

# Combined hormonal contraceptives CHC Session II

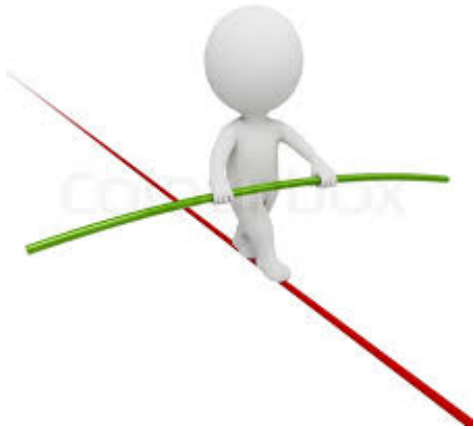
How to take a detailed risk history  
understanding VTE and ATE risk  
balance risks / benefits

Advanced slide kit complementing the  
WHO training tool [www.fptraining.org](http://www.fptraining.org)

# Contents

- How to take a history before contraceptive counselling
- Special risk screening for use of CHCs (higher risks / lower risks and WHO MEC category 4 criteria)
- There are two types of risks: one affecting the arterial system and one the venous system
- **VTE risk in healthy young women without contraception and in pregnancy**
  - EMAS recommendation: VTE risk according to progestin type and method of application
  - VTE risk according to estrogen dose and type of estrogen
  - Understand what is meant by a positive family history and what it means for risk counselling
  - VTE risk in women with thrombophilia
  - Overview risk for VTE in numbers and multiplication of risks
  - VTE risk with age, obesity and duration of CHC use
- **Arterial risk:** stroke and myocardial infarction in numbers, in relation to age and obesity
- Balancing risks against other contraceptive options and benefits during counselling

## Balancing risks and benefits



- This session discusses a lot of potential risks associated with use of CHC
- Only a subgroup of women will experience complications with CHC use
- CHCs are not dangerous for healthy young women

# Taking a history before contraceptive counselling

**General  
History**

**Gynaecologic  
history**

**Reproductive  
health goals**

**Personal  
situation**

# General history

Most important aspects to avoid severe complications

## General history

Exclude:

1. Previous venous blood clot (venous thrombosis), stroke or heart attack
2. Thrombogenic mutations
3. Migraine with aura
4. Hypertension ( $\geq 160/ \geq 100$  mm Hg)
5. Severe liver or gall bladder disease
6. Systemic lupus erythematoses
7. Diabetes with vascular complications
8. Smoking and age  $> 35$  years
9. A venous blood clot, stroke or heart attack in any first degree relative aged  $\leq 50$  years

# General history

Further issues important to address before balancing risks and benefits

## General history

1. Medical conditions
2. Surgery
3. Medication (include phytotherapeutics): consider potential interactions
4. Psychic disorders and eating disorders
5. Alcohol, drugs and allergies
6. Smoking and weight

# Gynaecological history

The most important aspects to optimise counselling and use benefits of CHC

## Gynaecological History

1. Menstrual cycle: interval, duration, intensity of bleeding, symptoms and date of last menstruation
2. Pregnancies: births, abortions, breastfeeding
3. Breast, cervical, ovarian and endometrial cancer
4. Ovarian cysts
5. Previous contraceptive methods: tolerability and adherence
6. Previous use of emergency contraception

# Personal situation and reproductive health goals

## Reproductive health goals

1. Duration of relationship with partner
2. Plans for motherhood
3. Need for long-term contraception
4. Financial issues
5. Wish for permanent contraception
6. STI protection

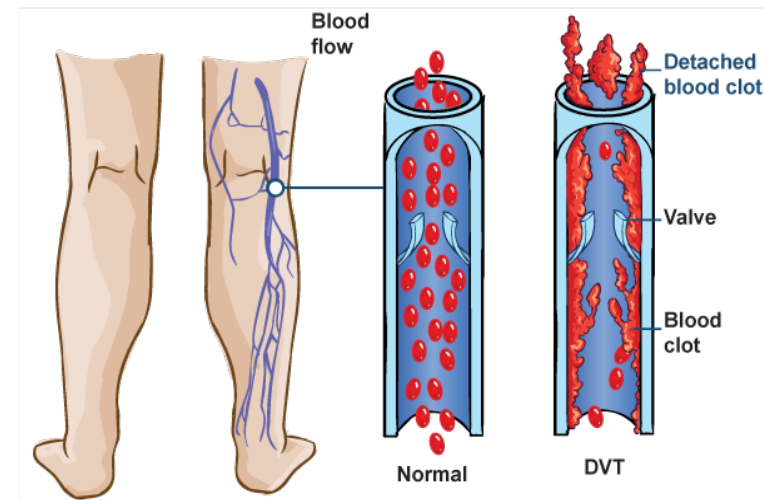


## More detailed cardiovascular risk screening for use of CHC

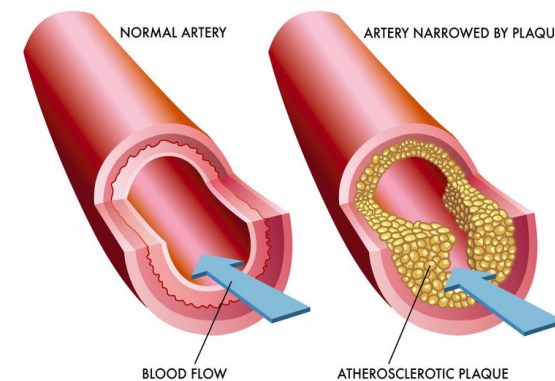
- History of venous thromboembolism (VTE), pulmonary embolism, myocardial infarction (MI) or stroke: **WHO MEC category 4**
- Known thrombophilia: **WHO MEC category 4**
- Migraine with aura: **WHO MEC category 4**
- Hypertension  $\geq 160/\geq 100$  mmHg: **WHO MEC category 4**
- Positive family history of VTE, pulmonary embolism, MI, stroke: **strong contraindication**
- Obesity
- Age  $>35$  years
- Smoking
- Migraine without aura
- Multiplicative effect of less strong risk factors (smoking and age)

# Differentiate arterial from venous risks

- **VTE** in CHC users is an acute event which results from the effects of hormones on the coagulation system.
- VTE typically affect younger users and newstarters.
- **Arterial** events typically occur when the arteries are already damaged by atherosclerosis and a thrombus develops on the plaques potentially promoted from the effects of CHC on coagulation.
- Age >35 and any condition related to atherosclerosis are important risk factors.



ATHEROSCLEROSIS



# 1. VTE and deep venous thrombosis (DVT)

Risks, in numbers, according to :

- Type of CHC
- Type of risk factor

## VTE risk in healthy young women not using CHC

### Risk of developing a VTE in a year

	Incidence	Relative risk
1. Healthy young women	2-3/10.000	1
2. Pregnancy	48-60/10.000	12
3. Healthy user of CHC	5-12/10.000	2-4

**CHC use in healthy women is associated with a two-fourfold VTE risk**

# Risk with different types of CHC

<b>Risk of developing a blood clot (VTE) in a year in 10.000 women</b>	
<b>Women not using CHC pill / patch / ring</b>	<b>About 2 / 10.000</b>
<b>Women using a CHC containing ethinylestradiol/levonorgestrel, norethisterone, norgestimate</b>	<b>About 5-8.9 / 10.000</b>
<b>Women using a CHC containing ethinylestradiol/drospirenone, gestoden, desogestrel</b>	<b>About 9-12 / 10.000</b>
<b>Women using a CHC containing estradiol/nomegestrolacetate*</b>	<b>About 4.8 / 10.000</b>
<b>Women using a CHC containing estradiolvalerate/dienogest</b>	<b>About 7.7 / 10.000</b>
<b>Women using a CHC containing estetrol/drospirenone</b>	<b>Not yet known</b>

\* More information next slide, comments in the notes

## VTE risk and progestin type in CHCs

CHC with ethinylestradiol and a third or fourth generation progestin are associated with the **twofold higher VTE** risk in comparison with those containing a second generation progestin

The pill with estradiol / nomegestrolacetate is associated with the same VTE risk as pills with EE/LNG

The exact VTE risk for the combined pill with estetrol is not yet known

## Consequences for prescription of CHCs

- CHCs with third and fourth generation progestins are associated with a twofold higher risk of VTE in comparison with CHCs containing levonorgestrel
- The differences in VTE risks between CHC with different progestins are low (odds ratio 2). In numbers these are 3-5 events in 10.000 women/year
- It is recommended to start women on a product containing a second generation progestin (levonorgestrel) or a pill with estradiol / nomegestrolacetate, if there is no reason to prescribe a CHC associated with a slightly higher VTE risk
- Regular re-assessment of risk factors is needed

## VTE and estrogen type and dosage

- No difference in VTE risk was found between pills containing 20  $\mu\text{g}$  or 30  $\mu\text{g}$  ethinylestradiol
- CHCs with estradiol-valerate are not associated with a higher risk for VTE in comparison with third generation CHCs
- The VTE risk with the pill with estradiol / norgestrolacetate is comparable with that of second generation CHCs



## Risk factors for VTE

- a. Family history (1st degree relative <50 years)
- b. Thrombophilia
- c. Obesity
- d. *Age? → risk is more on the arterial side*
- e. *Smoking? → risk is more on the arterial side*

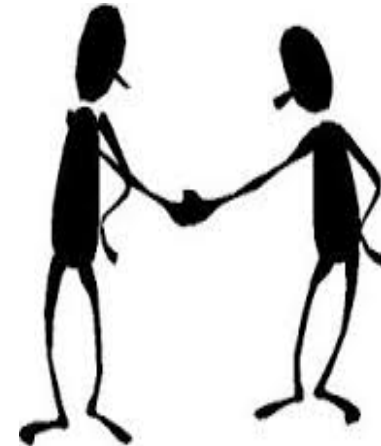
Consider the multiplicative effect of risk factors

## Risk factors for VTE

- a. Family history (1st degree relative <50 years)

## Positive family history Definition

- A family history for VTE is positive, if a first-degree relative has experienced a VTE
- There is no general agreement about the age of this first-degree relative
- Age <50 years is typically used in haematological studies



**In the context of CHC use it makes sense to limit the age of the first-degree relative to 50 years, however in some situations additional aspects have to be considered**

# Positive family history

## How high is the VTE risk in non-CHC users?

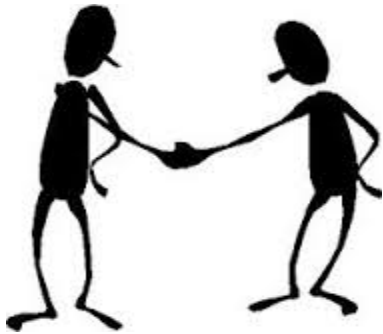
Family history	VTE-Risk odds ratio (1)	Relation to proband	VTE-Risk odds ratio (2)
negative	1	Sibling	2.5
positive any relative	2.2	Son/daughter	2.6
positive relative <50 years	2.9	Parent	2.1
>1 relative	2.9	Second degree relative	1.5-2.3
2 relatives, one <50 years	4	2 relatives, one <50 years	4

Note, that age of the first degree relative <50 or not, does not make such a difference!

## Positive family history Probable risk for CHC users

- The VTE risk with a first-degree relative is two- to threefold
- The risk with additional use of CHC is 15 fold
- CHC should rather not be prescribed in such a situation
- Progestin-only methods and intrauterine devices can be used

# Medical condition Positive Family history



## Efficient and safe options for contraception

- Copper IUD and LNG-IUS
- POP Desogestrel
- Implant
- DMPA
- Permanent methods

Should women with positive family history be screened for hereditary thrombophilia? **NO**

- 29.7 % of women with family history (1st degree relative) and VTE are diagnosed with thrombophilia (genetic risk)
- The classical five thrombophilias are not a typical cause for a positive family history
- A positive family history is the stronger predictor for VTE than cost-intensive thrombophilia screening
- Testing women with positive family history may give wrong reassurance if the patient is tested negative. She nevertheless will have a markedly increased risk of CHC-related VTE compared with the general population. CHCs therefore should not be prescribed.

# Risk factors for VTE

b. Thrombophilia



# Hereditary thrombophilia

Incidence and VTE risk without CHC  
(heterozygous carriers)

	<b>Prevalence</b>	<b>Risk for VTE</b>
• Protein C deficiency	0.1%	10 fold
• Protein S deficiency	0.1%	10 fold
• Antithrombin III deficiency	0.1%	10 fold
• Prothrombin 20210 A Mutation	2-3%	3-8 fold
• Factor V Leiden	5-10%	3-8 fold

# Severe hereditary thrombophilia

## Incidence and VTE risk in CHC users

Type of thrombophilia	Incidence / 10.000 woman years CHC users	Incidence / 10.000 woman years Non- HC users <small>(all are relatives and thus have a positive family history and a higher baseline risk in comparison to young healthy women)</small>
<b>Severe</b> Antithrombin deficiency Protein C deficiency Protein S deficiency	430-462	48-70
<b>Mild</b> Factor V Leiden Prothrombin 20210 A Mutation	49-200	19

# Hereditary thrombophilia

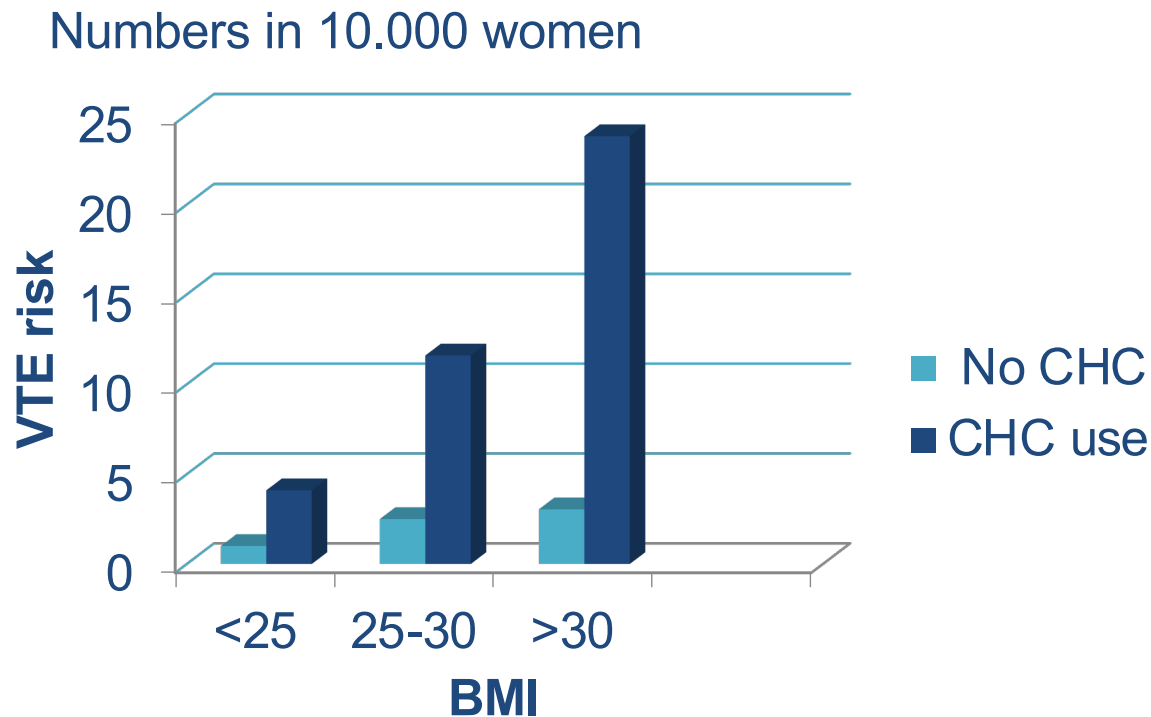
## Recommendation for CHC use

- Based on the high additive risk for VTE CHC-use should be **avoided** in asymptomatic women with severe thrombophilia
- Testing women with positive family history may give wrong reassurance if the patient is tested negative. She nevertheless will have a markedly increased risk of CHC-related VTE compared with the general population.

# Risk factors for VTE

c. Obesity

# VTE and Obesity



**Obesity increases the risk for VTE 2-3 fold.**  
**The risk strongly increases with CHC use and can multiply with other risks like age. The degree of obesity has an impact as well.**

## Risk factors for VTE

- d. *Age? → risk is more on the arterial side*
- e. *Smoking? → risk is more on the arterial side*

## VTE risk Age and smoking

**Smoking** as risk factor for VTE is discussed controversial, in heavy smokers some studies indicate an increased risk HR 1.5.

**Age** is not important as risk factor for VTE in women from age 35 onwards. For younger women other additional risk factors, like obesity have to be excluded.

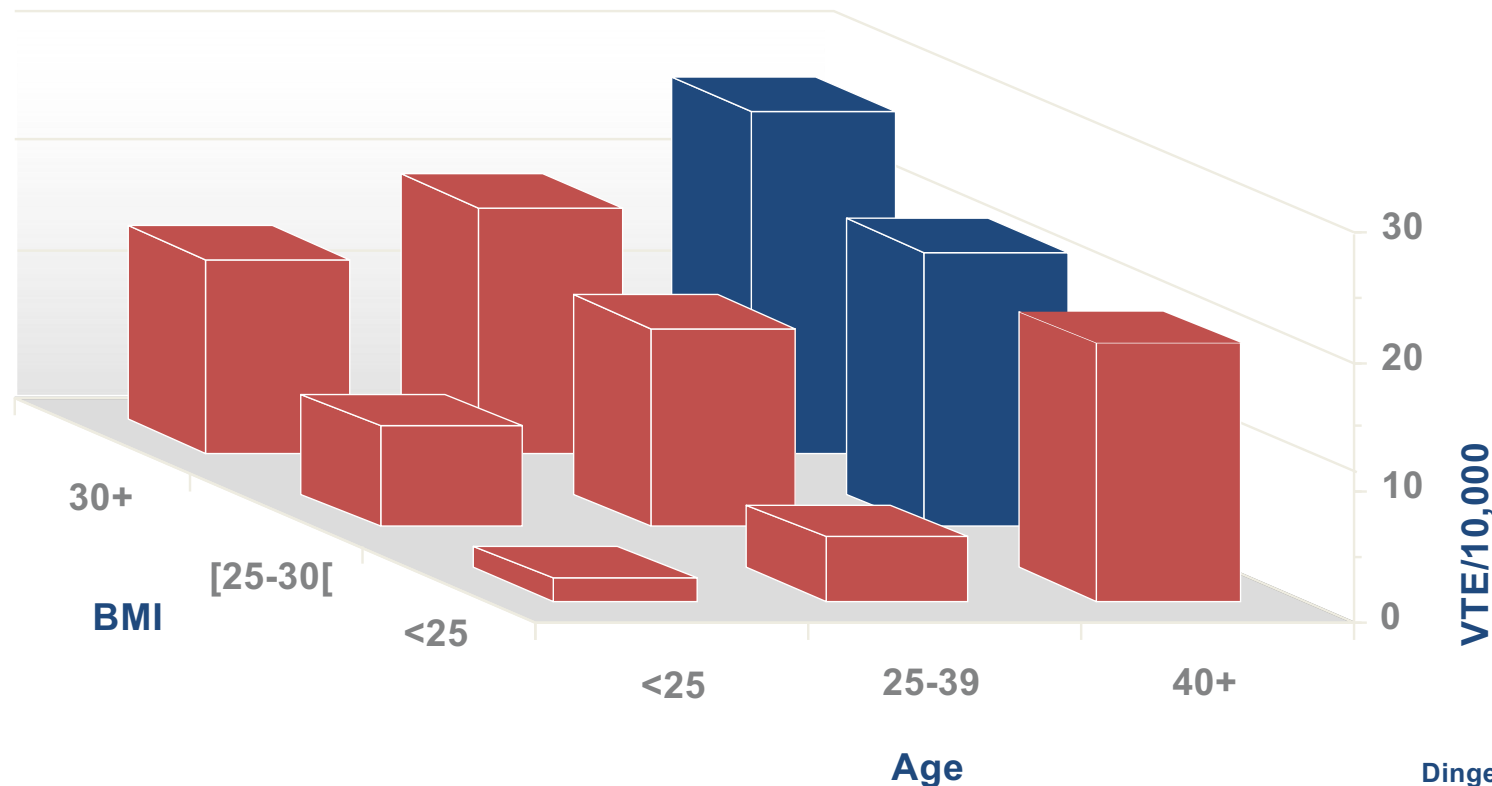
Incidence in non-CHC users:

Incidence age 20-24            2.7/10.000

Incidence age 35-39            3.9/10.000

# Multiplication of risk factors

Increasing impact of age and BMI on VTE risk in COC users\*



Dinger, EURAS Study

\* Risk estimates based on 115 VTEs in 116,708 WY of exposure



## VTE risk age and smoking

- Age and smoking are not strong as single risk factors for VTE in fertile women
- However, take into account the multiplicative effect of less strong risk factors and consider the arterial risk as well

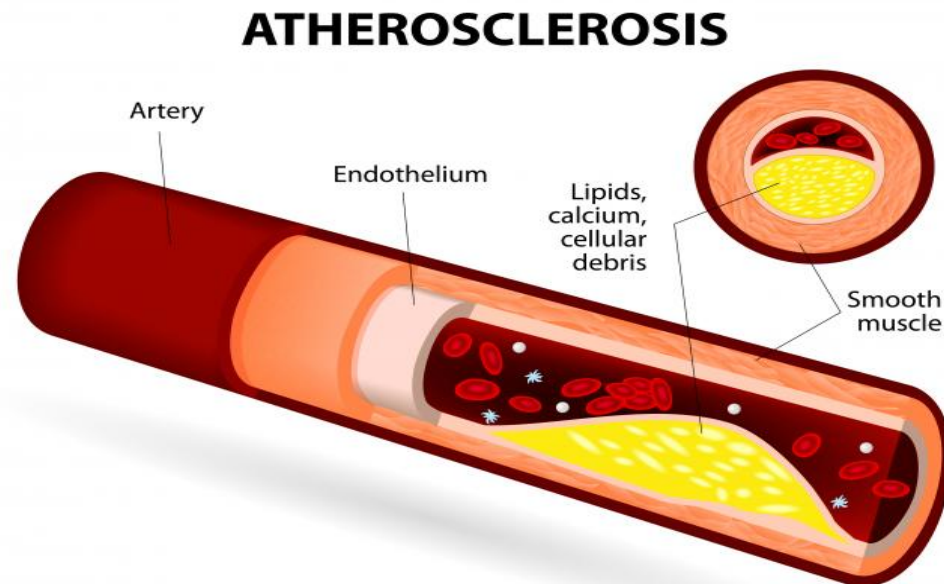
## Risk of cerebral venous thrombosis (CVT)

- CVT incidence among adults 0.13/10.000 years
- Women and persons younger than 50 years are at greater risk
- Risk factors: hereditary thrombophilia, CHC use, anaemia, trauma
- Typical symptoms include: headache, papilloedema, epileptic seizure

The OR for CVT risk in CHC users is 5.5, but the risk is very small, as baseline incidence is low

## 2. ATE risks in numbers

Myocardial infarction and ischemic stroke



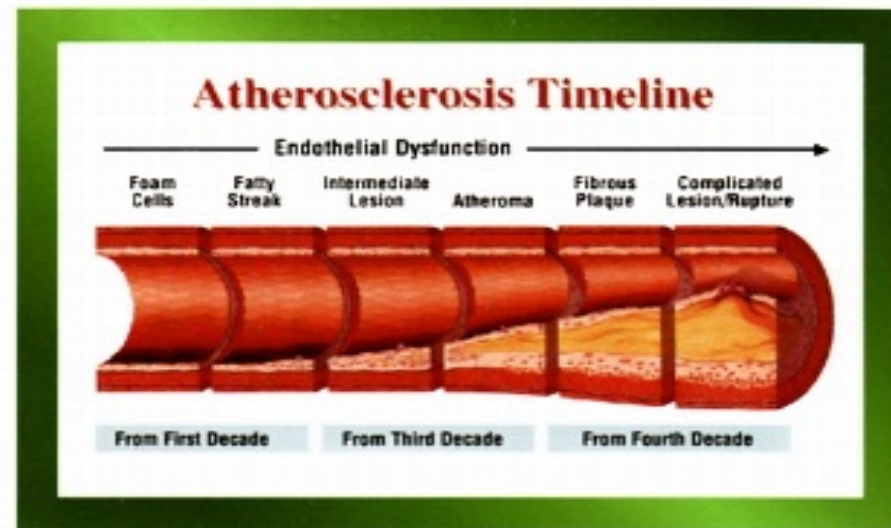
# Arterial events

Myocardial infarction and thrombotic stroke  
in CHC users – Important risk factors

- Age >35 years
- Obesity
- Migraine with/without aura
- Smoking
- Hypertension
- Diabetes
- Dyslipidaemia
- Family history

# Myocardial infarction

The development of atherosclerotic plaques progresses over the years. Therefore age and longlasting risk factors over the years are important for the individual risk.



When balancing risks it has to be considered that MI is associated with a much higher mortality in comparison to VTE. However, MI is rare in young women. Special risk factors for atherosclerosis are high blood pressure, smoking, diabetes and hyperlipidemia

# Age-related incidence of MI in none-CHC users

Incidence per 100 000 women per year / 2 independent studies 1999 and 2012

	Age 20-24	Age 40-44
Myocardial infarction (1)	0.2	30 ←
Myocardial infarction (2)	0.7	25.4 ←

- Age has a major impact on risk for MI. This risk increases strongly with other risk factors like smoking, obesity or hypertension or dyslipidemia.
- Check carefully for risk factors if you prescribe CHC in women aged > 35 years
- Discuss contraceptive options without risk (POP; IUD; permanent methods)

# Ischemic stroke in CHC users

## Role of pill type

- Use of low-dose CHC is associated with a **twofold** risk for ischemic stroke
- Risk for ischemic stroke in CHC is the same with all types of progestins
- Progestin-only pills are not associated with an increase of risk

## Multiplicative influence of age, smoking and CHC use on incidence of myocard infarction

Incidence per 1.000.000 woman-years	Age <35	Age >35
No pill, no smoking	0.8	10
Pill use, no smoking	4	40
No pill, smoking	8	88
<b>Pill use and smoking</b>	<b>43</b>	<b>485</b>



# Migraine and stroke with CHC use

## Multiplication of risks

	<u>Odds Ratio</u>
All migraine	2.3 - 3.7
Migraine without aura	2.3 – 3.8
Migraine with Aura	3.8 – 8.6
Migraine and COC	5 – 17
Migraine and smoking	10.2
Migraine, smoking and COC	34.4

**Migraine with aura and use of CHC are associated with a considerable increase in risk for ischemic stroke. This risk already exists in young women.**

# Arterial events

## Counselling under consideration of age

	Age <35 years	Age >35 years	Age >35 years MEC if available for this situation
Obesity	possible	better not, consider DVT risk	
Migraine with aura	no	no	4
Migraine without aura	possible	no	3
Hypertension	possible if BP140-159/90-99	no	4
Smoking	possible	no	4
Diabetes	possible if no vascular complication	no	4
Dyslipidemia	possible	no	4

# Contraception in women with cardiovascular risk factors



Take time to collect all important information

**Effective estrogen-free method would be best**



Balance less effective method against the risk of pregnancy

In very difficult situations where the danger of pregnancy is high and no other option is applicable or available, consider prescribing CHCs despite the risk