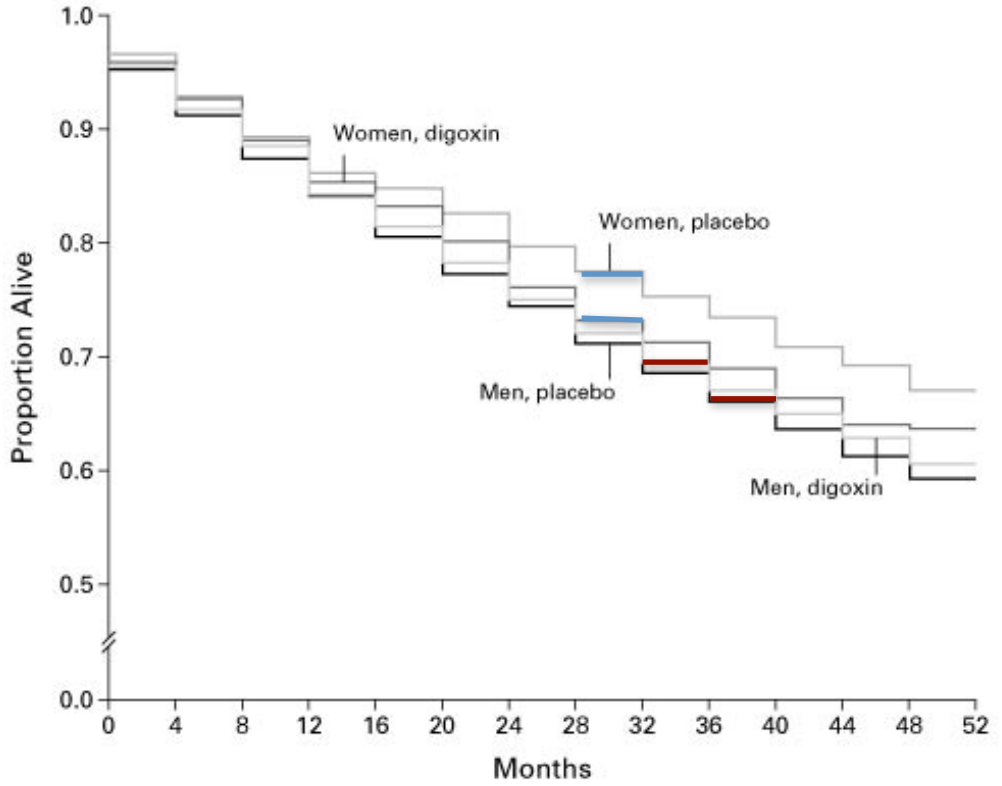
Table 1 Gender differences in pharmacokinetics

	Women	Men	Refs
Absorption	↓ gastric acid secretion ↑ GI transit time		[6–11]
Distribution	↓ body weight ↓ intravascular volume ↓ organ volume ↓ muscle volume ↑ adipose tissue		[6–8]
Metabolism	↑ CYP2D6 ↑ CYP3A	↑ CYP1A activity ↑ CYP2E1 activity ↑ P-gp activity	[7, 12, 13]
Excretion	↓ GFR		[6–8, 14]

↑, increased ↓, decreased

Cardiovasc Drugs Ther (2015) 29:403–410

Gender differences in the effect of cardiovascular drugs: **Digoxin**



No. at Risk

Men, placebo	2639	2510	2401	2301	2210	2111	2022	1944	1686	1438	1152	886	568	255
Men, digoxin	2642	2549	2449	2353	2243	2135	2047	1962	1685	1420	1129	870	572	249
Women, placebo	764	729	701	675	657	645	626	603	511	440	347	266	163	73
Women, digoxin	755	720	693	665	638	621	596	564	488	414	338	261	164	79

The increased risk of death among women was possibly related to the **relatively excessive dosage of digoxin**.

Although the increased mortality was correlated to the higher serum digoxin concentrations, **sex-based differences in digoxin PK were absent when actual or ideal body weight was used**.

N Engl J Med 2002;347:1403-1411

Gender differences in the effect of cardiovascular drugs: **Beta-blockers**

Although it is known that plasma levels of beta-blockers do not always correlate with therapeutic efficacy, women present **higher plasma level of metoprolol and propranolol due to a slower Clearance and lower volume of distribution**.

5474 patients (4353 men, 1121 women) have been studied during double-blind therapy with metoprolol 100 mg twice daily or matching placebo.
In total there were 223 deaths in the placebo-treated patients as compared to 188 deaths in the metoprolol-treated patients (P = 0.036). **The mortality reduction was found both in men and women.**

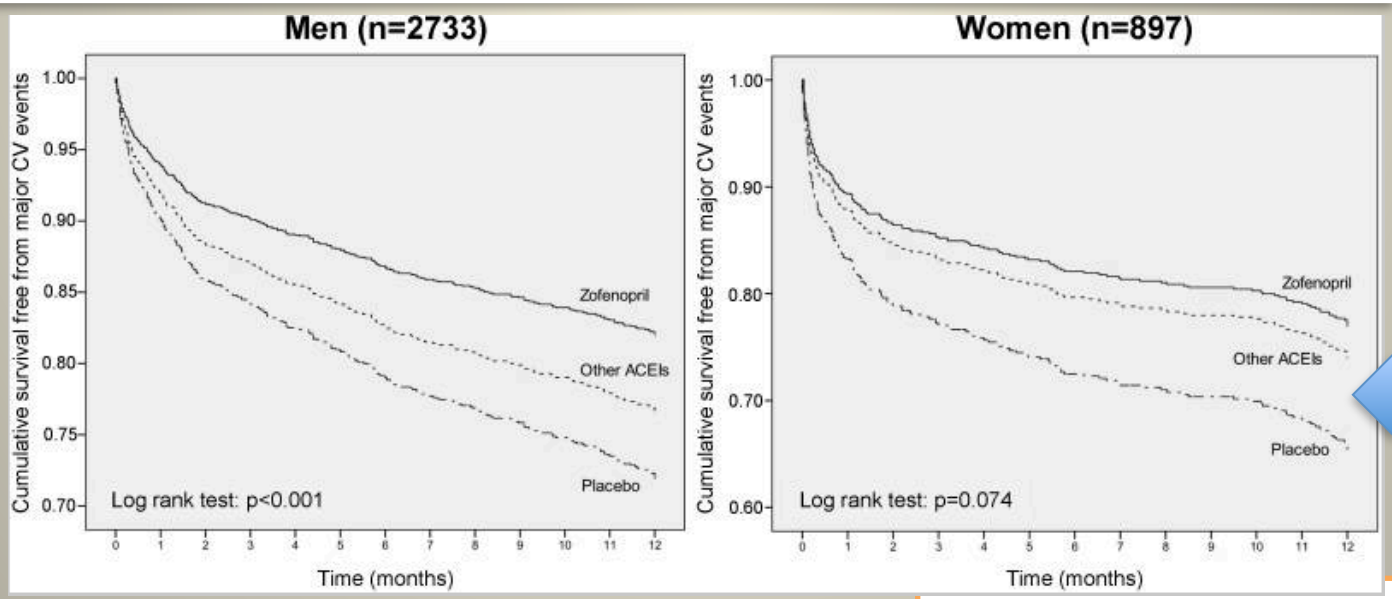
Eur Heart J 1992;13: 28–32.

Despite some trials suggested that beta-blockers improved survival only in males, but not in females, with hypertension or heart failure **several a meta-analysis confirmed that beta-blockers produced a similar survival benefit in heart failure or after MI in both sexes.**

Gender differences in the effect of cardiovascular drugs: Inhibitors of the renin-angiotensin-aldosterone system

RAAS are not recommended for use in women during childbearing

Retrospective pooled analysis of SMILE studies. Zofenopril vs. placebo or other ACE-inhibitors (ACEIs) in post-acute myocardial infarction (AMI).



PLoS One. 2014 Nov 3;9(11):e111558

Gender differences in the effect of cardiovascular drugs: Calcium-channel blockers

Gender-specific pharmacokinetics differences have been described for verapamil, nifedipine, and amlodipine.

Oral clearance of verapamil and amlodipine are faster in females compared with men, probably due to the higher activity of CYP3A4 or lower activity of P-gp in females.

Although amlodipine exhibited greater antihypertensive effect and higher incidence of oedema in females than in men, **major hypertension trials with calcium-channel blockers found no evidence for gender-specific differences in outcomes.**

Gender differences in the effect of cardiovascular drugs: Statins

Plasma concentrations of statins are generally 15–20% higher in women than in men, **but dose adjustments are not necessary**.
Women, however, have higher concentrations of CYP3A4 and therefore **are more capable of metabolizing these statins**.

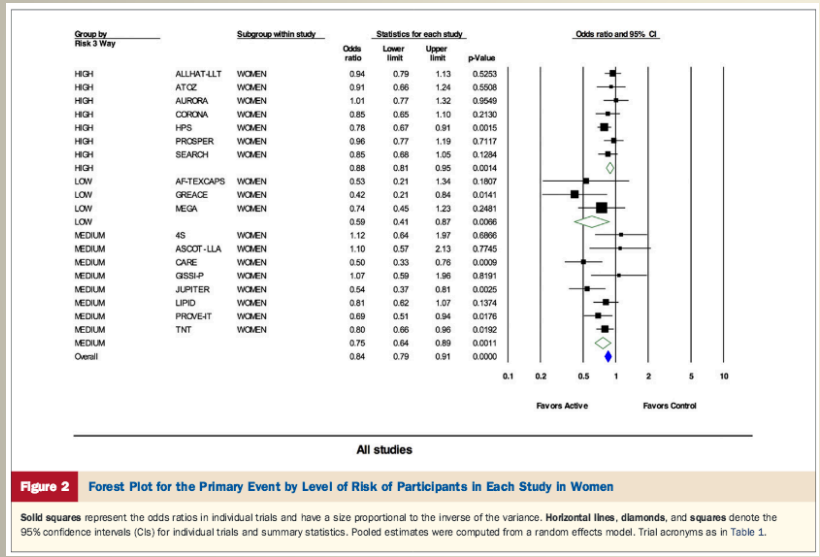


Figure 2 Forest Plot for the Primary Event by Level of Risk of Participants in Each Study in Women

Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. **Horizontal lines**, **diamonds**, and **squares** denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects model. Trial acronyms as in Table 1.

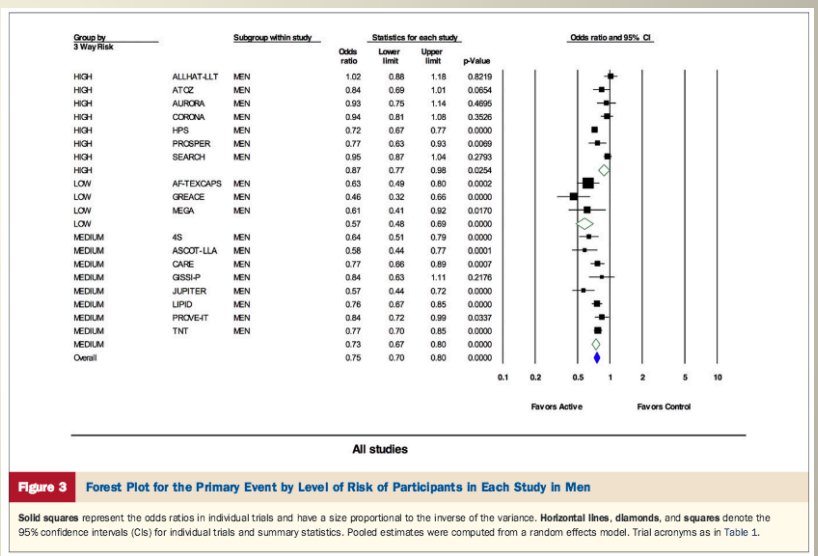


Figure 3 Forest Plot for the Primary Event by Level of Risk of Participants in Each Study in Men

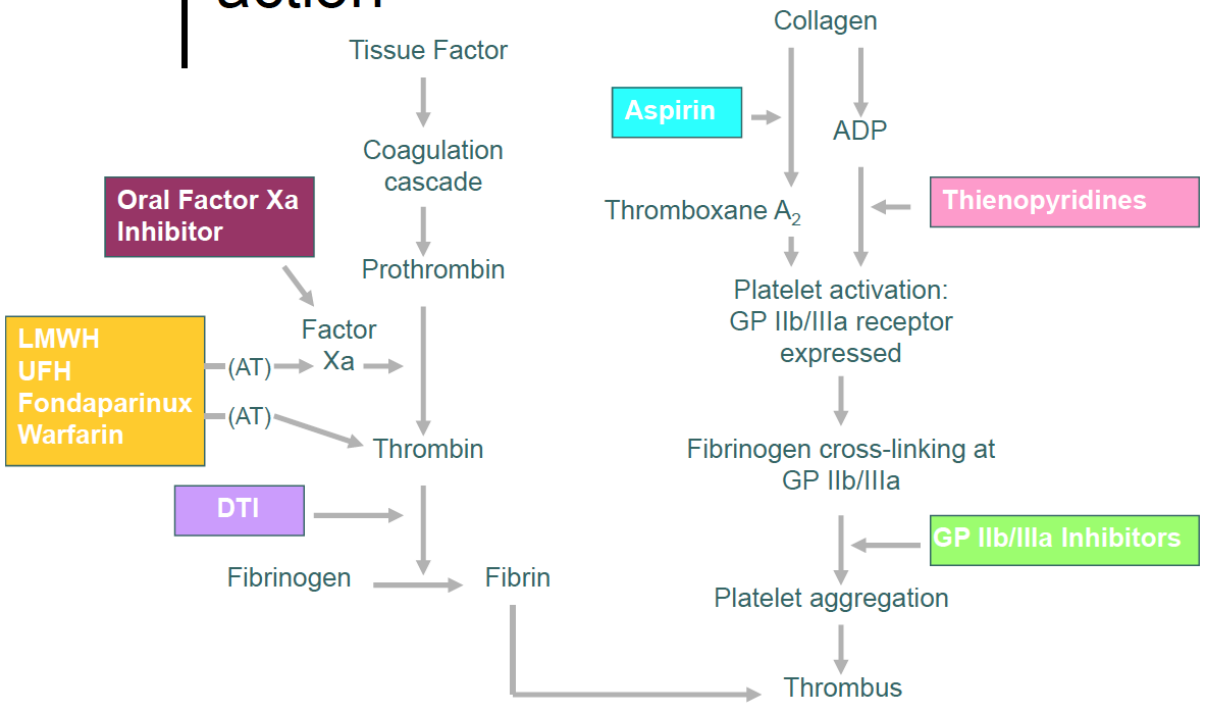
Solid squares represent the odds ratios in individual trials and have a size proportional to the inverse of the variance. **Horizontal lines**, **diamonds**, and **squares** denote the 95% confidence intervals (CIs) for individual trials and summary statistics. Pooled estimates were computed from a random effects model. Trial acronyms as in Table 1.

Statins decrease cardiovascular events and all-cause mortality in **both women and men**. The effect on cardiovascular events is present in both primary and secondary prevention trials.

J Am Coll Cardiol 2012;59:572–82

Antithrombotic Therapy

Coagulation cascade and sites of action

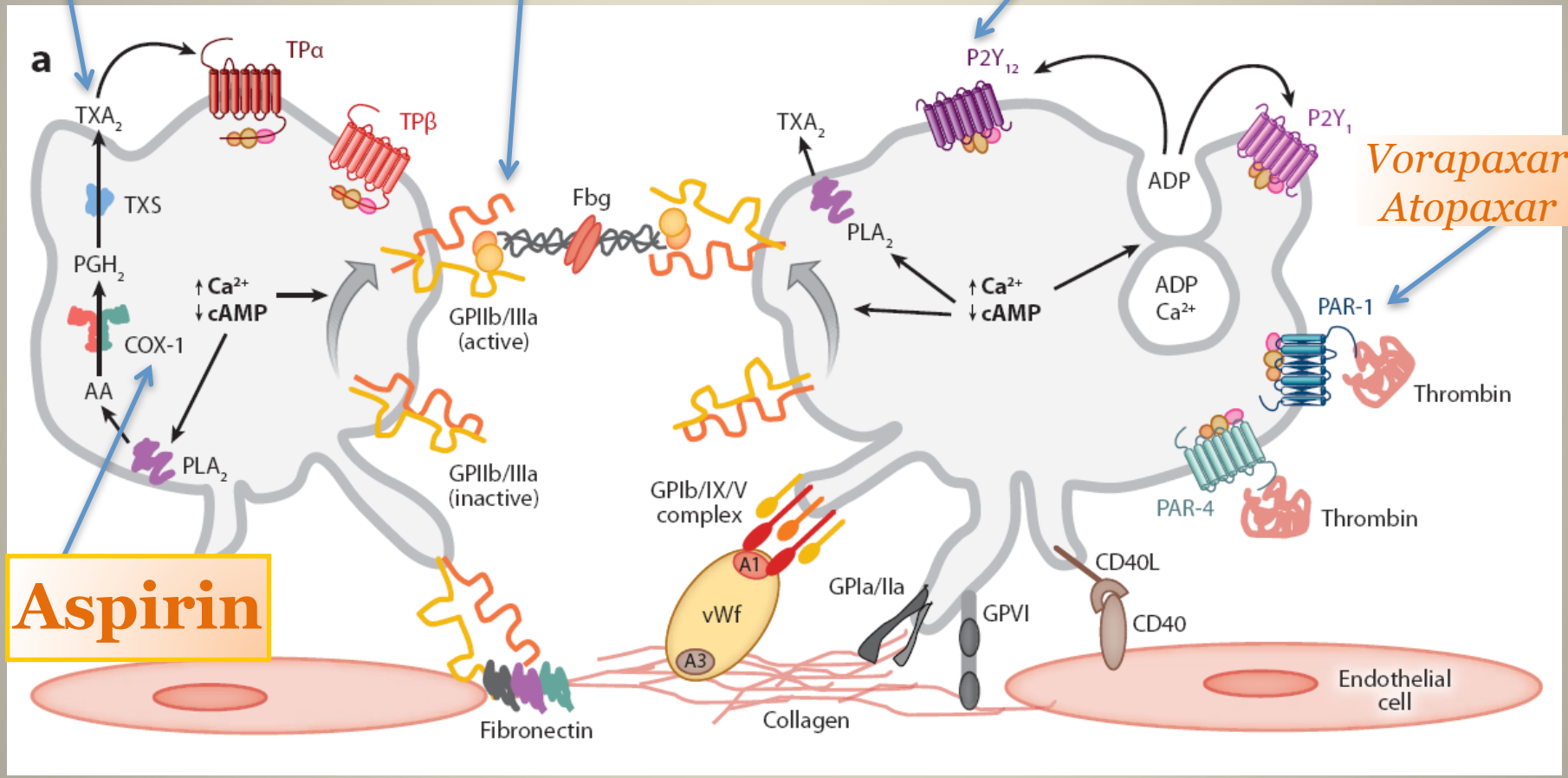


Oral Antiplatelet Agents

Picotamide

GP IIb/IIIa Antagonists

Clopidogrel
Ticlopidin
Ticagrelor
Prasugrel
elinogrel

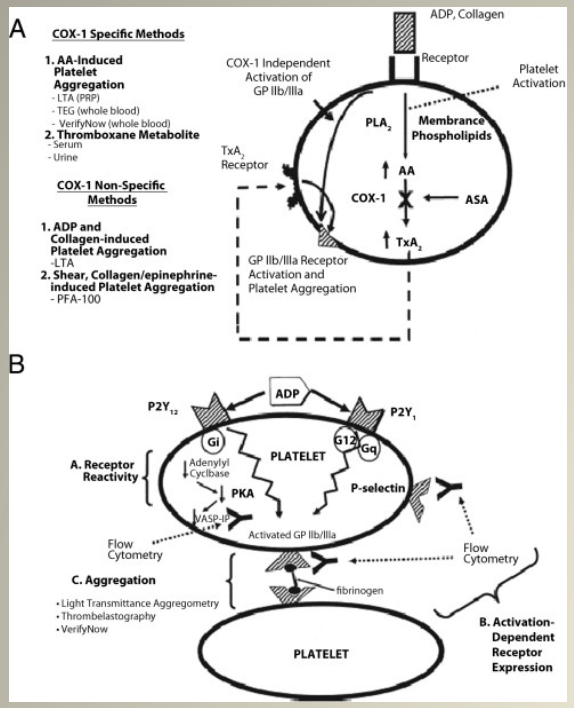


Aspirin

Vorapaxar
Atopaxar

Mod. From: Annu. Rev. Med. 2010. 61:49–61

Platelet Biology and Response to Antiplatelet Therapy in Women



Studies have shown a **higher prevalence of platelet reactivity and aspirin resistance** in women than in men, suggesting that hormonal differences may play a role.

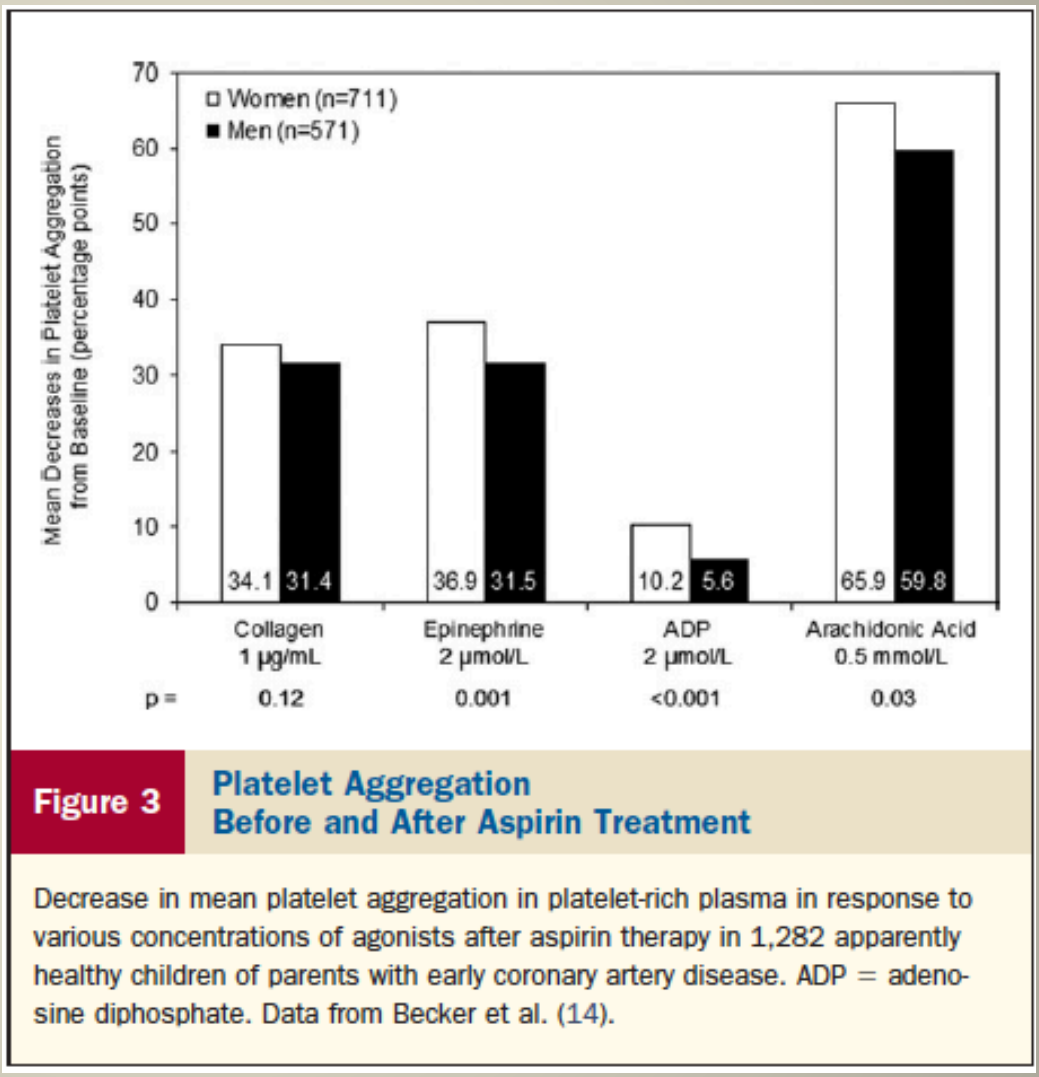


Figure 3 **Platelet Aggregation Before and After Aspirin Treatment**

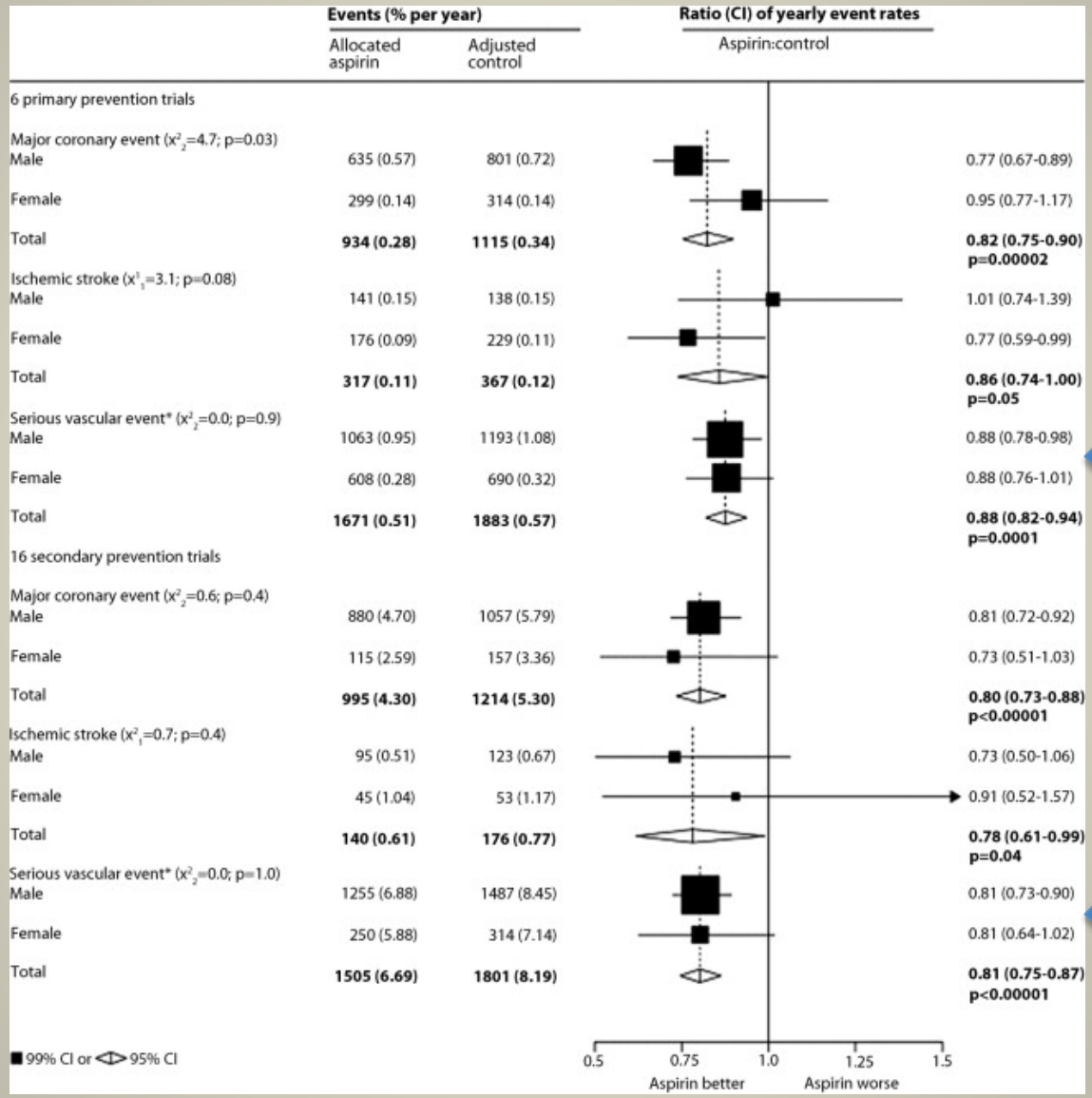
Decrease in mean platelet aggregation in platelet-rich plasma in response to various concentrations of agonists after aspirin therapy in 1,282 apparently healthy children of parents with early coronary artery disease. ADP = adenosine diphosphate. Data from Becker et al. (14).

J Am Coll Cardiol 2012;59:891–900

Selected Outcomes in Primary and Secondary Prevention Trials of Aspirin, by Sex.

Primary Prevention Trials

Secondary Prevention Trials



Journal of the American College of Cardiology, Volume 59, Issue 10, 2012, 891–900

Dual antiplatelet therapy in women and gender-stratified events analyses.

STUDY	YEAR	DESIGN	STUDY POPULATION	ACTIVE GROUP (dual antiplatelet therapy)	CONTROL GROUP (other antiplatelet drug or placebo)	PATIENTS ENROLLED (N)	WOMEN (%)	MEN (%)
CURE [56]	2001	RCT	ACS without ST-segment elevation	CLOP (300 mg loading dose followed by 75 mg/d) + ASA (75-325 mg/d)	ASA (75-325 mg/d) + Placebo	12,562	4,836 (39)	7,726 (61)
CREDO [58]	2003	RCT	Planned PCI or coronary angiogram	CLOP (300-mg loading dose followed by 75 mg/d through 12 months) + ASA (81-325 mg/d)	Placebo (loading dose followed by CLOP 75 mg/d until day 28 then placebo) + ASA (81-325 mg/d)	2,116	606 (29)	1,510 (71)
CHARISMA [62]	2006	RCT	Clinically evident cardiovascular disease or multiple risk factors	ASA (75-162 mg/d) + CLOP (75 mg/d)	ASA (75-162 mg/d) + Placebo	15,603	4,644 (30)	10,959 (70)
CURRENT OASIS-7 [68]	2010	RCT	ACS and intended early PCI	Double-dose CLOP (150 mg for 7 days followed by 75mg/d) High-dose ASA (300-325 mg/d)	CLOP-standard dose (75 mg/d) ASA-Low dose (75-100 mg/d)	17,263	4,234 (25)	13,029 (75)
PLATO [65, 66]	2009	RCT	ACS, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours	TIC (180 mg loading dose followed by 90 mg twice/d) + ASA (75-100mg/d)	CLOP (300-mg loading dose followed by a dose of 75mg/d) + ASA (75-100 mg/d)	18,624	5,288 (28)	13,336 (72)
TRITON-TIMI 38 [64]	2007	RCT	ACS with scheduled PCI	PRA (60 mg loading dose followed by 10 mg/d) + ASA (75-162 mg/d)	CLOP (300-mg loading dose followed by a dose of 75mg/d) + ASA (75-162 mg/d)	13,608	3,605 (27)	10,003 (73)
GRAVITAS [69]	2011	RCT	Stable CAD or non-ST-elevation acute coronary syndromes. Patients with high on-treatment reactivity 12 to 24 hours after PCI with drug-eluting stents	CLOP (600 mg followed by 150 mg/d) + ASA (75-162 mg/d)	CLOP (loading dose of placebo followed by 75 mg/d and placebo tablet daily) + ASA (75-162 mg/d)	2,214	773 (35)	1,441 (65)

Basili S, Raparelli V, Proietti M, Tanzilli G, Franconi F. J Atheroscler Thromb. 2015;22(2):109-25.

Sex differences in the clinical benefits of aspirin

There has been mention of using **higher doses** of aspirin in women to achieve the same level of platelet inhibition as in men.

However, studies have shown essentially **equal platelet inhibition** in both men and women after aspirin administration.

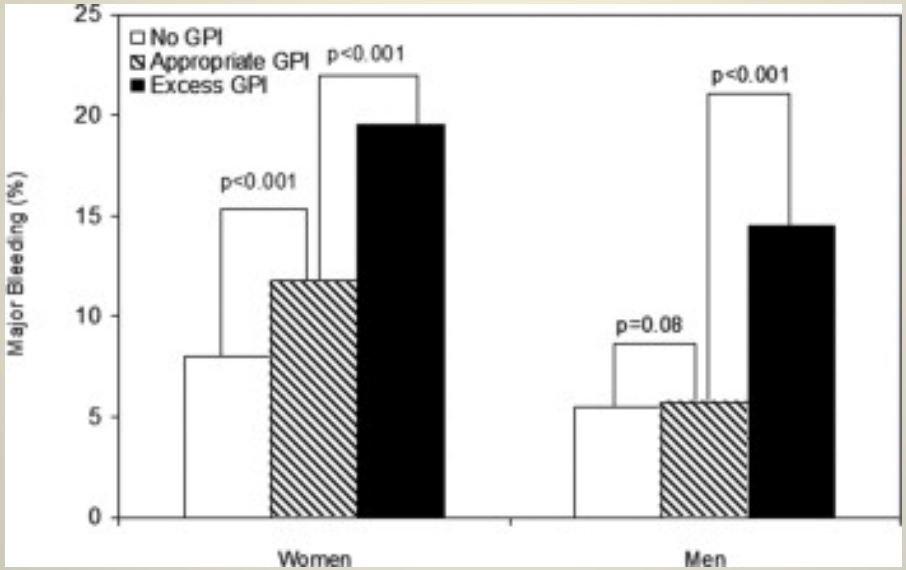
Therefore, **more work needs** to be done to better understand the observed sex differences in response to aspirin.

A clear trend to a higher incidence of ***bleeding complications*** *has been consistently reported in women,* ***which might be related to a more frequent over-dosage*** *of antithrombotic treatment in women than in men.*

Drugs – 2013; 73: 1921-1933.
Expert Rev Clin Pharmacol. 2014; 7: 469-85.

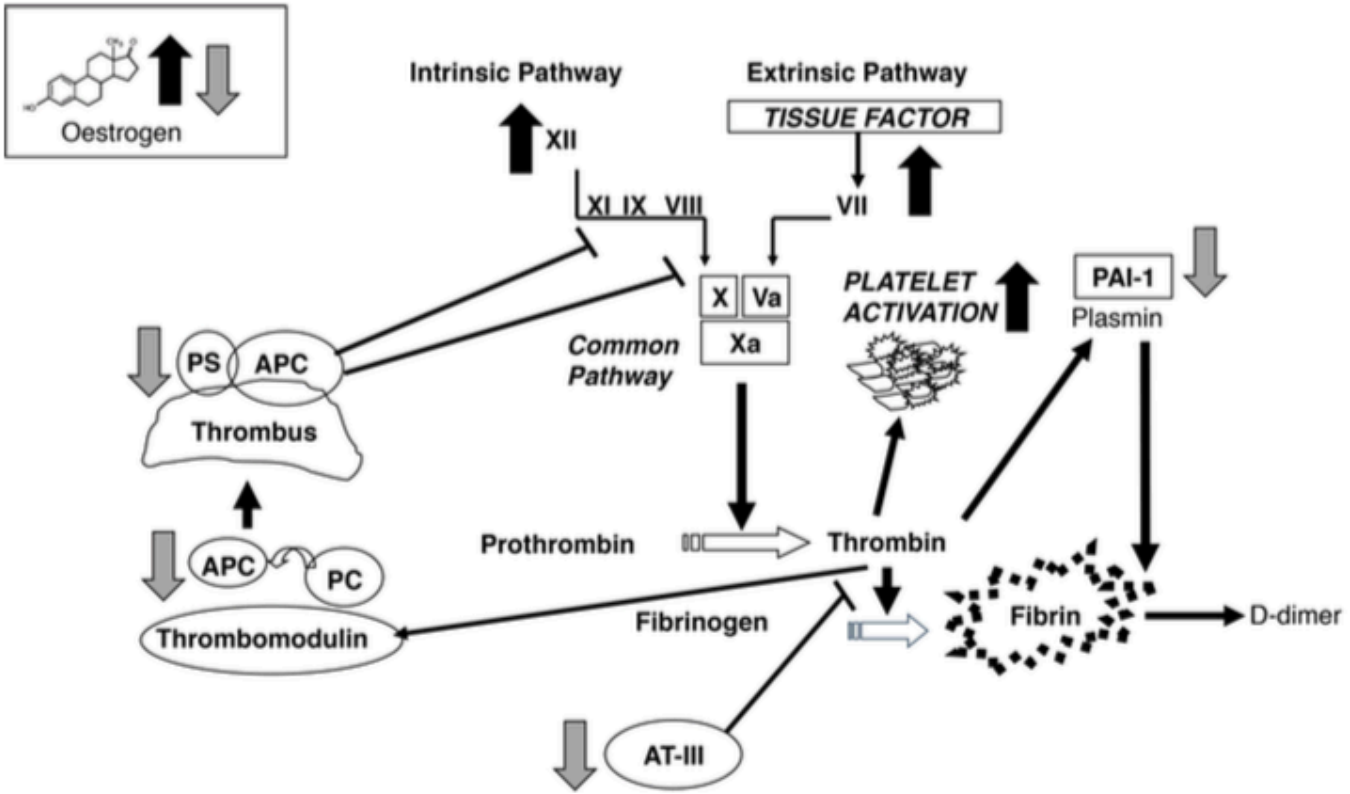
GP IIb/IIIa inhibitor

Major Bleeding by Sex and GPI Dosing Incidence of in-hospital major bleeding among women and men with acute coronary syndromes **who did not** receive a GP IIb/IIIa inhibitor (GPI), those who received **appropriate** GPI dosing, and those who received **excess** GPI dosing in the CRUSADE registry.



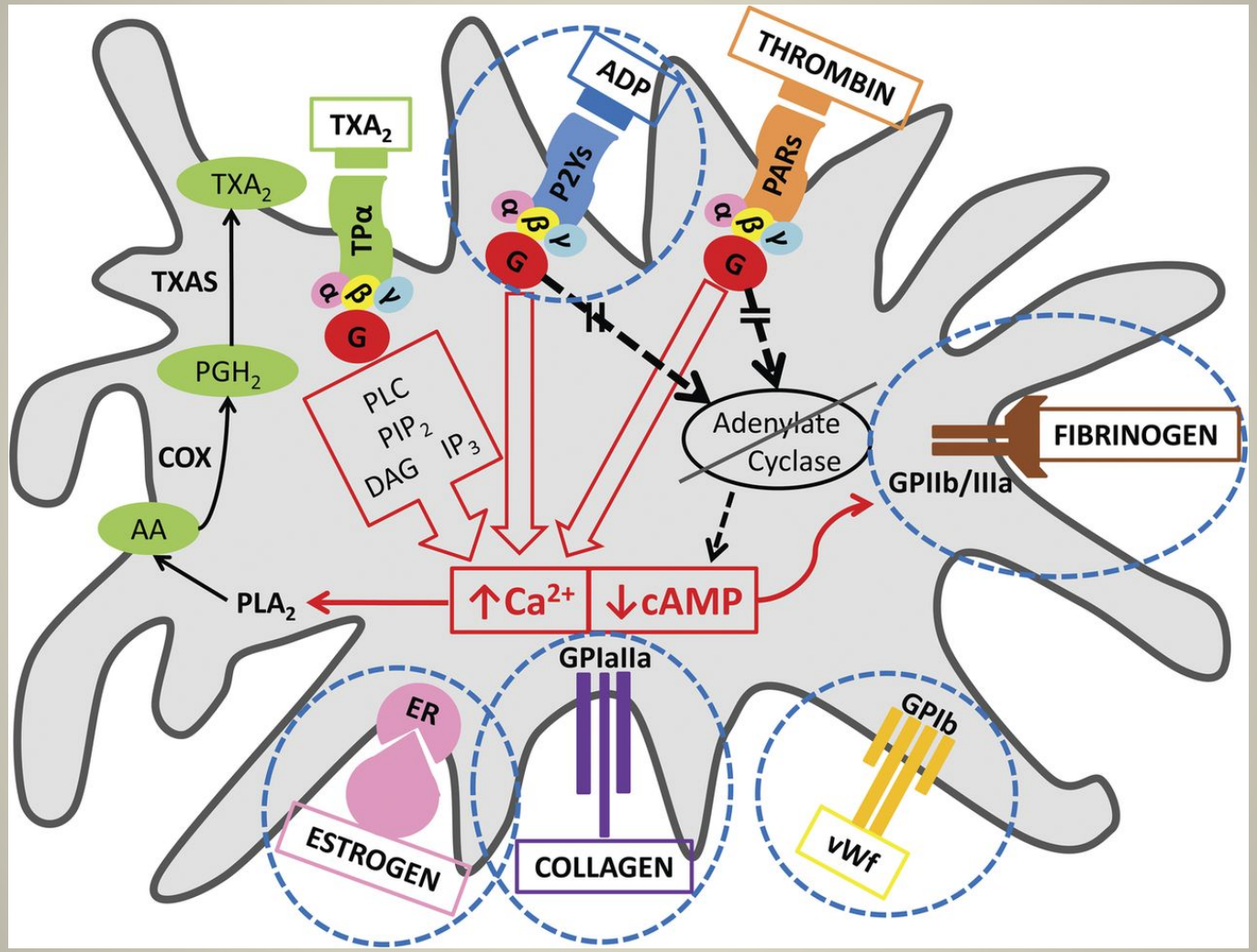
Journal of the American College of Cardiology, Volume 59, Issue 10, 2012, 891–900

Gender-based differences on the efficacy and safety of either "old" (i.e. vitamin K antagonist) or "new" oral anticoagulants (i.e. direct thrombin inhibitors and activated factor X inhibitors) may be relevant in atrial fibrillation management; nevertheless, they are underestimated. Effects of sexual hormones on haemostatic balance are under investigation to clarify the observed disparities in anticoagulation among sexes.



Basili S., Raparelli V., Proietti M., Napoleone L., Ferroni P, Franconi F. ***Old and New Oral Anticoagulants in Management of AtrialFibrillation: A Double-Edged Sword for Women***. Current Vascular Pharmacology, 2015, 13, 000-000.

Scheme of agonists, receptors, and effector systems participating in platelet activation.



Giuseppe Patti et al. Eur Heart J 2014;eurheartj.ehu279

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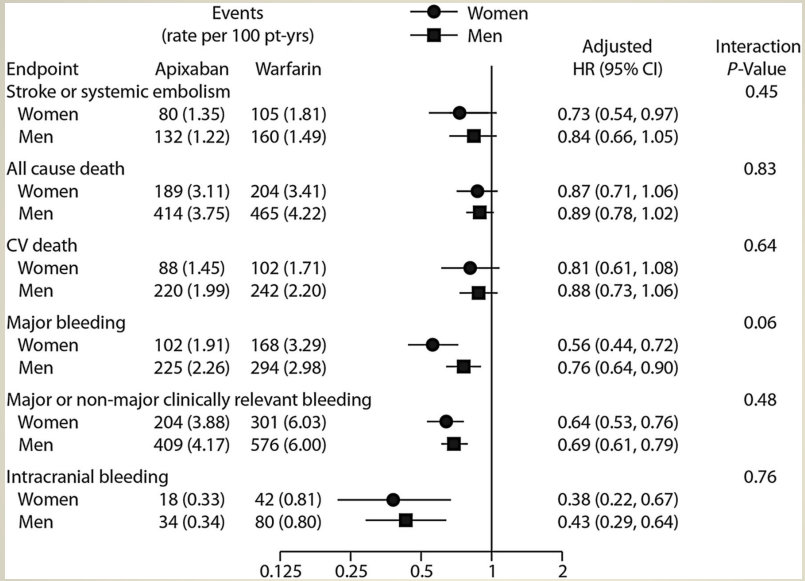
European Heart Journal

Gender Difference in Efficacy and Safety of Nonvitamin K Antagonist Oral Anticoagulants in Patients with Nonvalvular Atrial Fibrillation or Venous Thromboembolism.

Treatment effect of apixaban and warfarin on major study outcomes in men (N = 11785) and women (N= 6416) with NVAF.



Eur Heart J. 2015 Sep 14.

A total of 13 studies (> 100,000 patients) were included. **NOACs** appeared to have a similar efficacy **in female and male** patients treated for NVAF and acute VTE.
In the extended treatment of VTE NOACs had a RR of bleeding of 4.97 (95% CI 1.06, 23.41) in males and 1.33 (95% CI 0.63, 2.83) in females compared with placebo (subgroup difference chi-square test: 2.25, p = 0.13). Conclusions
No gender-related difference in the efficacy and safety of NOACs in patients with AF or acute VTE was found.

Semin Thromb Hemost. 2015 Oct;41(7):774-87

Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC

EUROPEAN SOCIETY OF CARDIOLOGY®

Data from observational and intervention studies, for instance in primary cardiovascular prevention, do not exclude gender-specific effects on clinical outcomes with antiplatelet agents; differences in platelet function, vascular factors, and coagulation mechanisms in different vascular beds, partly related to hormonal status, might contribute, although strong evidence is lacking.

For secondary cardiovascular prevention, although no significant gender-related differences in the efficacy of antiplatelet agents emerge, special attention should be paid to age, renal function, body weight, and dosing strategies when treating women in order to optimize benefits and minimize bleeding complications.

Eur Heart J. 2014 Sep 1;35(33):2213-23b.

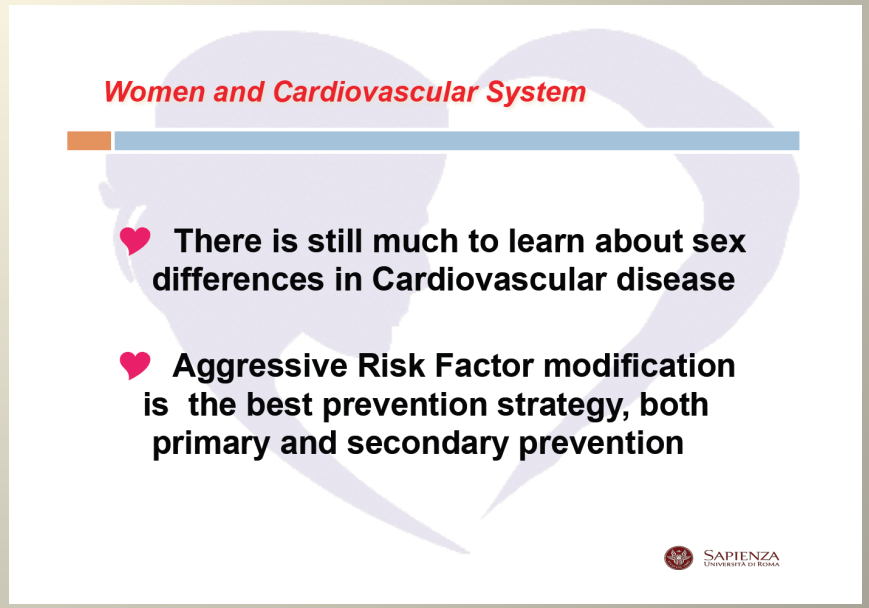
Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC

EUROPEAN SOCIETY OF CARDIOLOGY®

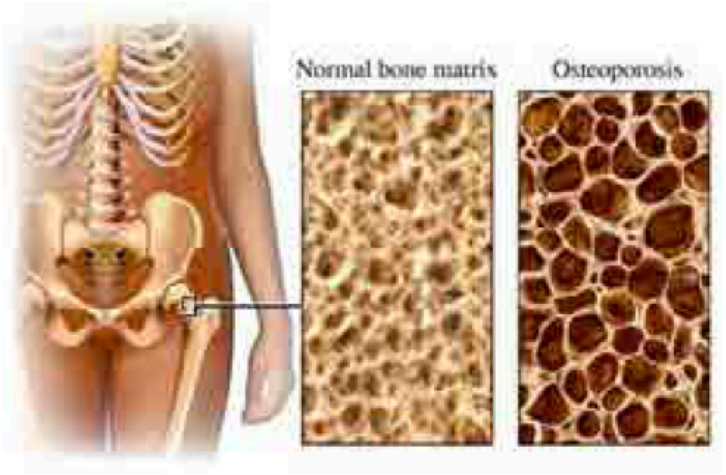
Gender differences in PD are difficult to quantify as women are often under-represented in trials and the role of sex hormones in the final response is not taken into consideration.
Unfortunately, the appropriate dosage and the gender differences in clinical outcomes are still not recognized for many drugs routinely used in clinical practice.

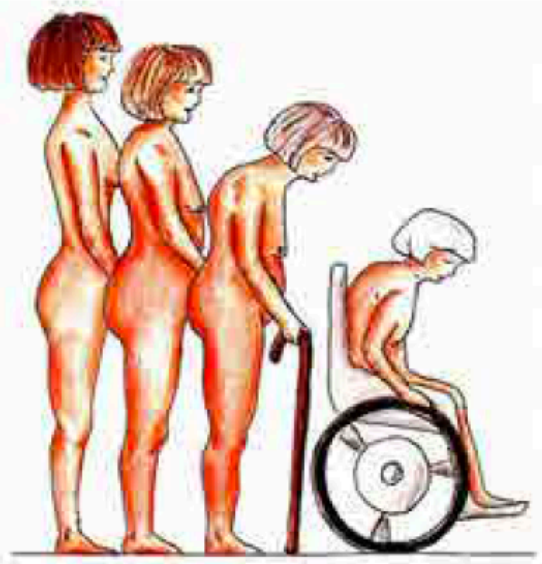
Eur Heart J. 2015 May 6. pii: eh

The development of a gender-based dosage guideline remains an unmet need in cardiology.

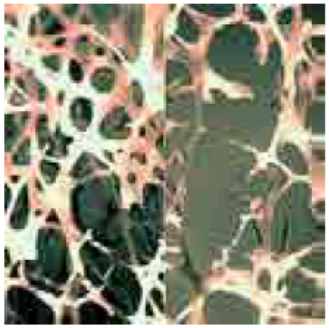


VIDEO





OSTEOPOROSI



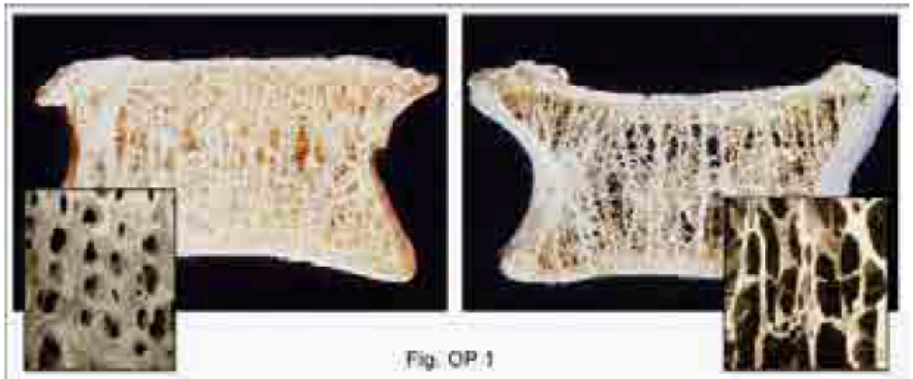


Fig. OP.1

Sezione di un corpo vertebrale normale con trabecole dense e ben calcificate (a sinistra) e una vertebra osteoporotica con rarefazione delle trabecole che indebolisce le proprietàmeccaniche del corpo vertebrale.

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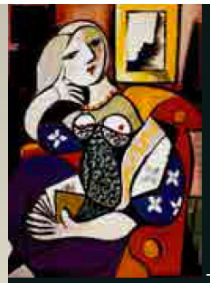
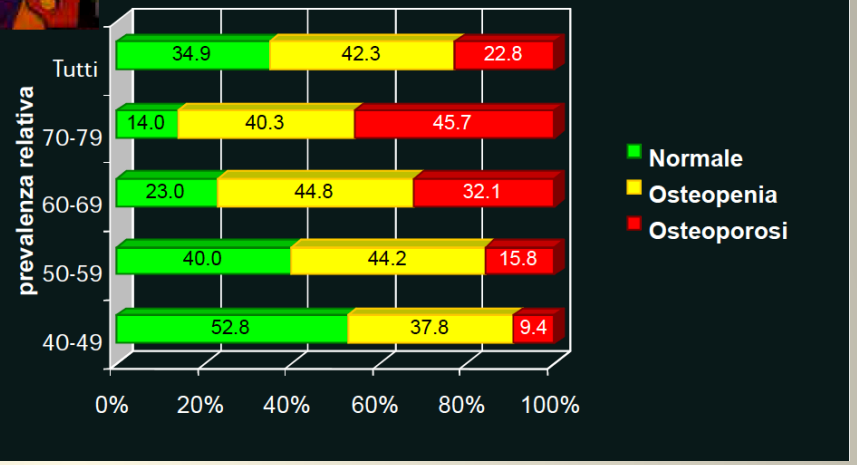
TUTTI GLI STUDI CONDOTTI SULLE DONNE

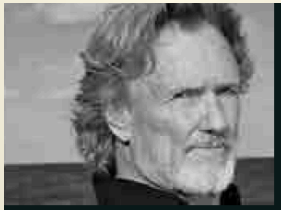


Prevalenza di Osteopenia ed Osteoporosi
Popolazione femminile in Italia
Studio E.S.O.P.O.

Maggi et al, Osteoporosis Int, 2006

Epidemiological Study on the Prevalence of Osteoporosis

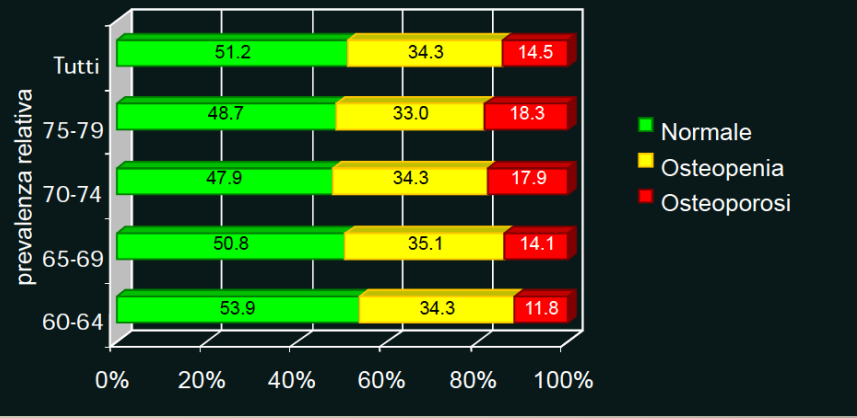


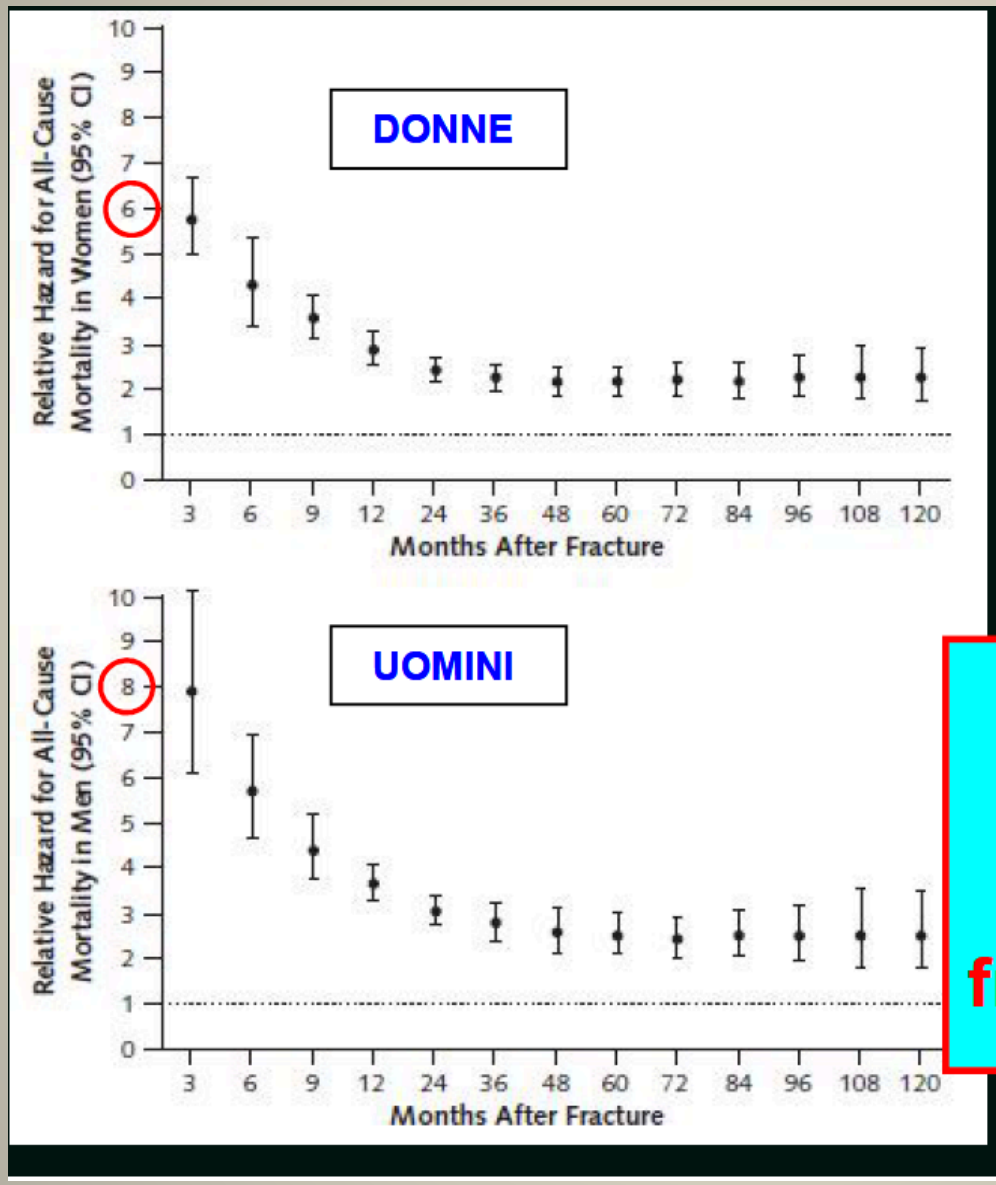


Prevalenza Osteopenia ed Osteoporosi
Popolazione maschile in Italia.
Studio E.S.O.P.O.

Maggi et al, Osteoporosis Int, 2006

Epidemiological Study on the Prevalence of Osteoporosis



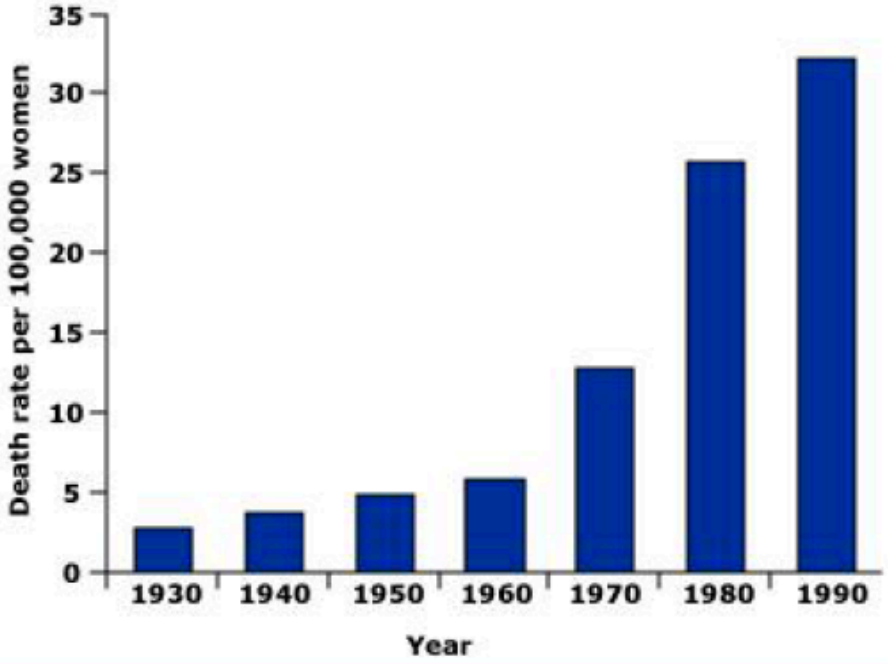


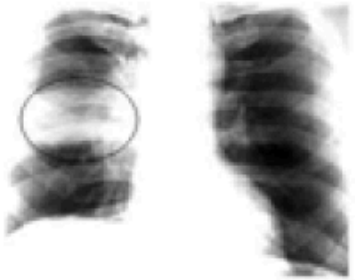
RISCHIO DI
MORTALITA'
per tutte le cause
per donne e
uomini con
frattura di femore
versus controlli

L'uomo muore di più dopo frattura di femore

Haentjens P et al., Ann Intern Med 2010

AUMENTO DELLA MORTALITA' PER TUMORE DEL POLMONE NEGLI ANNI NELLA DONNA



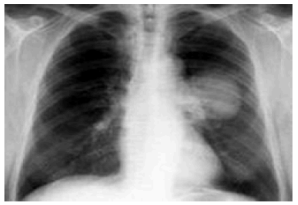


Lung cancer death rates per 100,000 women from 1930 to 1990 showing a dramatic and continuing increase since 1960.

Data from Parker, SL, Tong, T, Bolden, S, et al, CA - A Cancer Journal for Clinicians 1996; 46:5.

CANCRO DEL POLMONE NELLA DONNA

Prima causa di morte per tumore



Thomas L et al. Chest 2005;128:370-381

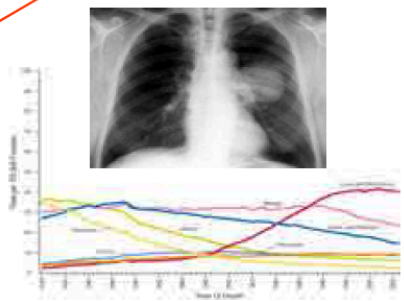
CHEST

Nel cancro del polmone nella DONNA

Differente metabolismo dei carcinogeni del tabacco

Minore capacità di riparare il DNA

Fumo di sigaretta più nocivo



STIAMO ATTUANDO UNA PREVENZIONE ADEGUATA? A LIVELLO CLINICO CI SONO INDICAZIONI DIVERSE?

Ruolo degli estrogeni e dei recettori per gli estrogeni

Possibile associazione con l'HPV (papilloma virus)?

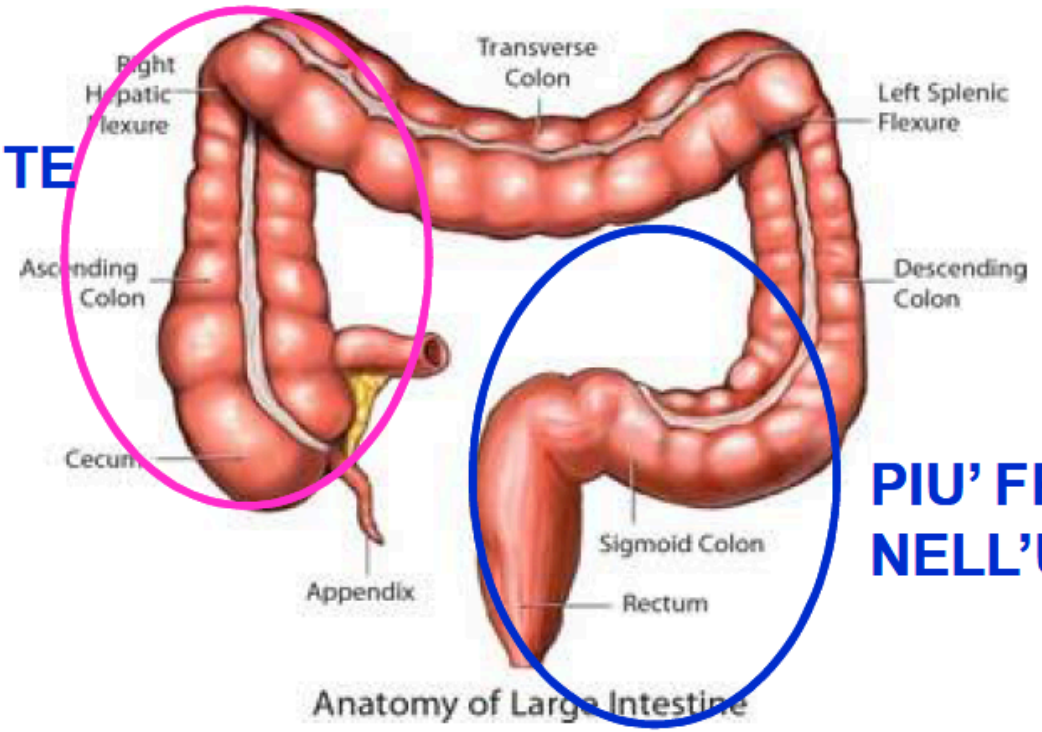
Maggiore risposta al cisplatino

Aumentata risposta ai k-ras

GENERE E LOCALIZZAZIONE del CCR

PIU' FREQUENTE NELLA DONNA

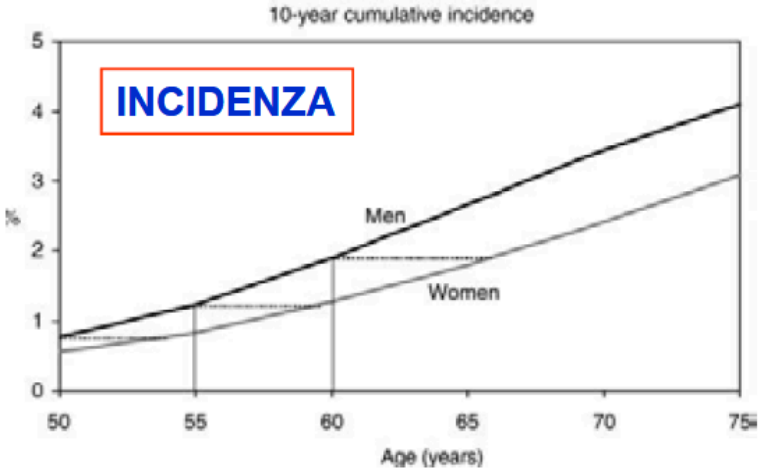
meno sintomatico

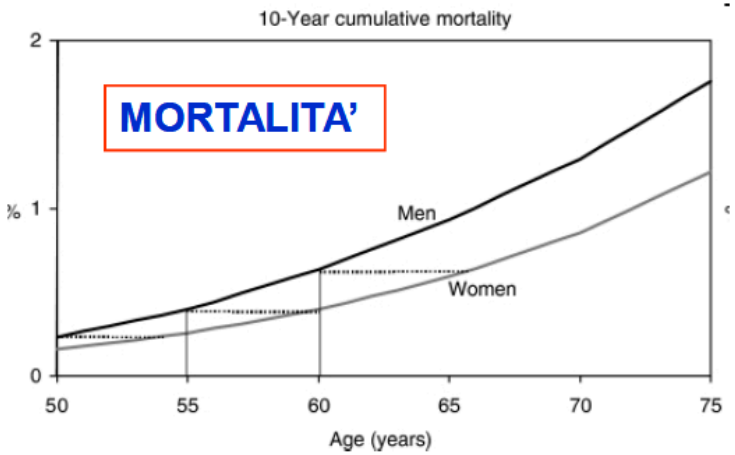


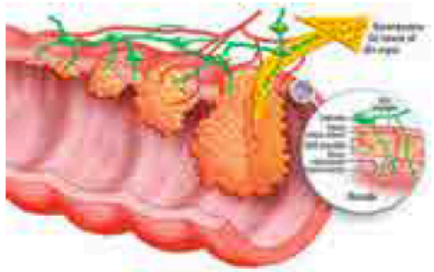
PIU' FREQUENTE NELL'UOMO

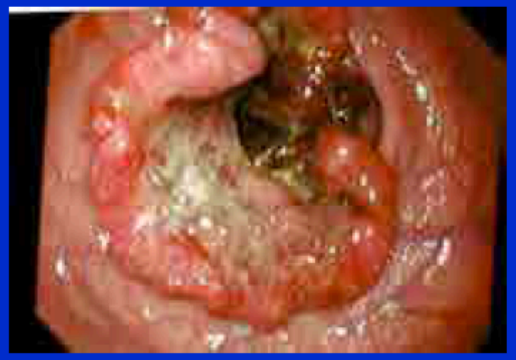
CANCRO DEL COLON RETTO

La donna ha <u>incidenza</u> e <u>mortalità</u> per cancro del colon retto ad età più avanzate rispetto all'uomo









Cancro del Colon Retto

- Differenze di età
- Differenze incidenza

NECESSITA' DI RIVEDERE LE RACCOMANDAZIONI E I PROGRAMMI DI SCREENING e TERAPIA ??

- Differenze di sintomatologia
- Differenze di relazione con terapia ormonale
- Differente risposta ai chemioterapici

Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Heart Transplant Report—2009

David O. Taylor, MD, Josef Stehlik, MD, Leah B. Edwards, PhD, Paul Aurora, MRCP, PhD, Jason D. Christie, MD, MS, Fabienne Dobbels, PhD, Richard Kirk, MA, FRCP, FRCPCH, Anna Y. Kucheryavaya, MS, Axel O. Rahmel, MD, and Marshall I. Hertz, MD

Advanced Heart Failure and Transplantation in Women

Mary Norine Walsh, MD

L'incrocio dei sessi nei trapianti NON è privo di ricadute sul risultato!!

Special Article

Gender Issues in Transplantation

Marie Csete, MD, PhD

C'è pochissima letteratura su questo argomento

The Impact of Donor-Recipient Sex Matching on Survival After Orthotopic Heart Transplantation

Analysis of 18 000 Transplants in the Modern Era

Eric S. Weiss, MD, MPH; Jeremiah G. Allen, MD; Nishant D. Patel, MD; Stuart D. Russell, MD; William A. Baumgartner, MD; Ashish S. Shah, MD; John V. Conte, MD

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Trombosi venosa profonda e embolia polmonare

Definizione di Tromboembolismo Venoso

- **EMBOLIA POLMONARE**

- **TROMBOSI VENOSA PROFONDA A. INFER**

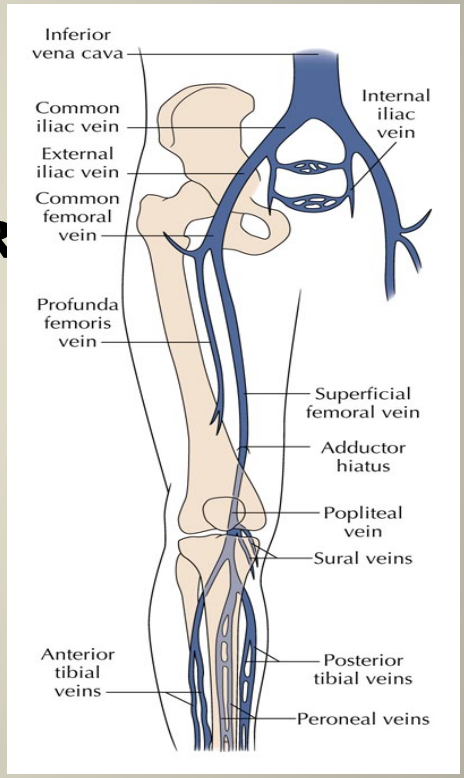
PROSSIMALE:

vene iliache, vena femorale, vena poplitea

DISTALE:

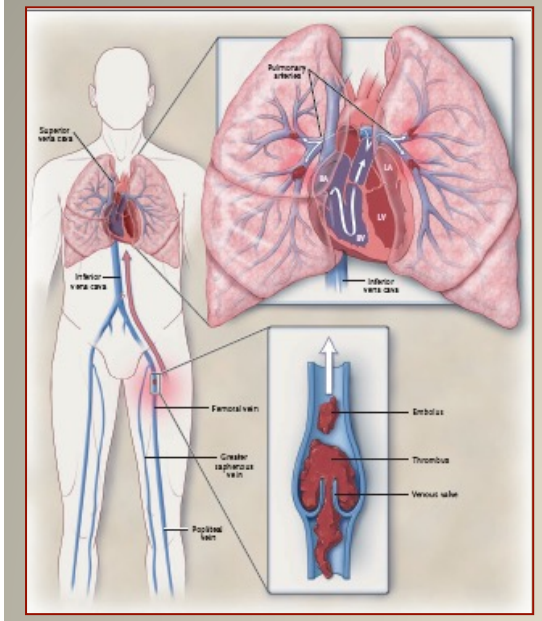
vene profonde del polpaccio

(peroniere e tibiali)



- **TROMBOSI VENOSA PROFONDA A. SUPERIORI**

Arterioscler Thromb Vasc Biol 2009;29:208-210



Venous ThromboEmbolic Disease (VTE)

Trombosi Venosa Profonda (DVT)/ Embolia Polmonare (EP)

Incidenza annuale (corretta per sesso ed età):

117 (in Italia 70) casi per 100.000 pazienti per anno

Trombosi Venosa Profonda (DVT) ~ **5.000.000/anno (in Italia 50000)**

- ~ 125.000/anno morti per PE
- **L'embolia polmonare rappresenta il 6 % di TUTTE le MORTI in ospedale**

TERZA PIU' COMUNE CAUSA DI MORTE CARDIOVASCOLARE

(European Journal of Haematology, 2012; 89: 281-7)

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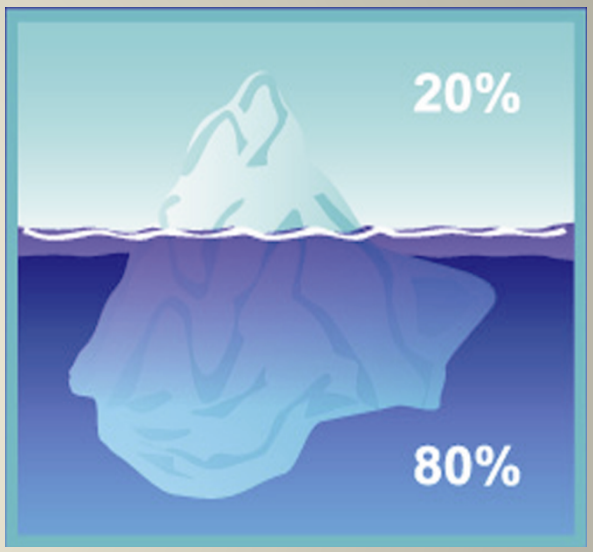
Risk Factors

- CHF
- Malignancy
- Obesity
- Estrogen/OCP
- Pregnancy (esp post partum)
- Lower ext injury
- Coagulopathy
- Venous Stasis
- Prior DVT
- Age > 70
- Prolonged Bed Rest
- Surgery requiring > 30 minutes general anesthesia
- Orthopedic Surgery

Nonostante il miglioramento della terapia, la mortalità è rimasta alta e costante negli ultimi 40 anni

Oltre il 70% delle EP fatali viene scoperto post mortem

1. Stein PD, et al. Chest 1995; 108(4): 978–81
2. Lethen H, et al. Am J Cardiol 1997; 80(8): 1066–9
3. Sandler DA, et al. J R Soc Med 1989; 82(4): 203–5



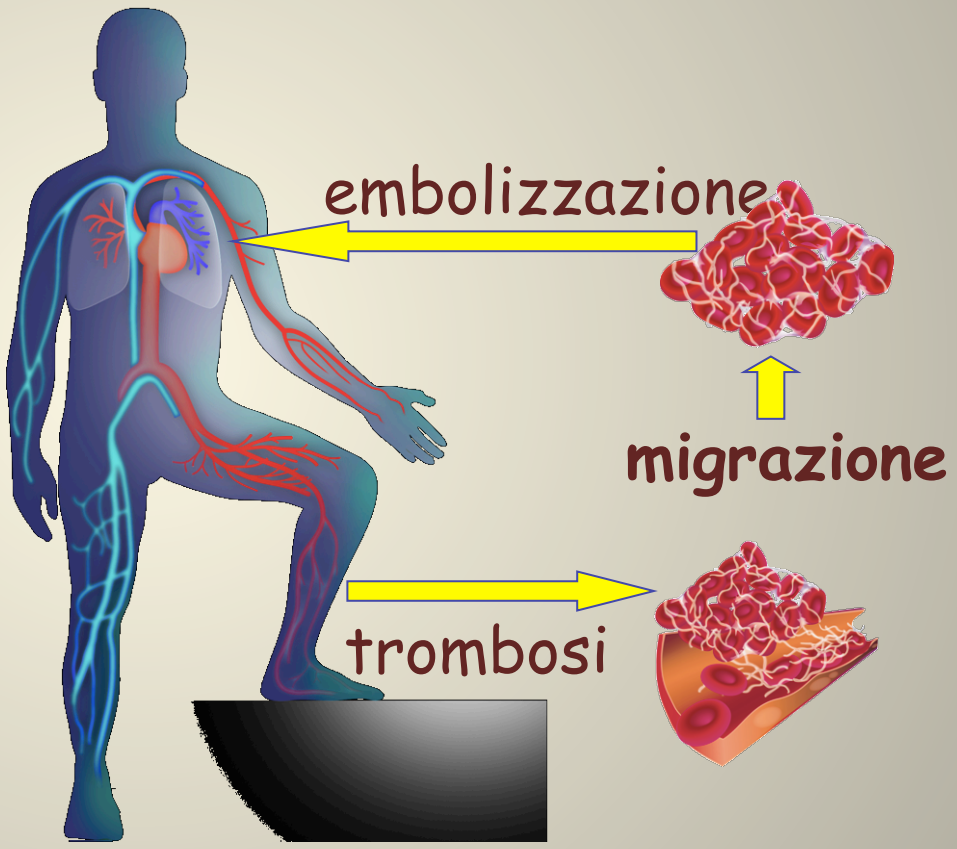
Circa l'80% delle TVP è clinicamente silente

PREVENZIONE e DIAGNOSI

Trombosi Venosa Profonda ⟷ Embolia Polmonare

Circa il 10 % delle TVP è complicata da Embolia Polmonare sintomatica (si stima il 50% di asintomatiche)

Una TVP (soprattutto se asintomatica) è presente in circa l' 80% dei pazienti con EP



Chest. 1999;116:903-908

Two-level DVT Wells score

Caratteristiche Cliniche	Punti
Cancro in atto (terapia in corso, o nei 6 mesi precedenti, terapia palliativa)	1
Paralisi, paresi o recente immobilizzazione di un arto inferiore	1
Recente allettamento (> 3 gg) o chirurgia maggiore (4 sett.) che abbia richiesto anestesia.	1
Dolorabilità localizzata lungo decorso vene profonde	1
Edema di tutto l'arto inferiore	1
Gonfiore di tutto il polpaccio (> 3 cm controlaterale)	1
Edema improntabile (più accentuato nell'arto sintomatico)	1
Circolo collaterale superficiale (non vene varicose)	1
Previously documented DVT	1
Diagnosi alternativa (verosimile quanto quella di TVP)	−2
ALTA PROBABILITA' = prevalenza 75%	**=>3**
MEDIA PROBABILITA' = prevalenza 17%	**1 O 2**
BASSA PROBABILITA' = prevalenza 3%	<=0

[a] Adapted from Wells PS et al. (2003) Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. New England Journal of Medicine 349: 1227–35

La diagnosi clinica e strumentale (CUS) deve essere tempestiva.

La terapia anticoagulante è la pietra miliare del trattamento (mortalità ridotta al 10%).

I nuovi anticoagulanti orali aprono nuove prospettive nel trattamento e nella prevenzione.

‘all men are created equal’

Declaration of Independence (1776)

Although Thomas Jefferson’s immortal phrase remains true today and includes both men and women having equal human rights, it is clear that important differences between the sexes exist, particularly with respect to venous thromboembolism (VTE) .

J Womens Health 2010; 6: 1059–72.

Triade di Virchow

Ipercoagulabilità

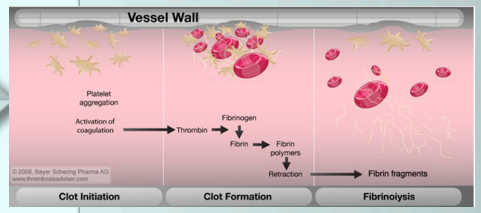
Ereditaria ***Acquisita***

Stasi

Acquisita

Lesione vascolare

Acquisita



Trombosi venosa

Virchow R. In Gesammelte Abhandlugen zur Wissenschaftlichen Medizin, 1856;
Frankfurt: Staatsdruckerei Rosendaal FR. Lancet 1999; 353:1167–1173

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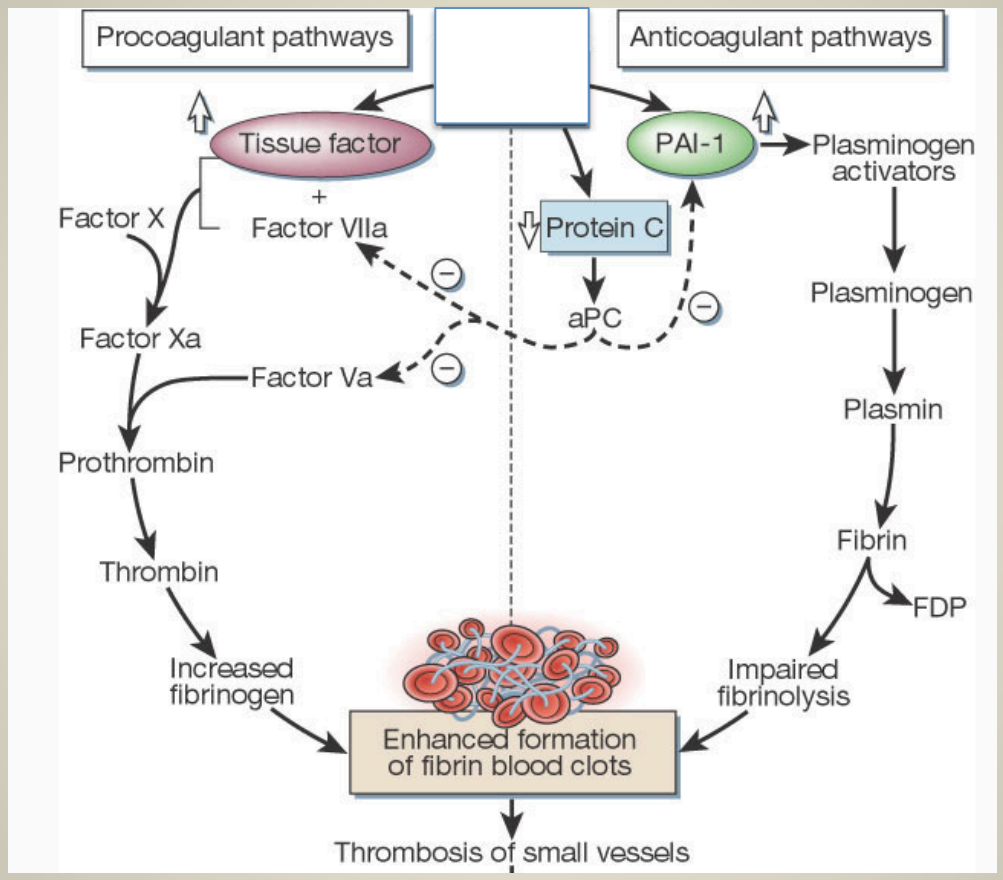
The cessation of menstrual bleeding

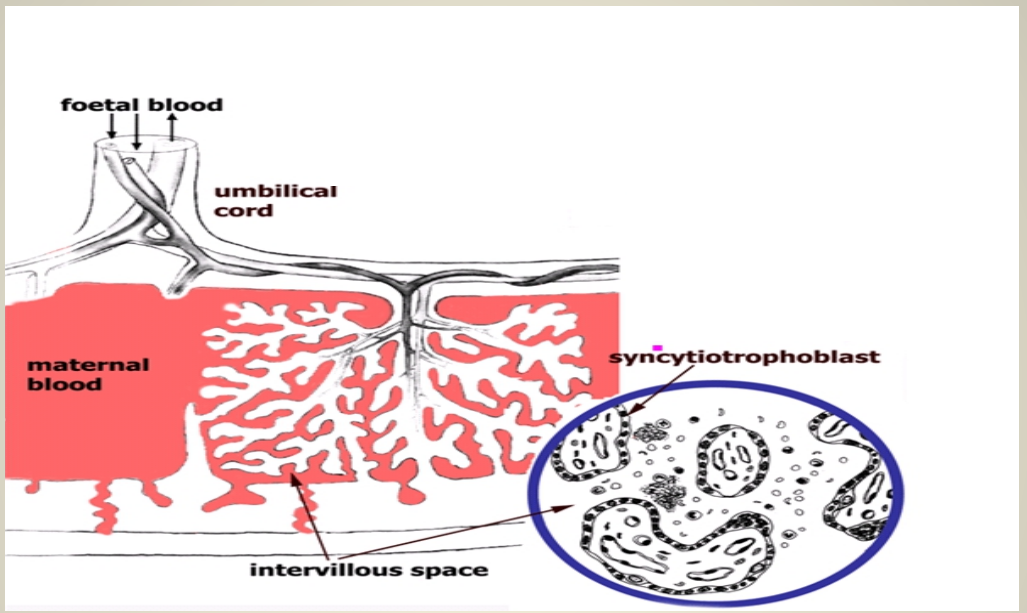
Reviews in Endocrine and Metabolic Disorders 2012; 13: 289-299



Tissue factor and thrombin play a key role locally in the cessation of menstrual bleeding through instigation of the coagulation factors.

On the other hand, fibrinolysis prevents clot organisation within the uterine cavity while plasminogen activator inhibitors (PAI) and thrombin-activatable fibrinolysis inhibitors control plasminogen activators and plasmin activity.

Pregnancy is associated with profound changes in uterine and systemic hemostatic potential.



These changes offer protection from potentially catastrophic hemorrhage during placentation and the third stage of labor.

It is considered that the placental separation provokes an acute maternal blood loss (10–15% of a woman's blood volume or 700 ml/minute)

Pregnancy

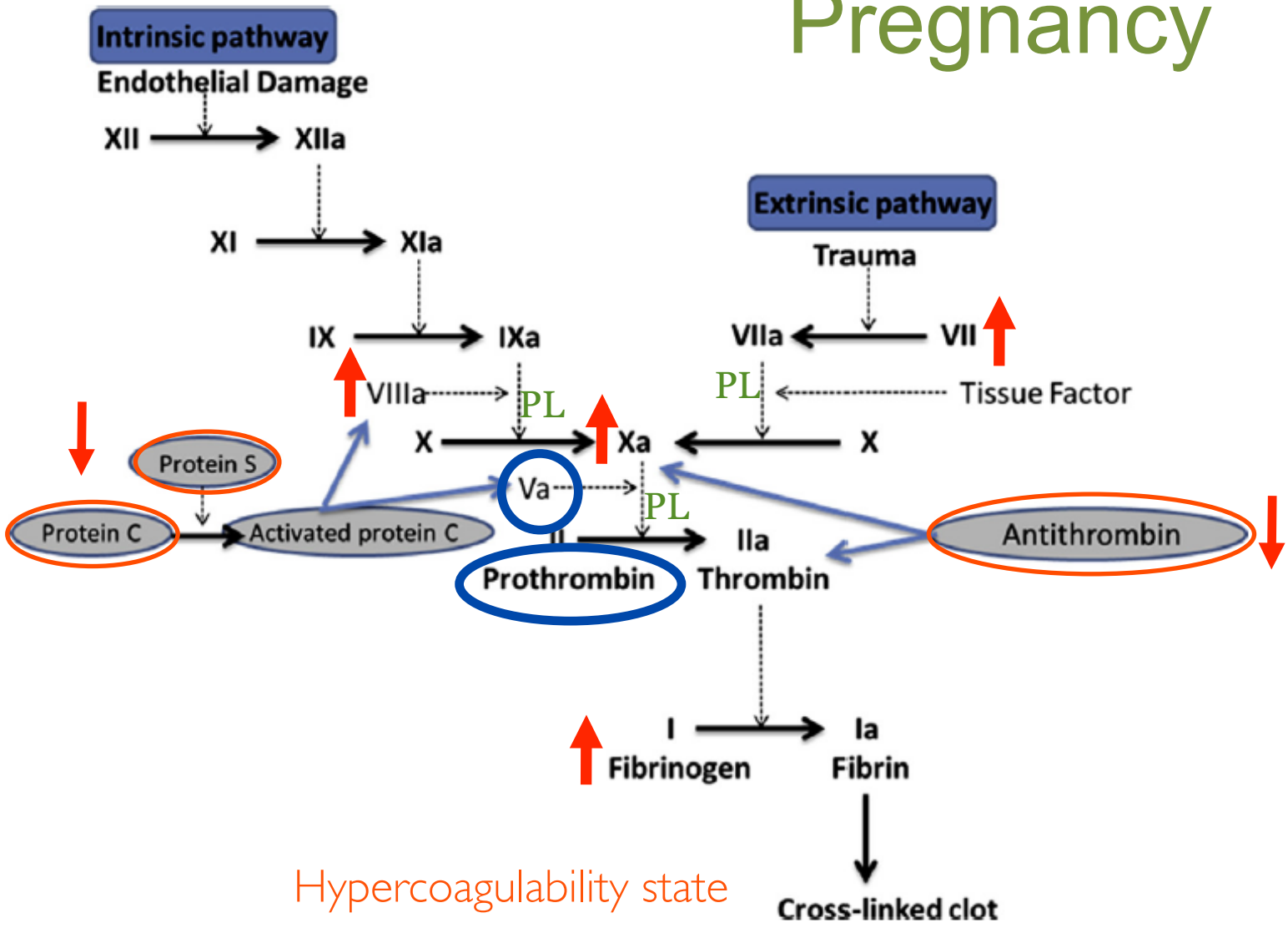
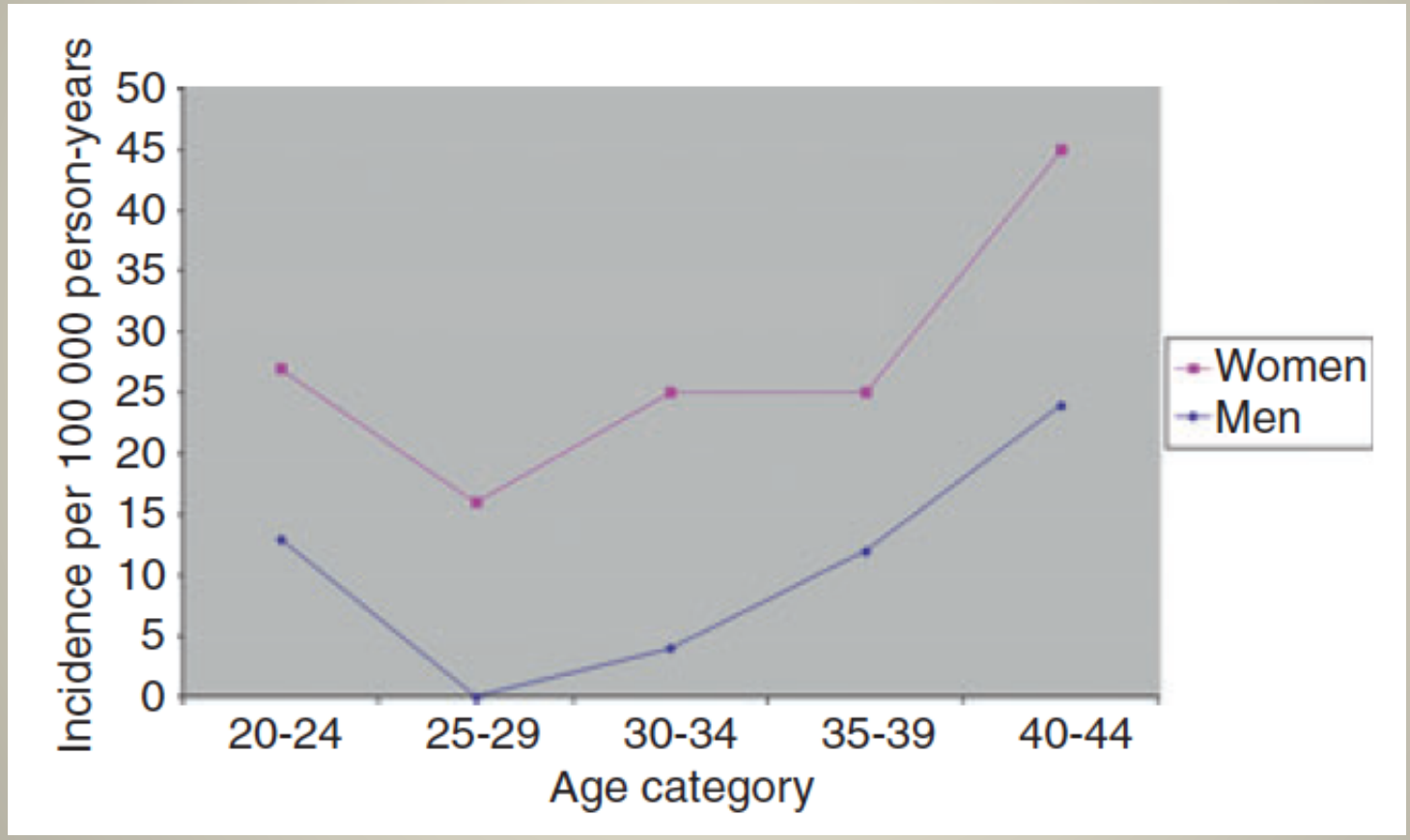


Fig. 1. Cascade of thrombus formation.

Anticoagulant

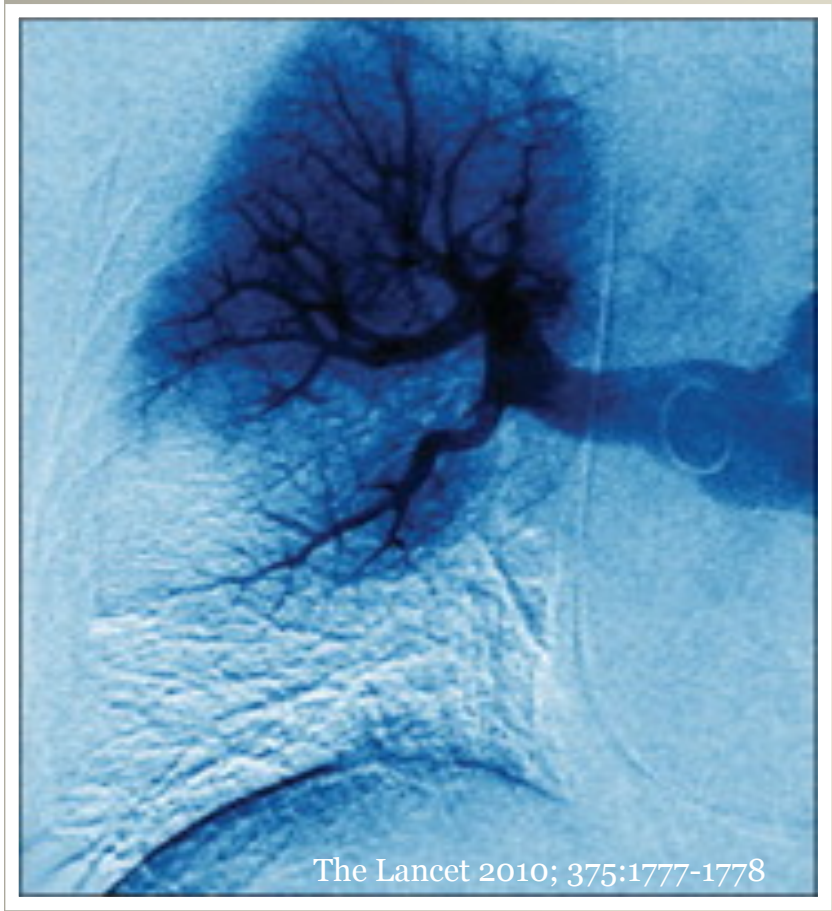
Thrombosis in women: what are the knowledge gaps?

Incidence of VTE in young women and men.



Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007; **4**: 692–9.

Le donne in gravidanza hanno un rischio di TEV di 4-6 volte più alto.
Durante il post-partum (6 settimane) il rischio è di 20 volte più alto.



The Lancet 2010; 375:1777-1778

Circa l'80% delle TEV è una trombosi venosa profonda (LEFT) mentre il 20% si complica con EP.

L'EMBOLIA POLMONARE È LA PIU' COMUNE CAUSA DI MORTE NELLE DONNE IN GRAVIDANZA NEI PAESI SVILUPPATI.

TASSO DI MORTALITA': 1.1 per 100.000 parti.
10% di tutte le morti materne.

Pre-existing risk factors
Previous recurrent VTE[a]
Previous VTE—unprovoked or oestrogen related[b]
Previous VTE—provoked
Family history of VTE
Known thrombophilia[c]
Medical co-morbidities, e.g.heart or lung diseases, SLE, cancer, inflammatory conditions, nephritic syndrome, sickle cell disease, i.v. drug use
Age >35 years
Obesity, BMI >30 kg/m^2 [d]
Parity ≥3
Smoker
Gross varicous veins
Obstetric risk factors
Pre-eclampsia
Dyhydration/hyperemesis/ovarian hyperstimulation syndrome
Multiple pregnancy or assisted reproductive therapy
Emergency caesarean section
Elective caesarean section
Mid-cavity or rotational forceps
Prolonged labour (>24 hours)
Peripartum haemorrhage (>1 L or transfusion)
Transient risk factors
Current systemic infection
Immobility
Surgical procedure in pregnancy or <6 weeks post-partum

Risk factor	Prevalence (%)	Odds ratio (confidence interval)
Factor V Leiden mutation		
Heterozygous	2.0–7.0	8.32 (5.44,12,70)
Homozygous	0.2–0.5	34.40 (9.86, 120.05)
Prothrombin G20210A mutation		
Heterozygous	2.0	6.80 (2.46, 18.77)
Homozygous	Rare	26.36 (1.24, 559.29)
Antithrombin deficiency (<80% activity)	<0.1–0.6	4.76 (2.15, 10.57)
Protein C deficiency (<75% activity)	0.2–0.3	4.76 (2.15, 10.57)
Protein S deficiency (<65% activity)	<0.1–0.1	2.19 (1.48, 6.00)

Regitz-Zagrosek V. et Al
ESC Guidelines on the management of cardiovascular diseases during pregnancy.
European Heart Journal (2011) 32, 3147–3197

Relevance of hormone use for VTE risk in the general population

- ***Can we safely prescribe female hormones with respect to VTE?***

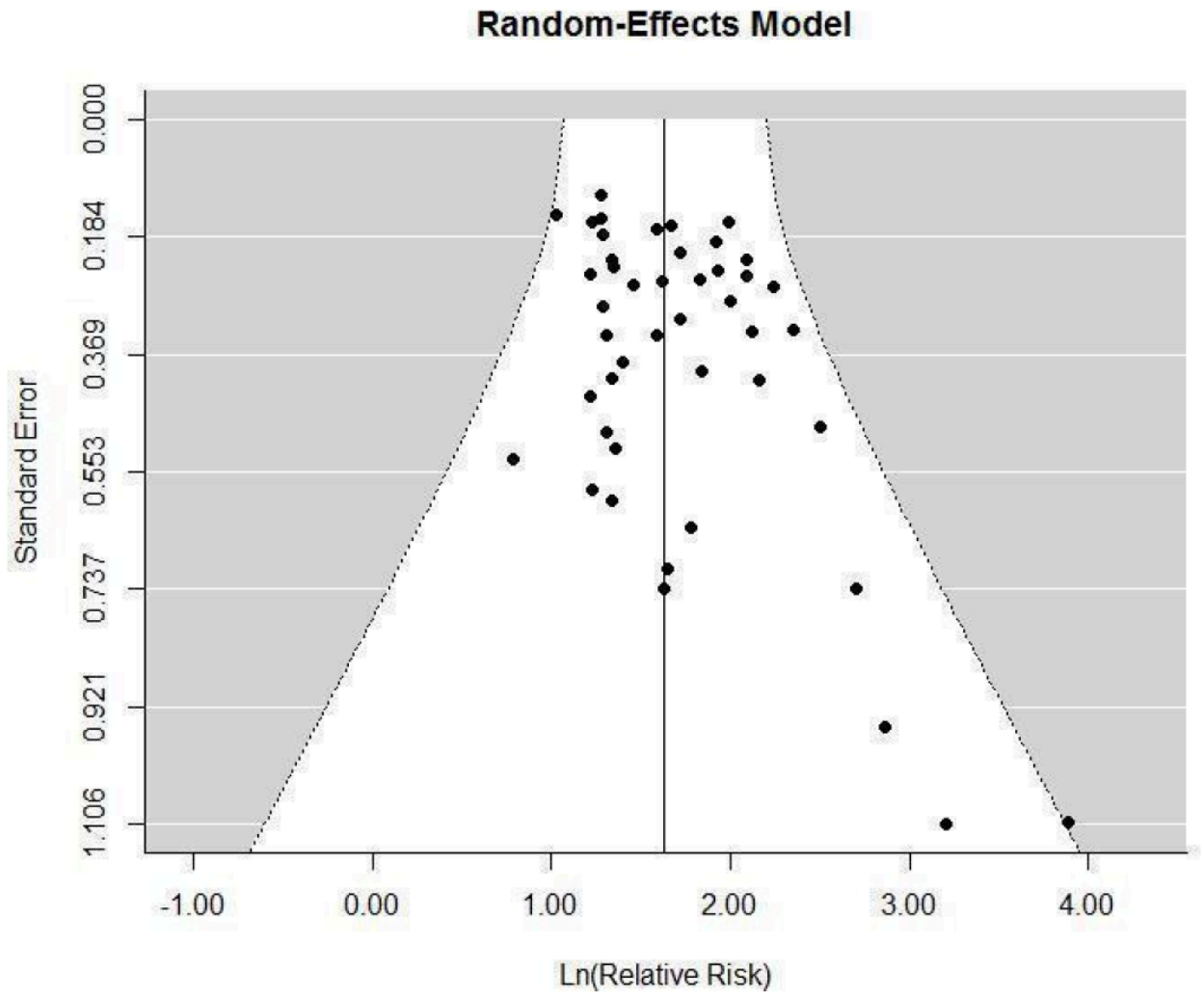
Combined oral contraceptives: venous thrombosis (Review)

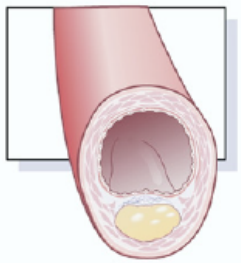
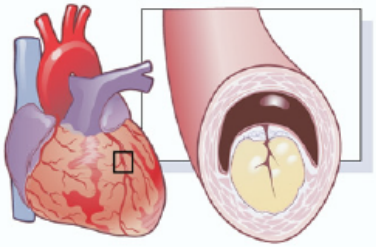
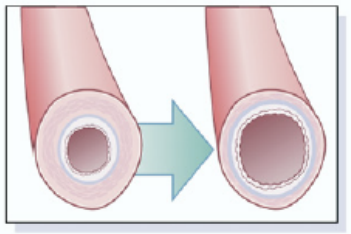
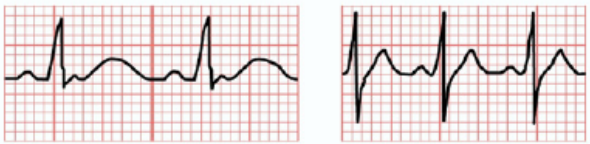
de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, Dekkers OM

THE COCHRANE COLLABORATION®

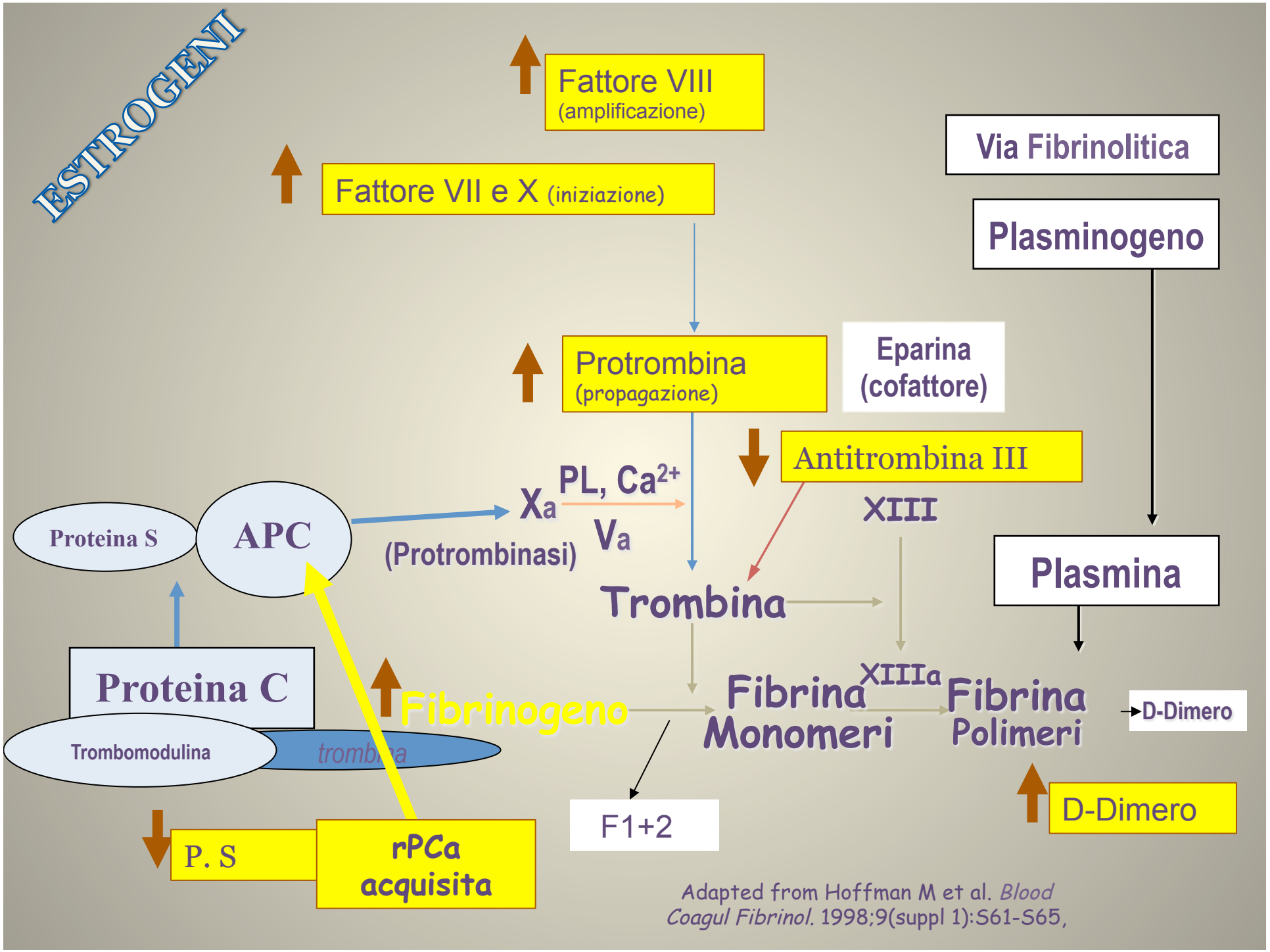
This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 3

Figure 3. Funnel plot of studies of combined oral contraceptive use and venous thrombosis risk



Estrogens		Progestins
↓ LDL oxidation ↓ LDL binding ↑↓ lipoprotein* *** ↑ blood pressure ↓ oxidation damage ↓ VSMC proliferation ↓ glucose tolerance***	**Atherosclerosis** 	↑↓ HDL effect* ** ↑↓ blood pressure** ↑ glucose tolerance**
↑ coagulation factors ↓ platelet aggregation	**Thrombosis** 	↑ coagulation factors ↓ platelet aggregation ↓ nitric oxide**
↑ nitric oxide ↓ endothelin ↑ Cox-2 ↓ neuroendocrine response ↓ VSMC proliferation	**Vasomotion** 	↑ vasoconstriction** ↓ nitric oxide**
↑ QT prolongation	**Arrhythmogenesis** 	↓ QT prolongation

J Am Coll Cardiol 2009;53:221–31



Adapted from Hoffman M et al. *Blood Coagul Fibrinol.* 1998;9(suppl 1):S61-S65,

COMPONENTE ESTROGENICA

COMPONENTE PROGESTINICA

Riduzione del rischio con basse dosi di EE

Variables	No. of studies	VTE risk OR (95% CI)	p-Value	I^2(%)[a]
Oestrogen dose <50 µg only	9	3.59 (3.01, 4.27)	<0.001	75
Cohort design[5,46]	2	3.23 (3.04, 3.45)	<0.001	0
Case-control design[4,6,37,48,54,57]	7	3.75 (2.90, 4.85)	<0.001	69
Oestrogen dose ≥50 µg only	5	5.21 (3.83, 7.47)	<0.001	35
Cohort design[54]	1	10.3 (1.74, 60.9)	0.01	NA
Case-control design[4,6,54]	4	5.11 (3.50, 7.46)	<0.001	43
Oestrogen dose ≥50 µg vs <50 µg	5	1.42 (1.15, 1.76)	0.001	0
Cohort design[33,34,37,46]	4	1.35 (1.07, 1.71)	0.01	0
Case-control design[6]	1	1.90 (1.08, 3.34)	0.03	NA

Drug Saf. 2012 Mar 1;35(3):191-205.

EE dose	Corrected OR	(95% CI)
50 µg EE	1.6	0.9-2.8
30-40 µg EE	1	REFERENCE
20 µg EE	0.6	0.4-0.9

Lidegaard et al, Contraception 2002

A van Hylckama Vlieg, BMJ, 2009.

S.N. Tchaikovski, J. Rosing / Thrombosis Research 126 (2010) 5–11

- The "total estrogenicity" rises with increasing dose of estrogen but decreases with increasing antiestrogenic activity of progestogen compound.

- It was suggested that **third generation progestogens**, as well as **drospirenone and cyproterone acetate possess** a weaker anti-estrogenic activity **than levonorgestrel** and, therefore, are less potent in the counterbalancing the prothrombotic effects of estrogen.

Effects of oral contraceptives on haemostatic parameters.

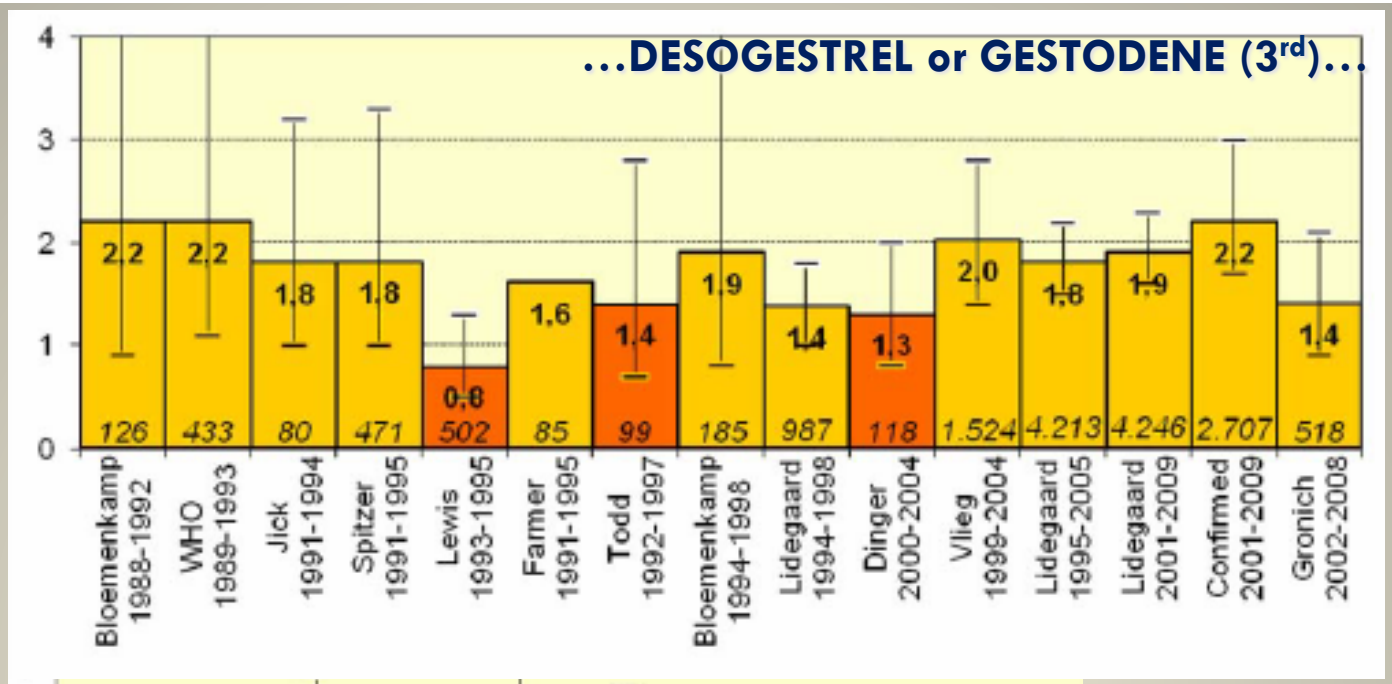
	2nd gen	3rd gen
Coagulation factors [a]		
Prothrombin	↑	↑*
Fibrinogen	↑	↑
Factor V	↓	↓*
Factor VII	↑	↑*
Factor VIII	↑↓	↑
Factor X	↑	↑
Anticoagulant system[b]		
Antithrombin	↑↓	↓
α_2-macroglobulin	↑	↑
α_1-antitrypsin	↑	↑
Protein C inhibitor	↑↓	↑
Protein C	↑	↑
Protein $S_{total\ and\ free}$	↓	↓*
APCsr (aPTT-based assay)	↑↓	↓*
APCsr (ETP-based assay)	↑	↑*
Fibrinolytic system[c]		
tPA, antigen	↓	↓
tPA, activity	↑	↑
PAI-1, Ag, ng/ml	↓	↓
PAI-1, act, U/ml	↓	↓
Plasminogen, act, %	↑	↑
TAFI, Ag, %	↑	↑*

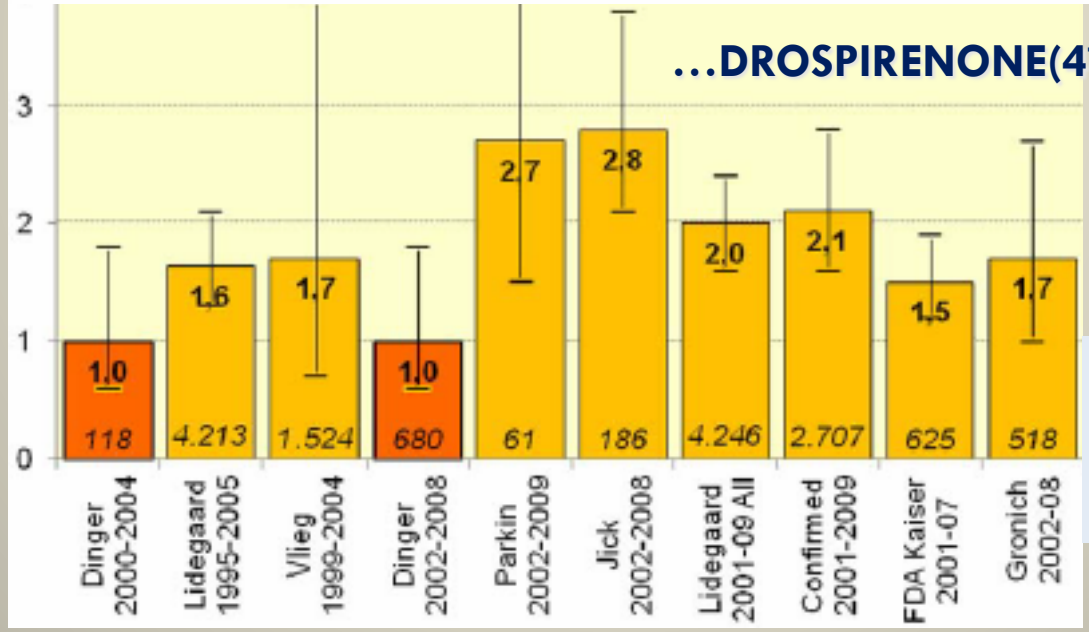
S.N. Tchaikovski, J. Rosing / Thrombosis Research 126 (2010) 5–11

J Thromb Haemost 2013; 11 (Suppl. 1): 180–91.

Hormonal contraceptives	Absolute risk (per 1000 person-years)*
Strong risk increase (odds ratio 5–8)	
Ethinylestradiol†/desogestrel	2.8 (2.1–3.9)
Ethinylestradiol†/cyproterone	2.7 (1.8–3.9)
Ethinylestradiol†/drosperidone	2.5 (1.1–5.3)
Ethinylestradiol†/norgestimate	2.3 (0.7–8.2)
Ethinylestradiol†/gestodene	2.2 (1.4–3.3)
Ethinylestradiol†/lynestrenol	2.2 (1.2–4.0)
Oral progestagen only, high dose (5–30 mg)	2.1 (0.6–7.3)
Moderate risk increase (odds ratio 2–5)	
Ethinylestradiol†/noresthisterone‡	1.5 (0.5–4.1)
Ethinylestradiol†/levonorgestrel	1.4 (1.1–1.8)
Injectable depot medroxyprogesterone‡	1.4 (0.7–2.8)
Transdermal ethinylestradiol/ norelgestromin§	1.5 (0.5–4.1)
No risk increase	
Levonorgestrel releasing IUD	0.1 (0.0–0.4)
Progestagen only, low-dose norethisteron 350 μg or levonorgestrel 30 μg	0.2 (0.1–0.4)
Progestagen only, low-dose desogestrel 75 μg¶	0.2 (0.1–0.7)
Uncertain	
Etonogestrel subcutaneous implant	0.5 (0.01–2.9)
Vaginal ring (ethinylestradiol/ etonogestrel)	1.5 (0.1–5.4)

Relative risk of VTE in current users of COCs with…





…versus COCs with LEVONORGESTREL

Acta Obstetricia et Gynecologica Scandinavica 2012

It should be kept in mind that all combined oral contraceptives increase the risk of venous thrombosis, which is not the case for the levonorgestrel intrauterine device.

However, if a woman prefers using combined oral contraceptives, only contraceptives with the lowest risk of venous thrombosis and good compliance should be prescribed, such as levonorgestrel with 30µg ethinylestradiol.

Skin patch and vaginal ring versus combined oral contraceptives for contraception - Cochrane Database Syst Rev. 2013 Apr 30;4.

The absolute increase for an individual is very modest for most women and needs to be balanced against the beneficial effects of avoiding unintended pregnancies.

- **Più alto nelle donne che fanno <u>per la prima volta</u> uso di COC**

- **Più alto <u>nel primo anno di terapia</u> con una riduzione del rischio del 50% negli anni successivi**

1 year, 7.0 -5.28

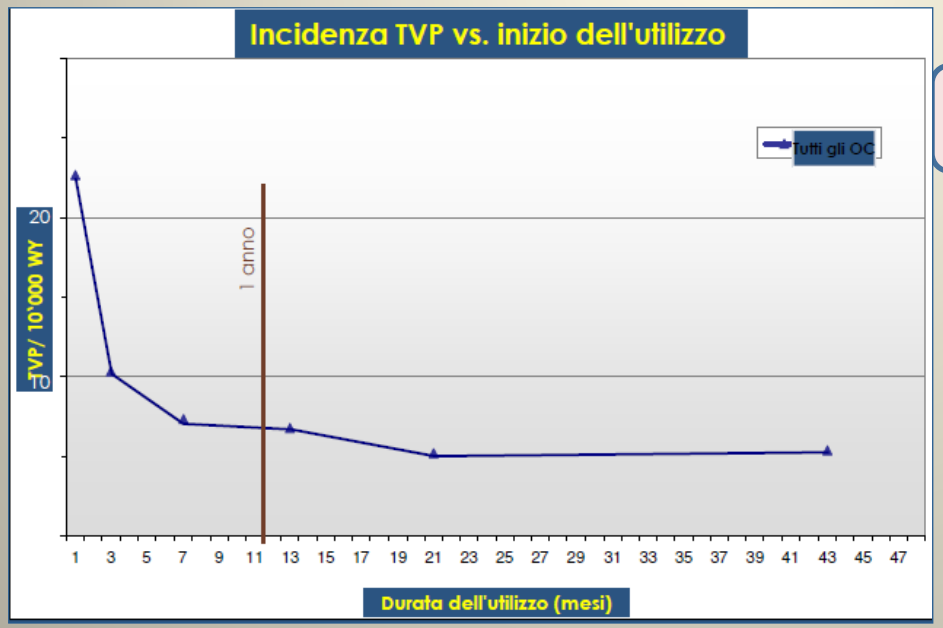
1–5 years, 3.6 -3.52

5 years, 3.1

Contraception 2002; 65:187–196, **Drug Saf. 2012 Mar 1;35(3):191-205.**

- **<u>Scompare con la sospensione</u> del trattamento**

(Report of a WHO Scientific group 1998. pp. 1–89)



Tempo utilizzo

Age category	Incidence of venous thrombosis in non-users of oral contraceptives (I_0) per 10 000 person-years*	Relative risk (95% CI) of oral contraceptive use†	Incidence of venous thrombosis in oral contraceptive users (I_1) per 10 000 person-years‡
<30 years	1.2	3.1 (2.2 to 4.6)	3.7
30-40 years	2.0	5.0 (3.8 to 6.5)	10.0
40-50 years	2.3	5.8 (4.6 to 7.3)	13.3

*I_0 is based on incidences published by Naess et al.
†Non-users of oral contraceptives are used as the reference category.
‡$I_1 = I_0 \times$ relative risk.

Age

A van Hylckama Vlieg, BMJ, 2009.

Obesity

Table IV. Combined effect of body mass index (BMI) and oral contraceptive (OC) use on the risk of venous thrombosis in women aged 18–39 years.

BMI (kg/m^2)	OC use	Patients	Control subjects	OR*	95% CI
<25	No	51	167	1	
≥25 & <30	No	27	34	2·52	1·38–4·57
≥30	No	28	30	3·04	1·66–5·57
<25	Yes	260	233	4·15	2·85–6·03
≥25 & <30	Yes	178	55	11·63	7·46–18·14
≥30	Yes	132	19	23·78	13·35–42·34

OR, odds ratio; CI, confidence interval.
*Analyses are performed with all patients and the random control subjects and adjusted for age.

Smoking increases the risk of venous thrombosis and ***acts synergistically with oral contraceptive use.***

Aged 18–39

Smoke

Smoking status	OC use	Patients (n=3,989)	Controls (n=4,900)	OR* (95%CI)
Never	no	105	168	1
Former	no	54	52	**1.63** (1.00-2.67)
Current	no	87	93	**2.03** (1.33-3.11)
Never	yes	257	189	**3.90** (2.63-5.79)
Former	yes	82	40	**4.83** (2.89-8.08)
Current	yes	271	94	**8.79** (5.73-13.49)

*Adjusted for age, BMI, and pregnancy.

Pomp E. *Am J Hematol. 2008*

Hormone use in women at increased risk of VTE

The presence of a hereditary thrombophilia increases the risk of a first episode of VTE in carriers.

Women with thrombophilia, selected from families with a **tendency for VTE**, have a higher absolute risk than women with the same defect identified by population testing.

Inherited thrombophilia

One should bear in mind that replacing oral contraceptives by less reliable contraceptive methods in young women with thrombophilia exposes them to the risk of unintended pregnancies and consequently to an increase in pregnancy-related VTE.

Best Practice & Research Clinical Endocrinology & Metabolism 27 (2013) 25–34

J Thromb Haemost 2013; 11 (Suppl. 1): 180–91.

Agenzia Italiana del Farmaco

AIFA

LISTA DI CONTROLLO PER I PRESCRITTORI - CONTRACCETTIVI ORMONALI COMBINATI

La preghiamo di utilizzare questa lista di controllo insieme al Riassunto delle Caratteristiche del Prodotto durante ogni consulto relativo ai Contraccettivi Ormonali Combinati (COC).

- La tromboembolia (per esempio trombosi venosa profonda, embolia polmonare, attacco cardiaco ed ictus) rappresenta un rischio importante associato all'uso dei COC.
- Il rischio di tromboembolia con un COC è più elevato:
  - durante il primo anno d'impiego;
  - quando se ne riprenda l'uso dopo una pausa nell'assunzione di 4 o più settimane.
- Si pensa che i COC contenenti etinilestradiolo in combinazione con levonorgestrel, norgestimato o noretisterone abbiano il rischio più basso di causare troemboembolia venosa (TEV).
- Il rischio per una donna dipende anche dal suo rischio basale di tromboembolia. La decisione di utilizzare un COC deve quindi prendere in considerazione le controindicazioni ed i fattori di rischio individuali, particolarmente quelli relativi alla tromboembolia – si vedano le caselle sotto riportate ed il relativo Riassunto delle Caratteristiche del Prodotto.
- La decisione di utilizzare un qualsiasi COC piuttosto che uno avente il rischio più basso di tromboembolia venosa (TEV) deve essere presa solo dopo un colloquio con la donna in modo da assicurarsi che comprenda:
  - il rischio di tromboembolia associato al suo COC;
  - l'effetto di qualsiasi fattore di rischio intrinseco sul suo rischio di trombosi;
  - che deve prestare particolare attenzione a segni e sintomi di una trombosi.

Non usi un COC se barra una qualsiasi casella di questa sezione. Nel caso in cui la donna abbia:	
☐	Riscontro anamnestico od in corso di un evento tromboembolico come ad esempio una trombosi venosa profonda, un'embolia polmonare, un attacco cardiaco, un ictus, un attacco ischemico transitorio, un'angina pectoris.
☐	Conoscenza personale di un disturbo della coagulazione del sangue.
☐	Storia di emicrania con aura.
☐	Diabete mellito con complicanze vascolari.
☐	Pressione arteriosa molto elevata, cioè una sistolica ≥160 od una diastolica ≥100 mmHg.
☐	Lipidemia molto elevata.
☐	Previsione di un intervento chirurgico maggiore o di un periodo di immobilizzazione prolungato. In tal caso, interromperne l'uso e consigliare un metodo contraccettivo non-ormonale per almeno 4 settimane prima e 2 settimane dopo la ripresa completa della deambulazione.

Discuta con la donna l'opportunità di utilizzare un COC nel caso in cui venga barrata una qualsiasi casella di questa sezione:	
☐	Se il suo indice di massa corporea (BMI) superi i 30 kg/m².
☐	Se ha un'età superiore ai 35 anni.
☐	Se sia una fumatrice. Qualora lo sia e sia anche oltre i 35 anni d'età, dovrà essere vivamente invitata a smettere di fumare o ad usare un metodo contraccettivo non-ormonale.
☐	Se ha una pressione arteriosa elevata, ad esempio una sistolica di 140-159 od una diastolica di 90-99 mmHg.
☐	Se ha un parente stretto che abbia presentato un episodio tromboembolico (vedere la lista sopra riportata) in giovane età (cioè al di sotto dei 50 anni).
☐	Se ha personalmente, o tra i familiari stretti, una lipidemia molto elevata.
☐	Se soffre di emicrania.
☐	Se ha una patologia cardiovascolare quale fibrillazione atriale, aritmia, malattia coronarica, malattia valvolare cardiaca.
☐	Se è affetta da diabete mellito.
☐	Se ha partorito nelle ultime settimane.
☐	Se ha intenzione di intraprendere un viaggio aereo a lungo raggio (oltre le 4 ore) o viaggia per oltre 4 ore al giorno.
☐	Se ha un qualsiasi altra condizione medica che possa aumentare il rischio di trombosi (come cancro, lupus eritematoso sistemico, anemia falciforme, morbo di Crohn, colite ulcerosa, sindrome emolitico-uremica).
☐	Se sta assumendo qualsiasi altro farmaco che possa incrementare il rischio di trombosi (come corticosteroidi, neurolettici, antipsicotici, antidepressivi, chemioterapici ed altri).

La presenza di più di uno di questi fattori di rischio può significare che un COC non deve essere usato.

Si ricordi che i fattori di rischio di una donna possono variare nel tempo. E' dunque importante utilizzare questa lista di controllo ad ogni consulto.

La preghiamo di assicurarsi che la Sua paziente sia pienamente consapevole di riferire agli operatori sanitari che sta assumendo un contraccettivo ormonale combinato qualora:

- Necessiti di un intervento chirurgico;
- Sia necessario che si sottoponga ad un periodo di immobilizzazione prolungato (come nel caso di incidente o malattia, oppure per un'ingessatura ad un arto inferiore).

➢ In questi casi sarebbe meglio riconsiderare se non fosse il caso di usare un contraccettivo non-ormonale sino a che il rischio non torni normale.

Agenzia Italiana del Farmaco

AIFA

INFORMAZIONI IMPORTANTI SUI CONTRACCETTIVI ORALI COMBINATI (COC) E SUL RISCHIO DI COAGULI DI SANGUE

Tutti i contraccettivi combinati aumentano il rischio di avere un coagulo di sangue. Il rischio complessivo di un coagulo di sangue dovuto all'assunzione di un contraccettivo ormonale combinato (COC) è piccolo, ma i coaguli possono rappresentare una condizione grave ed in rarissimi casi persino fatale.

E' molto importante che Lei riconosca quando potrebbe essere in una situazione di maggior rischio per la formazione di un coagulo di sangue, quali siano i segni ed i sintomi sui quali stare in guardia e quali azioni sia necessario intraprendere.

In quali situazioni è più alto il rischio di formazione di un coagulo di sangue?

- durante il primo anno d'uso di un COC (comprendendo anche quando si riprende l'uso dopo un intervallo di 4 o più settimane)
- se Lei è in sovrappeso
- se ha più di 35 anni d'età
- se ha un membro della famiglia che abbia avuto un coagulo di sangue in età relativamente giovane (cioè al di sotto dei 50 anni)
- se ha partorito nelle ultime settimane

Se fuma ed ha più di 35 anni, è vivamente invitata a smettere di fumare o ad usare un metodo contraccettivo non-ormonale.

Si rivolga immediatamente ad un medico se manifesta uno dei seguenti sintomi:

- Un dolore intenso od un gonfiore ad una delle gambe che può essere accompagnato da flaccidità, calore o cambiamenti del colore della pelle come la comparsa di pallore, di rossore o di colore bluastro. Potrebbe avere una **trombosi venosa profonda**.
- L'improvvisa ed inspiegabile mancanza di respiro o insorgenza di respirazione rapida; un dolore intenso al petto che può aumentare con la respirazione profonda; una tosse improvvisa senza una causa evidente (che può produrre sangue). Potrebbe essere una complicazione grave della trombosi venosa profonda chiamata **embolia polmonare**. Questo si verifica se il coagulo di sangue migra dalla gamba al polmone.
- Un dolore al petto, spesso acuto, ma che talvolta si manifesta come un malessere, un senso di pressione, di peso, un fastidio della parte alta del corpo che si irradia al dorso, alla mandibola, alla gola, al braccio con una sensazione di pienezza associata a indigestione o a soffocamento, sudorazioni, nausea, vomito o capogiri. Si potrebbe trattare di un **attacco di cuore**.
- Un intorpidimento od un senso di debolezza del viso, del braccio o della gamba, specialmente ad un lato del corpo; una difficoltà nel parlare o nel capire; un'improvvisa confusione mentale, una perdita improvvisa della vista o una visione offuscata; una cefalea/emicrania intensa e peggiore del solito. Si potrebbe trattare di un **ictus**.

Faccia attenzione ai sintomi di un coagulo di sangue, specialmente se:

- ha appena avuto un intervento chirurgico
- è stata immobilizzata per tanto tempo (come ad esempio per un incidente o una malattia, oppure perché ha avuto una gamba ingessata)
- ha fatto un lungo viaggio (per più di 4 ore)

Si ricordi di comunicare al Suo medico, all'infermiere o al chirurgo che sta assumendo un contraccettivo ormonale combinato se:

- Ha avuto o deve sottoporsi ad un intervento chirurgico
- Si trova una qualsiasi situazione in cui un operatore sanitario Le chiede quali farmaci sta assumendo

Per ulteriori informazioni è pregata di leggere attentamente il Foglietto Illustrativo che accompagna il farmaco e di riferire subito la comparsa di qualsiasi effetto indesiderato associato all'uso del contraccettivo ormonale combinato al Suo medico od al farmacista

National DVT Risk Assessment Screening Program

NAME:_____

DVT Risk Assessment/Patient Questionnaire

Date:_____ **Age:**_____ **SEX:** Male / Female **Your home ZIP code** _____

Height: Feet_____ Inches_____ **Weight in pounds:**_____

Race: Caucasian / African-American / Asian / Hispanic / Native American / Other

What specialty is your personal doctor or primary care physician? (Circle one)

Internist / Family practitioner / Cardiologist / Clinic doctor / HMO doctor

Osteopath / Other / I don't have a doctor

Do you have? Diabetes Y/N High blood Pressure Y/N Heart failure Y/N Smoker? Never / Now / Quit

Do you take blood thinner? None / Coumadin / Aspirin / Plavix / Ticlid / Pletal / Aggrenox

Why are you here today? (circle most appropriate):

Do you have leg pain? (None) (Occasional) (Daily) (Limit activities)

Do you have swelling? (None) (Evenings/ankle only) (Afternoon/leg) (Morning/leg)

Do you use compression stockings? (Not used) (Intermittent use) (Most days) (Continually)

Medical History

(Circle appropriate answers)

				Points for "yes" answer
1.	Have you ever had a blood clot in your legs or lungs?	Yes	No	(3)
2.	Do you have a family history of blood clots in the veins?	Yes	No	(3)
3.	Do you have leg swelling every day?	Yes	No	(1)
4.	Do you have visible varicose veins or spider veins?	Yes	No	(1)
5.	Do you have inflammatory bowel disease?	Yes	No	(1)
6.	Do you have emphysema or COPD?	Yes	No	(1)
7.	Have you had more than three days of continuous bed rest due to injury or illness in past month?	Yes	No	(1)
8.	Have you had a pelvic fracture or a plaster leg cast in the last month?	Yes	No	(1)
9.	Have you had a heart attack or heart failure?	Yes	No	(1)
10.	Have you had major surgery lasting over an hour in the last month?	Yes	No	(1)
11.	Do you have or have you had a malignant disease (cancer)?	Yes	No	(1)
12.	Do you weigh over 250 pounds?	Yes	No	(1)
13.	AGE (Circle) Under 40 40-59 (1) 60-69 (2) Over 70 (3)	(0)	(1) (2)	(3)

The following questions are for WOMEN only

14.	Do you use birth control pills or estrogen replacement therapy?	Yes	No	(1)
15.	Are you pregnant or had a baby within the last month?	Yes	No	(1)

adapted from Caprini risk assessment

Total: _____

(Add all points for "Yes" answer and "Age" group.)

Sponsored by sanofi-aventis U.S.

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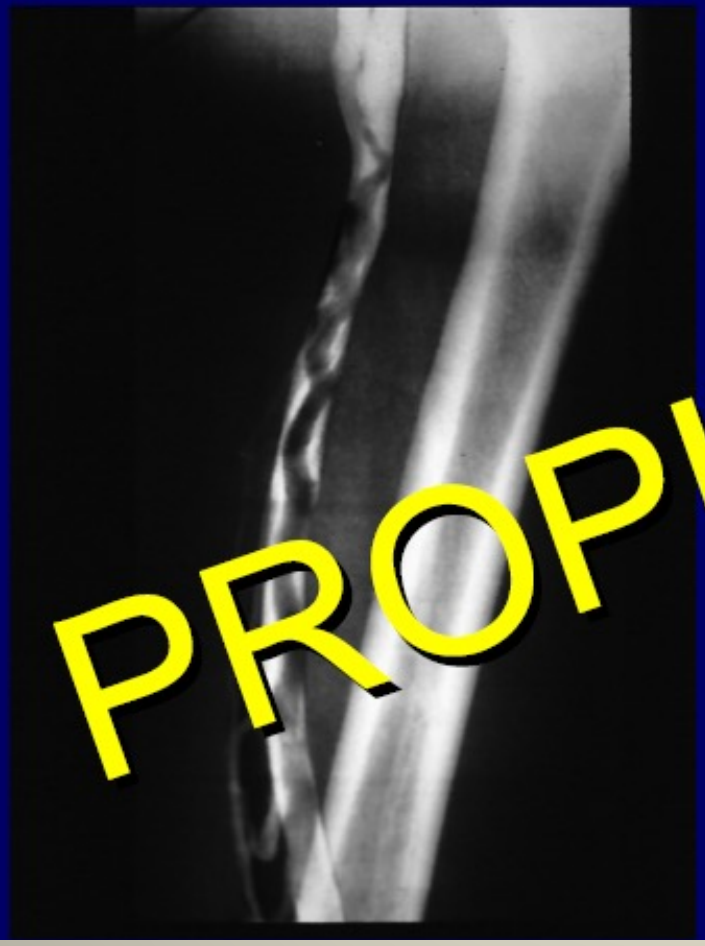
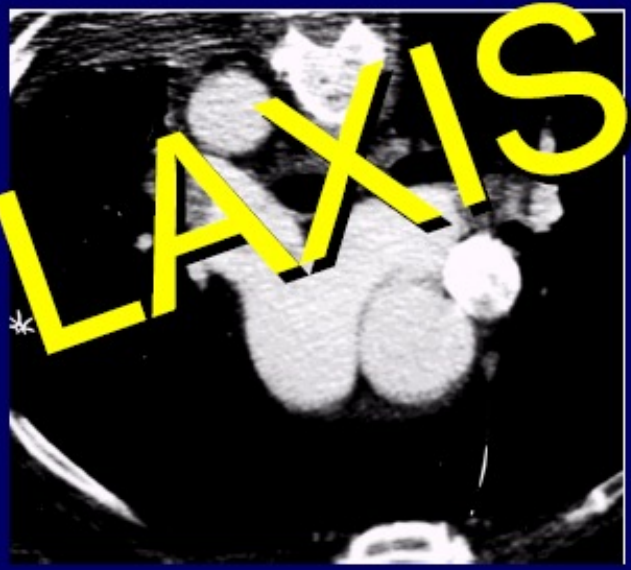
Deep vein thrombosis

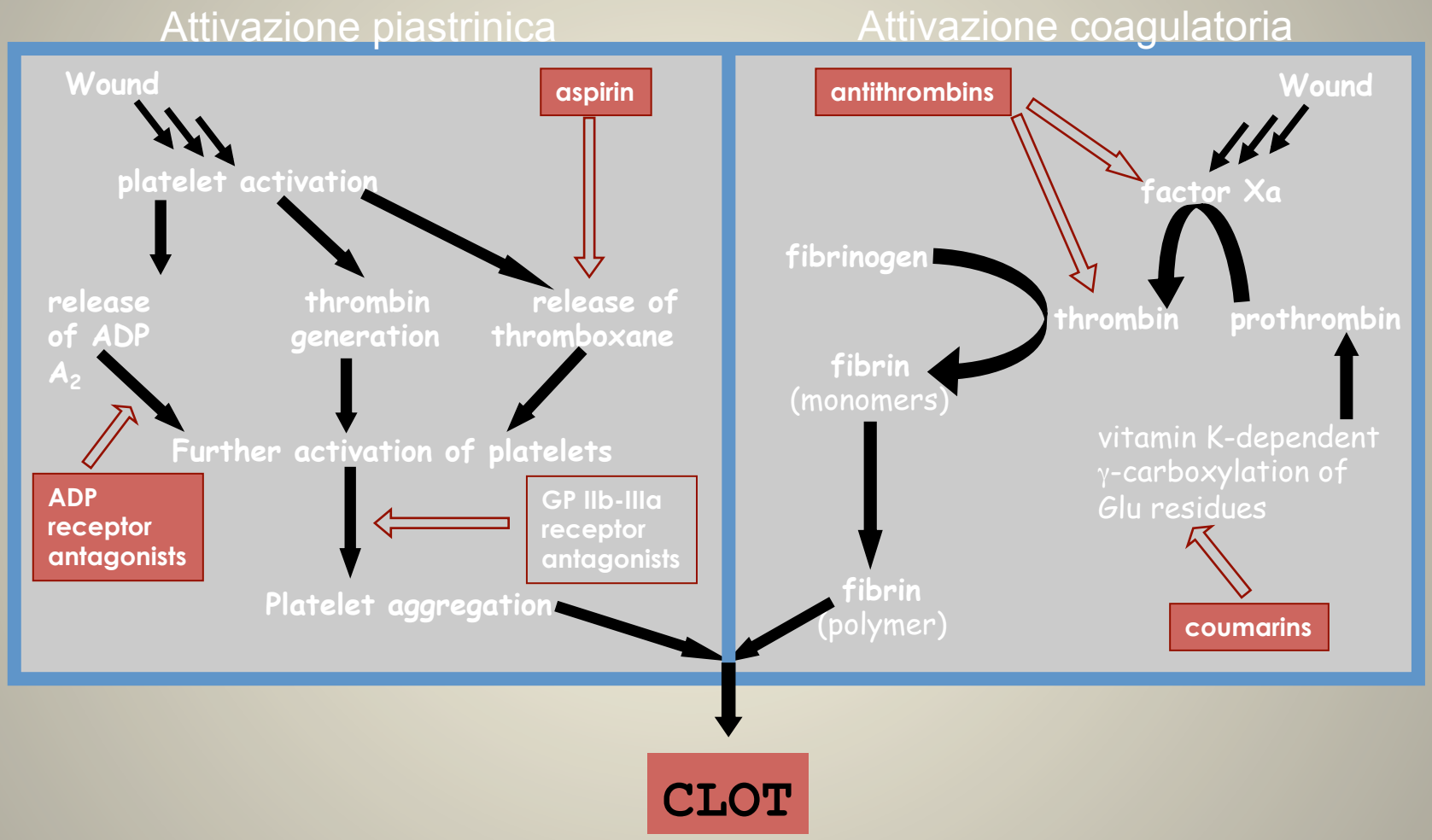


Pulmonary embolism



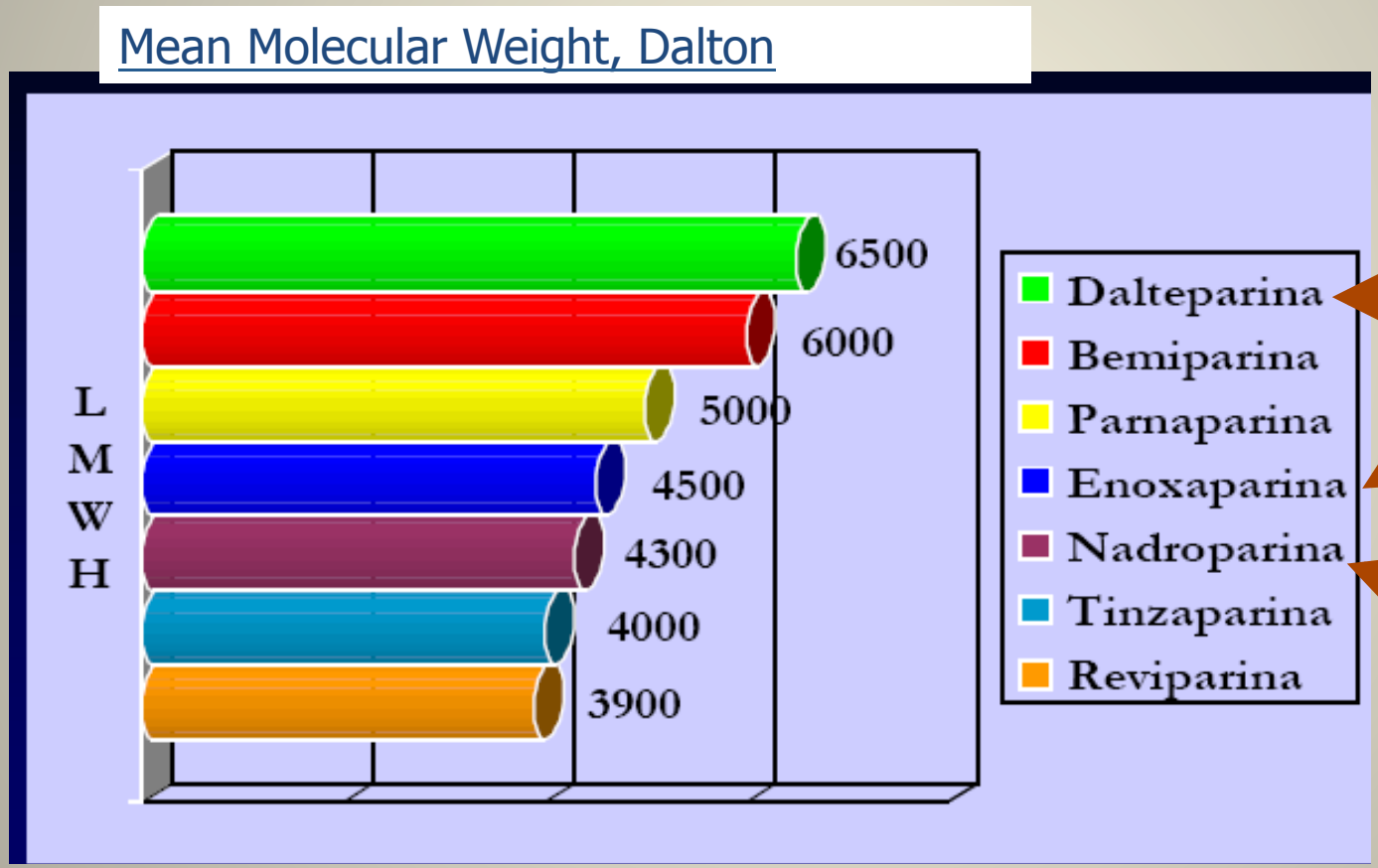
PROPHYLAXIS

Interventi terapeutici sulla modulazione dell' emostasi



Taken from ***Desai UR (2004) Med. Res. Rev. 24, 151-181.***

Are All Low Molecular Weight Heparins Equivalent? 1



Method of Preparation

Nitrous acid depolymerization

Benzylation followed by alkaline hydrolysis

Nitrous acid depolymerization

Clinical and Applied Thrombosis/Hemostasis / Vol. 14, No. 4, October 2008

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Are All Low Molecular Weight Heparins Equivalent? 2

POTENZA anti-Xa e anti-IIa

	UHF	Tinzaparine	Dalteparine	Enoxaparine	Nadroparine
Anti Xa:IIa	1:1	1.9:1	2.7:1	3.8:1	3.6:1
Inizio azione	20-30 min	4-6 h	4 h	3 h	3 h
Emivita	30-90 min	2-4 h	2-5 h	3-6 h	2-3.5 h
Via eliminazione	SRE + rene	Rene	Rene	Rene	Rene
Dose Terapia Embolia Polmonare	80 U/kg + 18 U/kg/h	175U/kg die	100 U/kg x 2	100 U/kg x 2	90 U/kg x 2

ACCP 2008 Dosaggi

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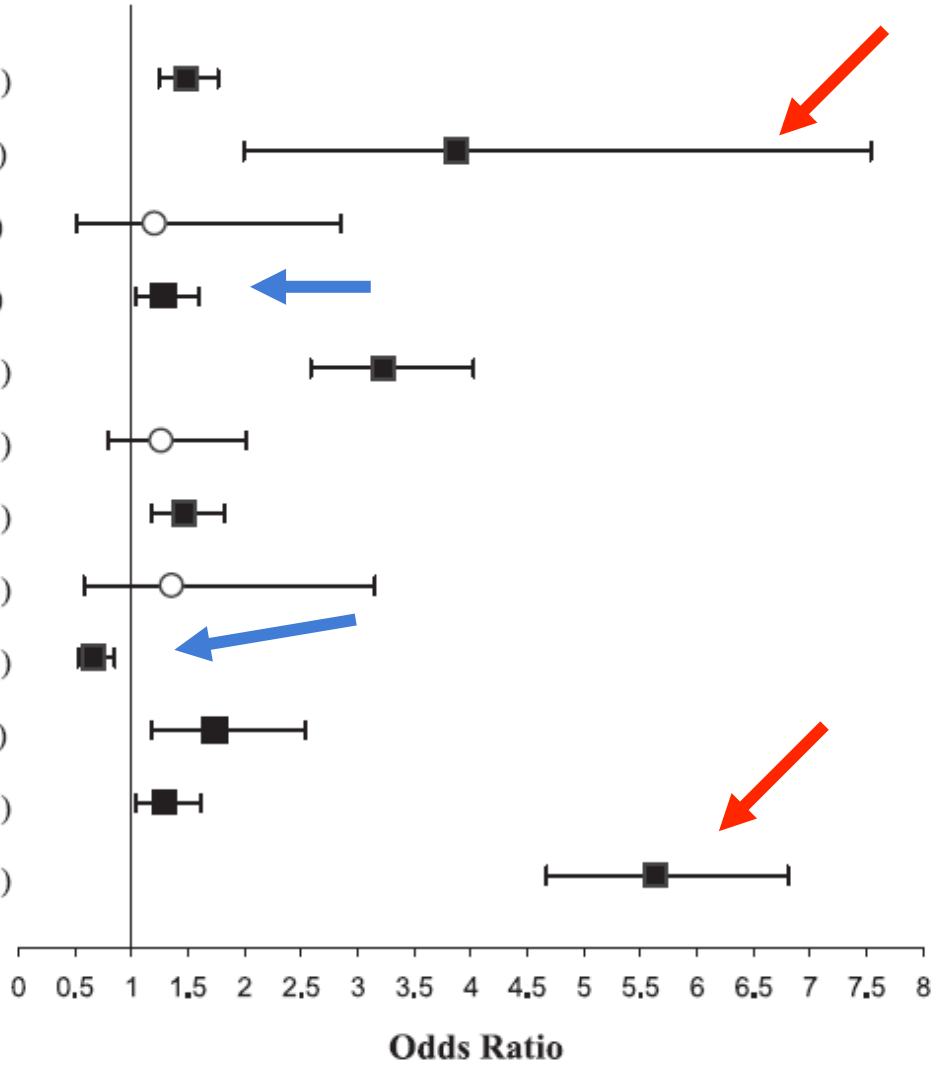
Eparina	Dosi Profilattiche	Dosi Intermedie	Dosi in base al peso
LMWH	Dalteparina: 5,000U S.C. AL GIORNO Tinzaparin: 4500U S.C. AL GIORNO Enoxaparina: 40mg S.C. AL GIORNO	Dalteparina: 5,000U S.C. OGNI 12 ORE Enoxaparina: 40mg S.C. OGNI 12 ORE	Dalteparina: 200U/kg S.C. ogni 24 ORE 100U/kg S.C. ogni 12 ore Tinzaparin: 175U/kg SQ q24 Enoxaparina: 1mg/kg S.C. ogni 12 ore
UFH	5000 U S.C. OGNI 12 ORE	SQ q12 adjusted to Anti-Xa of 0.1-0.3U/mL	SQ q12 adjusted to mid-interval PTT in therapeutic range

GEMINI STUDY - 27 Internal Medicine Departments (all in Italy) (4,846 patients)

58.7% of those for whom prophylaxis was recommended

Thromb Haemost. 2009 May;101(5):893-901

Effect	Odds Ratio	(95% CI)
Age class	1.48	(1.24 – 1.76)
Previous VTE	3.87	(1.99 – 7.54)
Recent surgery	1.2	(0.51 – 2.9)
Obesity	1.28	(1.04 – 1.6)
CHF	3.22	(2.58 – 4.03)
Acute MI	1.26	(0.79 – 2.01)
COPD	1.46	(1.12 – 1.82)
IBD	1.35	(0.58 – 3.15)
Cancer	0.67	(0.52 – 0.85)
Hemi-paraparesis/Hemi-paraplegia	1.73	(1.19 – 2.53)
Fever	1.29	(1.04 – 1.60)
Bed rest	5.64	(4.67 – 6.81)



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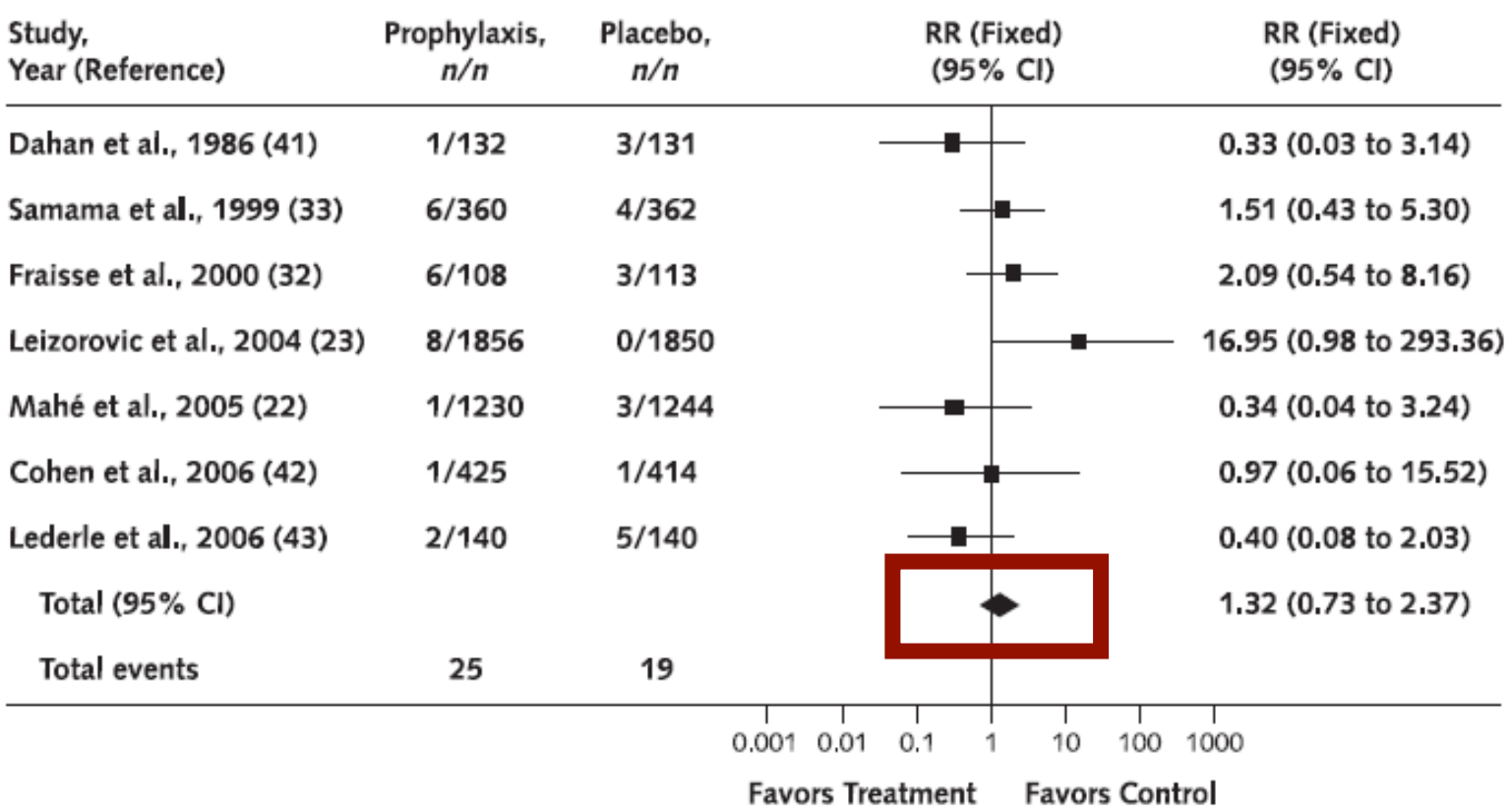
Meta-analysis: Anticoagulant Prophylaxis to Prevent Symptomatic Venous Thromboembolism in Hospitalized Medical Patients (*Ann Intern Med.* 2007;146:278-288)

Major bleeding during anticoagulant prophylaxis. **9 studies (*n* = 19,958)**

M

P

A



In 25 of 4301 (0.58%) patients who received prophylaxis and in 19 of 4304 (0.44%) patients who received no prophylaxis (relative risk, 1.32 [CI, 0.73 to 2.37], ns)

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Tromboembolia venosa

Triade di Virchow

1821-1902

Rudolf Virchow's Triad

Ipercoagulabilità

Ereditaria *Acquisita*

Stasi

Acquisita

Lesione vascolare

Acquisita

Trombosi venosa

Virchow R. In Gesammelte Abhandlugen zur Wissenschaftlichen Medizin, 1856; Frankfurt: Staatsdruckerei
Rosendaal FR. Lancet 1999; 353:1167–1173

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Ipercoagulabilità

TROMBOFILIA

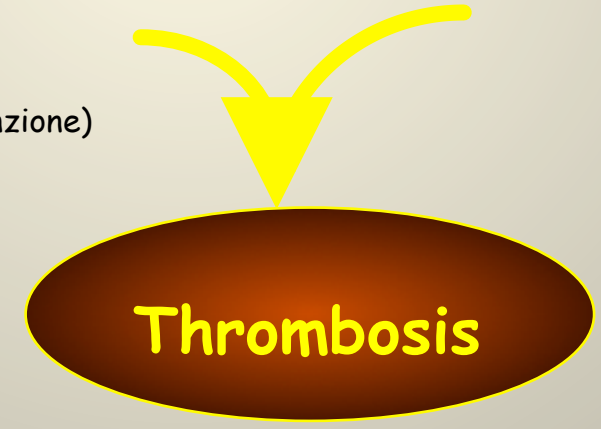
Inherited Prothrombotic Mutation(s)

1. **FACTOR V LEIDEN/ Cambridge/ Hong Kong** (aumento di funzione)
2. **PROTHROMBIN 20210A** (aumento di funzione)
3. **PROTEIN C DEFICIENCY** (perdita di funzione)
4. **PROTEIN S DEFICIENCY** (perdita di funzione)
5. **ANTITHROMBIN DEFICIENCY** (perdita di funzione)

Acquired Prothrombotic Stimulus

- **ANTIPHOSPHOLIPID ANTIBODIES/LAC**
- **Elevated levels of FVIII**

(Combined)



(*International Consensus Statement. Int J Angiol 2005; American Society of Haematology, 2005*)

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Prevalenza delle alterazioni trombofiliche.

	popolazione generale	TEV
ATIII	0.02%	1%
PC	0.2-0.4%	3%
PS	0.02% (?)	1-2%
FV Leiden	4-7 %	15-20%
PT 20210A	1-3%	6%
Fattore VIII	10%	25%
Hcy	5%	10%
LAC/ACA	?	5%

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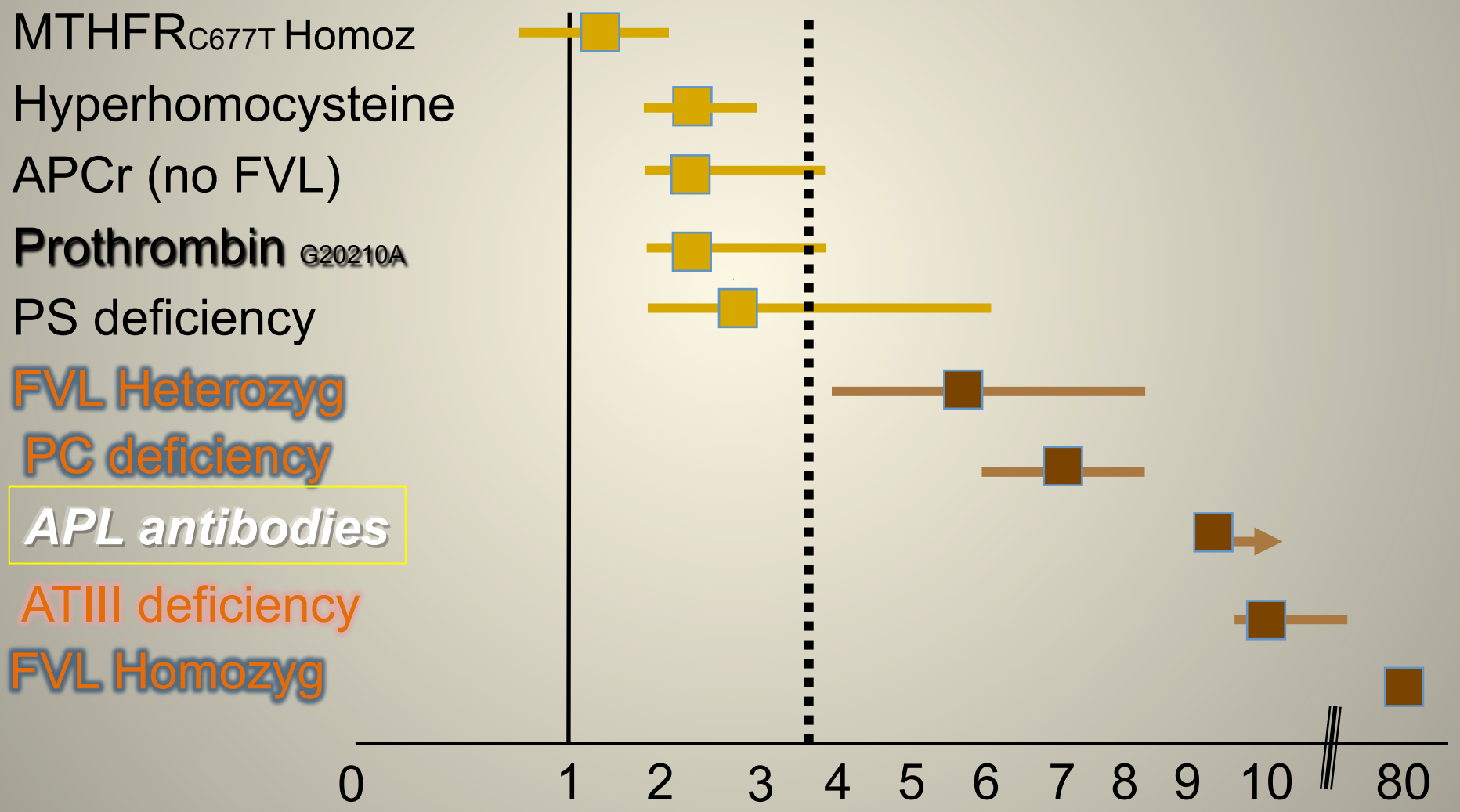
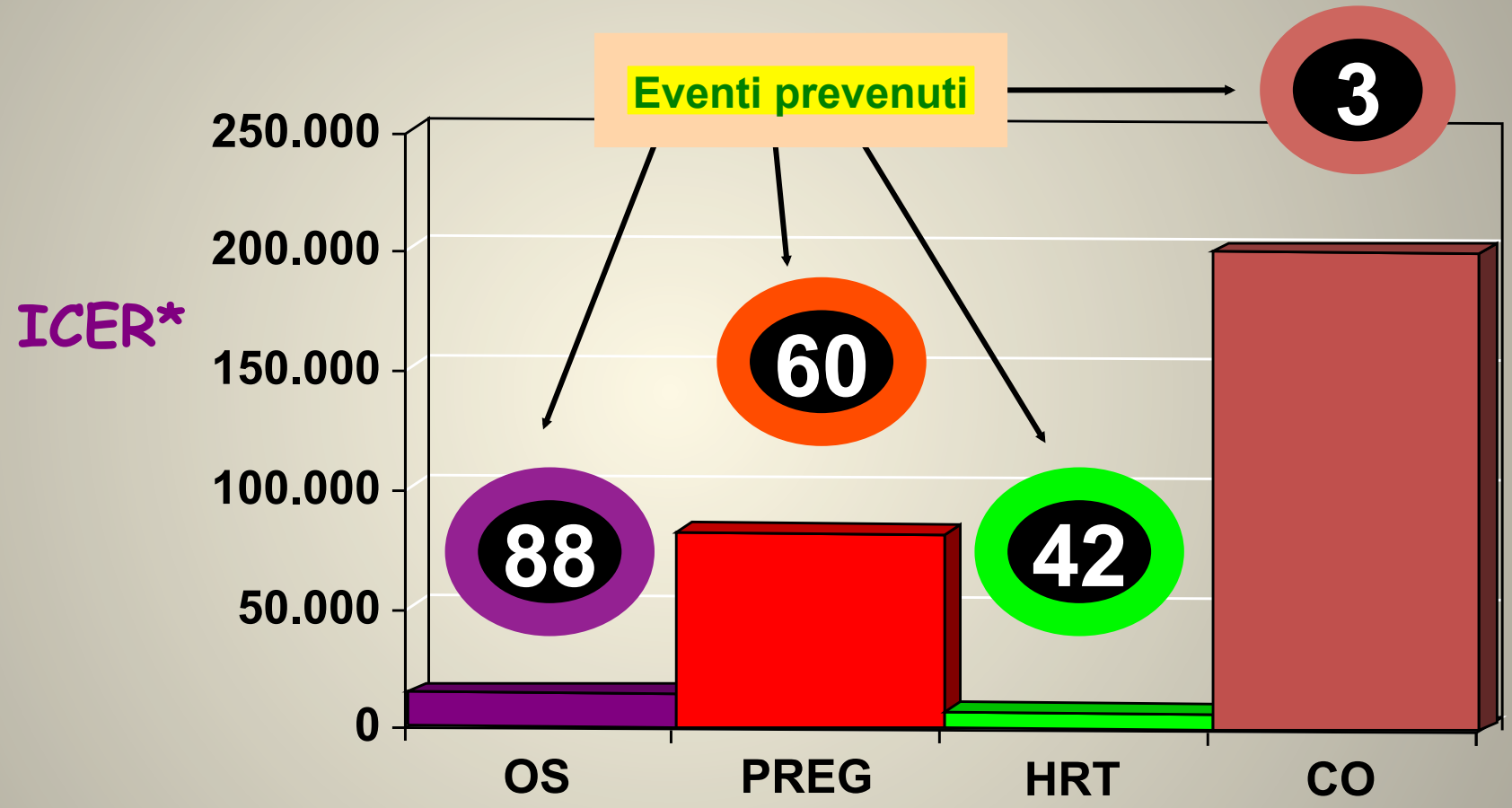
Estimated Prevalence of Thrombophilic Disorders (OR for VTE) -Review

*(American Journal of Obstetrics and Ginecology **2004**; 191: 412-24)*



RAPPORTO COSTO-BENEFICIO NELLO SCREENING UNIVERSALE. (N=10.000)



* Incremental Cost-Effectiveness Ratios (ICER) = Δcosts/Δbenefits; i.e. costs (screening -no screening)/clinical complications prevented (screening - no screening).

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APS: impact on real life

*There are two major 'new' diseases of the late twentieth century – AIDS and Hughes Syndrome.(**APS**).."*

…… accounts for approximately:

1 in 5 Deep Vein Thrombosis ('DVTs')

1 in 5 young strokes (under 45)

1 in 5 recurrent miscarriages

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Antiphospholipid syndrome (APS)

ACQUIRED AUTOIMMUNE THROMBOPHILIA in which

vascular thrombosis and/or recurrent pregnancy losses

occur in patients having laboratory evidence for antibodies against phospholipids or phospholipid-binding protein cofactors in their blood.

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APS

SAPPORO 1998 + ISTH 2006 - Ann Rheum Dis. 2007 Mar 2

AT LEAST ONE OF THE CLINICAL CRITERIA:

1. Vascular Thrombosis

2. Pregnancy Morbidity

   a) death of normal fetus at > 10 wks
   b) premature birth at < 34 wks due to preeclampsia
   c) >3 consecutive abortions at <10wks
   d) placental insufficiency at < 34 wks

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APS

AND AT LEAST ONE OF THE LABORATORY CRITERIA:

1. Lupus anticoagulant (LA) on >two occasions at least 12 weeks apart.

2. Anticardiolipin (aCL) antibody of IgG and/or IgM present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart.

3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart.

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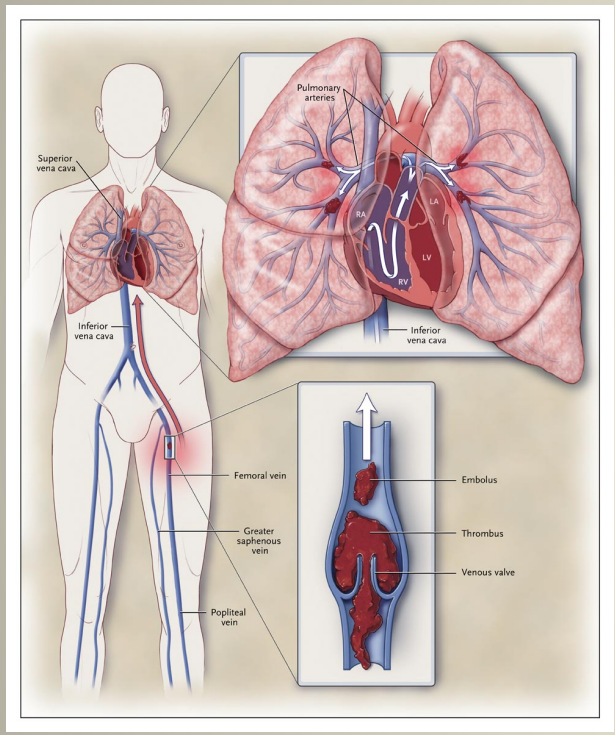
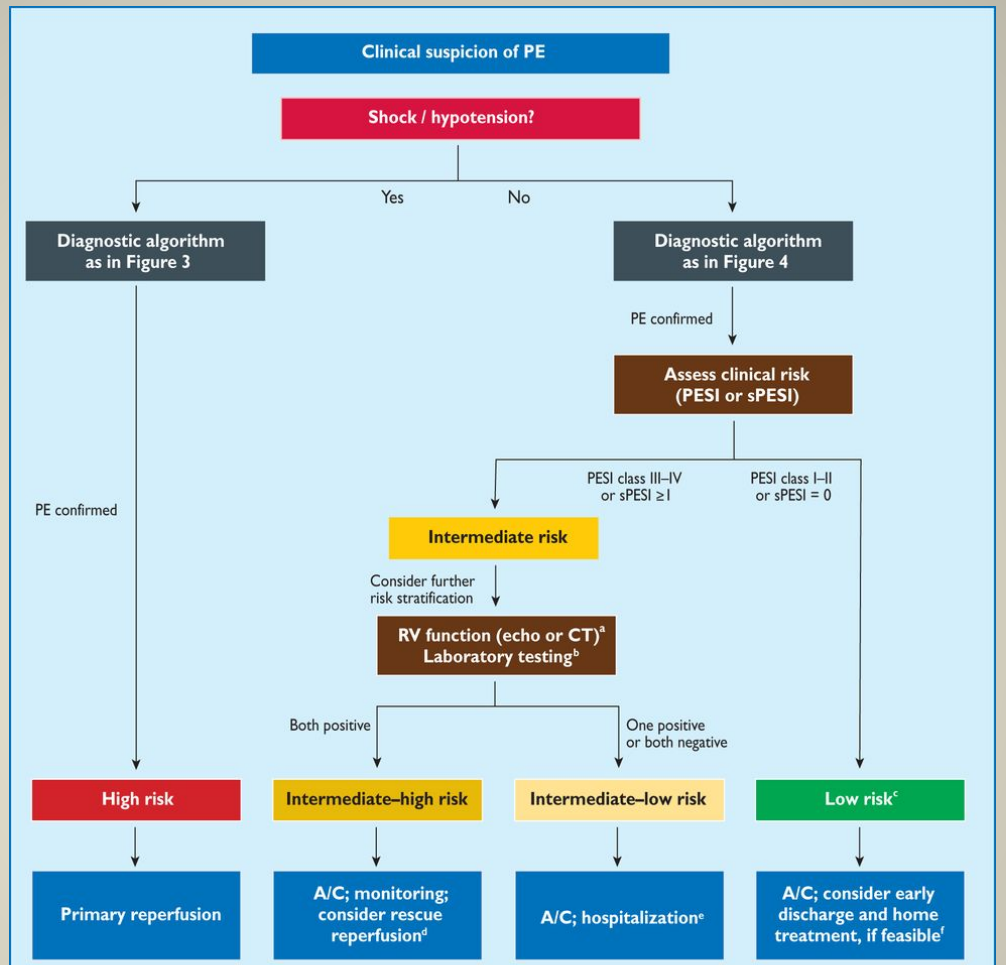


- Both Pulmonary embolism and DVT are treated the same
- An adequate level of anticoagulation is essential
- There are no randomized studies investigating the timing of anti-coagulation therapy initiation in patients with suspected DVT/EP.

JAMA Intern Med. doi:10.1001/jamainternmed.2015.1687 Published online May 18, 2015.

European Heart Journal

Risk-adjusted management strategies in acute PE



A/C = anticoagulation; CT = computed tomographic pulmonary angiography; PE = pulmonary embolism; PESI = pulmonary embolism severity index; RV = right ventricular; sPESI = simplified pulmonary embolism severity index.

[a]If echocardiography has already been performed during diagnostic work-up for PE and detected RV dysfunction, or if the CT already performed for diagnostic work-up has shown RV enlargement (RV/LV (left ventricular) ratio ≥0.9), a cardiac troponin test should be performed except for cases in which primary reperfusion is not a therapeutic option (e.g. due to severe comorbidity or limited life expectancy of the patient).

[b]Markers of myocardial injury (e.g. elevated cardiac troponin I or T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma). If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic work-up (e.g. in the chest pain unit) and was positive, then an echocardiogram should be considered to assess RV function, or RV size should be (re)assessed on CT.

[c]Patients in the PESI Class I–II, or with sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate–low risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index. These patients are probably not candidates for home treatment.

[d]Thrombolysis, if (and as soon as) clinical signs of haemodynamic decompensation appear; surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high.

[e]Monitoring should be considered for patients with confirmed PE and a positive troponin test, even if there is no evidence of RV dysfunction on echocardiography or CT.

[f]The simplified version of the PESI has not been validated in prospective home treatment trials; inclusion criteria other than the PESI were used in two single-armed (non-randomized) management studies.

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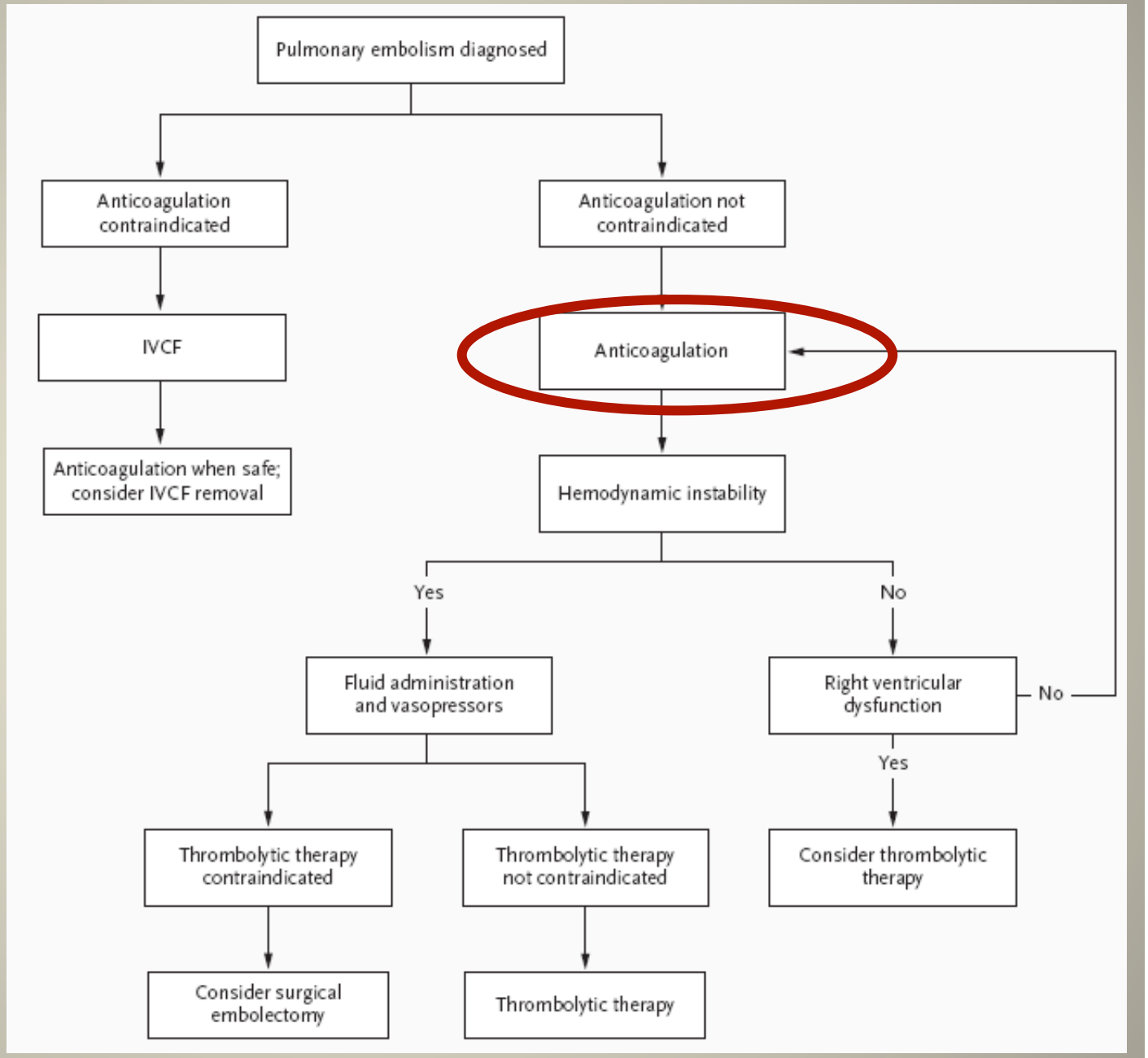
Flow chart trattamento embolia polmonare



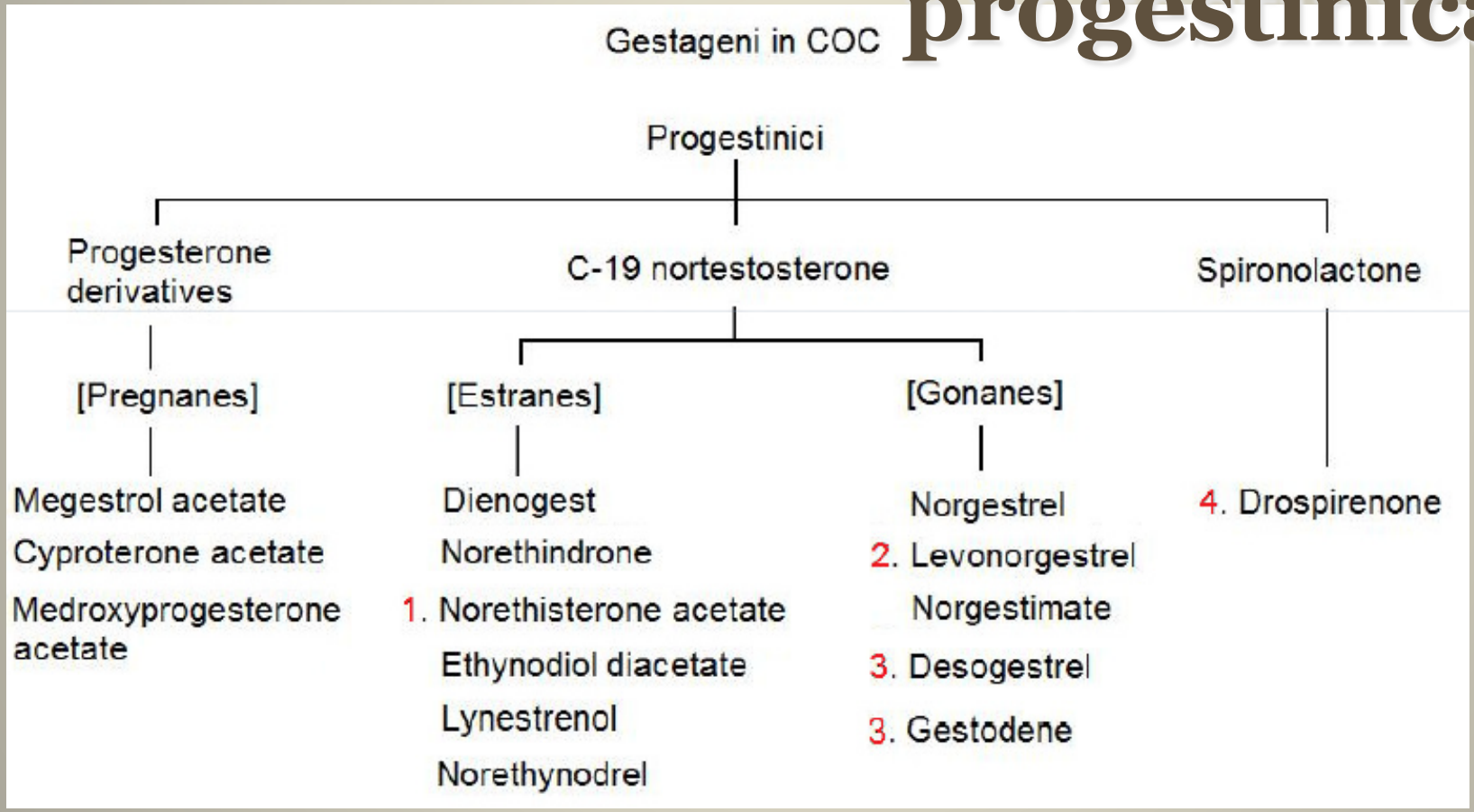
The NEW ENGLAND JOURNAL of MEDICINE

2008;358:1037-52.

COMPONENTE ESTROGENICA

COMPONENTE PROGESTINICA

Effetto componente progestinica



Relative risk of venous thromboembolism in current users of different combined oral contraceptives according to study

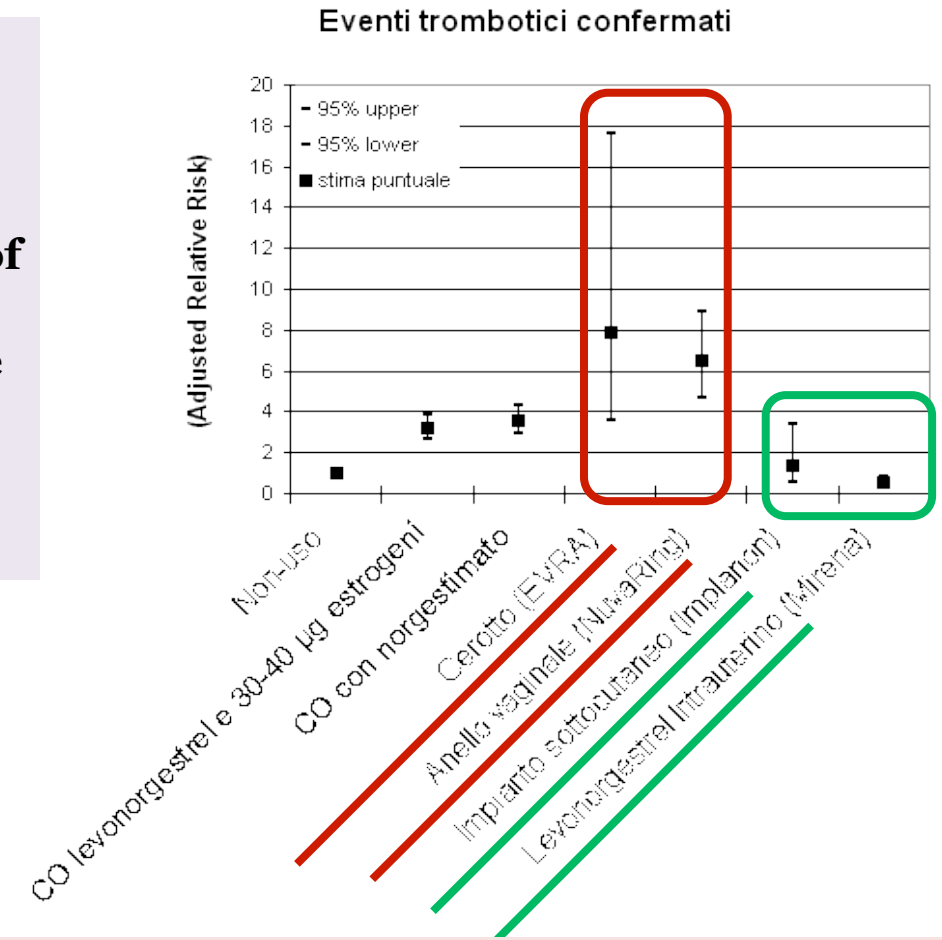
Study	Sampling period	No of events*	Relative risk (95% CI)		
			COC with levonorgestrel	COC with third generation progestogens†	COC with drospirenone
Bloemenkamp[1]	1988-92	126	3.8 (1.7 to 8.4)	8.7 (3.9 to 19.3)	NA
WHO[4]	1989-93	433	3.6 (2.5 to 5.1)	7.4 (4.2 to 12.9)	NA
Jick[2]	1991-4	80	1 (Reference)	1.8 (1.0 to 3.2)	NA
Spitzer[5]	1991-5	471	3.7 (2.2 to 6.2)	6.7 (3.4 to 13)	NA
Farmer[6]	1991-5	85	3.1‡ (2.1 to 4.5)	5.0‡ (3.7 to 6.5)	NA
Lewis[8]	1993-5	502	2.9 (1.9 to 4.2)	2.3 (1.5 to 3.5)	NA
Todd[9]	1992-7	99	1 (Reference)	1.4 (0.7 to 2.8)	NA
Bloemenkamp[7]	1994-8	185	3.7 (1.9 to 7.2)	5.6 (NA)	NA
Lidegaard[13]	1994-8	987	2.9 (2.2 to 3.8)	4.0 (3.2 to 4.9)	NA
Dinger[14]	2000-4	118	1 (Reference)	1.3 (NS)	1.0 (0.6 to 1.8)
Vlieg[17]	1999-2004	1524	3.6 (2.9 to 4.6)	7.3 (5.3 to 10.0)	6.3 (2.9 to 13.7)
Lidegaard[18]	1995-2005	4213	2.0 (1.8 to 2.3)	3.6 (3.3 to 3.8)	4.0 (3.3 to 4.9)
Dinger[19]	2002-8	680	1 (Reference)	NA	1.0 (0.6 to 1.8)
Parkin[20]	2002-9	61	1 (Reference)	NA	2.7 (1.5 to 4.7)
Jick[21]	2002-8	186	1 (Reference)	NA	2.8 (2.1 to 3.8)
Present study:					
All reported events*	2001-9	4246	2.2 (1.7 to 2.8)	4.2 (3.6 to 4.9)	4.5 (3.9 to 5.1)
Confirmed events only*	2001-9	2707	2.9 (2.2 to 3.8)	6.8 (5.7 to 8.1)	6.3 (5.4 to 7.5)

COC containing DRSP X 2-3 times

Lidegaard Ø et al BMJ. 2011 Oct 25;343:d6423

Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10

Danish non-pregnant women AGED 15-49 (n=1 626 158), free of previous thrombotic disease or cancer, were followed from 2001 to 2010 (*Four national registries*)



- **TRANSDERMAL PATCHES containing norelgestromin (the active metabolite of norgestimate) and EE**
- **VAGINAL RING with etonogestrel (3rd generation progestogen) and EE**
- **SUBCUTANEOUS IMPLANTS containing etonogestrel only**
- **LEVONORGESTREL INTRAUTERINE SYSTEM (hormone intrauterine device).**

BMJ 2012;344:e2990 (Published 10 May 2012)

WHO medical eligibility criteria for contraceptive use 2010

1 : no restriction for the contraceptive method;

2: the advantages of using the method generally outweigh the theoretical or proven risks;

3: theoretical or proven risks usually outweigh the advantages of the method;

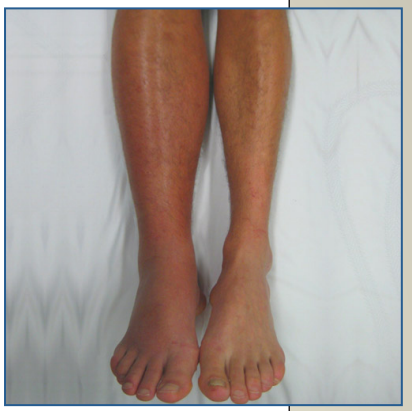
4: unacceptable hea
contraceptive method

World Health Organization

2010

IL CUORE MALATO È MASCHIO O FEMMINA?"
THE SICK HEART IS MALE OR FEMALE?

CONDITION * additional comments at end of table	CATEGORY I = initiation, C = continuation				CLARIFICATIONS/EVIDENCE
	COC	P	R	CIC	
COC = combined oral contraceptives **P** = combined contraceptive patch **R** = combined contraceptive vaginal ring **CIC** = combined injectable contraceptives					
DEEP VENOUS THROMBOSIS (DVT)/ PULMONARY EMBOLISM (PE)*					
a) History of DVT/PE	4	4	4	4	
b) Acute DVT/PE	4	4	4	4	
c) DVT/PE and established on anticoagulant therapy	4	4	4	4	
d) Family history (first-degree relatives)	2	2	2	2	
e) Major surgery					
(i) with prolonged immobilization	4	4	4	4	
(ii) without prolonged immobilization	2	2	2	2	
f) Minor surgery without immobilization	1	1	1	1	
KNOWN THROMBOGENIC MUTATIONS (e.g. factor V Leiden; prothrombin mutation; protein S, protein C, and antithrombin deficiencies)	4	4	4	4	**Clarification**: Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening. **Evidence**: Among women with thrombogenic mutations, COC users had a two to twenty-fold higher risk of thrombosis than non-users. (191;222-244)
SUPERFICIAL VENOUS THROMBOSIS*					
a) Varicose veins	1	1	1	1	
b) Superficial thrombophlebitis	2	2	2	2	



Additional studies are needed to define the mechanisms that control sex-based differences in thrombosis at the molecular, cellular, and whole organismal level.

Bullet point summary

- Hormonal contraceptives are used by millions of women worldwide
- Venous thromboembolism is the most important determinant of the benefit/risk profile of hormonal contraceptive
- Familial history of VTE has to be systematically assessed before prescribing combined hormonal contraception
- Reducing the daily dose of ethinyl-estradiol from 100 μg to 50 μg and from 50 μg to 30 μg leads to a decrease in the risk of venous disease
- The risk of venous disease is higher among users of third generation pills, drospirenone and cyproterone acetate combined pill compared with second generation pills
- Non-oral routes of EE administration (vaginal or patch) seem to be more thrombogenic than oral route
- Progestin-only oral pills and levonorgestrel intra-uterine device are not associated with VTE risk

Research agenda

Future research on the association of hormonal contraceptive with venous thromboembolism should focus on:

- The impact of reducing the daily dose of ethinyl-estradiol from 30–40 μg to 20 μg
- The impact of pills containing natural 17β-estradiol on thrombotic risk
- The route of administration of hormonal combined contraception and progestin only contraception (implant)
- The potential hormonal contraceptives for women with a personal history of venous thromboembolism

Best Practice & Research Clinical Endocrinology & Metabolism 27 (2013) 25–34

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 October 2013
EMA/607314/2013

PRAC confirms that benefits of all combined hormonal contraceptives (CHCs) continue to outweigh risks

Committee recommends that women and prescribers be better informed of the known risk of thromboembolism and alert for signs and symptoms

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the risk of venous thromboembolism (VTE or blood clots in veins) with combined hormonal contraceptives (CHCs). The PRAC concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks.

There is no reason for women who have been using CHCs without any problem to stop taking them on the basis of this review. It is important that women are made aware of the risk of VTE and its signs and symptoms, and that doctors take into consideration a woman's individual risk factors when prescribing a contraceptive.

This review has confirmed that the risk of VTE with all CHCs is small and has shown that there are small differences between the CHCs depending on the type of progestogen they contain. It has reinforced the importance of ensuring good information for women who use these medicines and for the healthcare professionals providing advice and clinical care.

When prescribing a CHC, doctors should assess a woman's individual risk for blood clots regularly, as the risk changes over time. Risk factors include among others smoking, being overweight, increasing age, having migraines, family history of VTE and having given birth in the previous few weeks. Doctors should also consider how the risk of VTE compares with other CHCs.

It is important that women and doctors remain alert for the signs and symptoms of thromboembolism, which may include severe pain or swelling in the legs, sudden unexplained breathlessness, rapid breathing or cough, chest pain, and face, arm or leg weakness or numbness. In case a woman develops any of these signs and symptoms she should seek medical advice immediately.

The PRAC recommendation will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP) which is expected to adopt an EMA final opinion at its plenary meeting of 18-21 November 2013.[1]

Gender Medicine

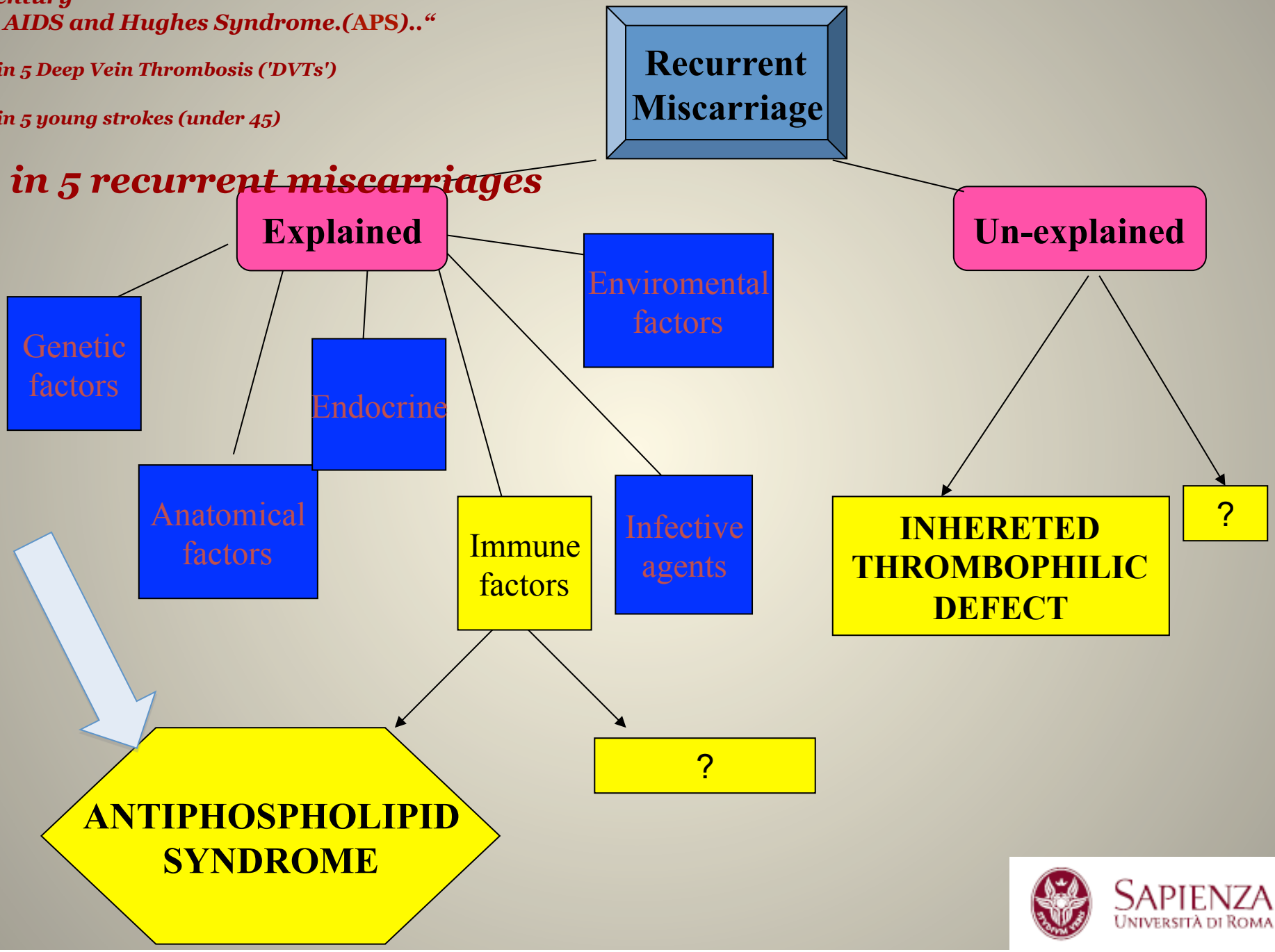
MISCARRIAGES

There are two major 'new' diseases of the late twentieth century
– AIDS and Hughes Syndrome.(APS)..“

1 in 5 Deep Vein Thrombosis ('DVTs')

1 in 5 young strokes (under 45)

1 in 5 recurrent miscarriages



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ANTIPHOSPHOLIPID SYNDROME: CRITERIA

1. *Vascular Thrombosis*

2. Pregnancy Morbidity

a) death of normal fetus at ≥ 10 wks
b) premature birth at ≤ 34 wks due to preeclampsia
c) ≥3 consecutive abortions at <10wks
d) placental insufficiency at < 34 wks

3. AND AT LEAST ONE OF THE LABORATORY CRITERIA:

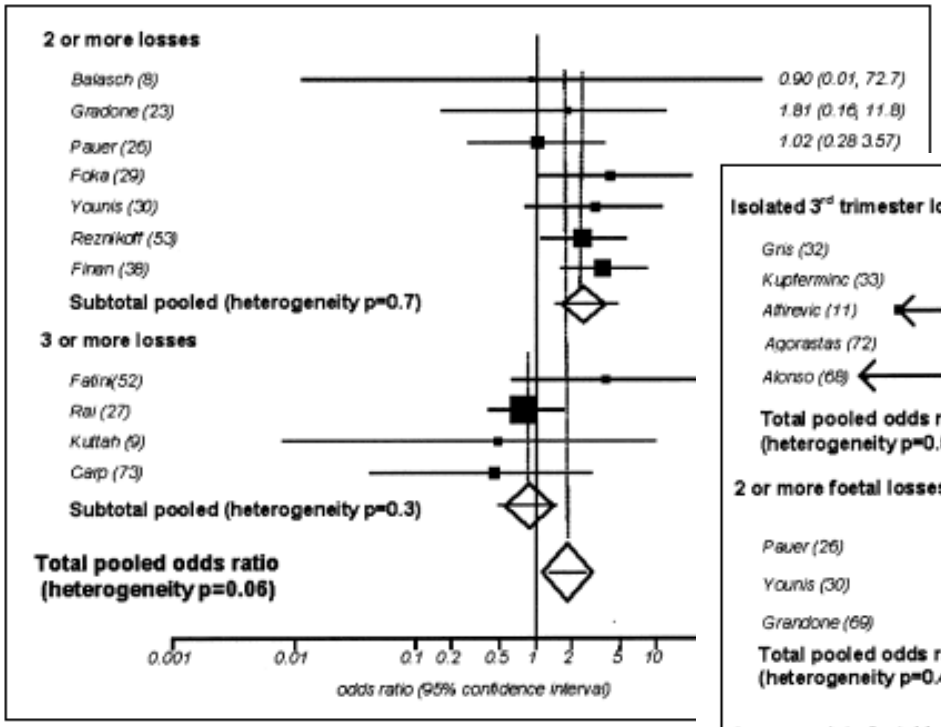
1. **Lupus anticoagulant (LA) on >two occasions at least 12 weeks apart.**

2. **Anticardiolipin (aCL) antibody of IgG and/or IgM present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart.**

3. **Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart.**

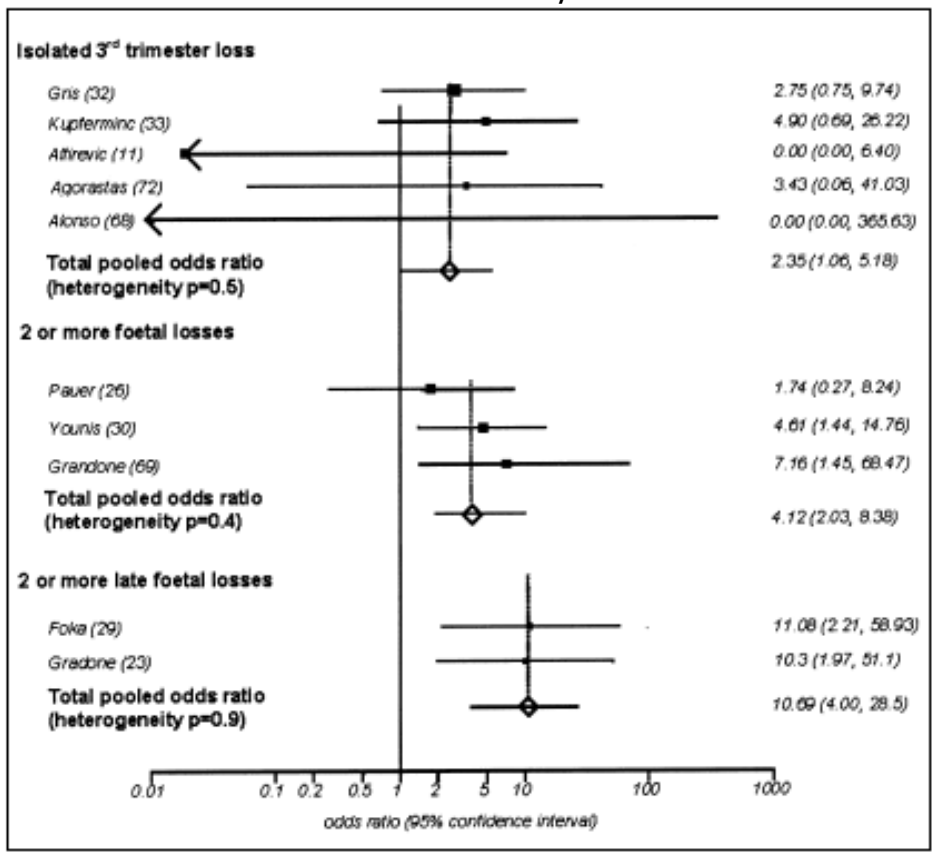
7,167 women (metanalysis)

FVL



1th trimester

second/third trimester



Thromb Haemost 2004; 91: 700–11

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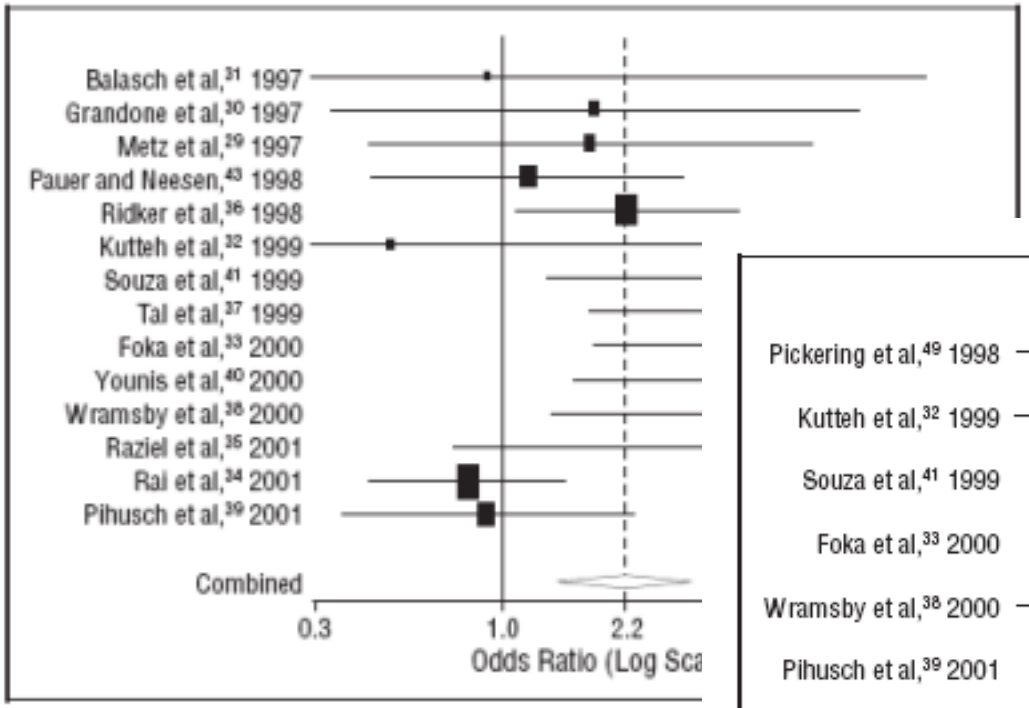
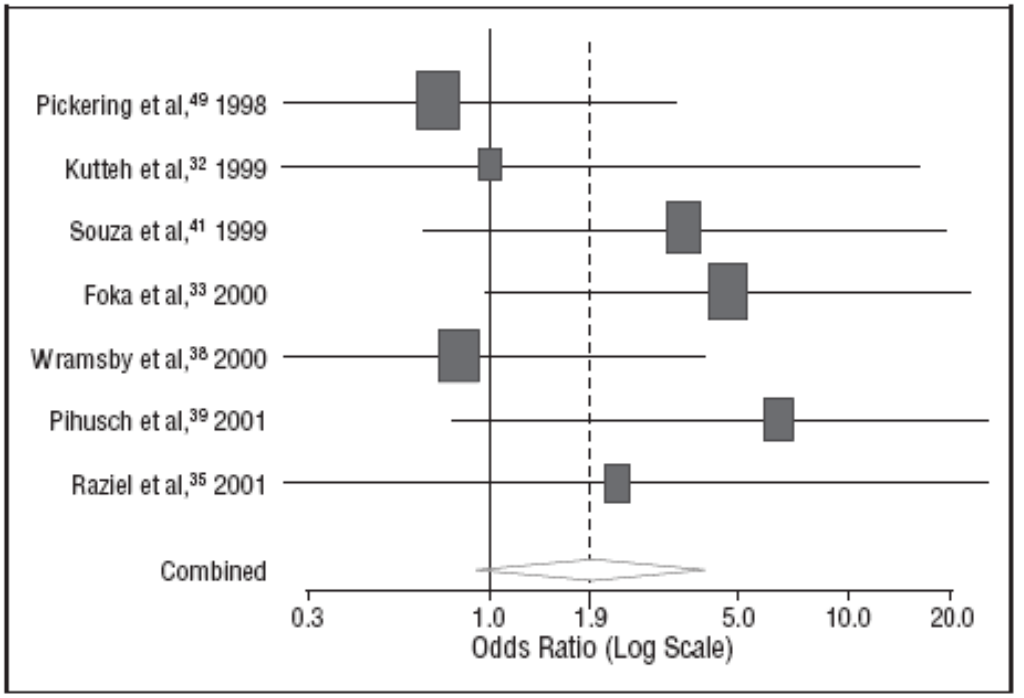
FVL or *PROTHROMBIN G20210A*





Arch Intern Med. 2004;164:558-563

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Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia

	Patients no.	Miscarriages no. (%)	Start of medication	Treatment	Live birth	P-value
ALIFE	364 itt* 299 pregnant	2 (40.1) ≥3 (59.9)	<6 weeks	1. LMWH+ aspirin 2. Aspirin 3. Placebo	69% 62% 67%	0.63
HABENOX	207	2 (1.0) ≥3 (99.0)	<7 weeks	1. LMWH+ aspirin 2. Aspirin 3. LMWH	65% 61% 71%	0.45
SPIN	294	2 (57.1) ≥3 (42.9)	<7 weeks	1. LMWH+ aspirin 2. Placebo	78% 80%	0.85

*intention-to-treat

Visser et al. Thromb Haemost 2011; 105: 295–3

ALIFE: nadroparin 2850UI daily

SPIN: enoxaparin 40 mg sc daily

HABENOX: enoxaparin 40 mg daily

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Use of Heparin in Women With Early and Late Miscarriages With and Without Thrombophilia

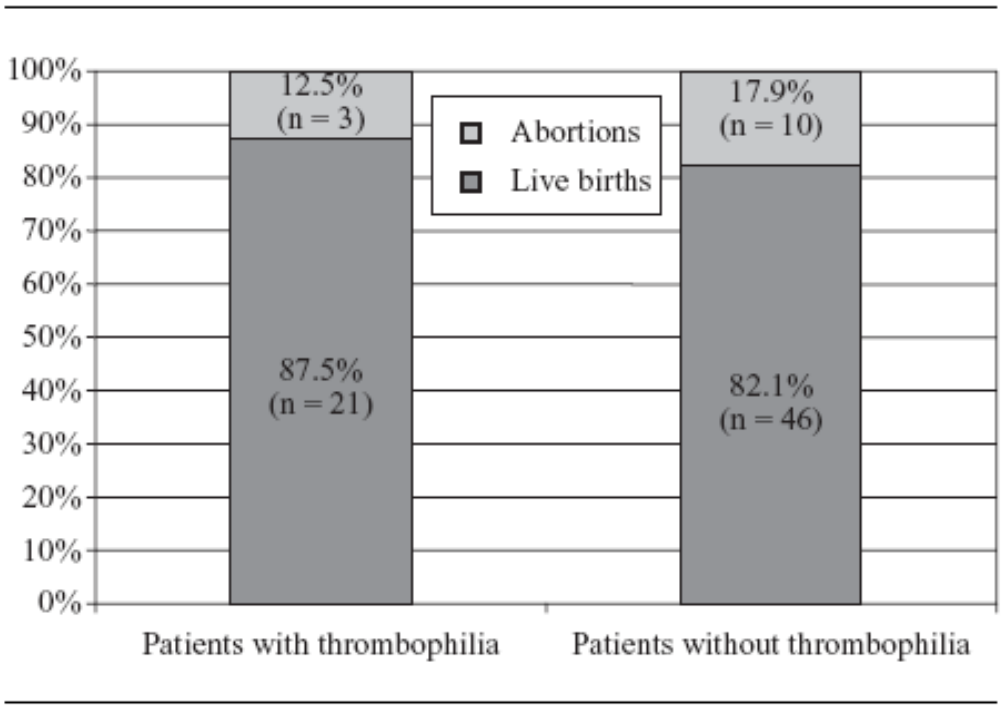

Figure 1. Comparison of the outcome of 24 pregnancies with thrombophilia and 56 pregnancies without thrombophilia under low-molecular-weight heparin (LMWH).

164 women with unexplained early and late miscarriages.
subsequent pregnancies in 79 patients were treated with 5000 U dalteparin / day subcutaneously independently of thrombophilia.

Monien S, et al. Clin Appl Thromb Hemost 2009; 15:636-44.

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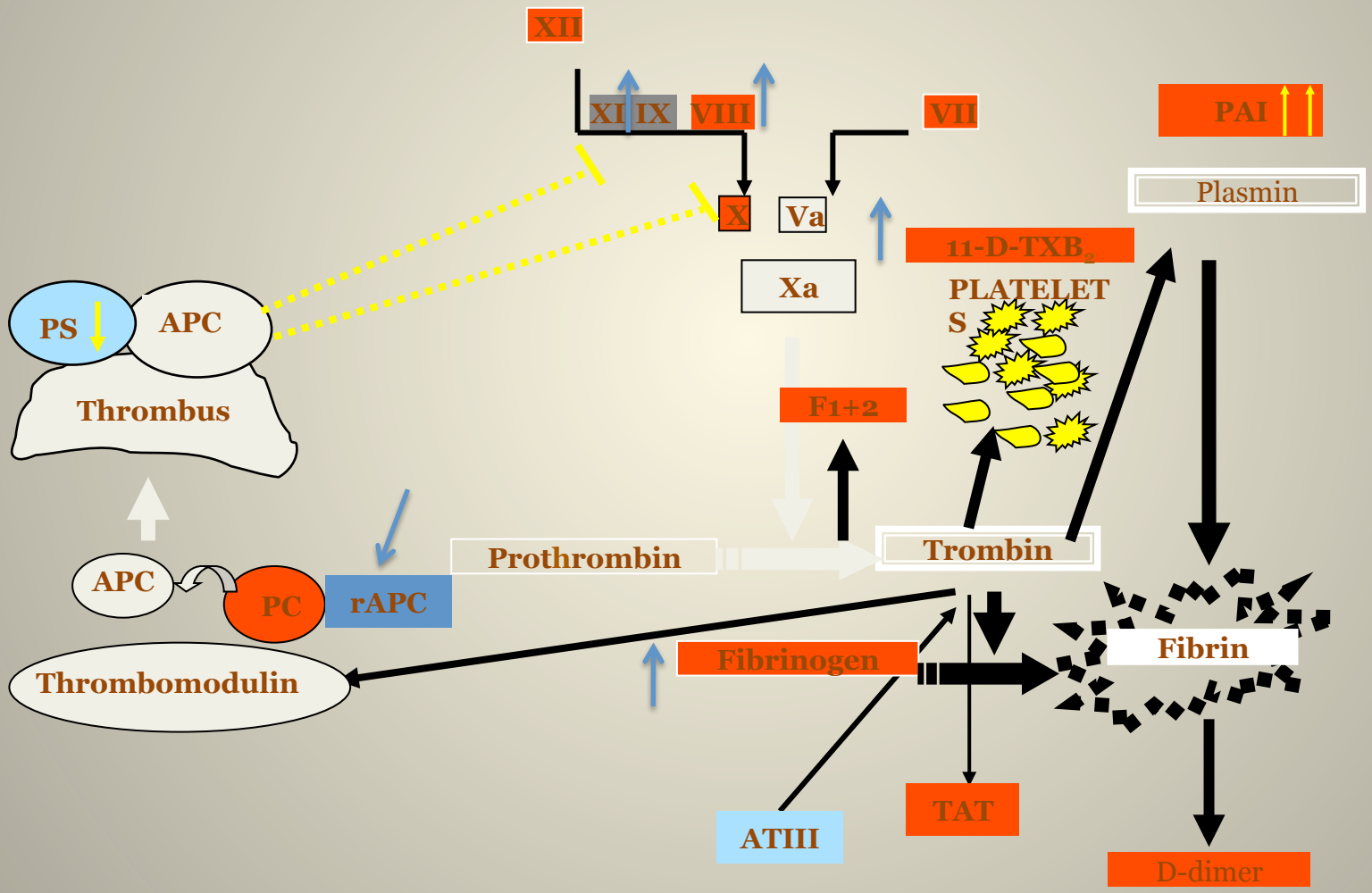
Gender Medicine

PREGNANCY

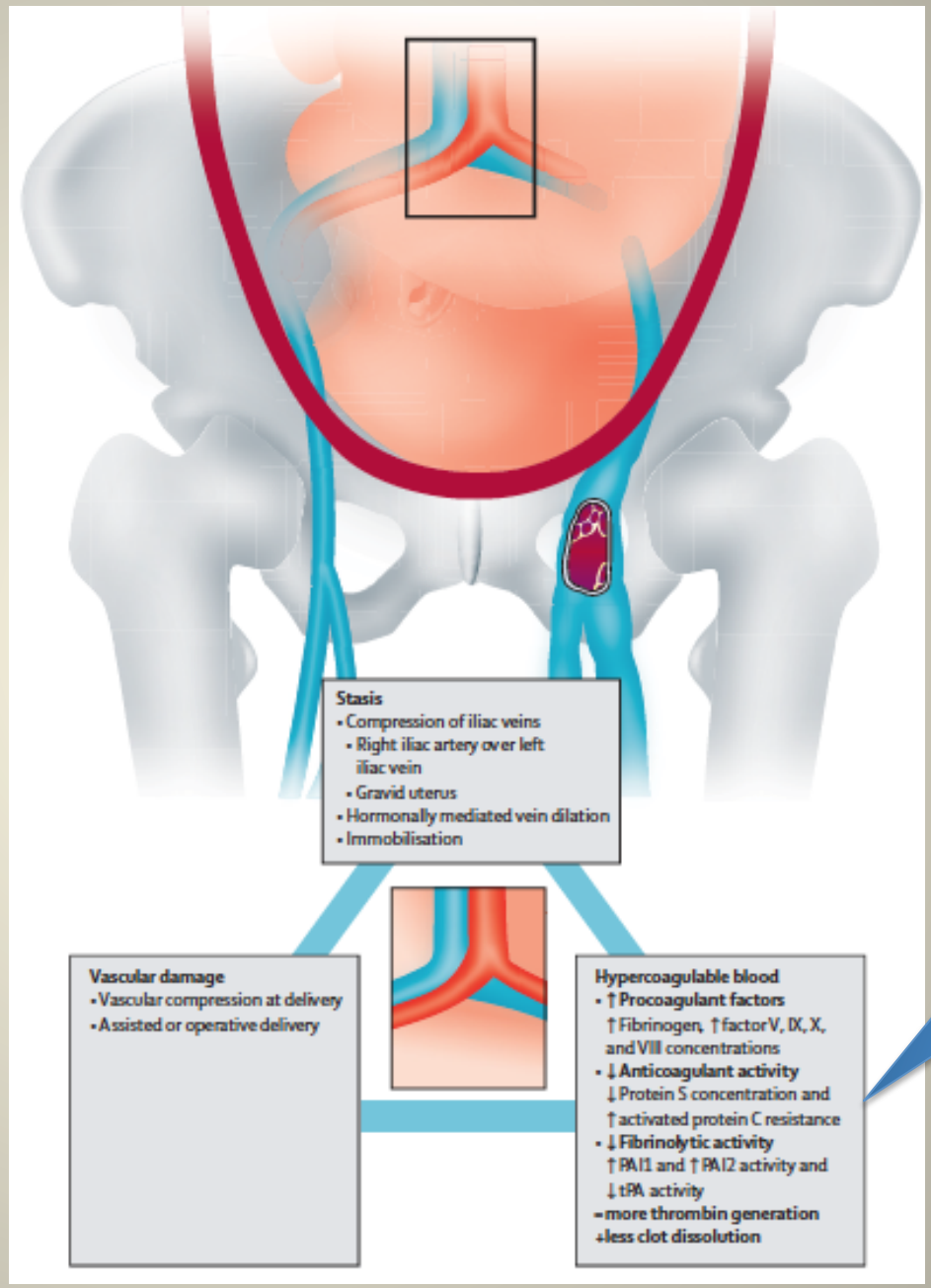
Pregnancy is accompanied by changes in both clotting and anti-clotting factors that maximize hemostasis.



haematologica reports 2005; 1(issue 10):November 2005

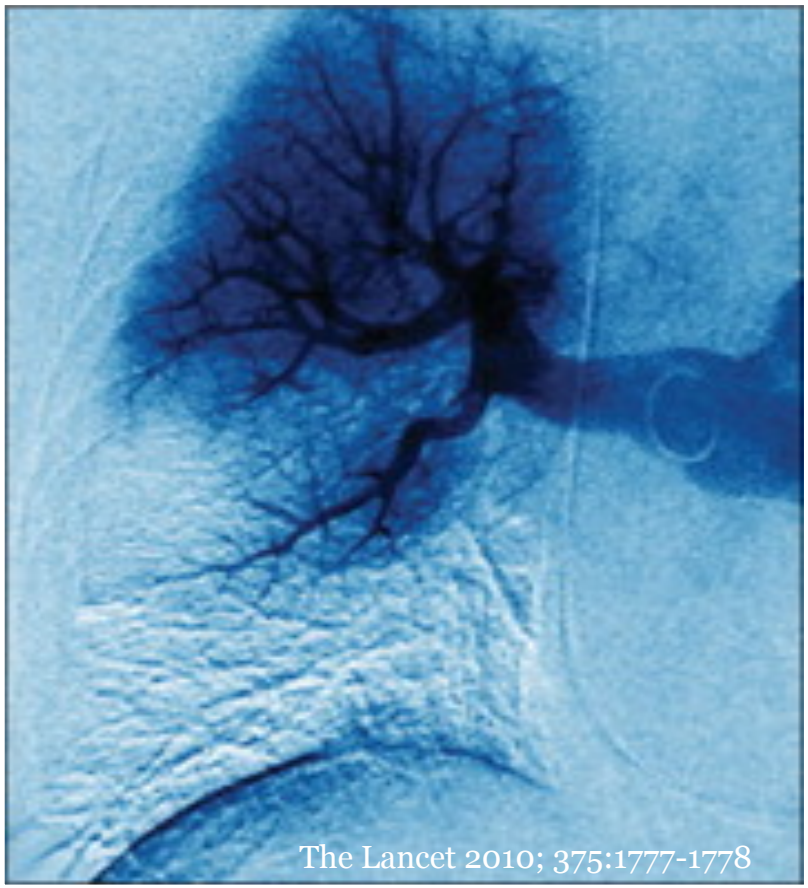
IL CUORE MALATO È MASCHIO O FEMMINA?"
"THE SICK HEART IS MALE OR FEMALE?

Pregnancy is an example of Virchow's triad: hypercoagulability, venous stasis, and vascular damage.



The Lancet 2010; 375:1777-1778

Le donne in gravidanza hanno un rischio di TEV di 4-6 volte più alto.
Durante il post-partum (6 settimane) il rischio è di 20 volte più alto.


The Lancet 2010; 375:1777-1778

Circa l'80% delle TEV è una trombosi venosa profonda (LEFT) mentre il 20% si complica con EP.

L'EMBOLIA POLMONARE È LA PIU' COMUNE CAUSA DI MORTE NELLE DONNE IN GRAVIDANZA NEI PAESI SVILUPPATI.

TASSO DI MORTALITA': 1.1 per 100.000 parti.
10% di tutte le morti materne.

Specific risk factors for antepartum and postpartum

	Odds Ratio (95% CI)
Medical Complications	
Hypertension	1.8 (1.4–2.3)
Diabetes	2.0 (1.4–2.1)
Obesity	4.4 (3.4–5.7)
Sickle cell disease	6.7 (4.4–10.1)
Heart disease	7.1 (6.2–8.3)
Lupus	8.7 (5.8–13.0)
Antiphospholipid syndrome	15.8 (10.9–22.8)
History of thrombosis	24.8 (17.1–36.0)
Thrombophilia	51.8 (38.7–69.2)
Antepartum risk	
Body mass index (BMI) >25	1.8 (1.3–2.4)
Smoking (10–30 cigarettes/d)	2.1 (1.3–3.4)
Spontaneous twin gestation	2.6 (1.1–6.2)
ART twin gestation	6.6 (2.1–21.0)
Antepartum immobilization	7.7 (3.2–19.0)
BMI >25 and antepartum immobilization	62.3 (11.5–337.6)
Postpartum risk	
Planned cesarean	1.3 (0.7–2.2)
Acute cesarean	2.7 (1.8–4.1)
Smoking (10–30 cigarettes/d)	3.4 (2.0–5.5)
Hemorrhage (without surgery)	4.1 (2.3–7.3)
Infection (cesarean delivery)	6.2 (2.4–16.2)
Hemorrhage (with surgery)	12.0 (3.9–36.9)
Infection (vaginal delivery)	20.2 (6.4–63.5)

Obstet Gynecol Clin N Am 37 (2010) 333–343 - Arterioscler Thromb Vasc Biol (2009);29;326-331

Assessment of risk factors for VTE before pregnancy or in early pregnancy.

Pre-existing risk factors
Previous recurrent VTE[a]
Previous VTE—unprovoked or oestrogen related[b]
Previous VTE—provoked
Family history of VTE
Known thrombophilia[c]
Medical co-morbidities, e.g.heart or lung diseases, SLE, cancer, inflammatory conditions, nephritic syndrome, sickle cell disease, i.v. drug use
Age >35 years
Obesity, BMI >30 kg/m^2 [d]
Parity ≥3
Smoker
Gross varicous veins
Obstetric risk factors
Pre-eclampsia
Dyhydration/hyperemesis/ovarian hyperstimulation syndrome
Multiple pregnancy or assisted reproductive therapy
Emergency caesarean section
Elective caesarean section
Mid-cavity or rotational forceps
Prolonged labour (>24 hours)
Peripartum haemorrhage (>1 L or transfusion)
Transient risk factors
Current systemic infection
Immobility
Surgical procedure in pregnancy or <6 weeks post-partum

Risk factor	Prevalence (%)	Odds ratio (confidence interval)
Factor V Leiden mutation		
Heterozygous	2.0–7.0	8.32 (5.44,12,70)
Homozygous	0.2–0.5	34.40 (9.86, 120.05)
Prothrombin G20210A mutation		
Heterozygous	2.0	6.80 (2.46, 18.77)
Homozygous	Rare	26.36 (1.24, 559.29)
Antithrombin deficiency (<80% activity)	<0.1–0.6	4.76 (2.15, 10.57)
Protein C deficiency (<75% activity)	0.2–0.3	4.76 (2.15, 10.57)
Protein S deficiency (<65% activity)	<0.1–0.1	2.19 (1.48, 6.00)

Regitz-Zagrosek V. et Al
ESC Guidelines on the management of cardiovascular diseases during pregnancy.
European Heart Journal (2011) 32, 3147–3197

PREVENTION OF VTE

Early mobilization and **graduated compression stockings** are mildly effective, safe, and non-invasive methods for prevention of VTE; they are probably all that is needed to prevent VTE in low-risk groups!!!

Prevention of Recurrent VTE in Pregnant Women

For pregnant women at moderate to high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term anticoagulation), we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH rather than clinical vigilance or routine care (Grade 2C).

Women with no prior VTE and one of the following thrombophilic defects:
Deficiency of Protein C,
Deficiency of Protein S
Double heterozygous carriers of FVL and PTM
Homozygous carriers of FVL or PTM (Grade D).

Prophylactic doses of LMWH ante-partum plus postpartum for 6 weeks after delivery.

Women with no prior VTE and deficiency of antithrombin

Moderate doses of LMWH ante-partum plus postpartum for 6 weeks after delivery
(at the time of delivery the use of antithrombin concentrates should be evaluated, in order to allow reduction of LMWH to prophylactic doses and decrease the haemorrhagic risk).

Asymptomatic women with APLA

Ante-partum prophylactic doses of LMWH and/or aspirin.
Post-partum prophylactic doses of LMWH for 6 weeks after delivery

9th ed: American College of Chest Physicians 2012© Chest. 2012 Feb;141(2 Suppl):e419S-94S

Guidelines of the Italian Society for Haemostasis and Thrombosis Thrombosis Research 124 (2009) e19–e25

Indications to Thrombophilic work up

- Unexplained venous thromboembolism (VTE) at a younger age (< 50 years)
- Recurrent spontaneous VTE
- Unexplained VTE at an unusual site (portal, mesenteric, splenic, hepatic, sinus/cerebral,or renal veins)
- Unusually extensive spontaneous VTE
- Family history of spontaneous VTE
- Asymptomatic individual with family history of known stronger thrombophilia
  - Antithrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Homozygous factor V Leiden
  - Homozygous prothrombin mutation
  - Compound thrombophilias
- Recurrence of VTE while adequately anticoagulated
- Unexplained arterial thromboembolism in a younger patient who has no significant arteriosclerosis risk factors and no cardioembolic source
- ≥ 3 unexplained pregnancy losses before week 10, or ≥ 1 after week 10

The homocysteine controversy

- **A variable may predict disease without being causally related to the disease.**
- **The common term for such a predictor is biomarker.**
- **A biomarker commonly represents an early stage of the disease.**
- **Interventions aimed at optimizing a biomarker may or may not be associated with reduced disease incidence depending on whether the treatment has an effect on a causal mechanism that underlies both the appearance of the biomarker as well as the occurrence of disease.**
- **Treatment that reduces the biomarker without affecting disease incidence is useless.**

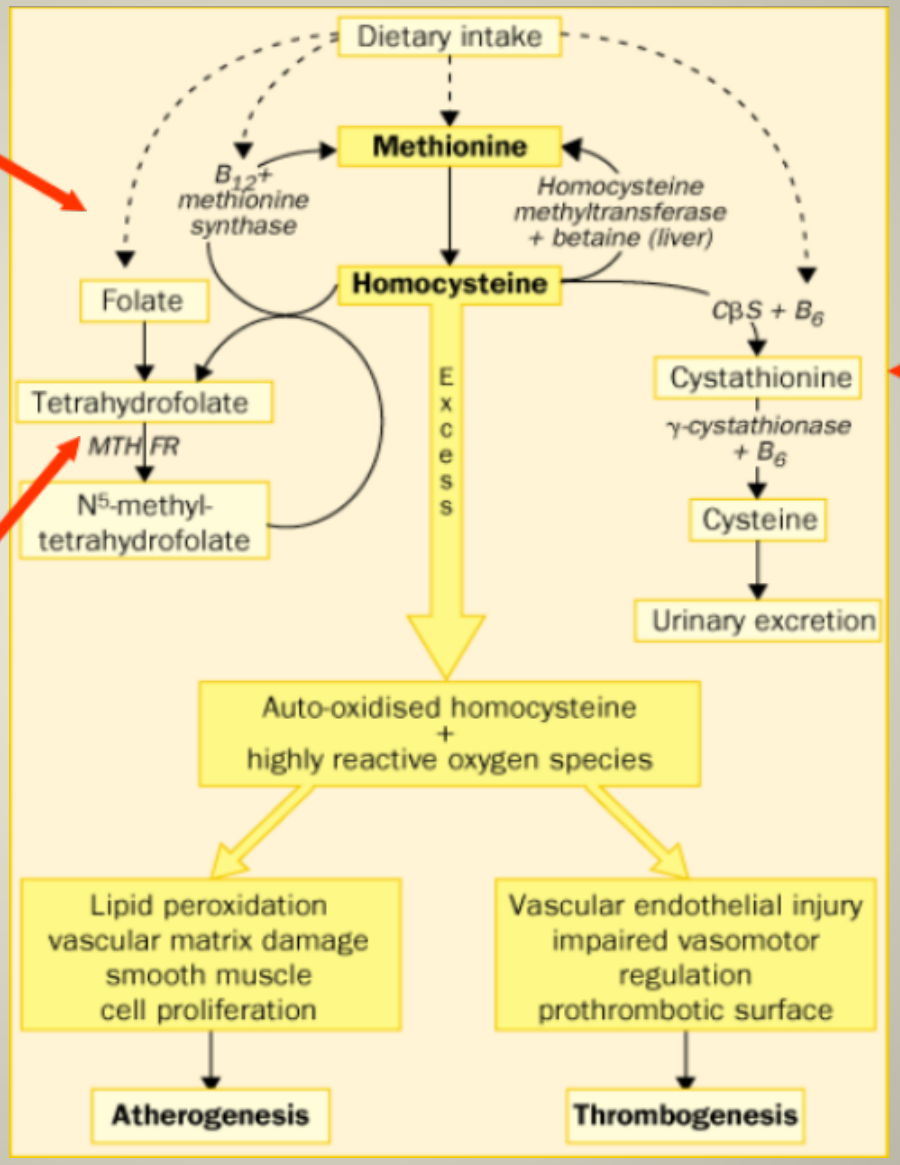
B12

Diet

Folate

Hyperhomocysteinemia: Possible mechanism for role in atherogenesis, thrombogenesis

Lancet Vol 354, 1999



B6

MTHFR C677T

(At III, PC, F VII, tPA)

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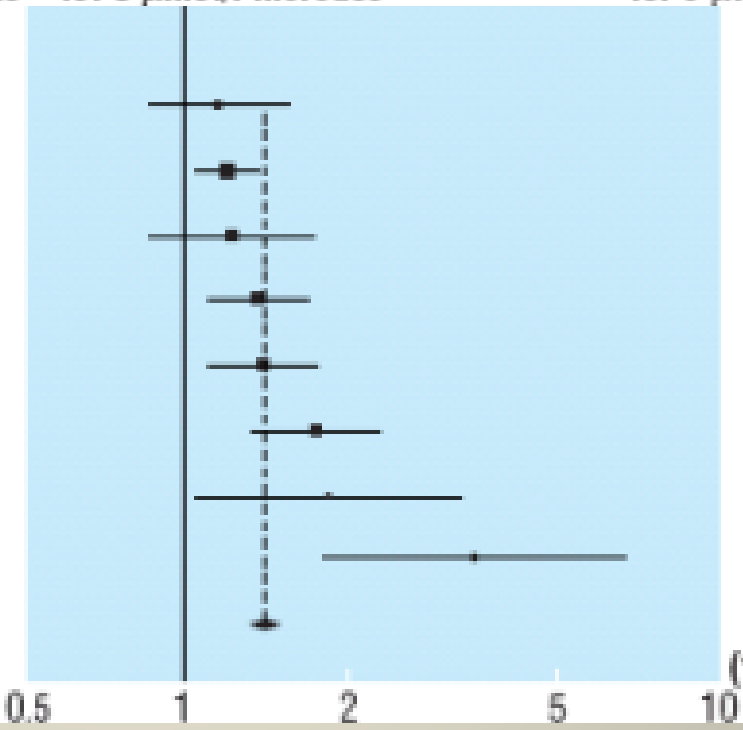
Hyperhomocysteinemia and Stroke

5 micromol

First author	Cohort size	Follow up (years)	No of events	Odds ratio for 5 μmol/l increase
Stroke				
Fallon[W112]	2254	10	107	1.15
Stehouwer[W102]	878	10	58	1.19
Alfthan[W98]	7424	9	74	1.21
Bostom[W113]	1947	10	165	1.36
Bots[W108]	7983	3	120	1.39
Vollset[W110]	4766	4	16	1.76
Petri[W114]	337	5	29	1.86
Perry[W115]	5661	12	107	3.52
Combined	**31 250**		**676**	**1.42 (1.21 to 1.66)**



Wald DS et al BMJ 2002; 325; 1202-1206

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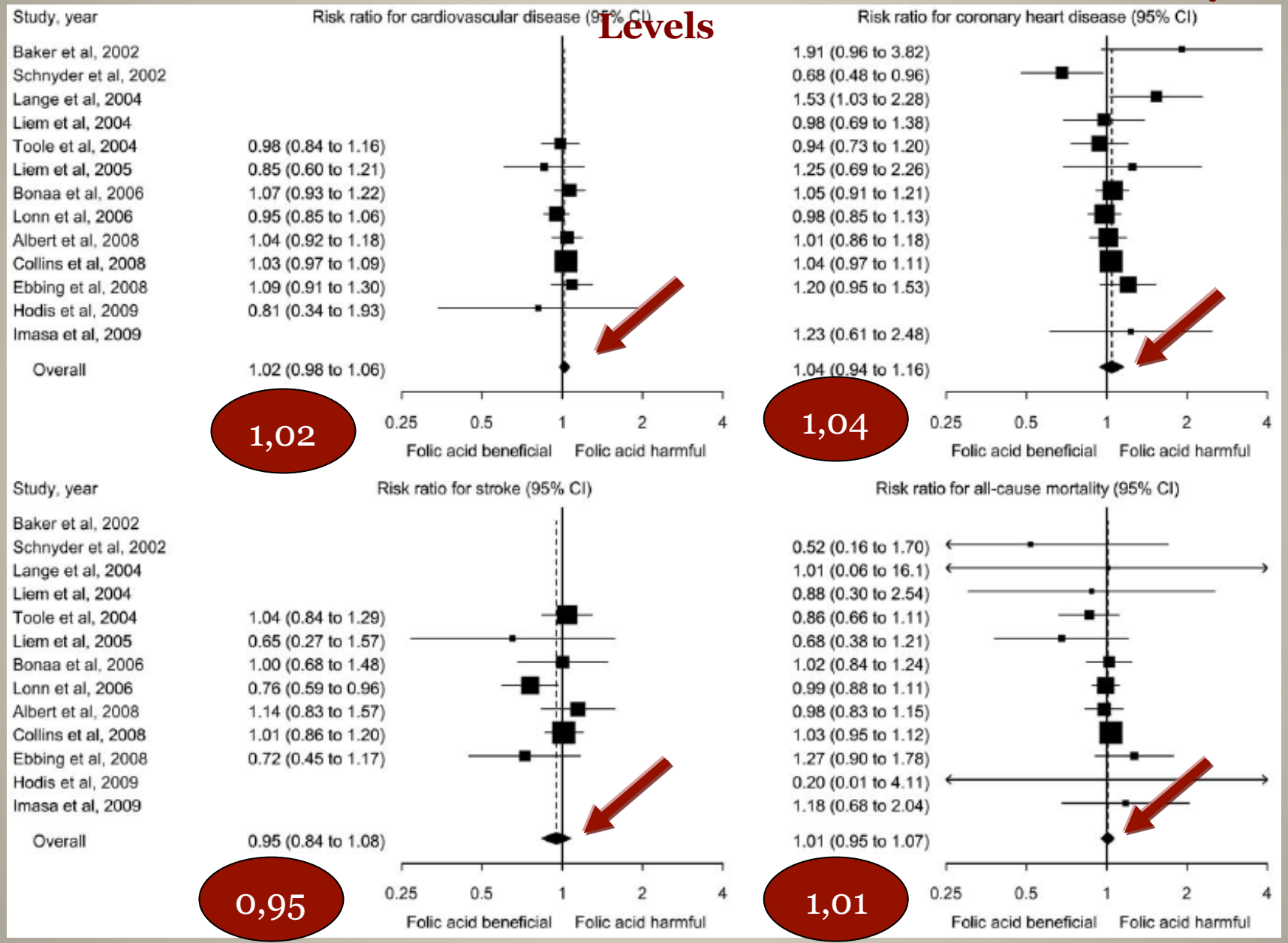
Meta-Analysis of Folic Acid Supplementation Trials on Risk of Cardiovascular Disease and Risk Interaction With Baseline Homocysteine Levels



Am J Cardiol 2010;106:517–52

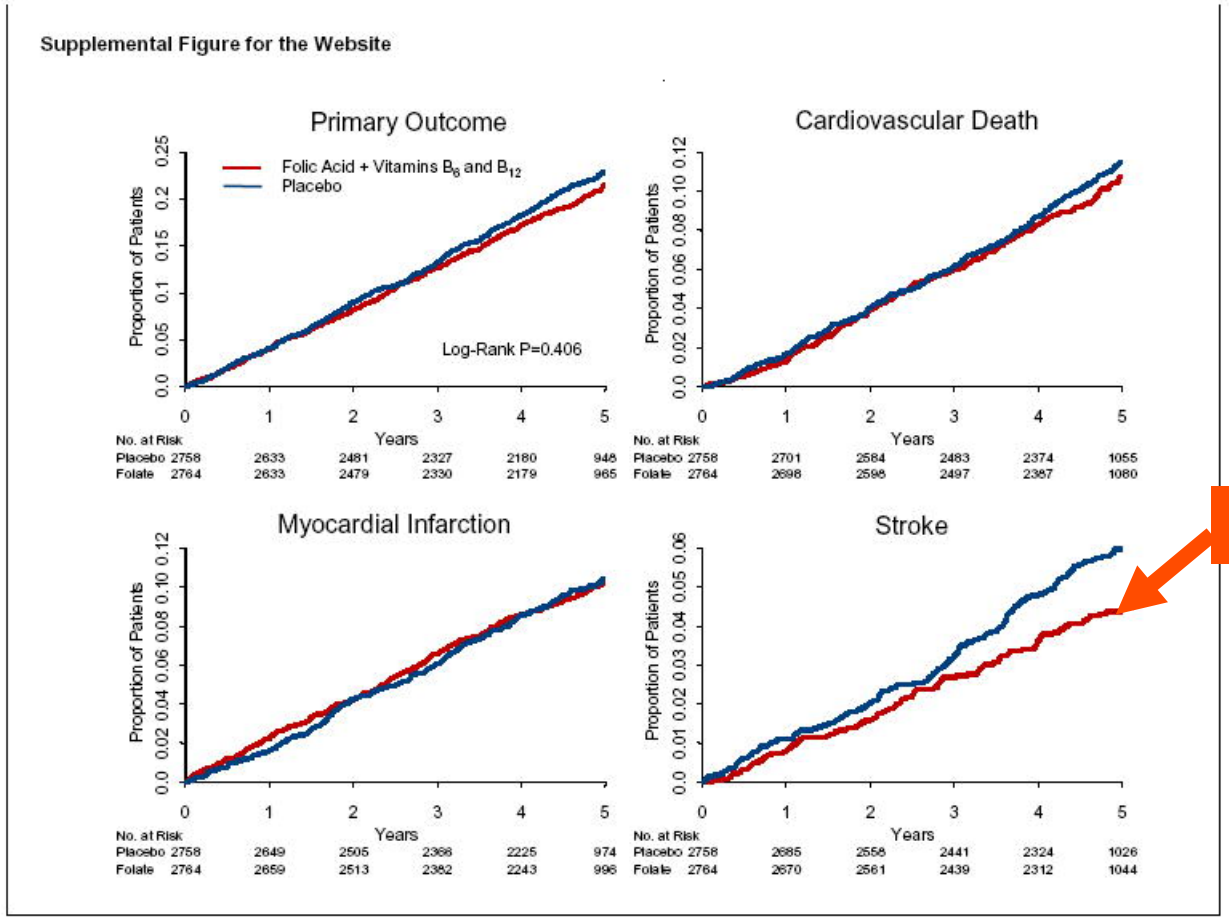
Individuals with homocysteine levels > 12 μmol/l *should increase and/or supplement* the dietary intake of folic acid

Patients with homocysteine levels > 30 μmol/l *should be treated* with daily doses of:

0.5–15 mg folic acid	(HOPE=2.5 mg) (NORVIT=0.8 mg)
50–400 mg vitamin B6	(HOPE=50 mg) (NORVIT=40 mg)
0.4–1 mg vitamin B12	(HOPE=1 mg) (NORVIT=0.4 mg)

Nutrition, Metabolism, and Cardiovascular Disease 1998, 8:212-271

Heart Outcomes Prevention Evaluation (HOPE 2)



Primary outcome events occurred in 519 patients (18.8 percent) assigned to active therapy and 547 (19.8 percent) assigned to placebo (relative risk, 0.95; P=0.41).

0.75

Stroke

4% vs. 5.3 %;
relative risk, 0.75; P=0.03

5,522 patients
>55 years of age
vascular disease or diabetes

N Engl J Med. 2006 Apr 13;354(15):1567-77

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Awaiting the results of studies to come, what should we do with our high-risk patient? Clearly, an evidencebased recommendation is impossible.

Homocysteine *should be measured* in patients with history of atherosclerotic and/or thromboembolic vessel diseases

Upon decision to treat (DIET), do not use high-dose B-vitamin preparations routinely, but start with a multivitamin containing moderate amounts of folate, B12, and B6

Acido Folico 5 mg
Acido folinico 15 mg (1 cp) se MTHFR C677T (omozigote)
Vit. B6 250 mg (1/2)
Vit. B12 500 mcg (1/2)

Switch to high-dose B vitamins only if homocysteine remains clearly elevated

Maternal Consequences of Antithrombotic Therapy Use During Pregnancy

For pregnant patients, we recommend LMWH for the prevention and treatment of VTE, instead of UFH (Grade 1B)**.**

For pregnant women, we suggest limiting the use of fondaparinux and parenteral direct thrombin inhibitors to those with severe allergic reactions to heparin (eg, HIT) (Grade 2C).

9th ed: American College of Chest Physicians 2012©

Treatment of Patients With Proven Acute VTE During Pregnancy

For pregnant women with acute VTE, we recommend therapy with adjusted-dose SC LMWH over adjusted-dose UFH (Grade 1B).

For pregnant women with acute VTE, we suggest that anticoagulants should be continued for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months) in comparison with shorter durations of treatment (Grade 2C).

9th ed: American College of Chest Physicians 2012©

Treatment of Patients With Proven Acute VTE During Pregnancy

For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 h prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (Grade 1B).

9th ed: American College of Chest Physicians 2012©

Prevention of Recurrent VTE in Pregnant Women

For all pregnant women with prior VTE, we suggest postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

9th ed: American College of Chest Physicians 2012©

Prevention of Recurrent VTE in Pregnant Women

For pregnant women at **low risk of recurrent VTE (single episode of VTE associated with a transient risk factor not related to pregnancy or use of estrogen),** we suggest clinical vigilance antepartum rather than antepartum prophylaxis (Grade 2C).

9th ed: American College of Chest Physicians 2012©

Prevention of Recurrent VTE in Pregnant Women

For pregnant women at moderate to high risk of recurrent VTE (single unprovoked VTE, pregnancy- or estrogen-related VTE, or multiple prior unprovoked VTE not receiving long-term anticoagulation), we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH rather than clinical vigilance or routine care (Grade 2C).

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Prevention of VTE in Pregnant Women With Thrompophilia and No Prior VTE

For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and have a positive family history for VTE, we suggest antepartum prophylaxis with prophylactic- or intermediate-dose LMWH and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than no prophylaxis (Grade 2B).

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Prevention of VTE in Pregnant Women With Thrompophilia and No Prior VTE

For pregnant women with all other thrombophilias and no prior VTE who have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or, in women who are not protein C or S deficient, VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2C).

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Prevention of VTE in Pregnant Women With Thrompophilia and No Prior VTE

For pregnant women with no prior history of VTE who are known to be homozygous for factor V Leiden or the prothrombin 20210A mutation and who do not have a positive family history for VTE, we suggest antepartum clinical vigilance and postpartum prophylaxis for 6 weeks with prophylactic- or intermediate-dose LMWH or VKAs targeted at INR 2.0 to 3.0 rather than routine care (Grade 2B).

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Prevention of VTE in Pregnant Women With Thrompophilia and No Prior VTE

For pregnant women with all other thrombophilias and no prior VTE who do not have a positive family history for VTE, we suggest antepartum and postpartum clinical vigilance rather than pharmacologic prophylaxis (Grade 2C).

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VTE in Patients Using Assisted Reproductive Technology

For women undergoing assisted reproduction, we recommend against the use of routine thrombosis prophylaxis (Grade 1B).

For women undergoing assisted reproduction who develop severe ovarian hyperstimulation syndrome, we suggest thrombosis prophylaxis (prophylactic LMWH) for 3 months postresolution of clinical ovarian hyperstimulation syndrome rather than no prophylaxis (Grade 2C).

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VTE Following Cesarean Section

For women undergoing cesarean section without additional thrombosis risk factors, we recommend against the use of thrombosis prophylaxis other than early mobilization (Grade 1B).

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VTE Following Cesarean Section

For women at increased risk of VTE after cesarean section because of the presence of one major or at least two minor risk factors (see next slide) we suggest pharmacologic thromboprophylaxis (prophylactic LMWH) or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in hospital following delivery rather than no prophylaxis (Grade 2B).

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Risk Factors for VTE Postpartum

1

Major Risk Factors (odds ratios >6): Presence of at least 1 risk factor suggests a risk of postpartum VTE of >3%

- Immobility (strict bed rest for a week or more in the antepartum period)
- Postpartum hemorrhage ≥1000 ml with surgery
- Previous VTE
- Preeclampsia with fetal growth restriction
- Thrombophilia
  - Antithrombin deficiency*
  - Factor V Leiden (homozygous or heterozygous),
  - Prothrombin G20210A (homozygous or heterozygous)
- Medical conditions
  - SLE
  - Heart disease
  - Sickle cell disease
- Blood transfusion
- Postpartum infection

Minor Risk factors (odds ratios > 6 when combined): Presence of at least 2 risk factors or 1 risk factor in the setting of emergency cesarean section suggests a risk of postpartum VTE of >3%

- BMI>30kg/M^2
- Multiple pregnancy
- Postpartum hemorrhage >1L
- Smoking >10 cigarettes per day
- Fetal growth restriction (Gestational age + sex adjusted birth weight <2.5th percentile)
- Thrombophilia
  - Protein C deficiency
  - Protein S deficiency
- Preeclampsia

2

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Prevention of VTE Following Cesarean Section

For selected high-risk patients in whom significant risk factors persist following delivery, we suggest extended prophylaxis (up to 6 weeks after delivery) following discharge from the hospital (Grade 2C).

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Venous filters

Recommendations	Class[a]	Level[b]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in case of recurrence of PE, despite therapeutic levels of anticoagulation.	IIa	C
Routine use of IVC filters in patients with PE is not recommended.	III	A

Venous filters are usually placed in the infrarenal portion of the inferior *vena cava* (IVC).

Early complications— 10% of patients.
Late complications - recurrent DVT in approximately 20% of patients and post-thrombotic syndrome in up to 40%.

Occlusion of the IVC affects approximately 22% of patients at 5 years and 33% at 9 years, regardless of the use and duration of anticoagulation.

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2014 ESC Guidelines

~~IVC filters~~

- **Non-permanent are classified as temporary or retrievable devices.**
- **Temporary filters must be removed within *few days*, while retrievable filters can be left in place for longer periods.**
- **When non-permanent filters are used, it is recommended that they be removed as soon as it is safe to use anticoagulants.**
- ***Despite this, they are often left in situ for longer periods, with a late complication rate of at least 10%.***

When should clinicians start anticoagulants?

- **In patients with a *high pretest probability of VTE* and *a low risk for bleeding*, it is reasonable to initiate a short-acting anticoagulant while awaiting the results of the diagnostic work-up, particularly if there is a delay in testing.**

- **In patients with *an intermediate clinical suspicion* of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).**

- **In patients with *a low clinical suspicion of acute VTE*, it is suggested not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).**

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- **In patients with *a low clinical suspicion of acute VTE*, it is suggested not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).**

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