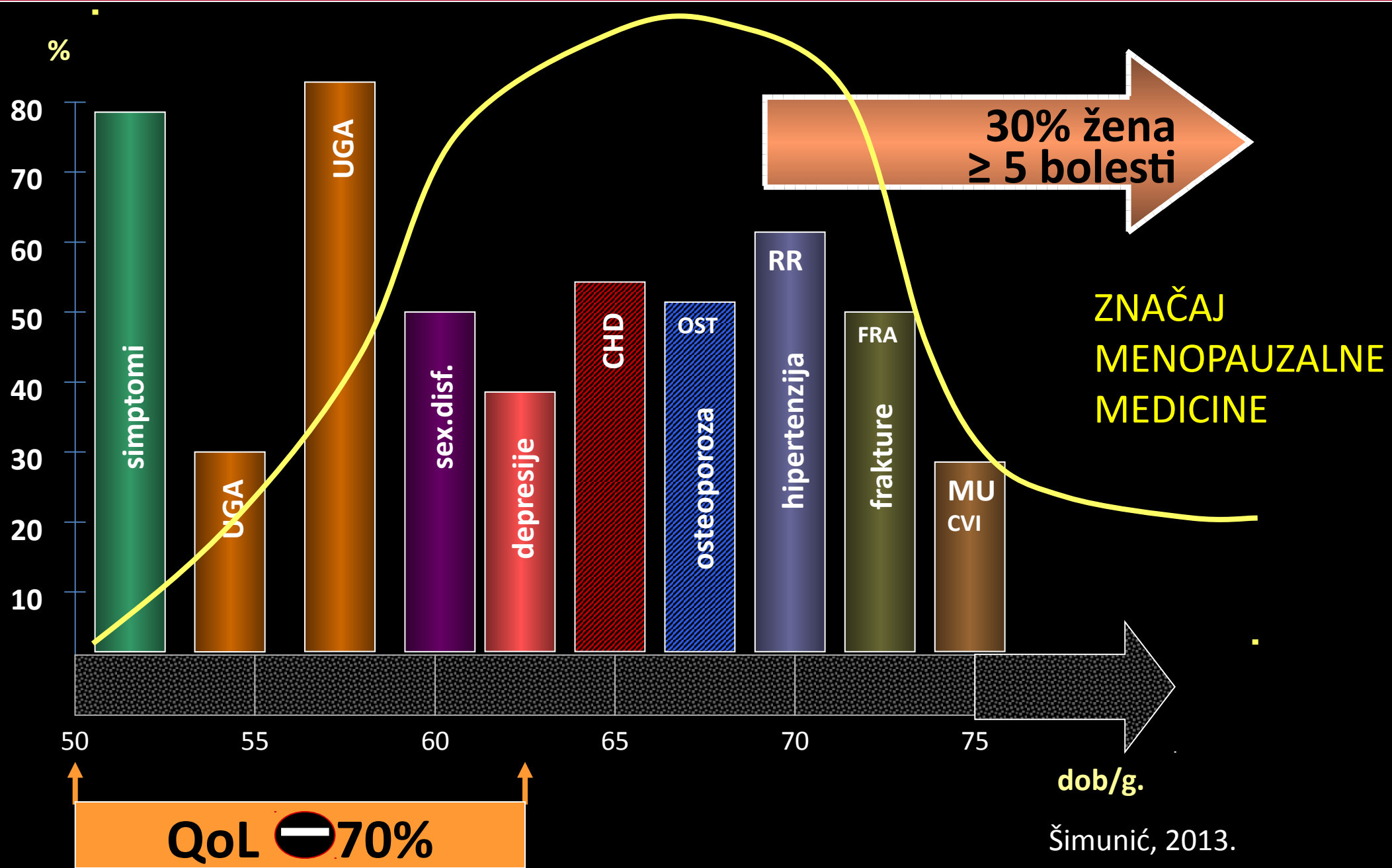
# Hormonsko nadomjesno liječenje danas transdermalno ili oralno

**Prof.dr. sc. Velimir Šimunić**
Medicinski fakultet u Zagrebu
Poliklinika IVF

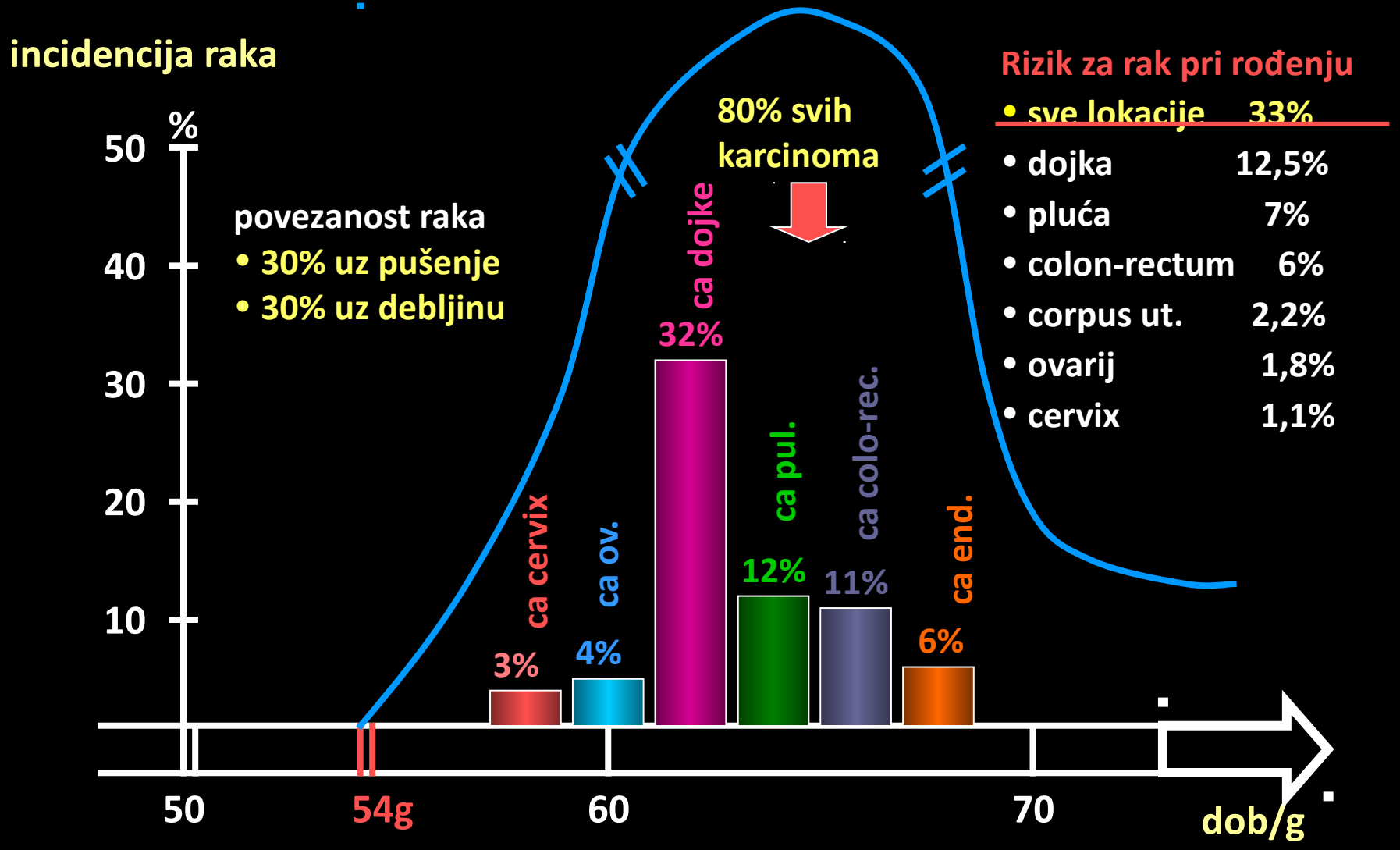
Travanj, 2016.

# STARENJE: UČESTALOST BOLESTI I SMETNJI




Šimunić, 2013.

# STARENJE: RIZIK ZA RAK



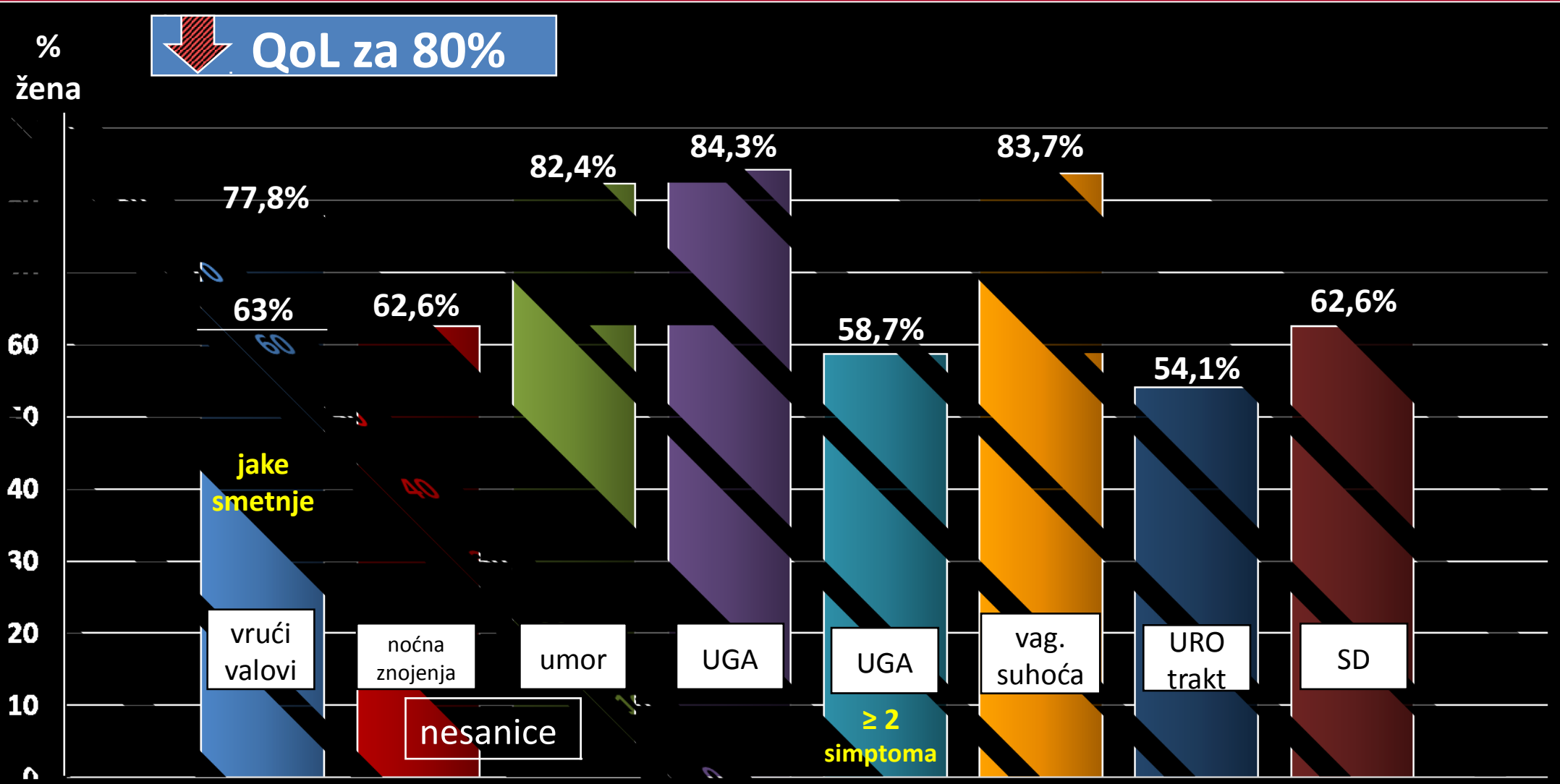

Rizik za rak pri rođenju

| | |
|---|---|
| • sve lokacije | 33% |
| • dojka | 12,5% |
| • pluća | 7% |
| • colon-rectum | 6% |
| • corpus ut. | 2,2% |
| • ovarij | 1,8% |
| • cervix | 1,1% |

raniji rak uz visoke obiteljske endogene i egzogene rizike

15-45 g. → Ca cervix 35%, tiroidea 50%, ovarij 15%, dojka 15%

# Učestalost simptoma rane postmenopauze




MHT → samo za simptome ?

Šimunić, 2003.

# PRIJEVREMENA MENOPAUZA – POF MENOPAUSIS PRAECOX

- prije 40. godine života

1-2%

## primarna

- kromosomske p.
- genski p.
- enzimski p.
- autoimune

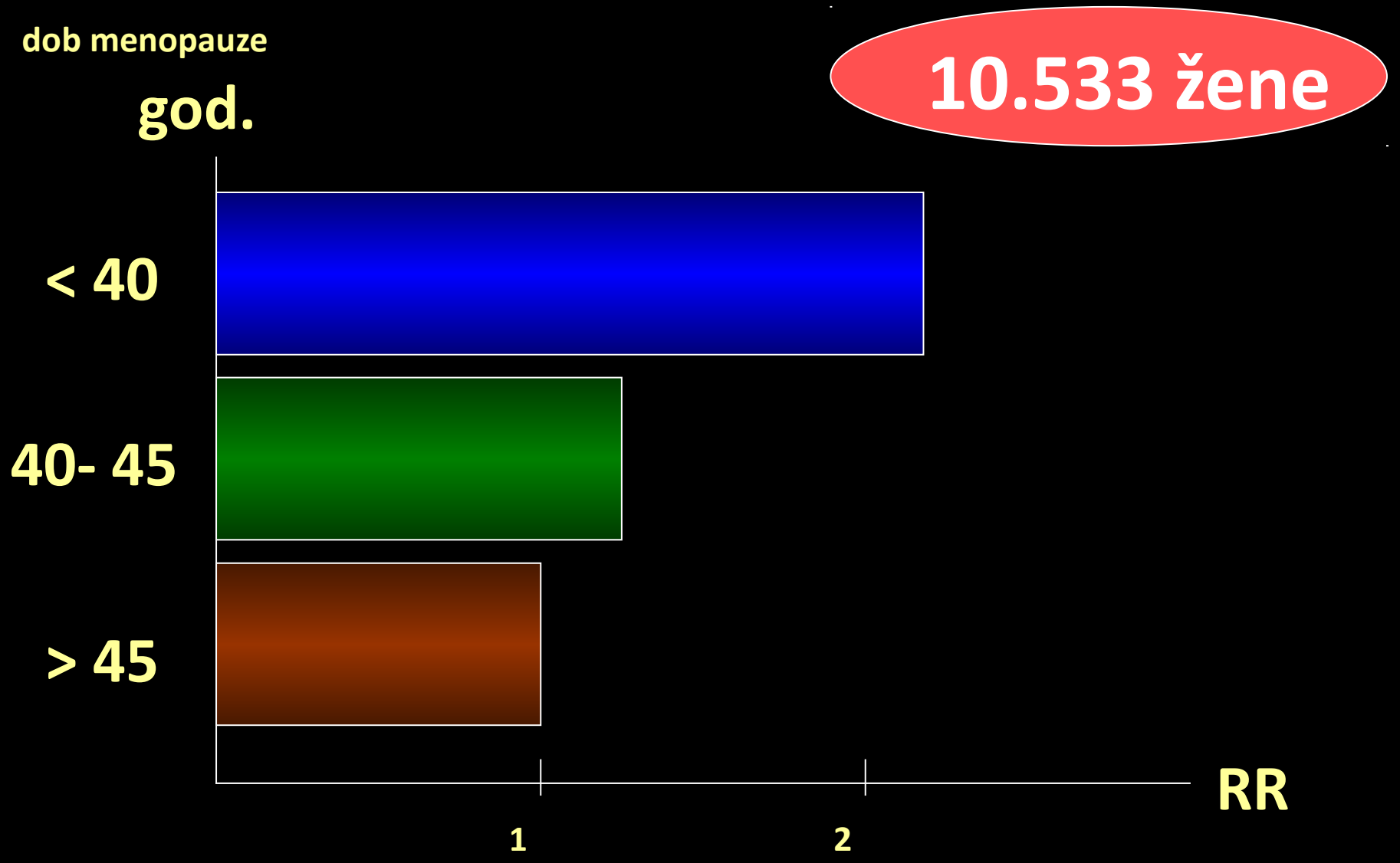
## jatrogena

- kemoterapija
- Ra terapija
- operacije
- embolizacija a.u.
- upale - parotitis

Rana menopauza (< 45 g.) → 5% ž.

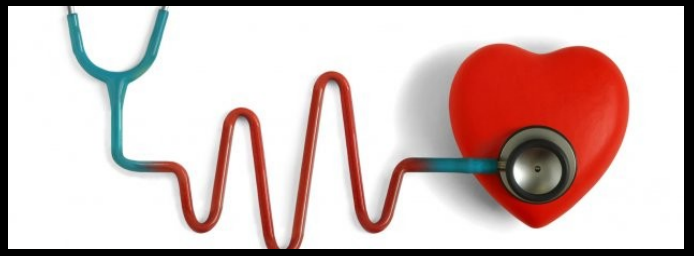
bez HNL-a smrtnost RR 1,94 (1,25-2,96)

# RANIJA MENOPAUZA ZA VIŠI RIZIK CHD




Lokkegaard, Mat, 2006.

# ŽENE BEZ HNL-a: RIZIK ZA KVB U RAZLIČITIM POPULACIJAMA



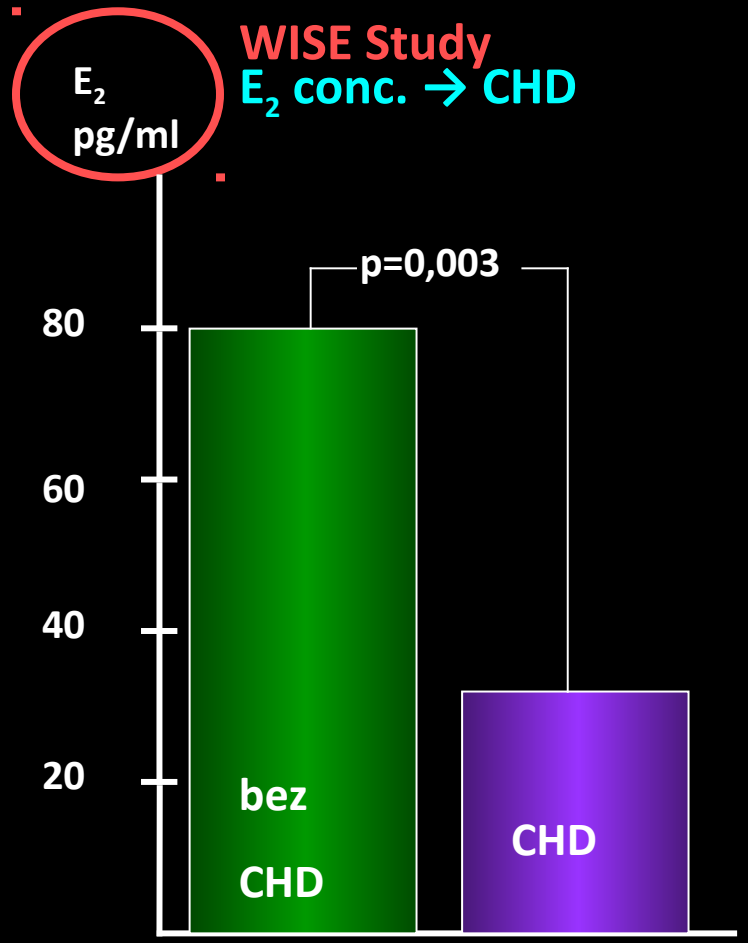



WHI studija

Nurse's Health Study

# STARENJE I MENOPAUZALNI STATUS: ATEROSKLEROZA I KORONARNA SRČANA BOLEST (CHD)

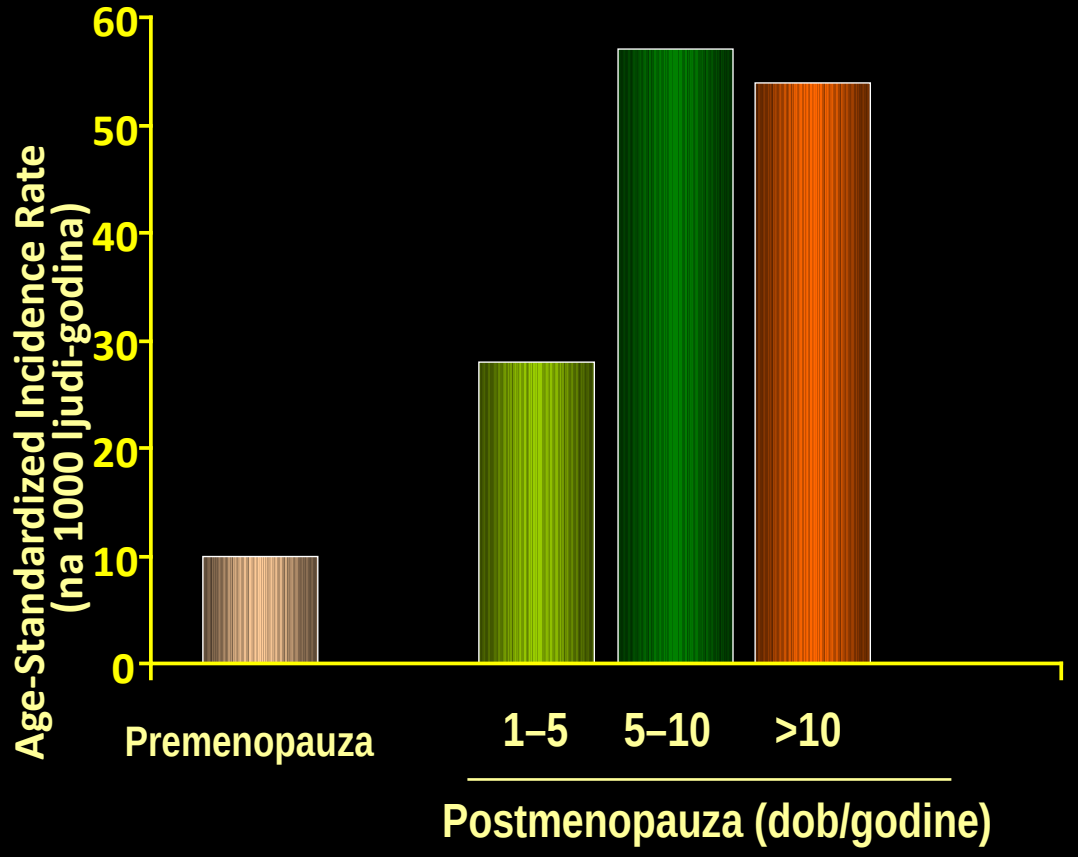
**WISE Study**
**$E_2$ conc. → CHD**




CHD – 70% stenoza (najmanje 1 cor.a.)

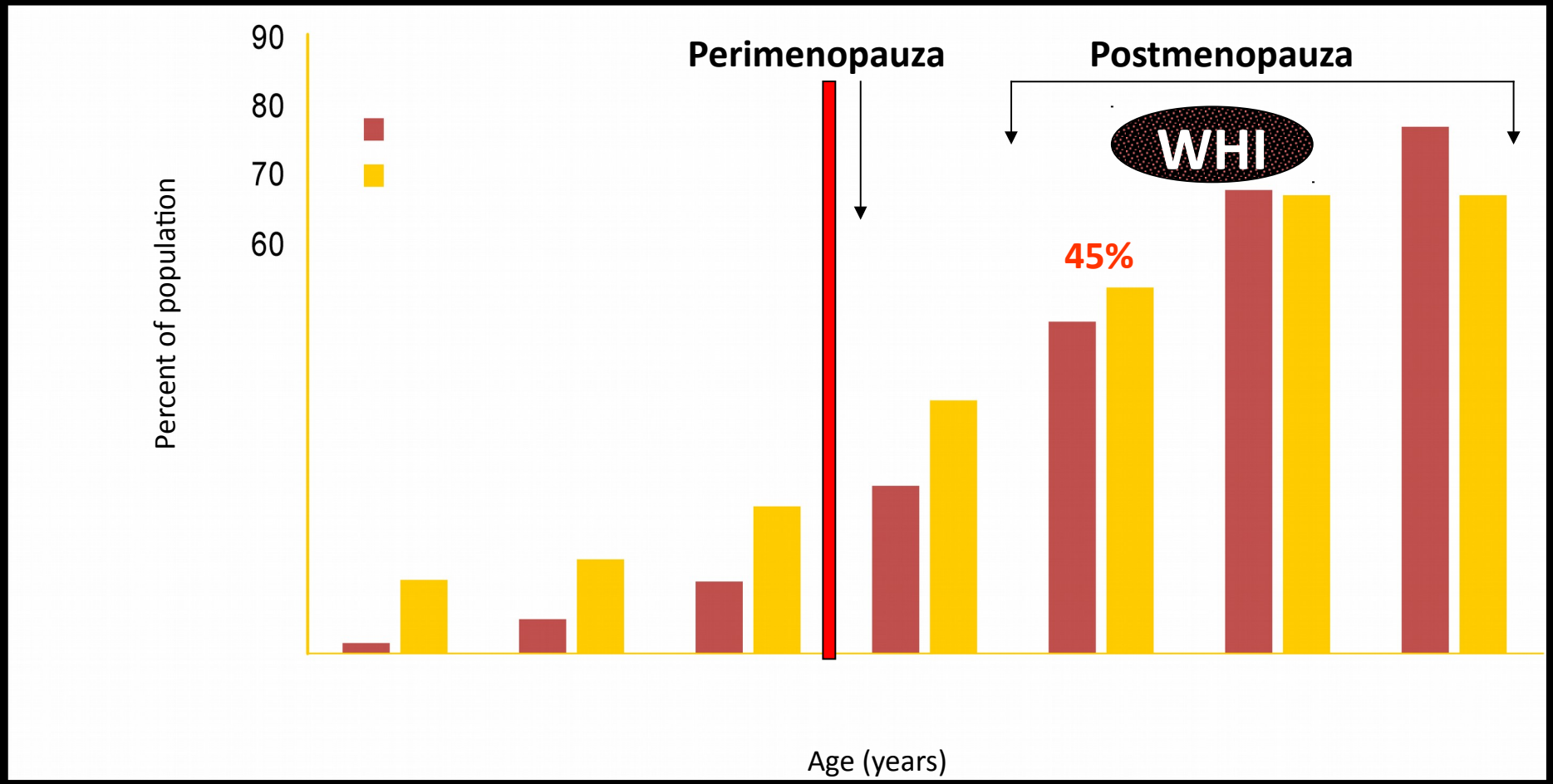
Merz et al, J. Am.Coll.Card, 2003

**Bruneck Study**
**dob→ plak karotidne arterije**




Kiechl S, Willeit J. *Arterioscler Thromb Vasc Biol.* 1999;19:1484-90.

# HIPERTENZIJA: učestalost




RR
- normalan ≤ 130/84
- prehipertenzija 130-139/85-89

Source: Health Survey for England 2003. See Department of Health website: http://www.dh.gov.uk/assetRoot/04/09/89/15/04098915.xls, Table 3A.

# KANDIDATI ZA HNL: INDIVIDUALIZIRANE INDIKACIJE

- **amenoreja ≥ 3 mj.** → centralne; uz lijekove/ add back th.
- **prijevremena menopauza** → sve žene
- **perimenopauza** → simptomi, krvarenja; 15-20% žena
- **postmenopauza** → simptomi, osteo-kardio-neuroprotekcija, UGA; 70% žena

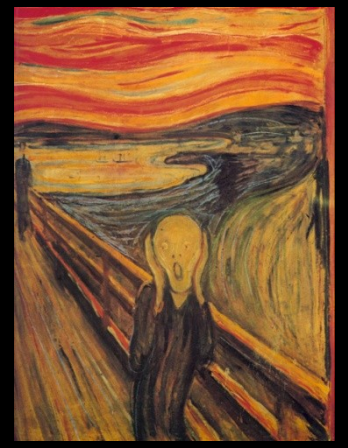
**za sve indikacije** HNL **bolji od** OHK

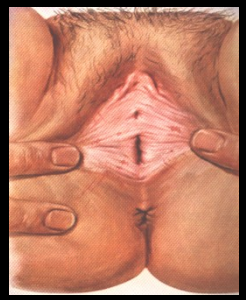
**deficit estrogena**

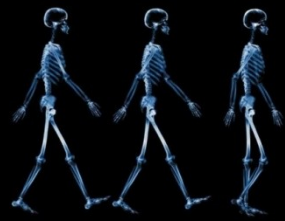
Šimunić, 2013.

# HNL IMA NEDVOJBENU DOBROBIT

| | | |
|---|---|---|
| simptomi | redukcija | 80-90% |
| Q o L | povišenje | 80% |
| urogenitalna atrofija | poboljšanje | 60-85% |
| C H D | redukcija | 40% |
| kost | BMD | +10% |
| | frakture | -50% |

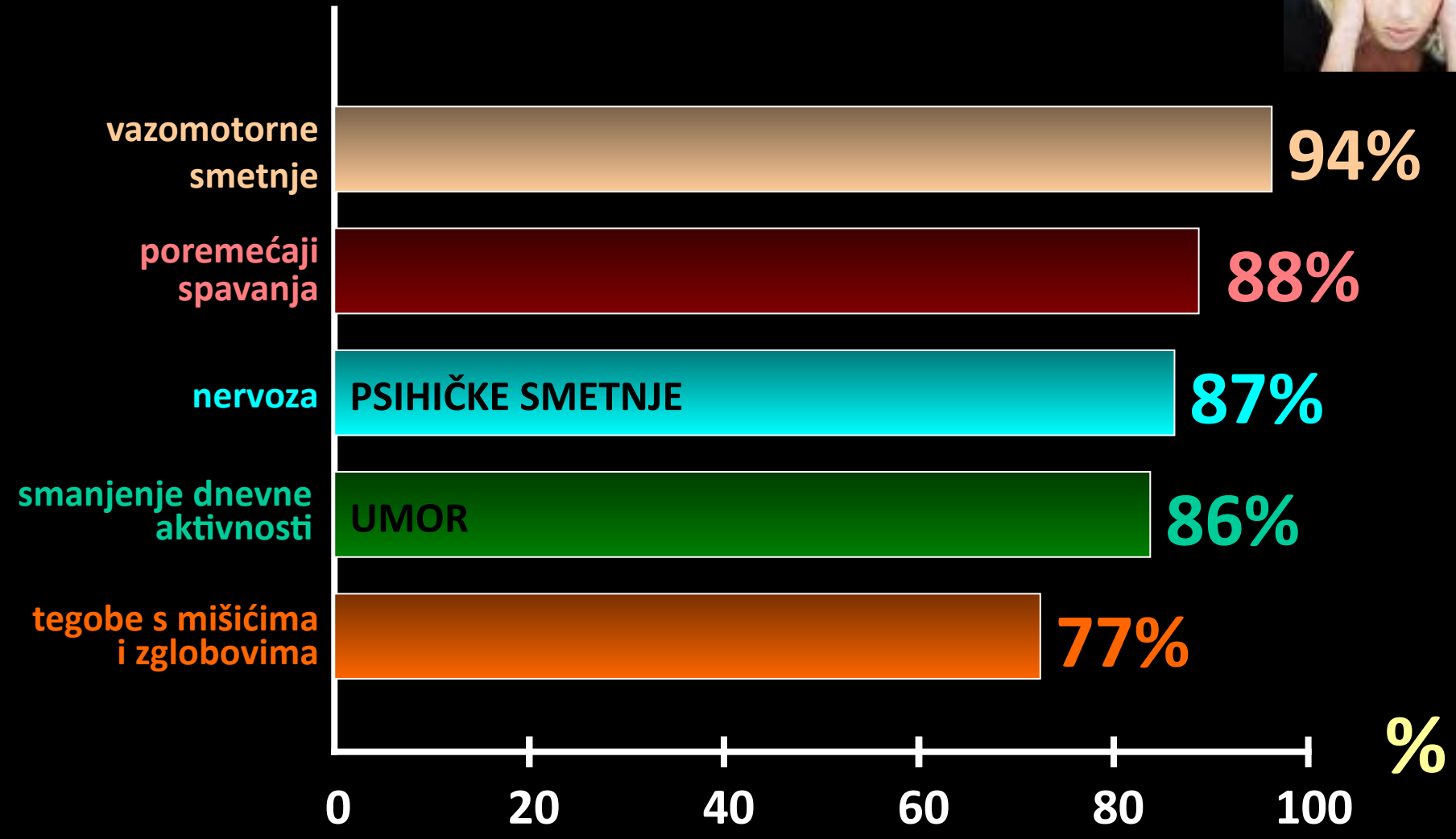






# SIMPTOMI: POBOLJŠANJE % ŽENA

Macleman, Cochrane, 2004.




**Izraženost i trajanje VM simptoma → povišena kalcifikacija žila**

Šimunić,1996
IMS Stat.,2011,NAMS,2010.

# KVALITETA ŽIVOTA: QOL

## HNL bez dvojbe poboljšava:

* QoL u perimenopauzi
* QoL u kasnijim godinama – zdravlje i QoL

- simptomi
- san
- opće zdravlje
- UGA
- libido
- koža
- anksioliza
- kognicija
- spolna disfunkcija
- emotivnost
- vitalnost

**Poboljšanje**

. **Kognitivne f.** (Le Blanc,2001)

. **Alzheimerova b.** (Zandi,2002)

Taylor,2011.

NAMS,2008(2010.

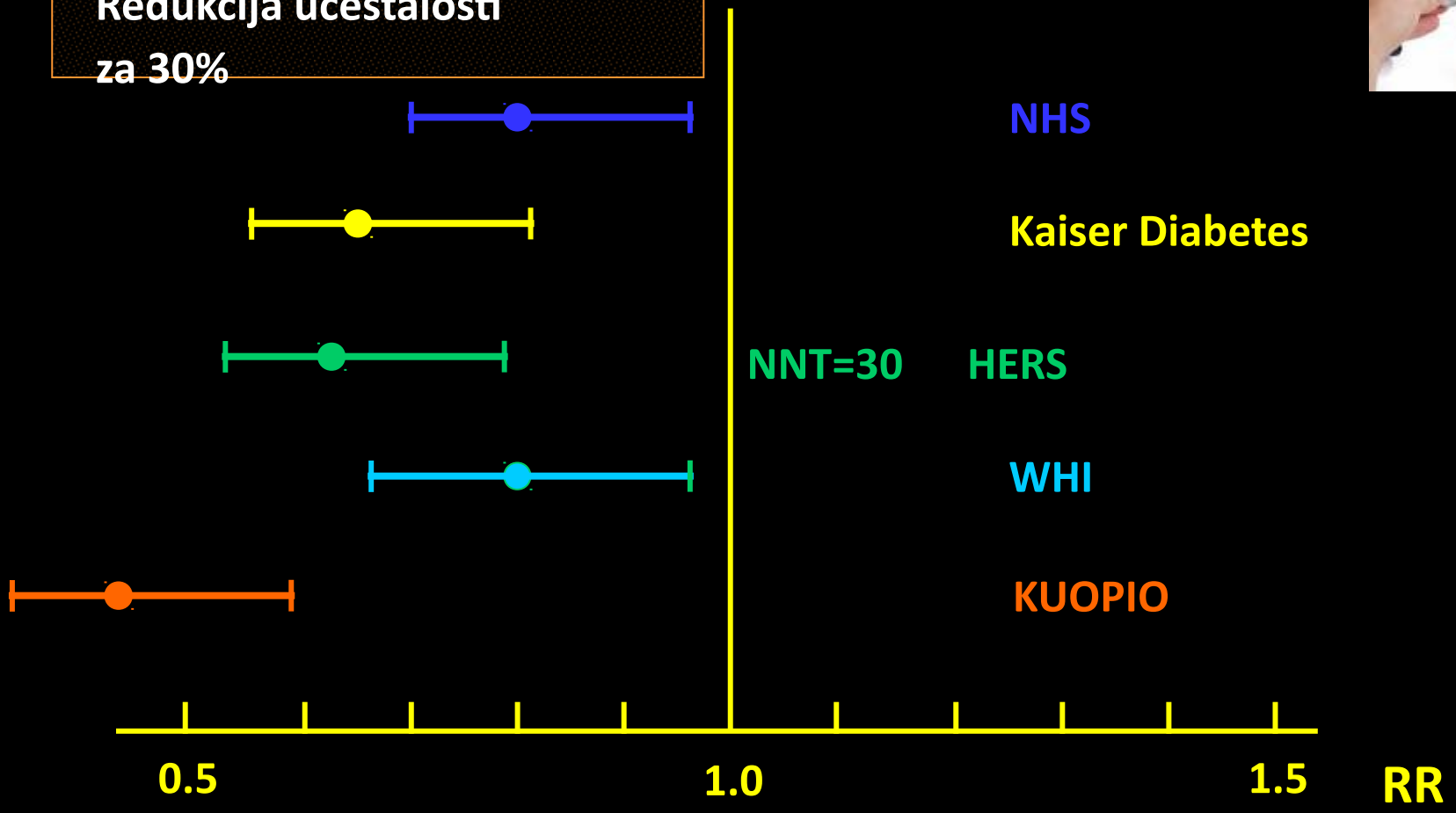
EMAS,2008

WISDOM Study,2008

Welton et al 2009

# HT I DIJABETES

Redukcija učestalosti
za 30%




Metabolic syndrome
- svi čimbenici

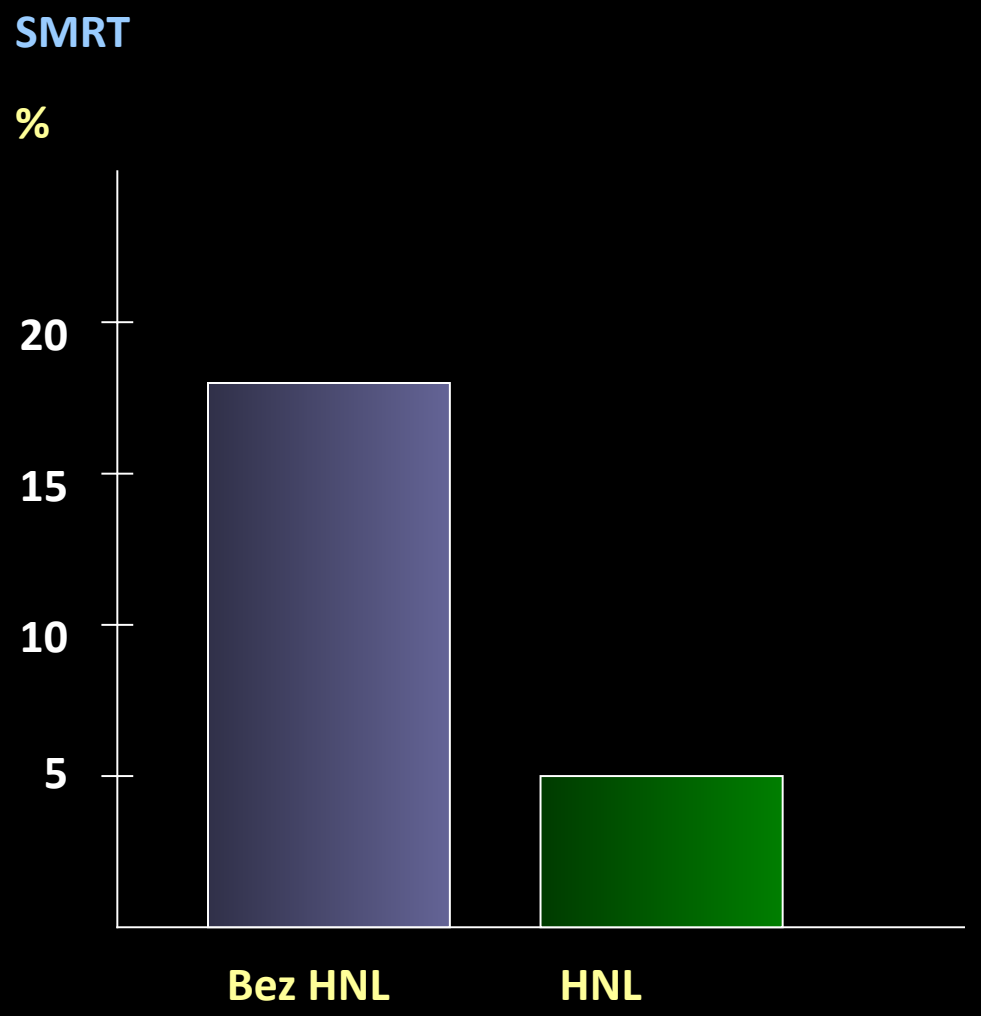
107 trials metaanalysis

Salpeter,Diab.2006.

Manson, 1992.
Ferrera, 2003.
Kanaya, 2003.
Margalis, 2004.
Reutti 2009

# INFARKT MIOKARDA - PREŽIVLJAVANJE

- 114.724 žene s IM
- dob > 55 g.
- 7.353 sa HNL
- OR 0,65 (CI 0,59 – 0,72)




Schlipak, Circul, 2001.

# HORMONSKO NADOMJESNO LIJEČENJE: ZDRAVLJE KOSTI - OSTEOPROTEKTIVNOST

⇒ početak u ranoj postmenopauzi / 2-3 godine HNL

1. BMD za 2 g. porast na svim lokacijama

   za **6 do 12 %**

2. PRIJELOMI – brzi učinak i trajan učinak ? na svim lokacijama

   redukcija rizika za **30 do 50 %**

Banks,JAMA,2004
Bagger,PERF,2004
DOPS,Mat.,2000

Metaanaliza,JAMA,2001
Metaanaliza,Matur.,2006
NORA,2003

# WHI Studije

**Primarni nalazi**

2002./2004.

**Učinci**

- reanalize
- korekcije

# WHI studija EPT
# Healthy Postmenopausal Women
## Principal results JAMA, 2002.

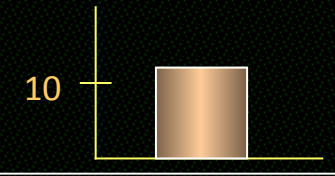
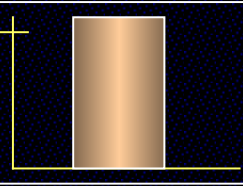
n ≈ 16.600 / dob (ẋ) = 63,2 g. → 68,4 g.

| HR (CI) početni rezultati | finalni rez. / korig. CI ‰ | AR |
|---|---|---|
| CHD | 1,29 (1,02-1,63) | 1,18 (0,95-1,45) | 0,6 |
| MU | 1,41 (1,07-1,85) | 1,37 [1,07-1,76 / 0,86-2,31] | 0,8 |
| VTE | 2,11 (1,58-2,82) | 2,06 (1,26-3,55) * | 1,1 SZ |
| Ca dojke | 1,26 (1,0-1,59) | 1,24 [0,83-1,92 / 0,97-1,54 / 1,01-1,53] | 0,8 |
| Global index | 1,15 (1,03-1,28) | 1,12 (1,02-1,24) | 2,1 |

AR 33 žene / 10.000 ž/g ≈ 3,3‰

Manson,JAMA,2013.

# KORISNICE HNL-a: različitost populacija

| | opservacijske st.<br>NHS / EU / RH | randomizirane st.<br>W H I<br>"healthy postmenopausal women" ? |
|---|---|---|
| dob (g) 51,8<br>perimenopauza 85% |  | < 10%  |
| debljina<br>(BMI) | 26,2<br>< 15%  | 29,6<br>> 30%  |
| hipertenzija | 8-10%  | 40%  |
| K V B | 3-4%  | 15-20%  |
| Framingham risk<br>indeks povišen 10-15% |  | 73%  |
| preparati | • niskodozirani - E2<br>• transdermalni<br>• NHS – Premarin 0,6/0,3 | • samo PremPro<br>standardna – viša doza |

# WOMEN'S HEALTH INITIATIVE, 2002.
# GENERALIZIRANI ZAKLJUČCI

→ Istraživanje na starijim ženama koje nisu zdrave

- HNL je štetna bez obzira na dob
- povisuje CHD
- povisuje VTE
- povisuje MU / CVI
- povisuje rak dojke

**Posljedice → pad korištenja za 70%**

WHI, 2002, JAMA
Stevenson, 2013.

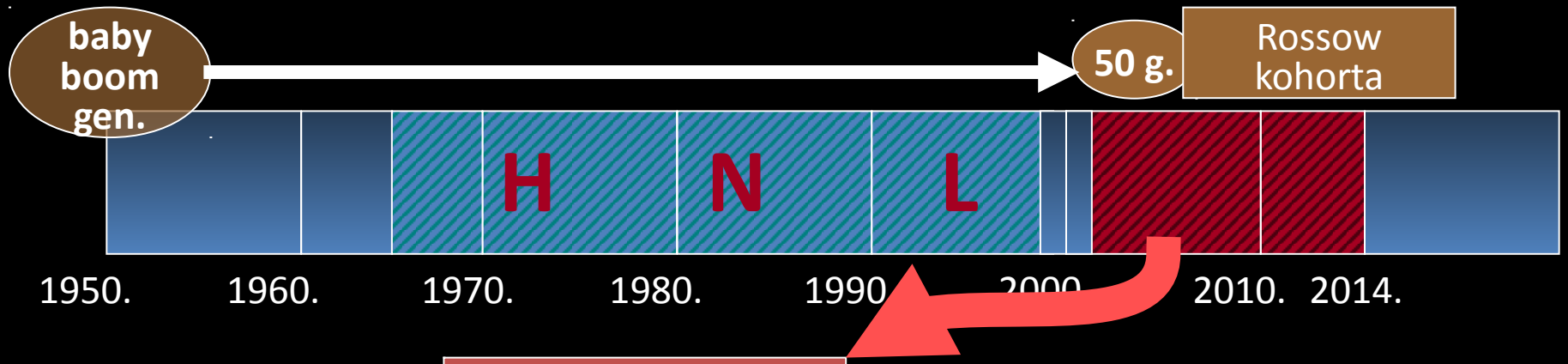
# HNL: RIZICI KOJI SU PROMIJENILI NAŠ STAV

R C T

| B O L E S T | R I Z I K |
| --- | --- |
| • rak dojke | nedokazano |
| • rak endometrija | ne postoji (uz progestagene) |
| • C H D | dobrobit |
| • moždani udar | doza / dob / put |
| • venske tromboze | doza / put primjene |

Stevenson, 2013.

# MENOPAUZALNA MEDICINA – 14 godina nakon WHI




**WHI bez dokaza visokih rizika**

**HNL 70 %**

| simptomi | UGA / SD | QoL | frakture | antidepresivi |
|---|---|---|---|---|
| bez alternative | zanemareno | nizak | + 50 % | + 50 % |

Editorial

# The WHI: have our worst fears come true?

*Nick Panay and Anna Fenton*

*EDITORS-IN-CHIEF*

The long-term health consequences of the Women's Health Initiative (WHI) studies appear to be finally revealing themselves more than a decade after publication.

In a recent analysis of US census data by Sarrel and colleagues[1], it is claimed that many thousands of excess deaths resulted in US women who had undergone bilateral oophorectomy without adequate hormone replacement. Given the hysterectomy rate and decline in estrogen use in this group of women, the authors extrapolated which deaths could have

tomy not only have reduced quality of life but also increased long-term morbidity and mortality[4].

Although less easy to prove causation, it is likely that the downturn in use of hormone replacement therapy also had significant consequences in women who had gone through natural menopause. A review from our special 'decade post-WHI' issue of *Climacteric* last year demonstrated adverse health outcomes thought to have resulted from the downturn in hormone therapy usage[5].

Estrogen-only therapy in women aged 50 to 59 declined nearly 79 percent between 2001 and 2011

Minimum 18,601 – maximum 91,610 (probably around 50,000) excess deaths can be attributed to estrogen avoidance!

Sarrel PM, Njike VY, Vinante V, Katz DL. The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years. Am J Public Health. 2013; 103(9): 1583-1588.

# Svjetska znanost –MHT: novi balans benefit - rizik

## B E N E F I T

- timing hipoteza
- selekcija pacijentica
  - personalizacija
- odabir hormona za MHT
  - vrsta (E / P)
  - doza (standard / niska)
  - put primjene (oral / transdermal)

## Progestageni problem rizik

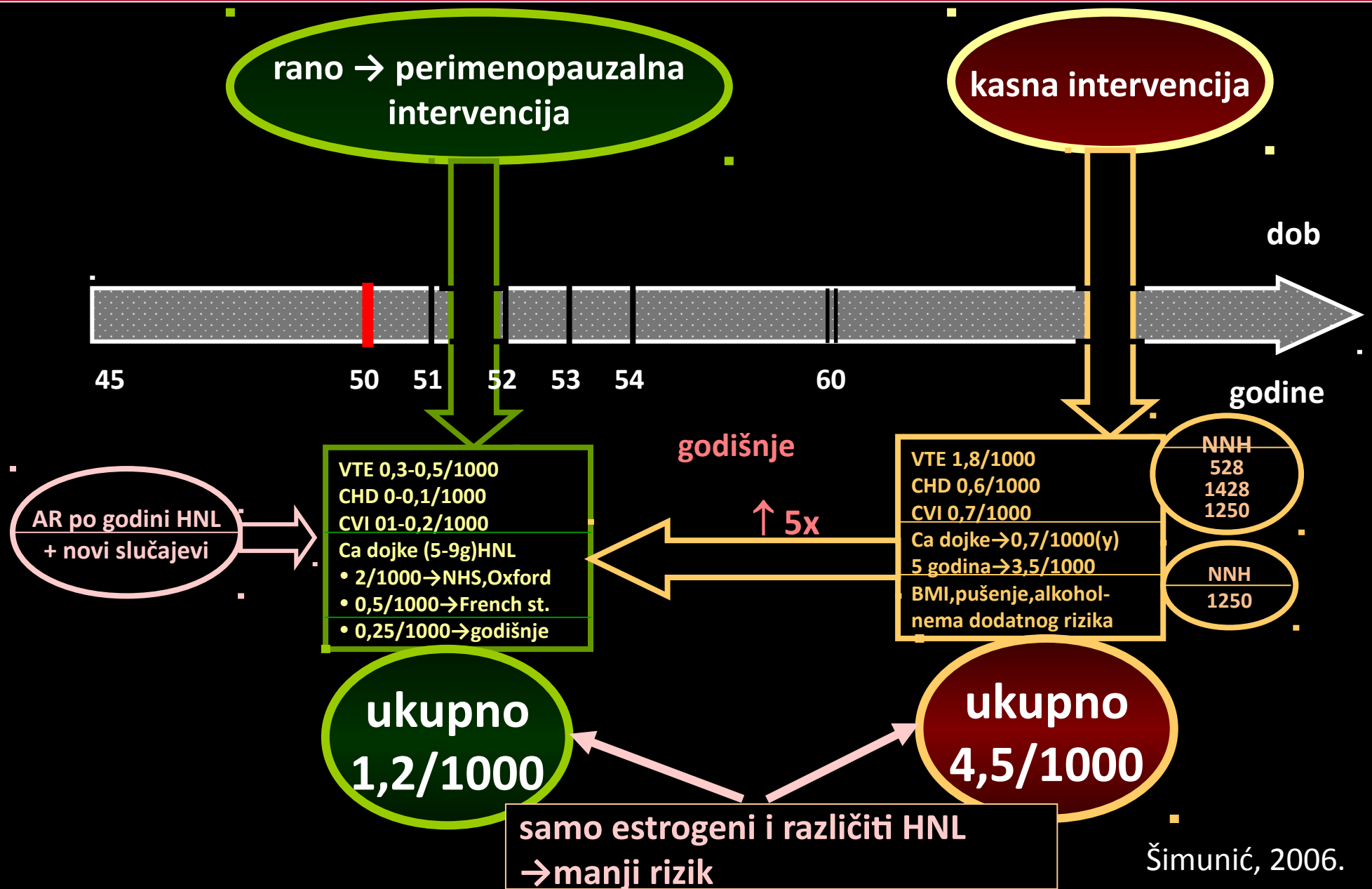
- progestageni razlika u rizicima
  - metabolic
  - vascular
  - DVT
  - CHD / CVI
  - breast Ca
- nuspojave
- MPA – glucocorticoidni efekt

**A**
- start u perimenopauzi (50-60g)
- estradiol 17 β

**B**
- transdermalna ET

**C**
- prirodni progestageni
- ne-androgeni

# TIMING HIPOTEZA
# POČETAK HNL: RAZLIKE U RIZICIMA




Šimunić, 2006.

# RIZICI ZA VTE: žene 50-60 g.

| preparat MHT | apsolutni rizik - dodatni |
|---|---|
| WHI | |
| - HNL (EPT) | 7 ‰ |
| - ENL (ET) | 3 ‰ |
| | u 5 g. |
| transdermalni | bez rizika |

WHI studije

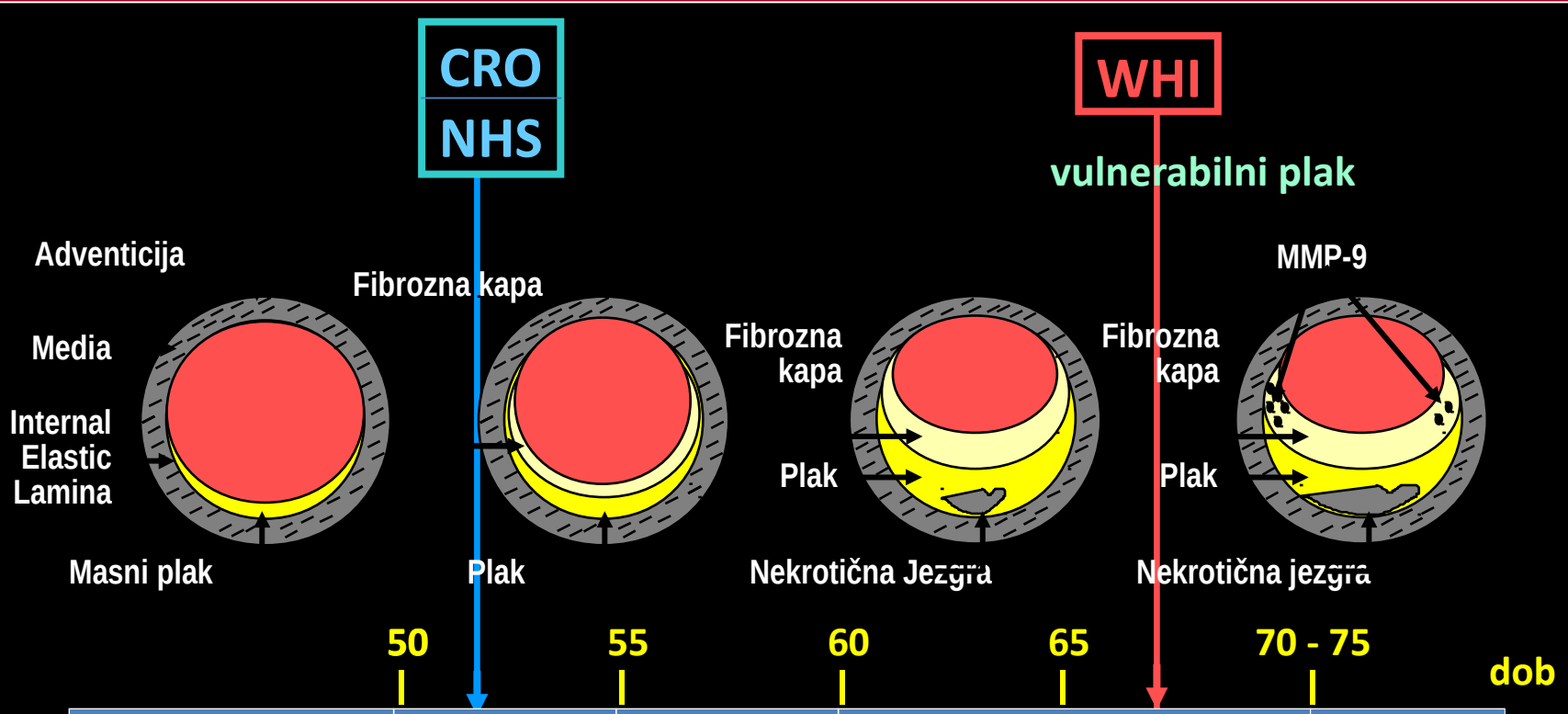
Cushman, JAMA, 2004.

**BMI > 30 kg/m2 → AR 5,1‰/ž-g**

**VTE RR 1,74 (1,11-2,73)**

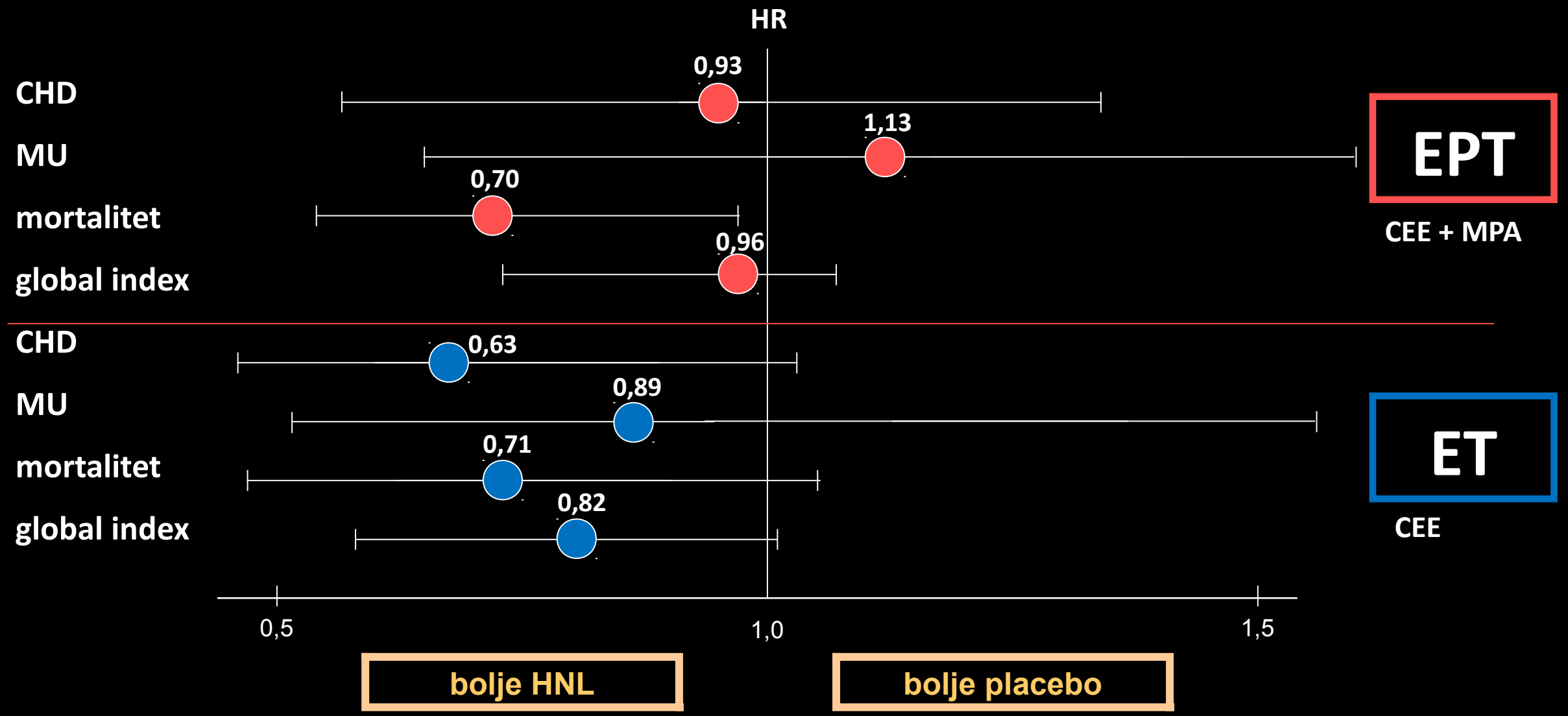
Cochrane,2015.

# STARENJE: PROGRESIJA KORONARNE ATEROSKLEROZE




| godine u postmenopauzi | < 5 | 5 - 10 | 10 – 15 | ≥ 15 |
|---|---|---|---|---|
| % populacije u WHI studiji | 17 % | 19% | 21% | 43% |

# WHI studija – KV rizici: žene 50 – 59 g.




Rossouw, Manson, JAMA, 2007.

# Rani početak HNL: redukcija CHD

| STUDIJE | rani POČETAK 50-59 g | E+P | E |
|---|---|---|---|
| RCT | < 10 g. od menopauze | HR 0,88<br>CI 0,54-1,43 | HR 0,48<br>CI 0,20-1,17 |
| OPSERVA-CIJSKE | perimenopauza | HR 0,71<br>CI 0,56-0,89 | HR 0,62<br>CI 0,52-0,76 |

| | |
|---|---|
| CHD mortalitet | RR 0,52 (0,29-0,96) |

Rossow,JAMA,2007.

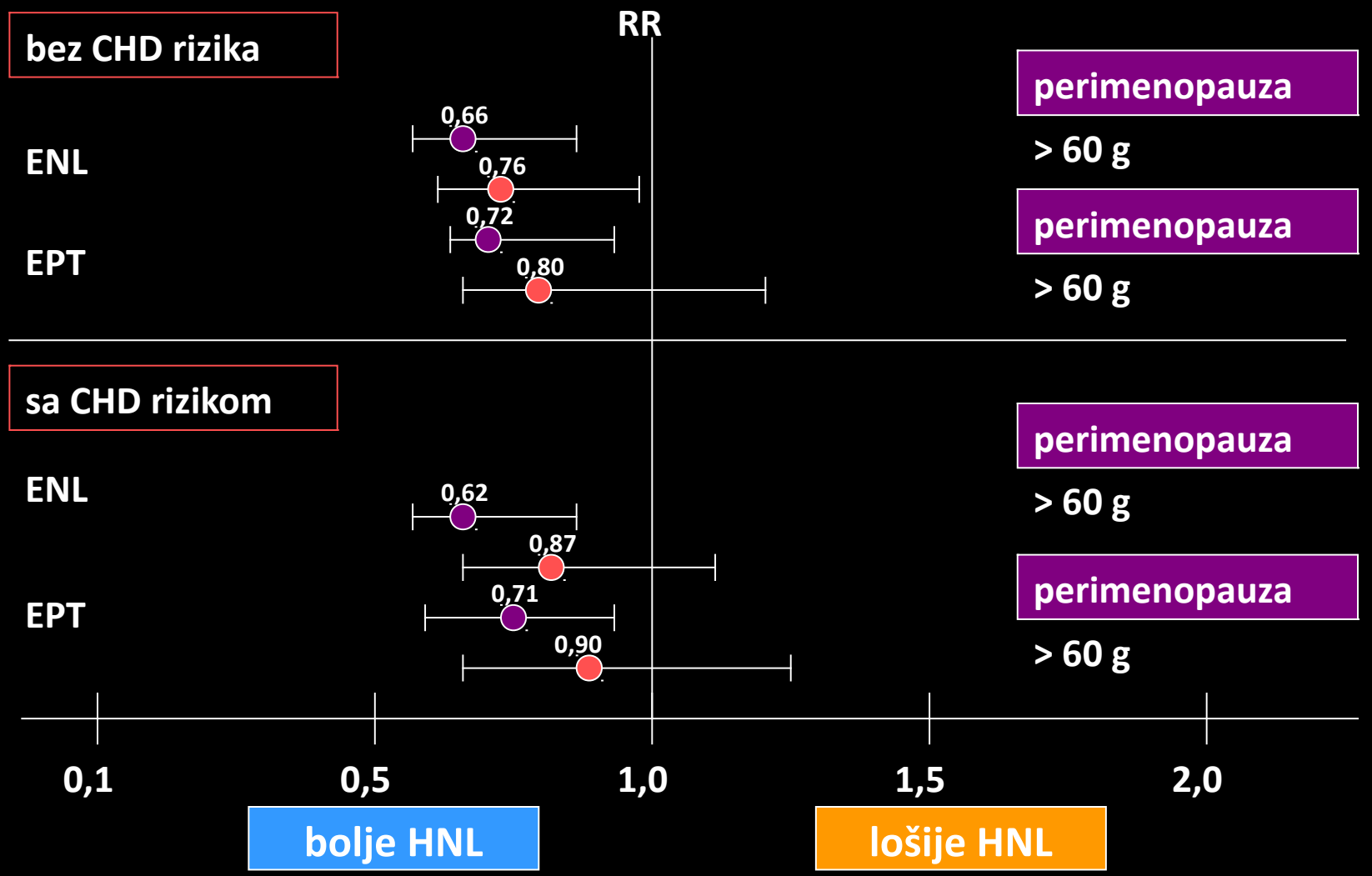
Stevenson, Athorosel, 2009.

Cochrane,2015.

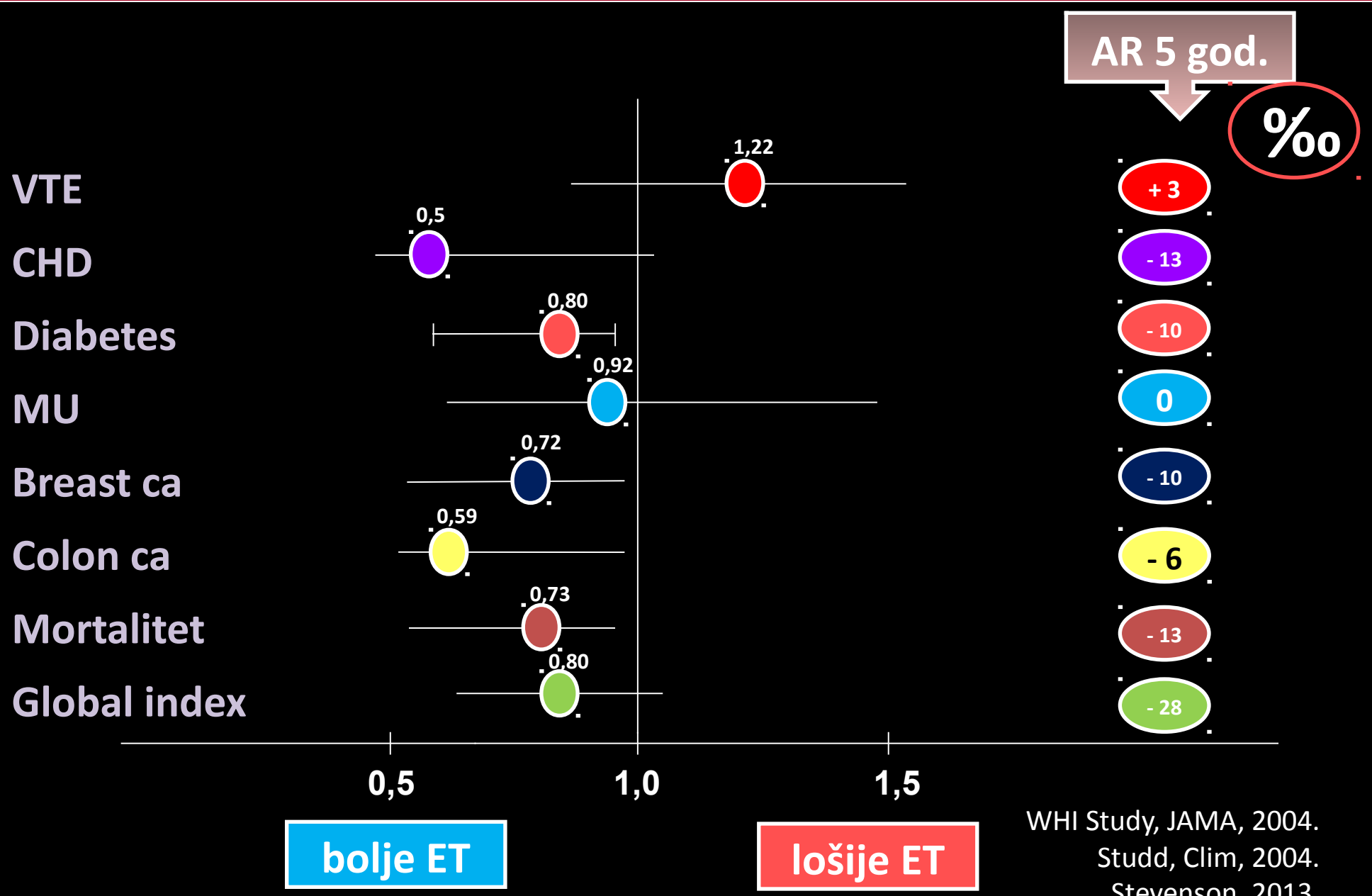
# Hormone therapy and CHD
# Timing of HRT
## Grodstein, Manson, Stampler, J.W.H., 2006.

NHS

NHS populacija / 121 tisuća ž./ 1976 - 2000

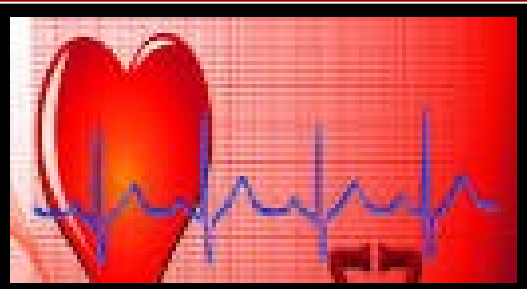


# ET – samo estrogeni – CEE ⇒ žene 50-59 g (WHI st)




WHI Study, JAMA, 2004.
Studd, Clim, 2004.
Stevenson, 2013.

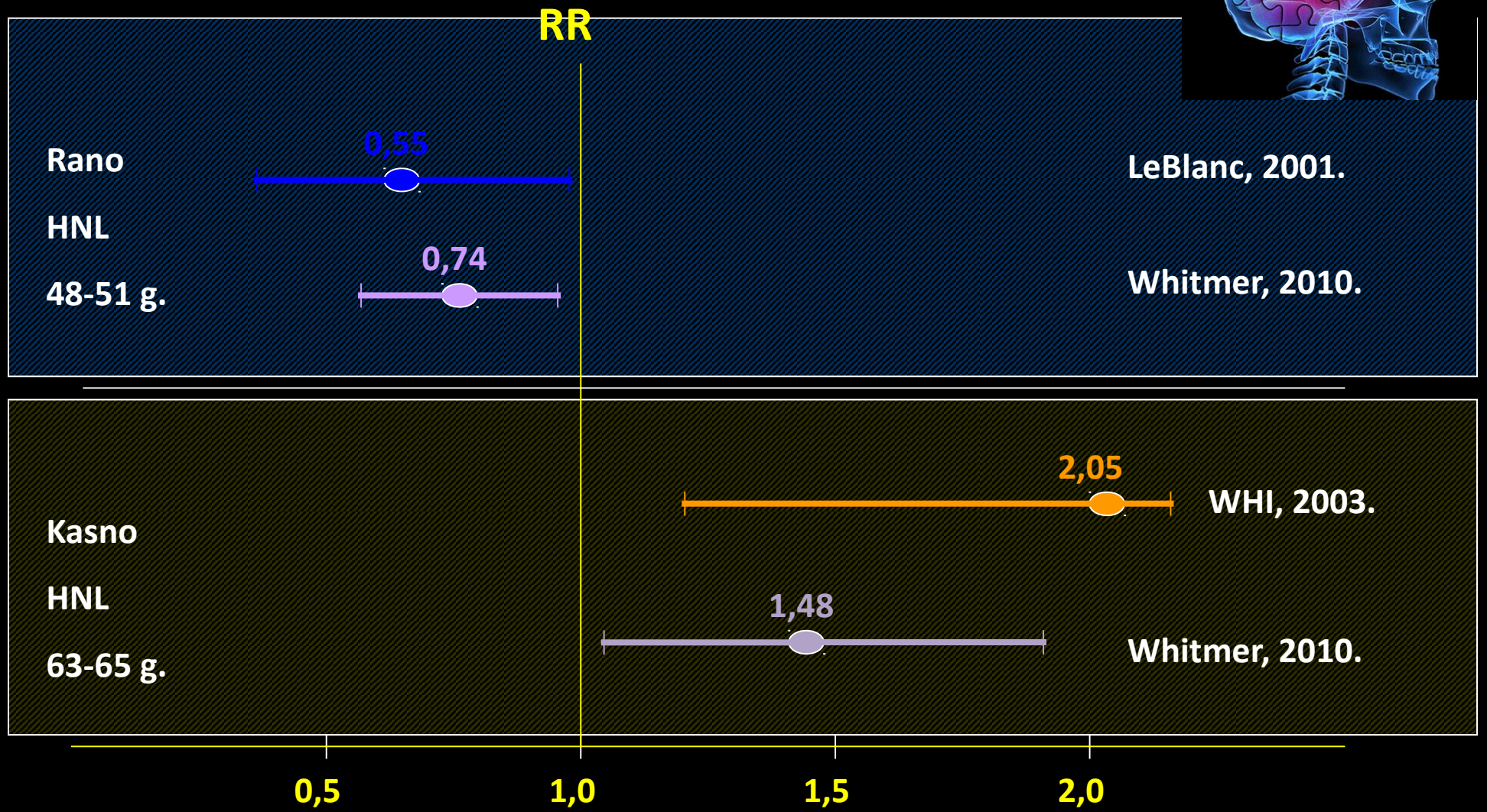
# WHI STUDIJA – SAMO ESTROGENI: niži rizik za KVB






Harman,FS,2014.

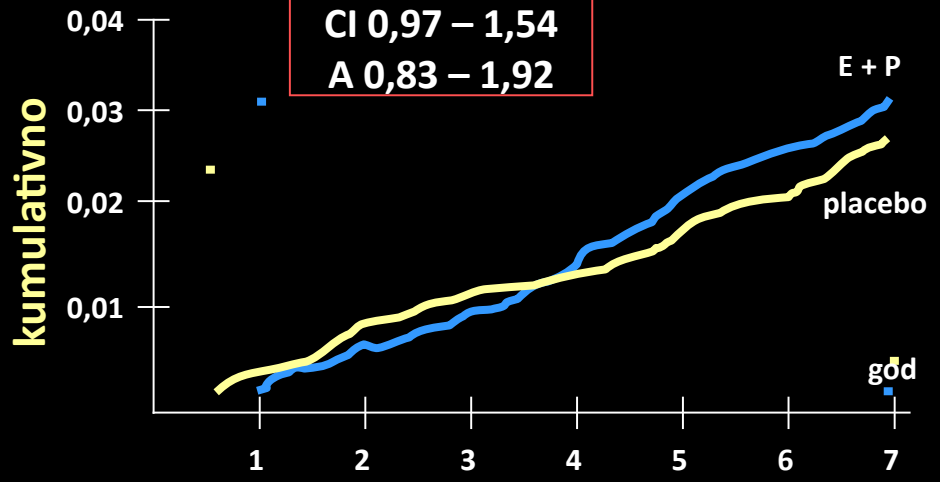
# HNL: RIZI ZA DEMENCIJU - AB



# Rizik za rak dojke u WHI studijama

**EPT**

**HR 1,24**
**CI 0,97 – 1,54**
**A 0,83 – 1,92**

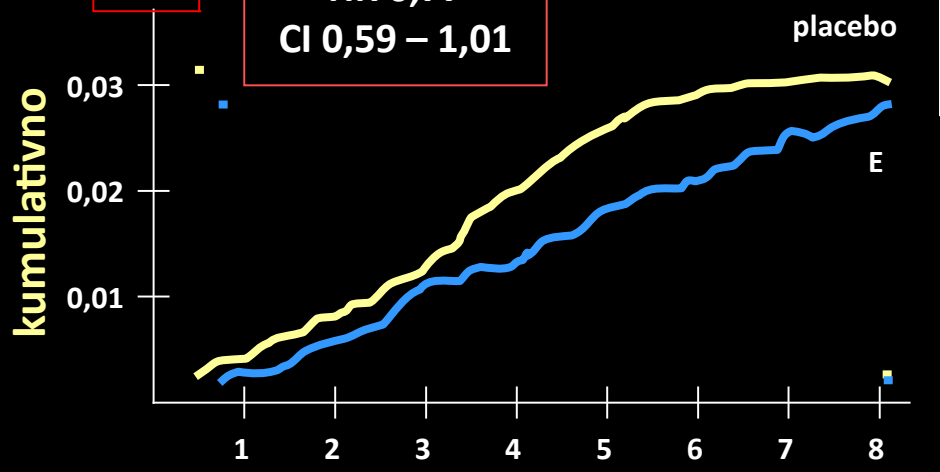



| HNL prvi put | |
|---|---|
| HR 1,06<br>CI 0,81 – 1,38 | 80 % |

| 50 – 59 g |
|---|
| HR 1,19 |

**ET**

**HR 0,77**
**CI 0,59 – 1,01**



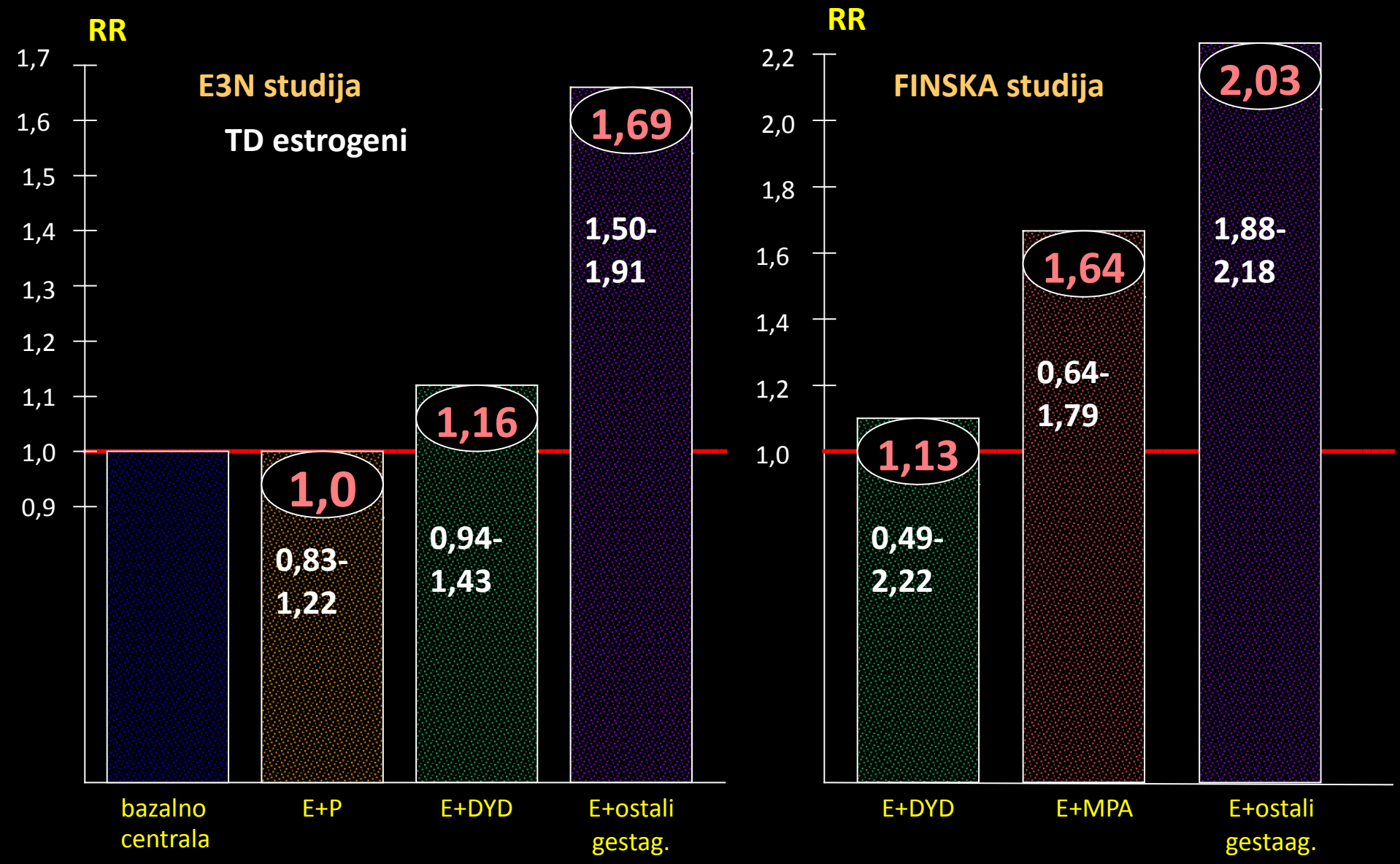

| post hoc | + 13 g. |
|---|---|
| HR 0,69<br>CI 0,51 – 0,95 | - 21% |

| 50 – 59 g |
|---|
| HR 0,72 |
| ↓ sve dobne skupine |

Estrogeni NE izazivaju rak dojke

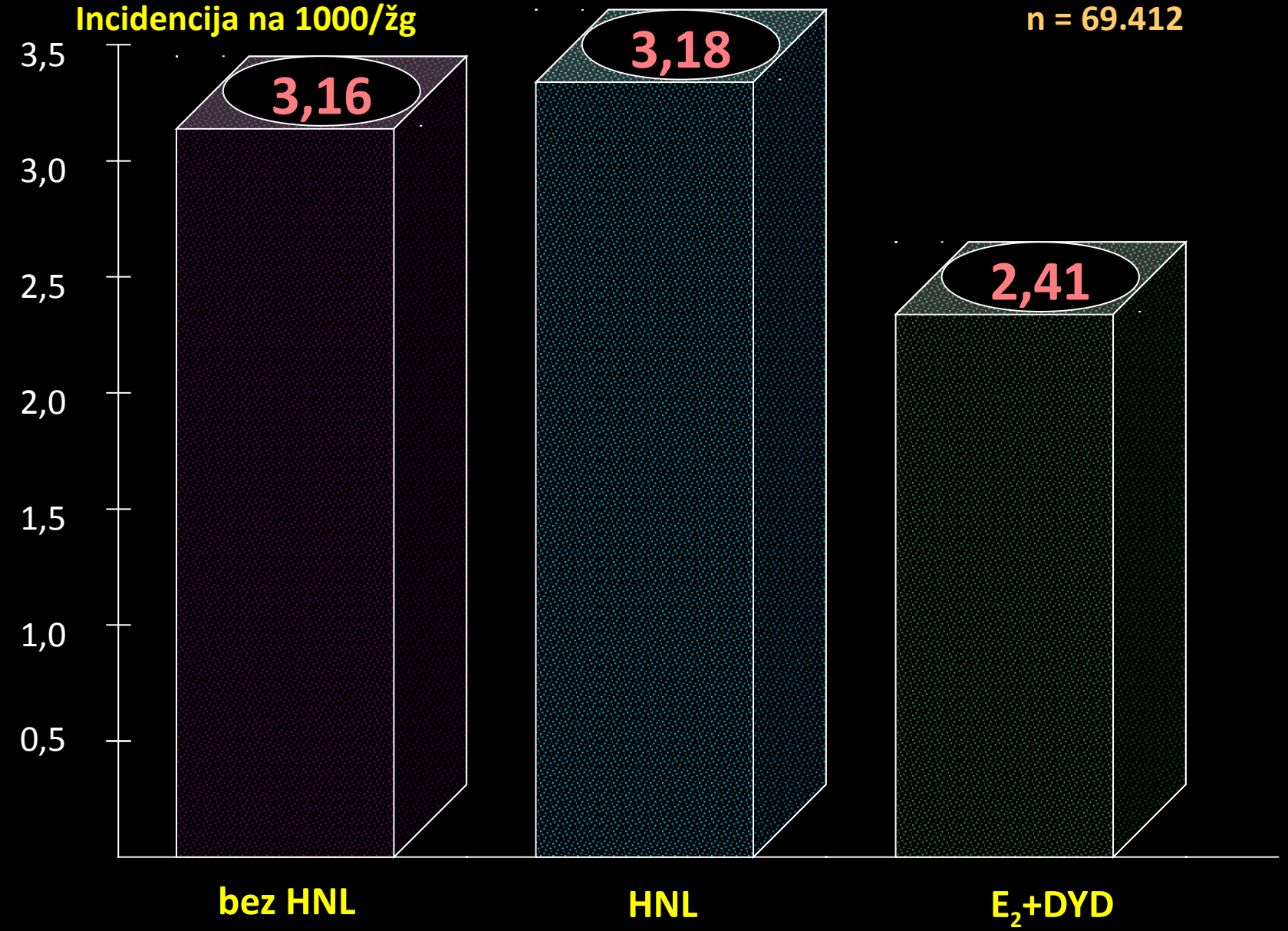
JAMA, 2002./2004.

# RAZLIČITI PROGESTAGENI: RIZIK ZA RAK DOJKE



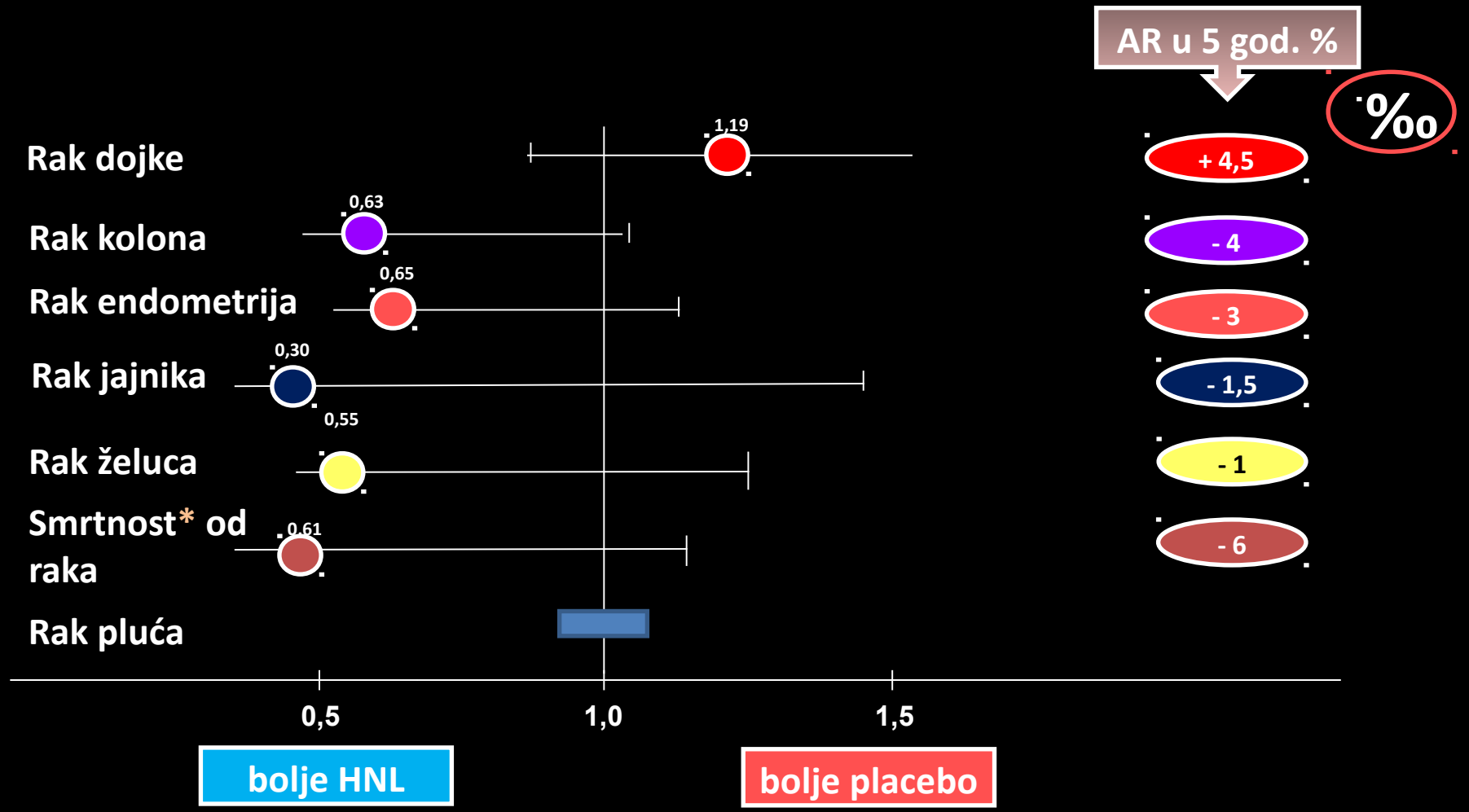

Fournier, 2008., Lyttinen, 2009.

# RAK DOJKE: UČESTALOST U UK-GPRD




Climacteric, 2009.

# HNL (EPT) u mlađih žena – 50-59 g: rizik za rak




* metaanaliza Salpeter

# HNL/MHT: redukcija smrtnosti

MHT HR 0,70 (0,52-0,95)

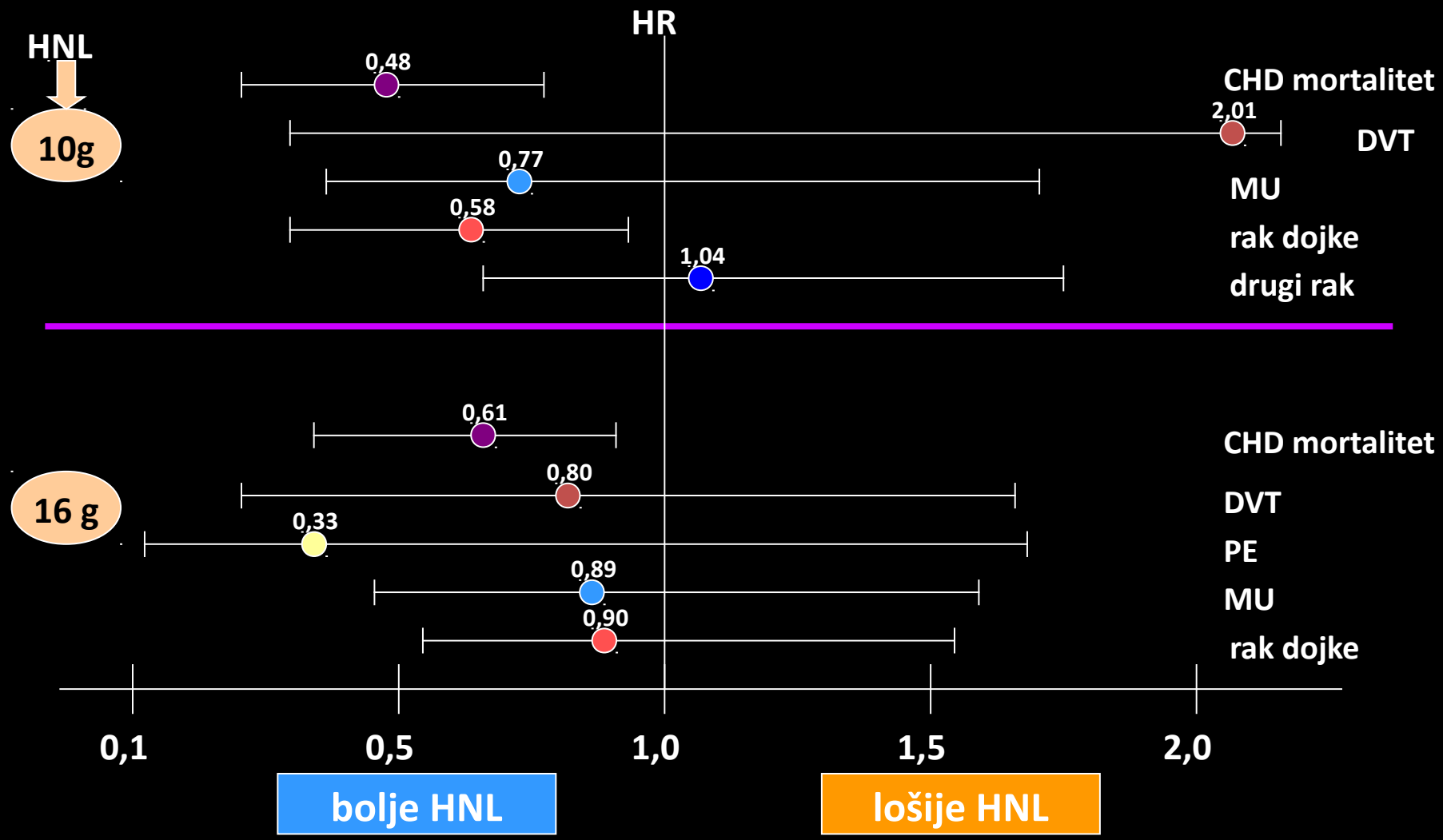
50-59 g Cochrane SR, 2015.

**Redukcija smrtnosti 30-40% za sve uzroke**

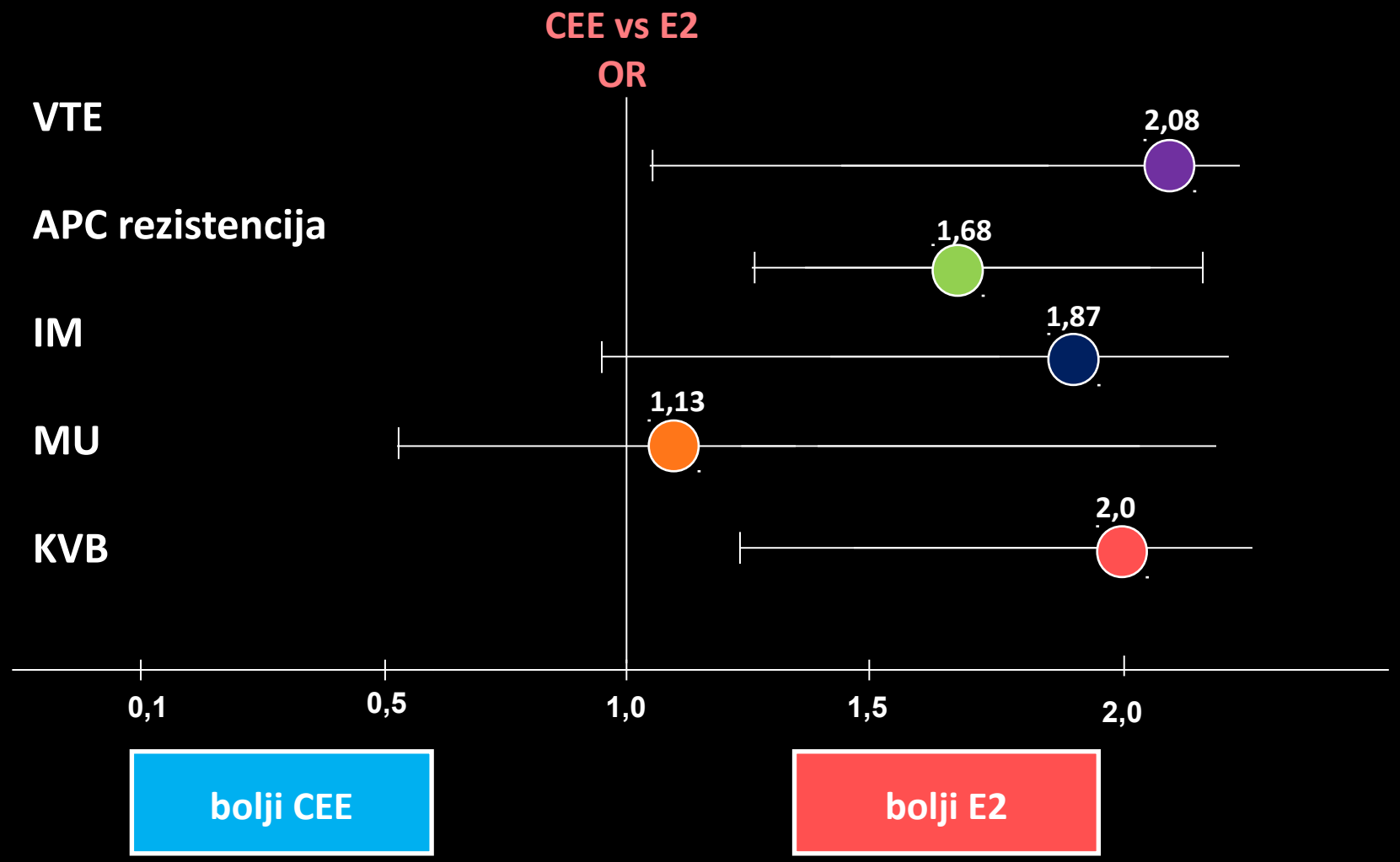
Baukhadra,JCEM,2015.
Boardman,2015.
Salpeter,AJM,2009.

# Effect of HRT – recently postmenopausal women
## Schierbeck et al / BMJ 2012. (DOPS)

RCT / 1006 ž / 7 mj u postmenopauzi / E2 + NETA



# CEE čini više rizika od Estradiola 17 β (Smith 2014)




Smith, JAMA, 2014.

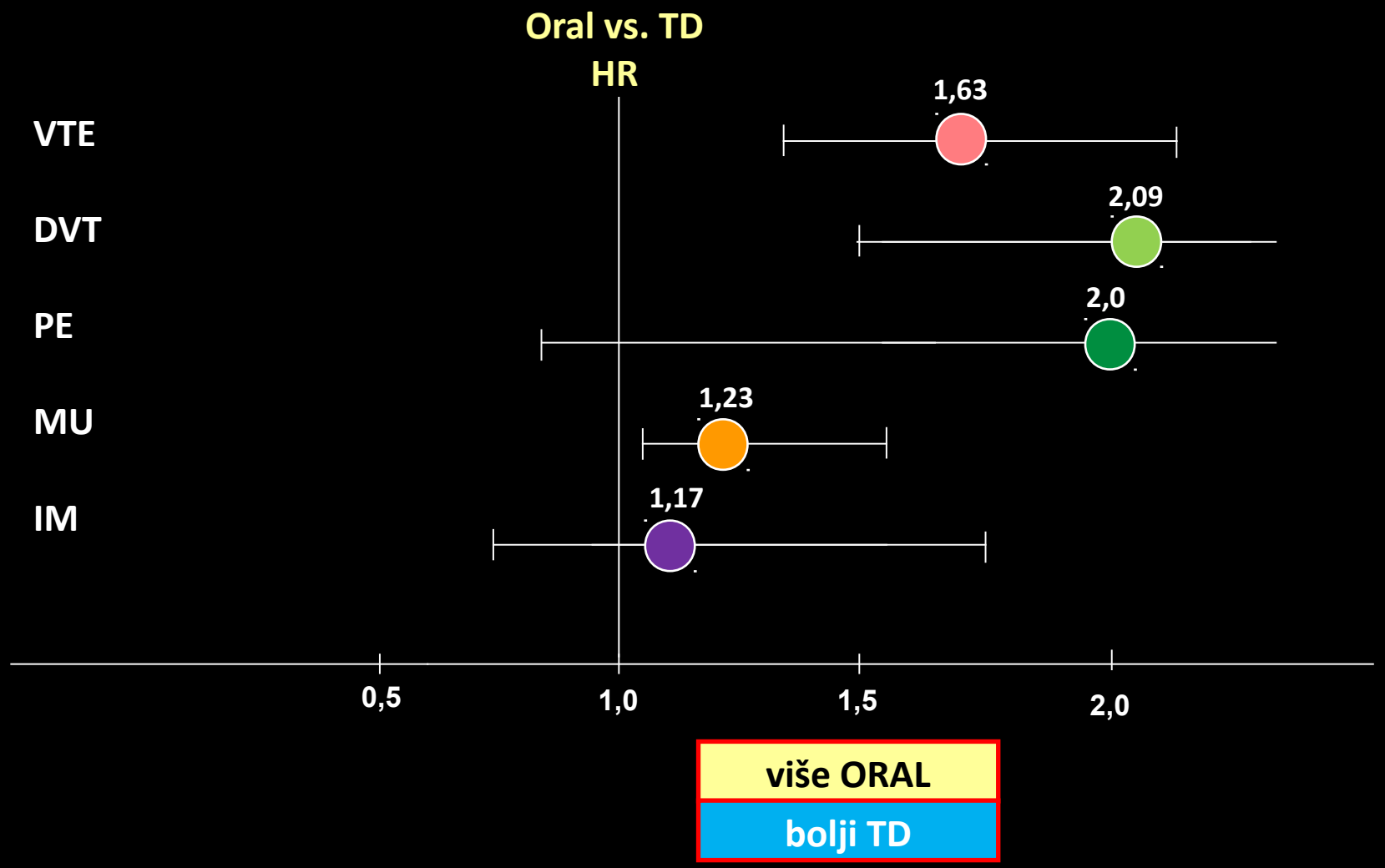
# Prednosti transdermalnog estradiola 17 β

- ne povisuje SHBG
- niži cirkulacijski E2
- kardioprotektivni efekt *
  - NO sintetaza
- anti-inflamatorni efekt *
- bez učinka na trigliceride
- bez učinka na CRP
- uz visok rizik za
  - KVB
  - rak dojke

- nema protrombotički efekt
  - niža APC rezistencija
  - niži trombin
  - niži endogeni potencijal trombina
  - niži PS
- pogodan u pacijentica
  - debljina
  - VTE rizik
  - mutacije – trombofilija
  - povišeni trigliceridi
  - ranije VTE

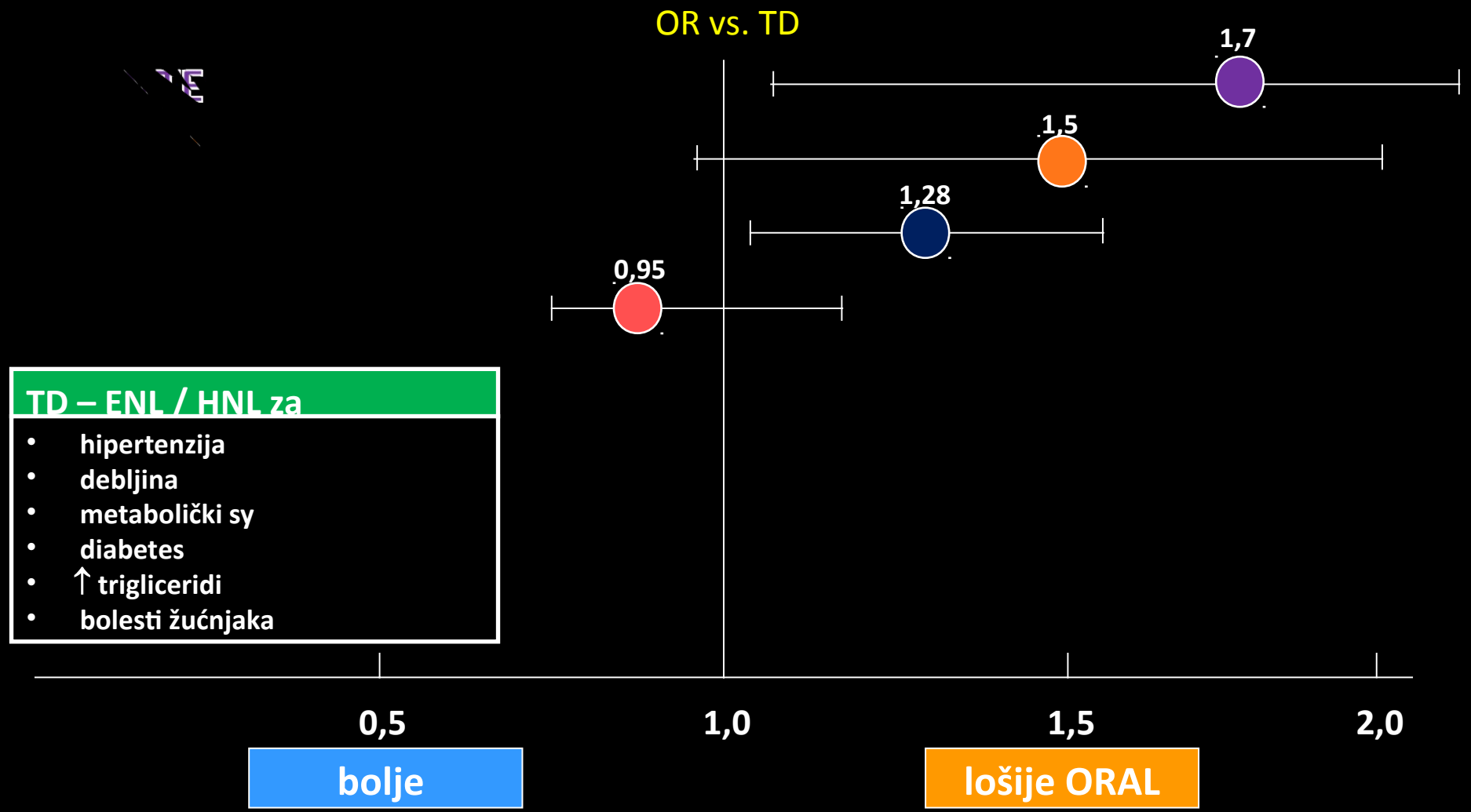
* MPA inhibira

# Oral vs. transdermal Estrogen therapy




Mohammed, JCEM, 2015.

# Oralni ili transdermalni estrogeni




**TD – ENL / HNL za**

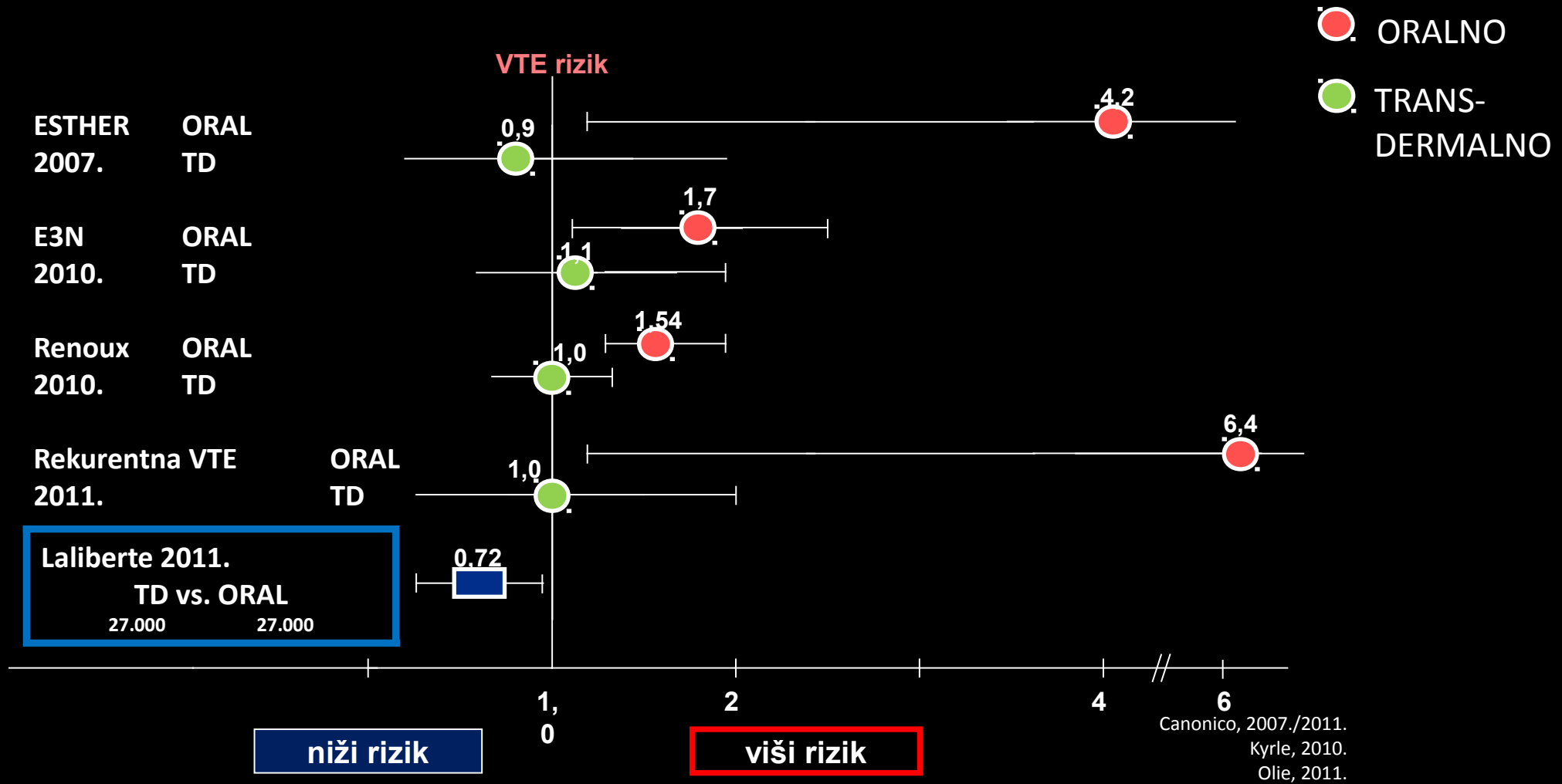
- hipertenzija
- debljina
- metabolički sy
- diabetes
- ↑ trigliceridi
- bolesti žućnjaka

**Oral E2 vs. TD-E2**

- 5 puta viši E1
- 15 puta viši E1 sulfat

Speroff,Clim,2010.
Renoux,BMJ,2010.

# HNL i tromboze: transdermalni estrogeni imaju nizak ili nikakav rizik




Canonico, 2007./2011.
Kyrle, 2010.
Olie, 2011.

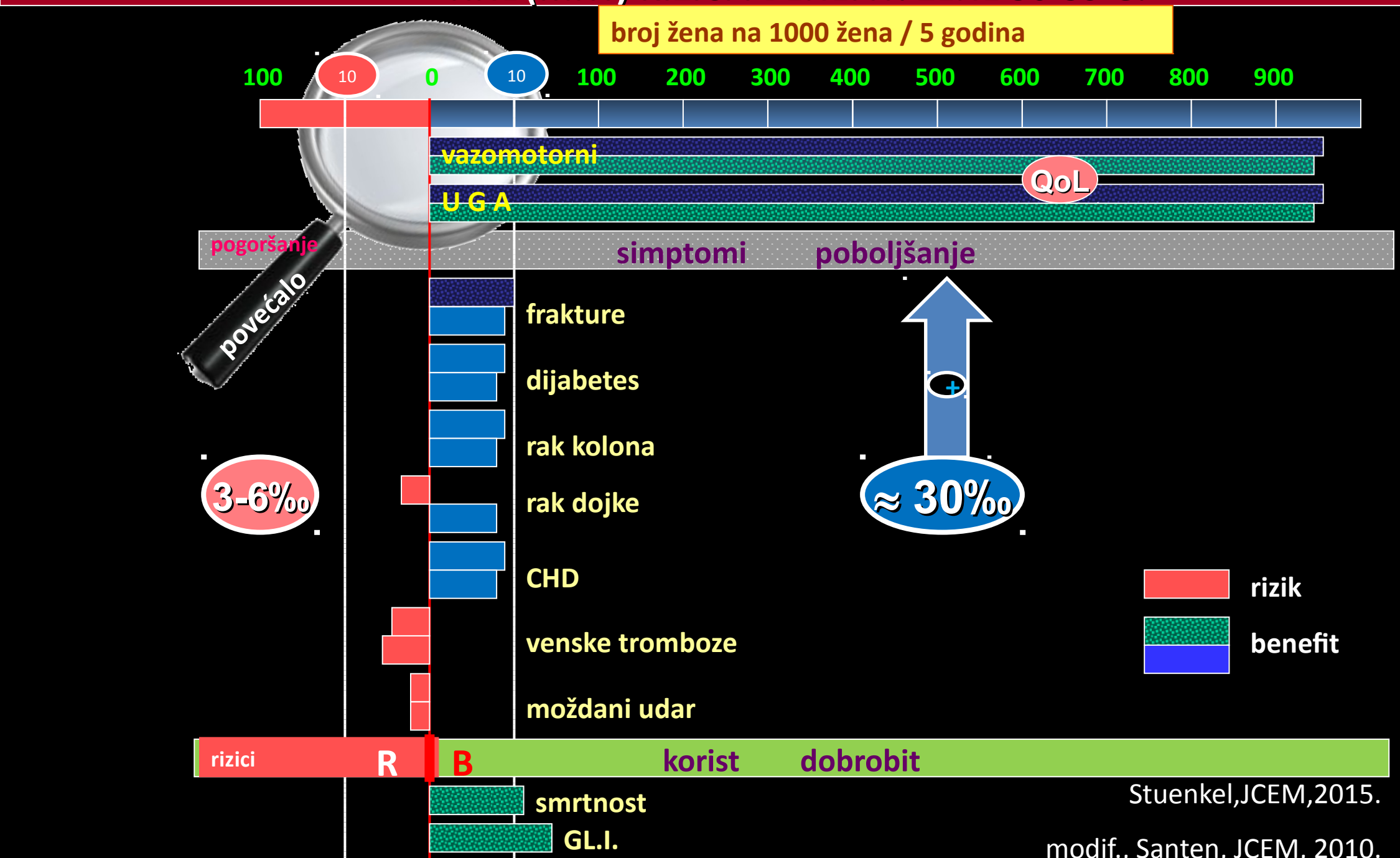
# HORMONSKO NADOMJESNO LIJEČENJE: KLINIČKO ODLUČIVANJE

rizik uzimanja HNL-a

ILI

rizik neuzimanja

# HNL (MHT) RIZICI I BENEFIT: ŽENE 50-59 G.




Stuenkel,JCEM,2015.

modif., Santen, JCEM, 2010.

# Promjene progestagena u HNL-u

- Prirodni – neandrogeni progestageni
  - Dydrogesterone
  - mikronizirani P.
- Niža doza – trajanje (10 dana)
- Lokalni progestageni
  - LNG – IUS
  - vaginal
- Estrogeni + SERM
  - Bazedoxiphene (Duavive)
- Novi SERM za simptome
  - Ospeniphen

Neki progestageni povisuju rizike KVB / rak

# GLOBAL CONSENSUS STATEMENT on MHT 2013.

RCT, opservacijske studije i metaanalize

su dokazale

da uz početak MHT / HNL i ENL
u perimenopauzi ili do 10 g. od menopauze

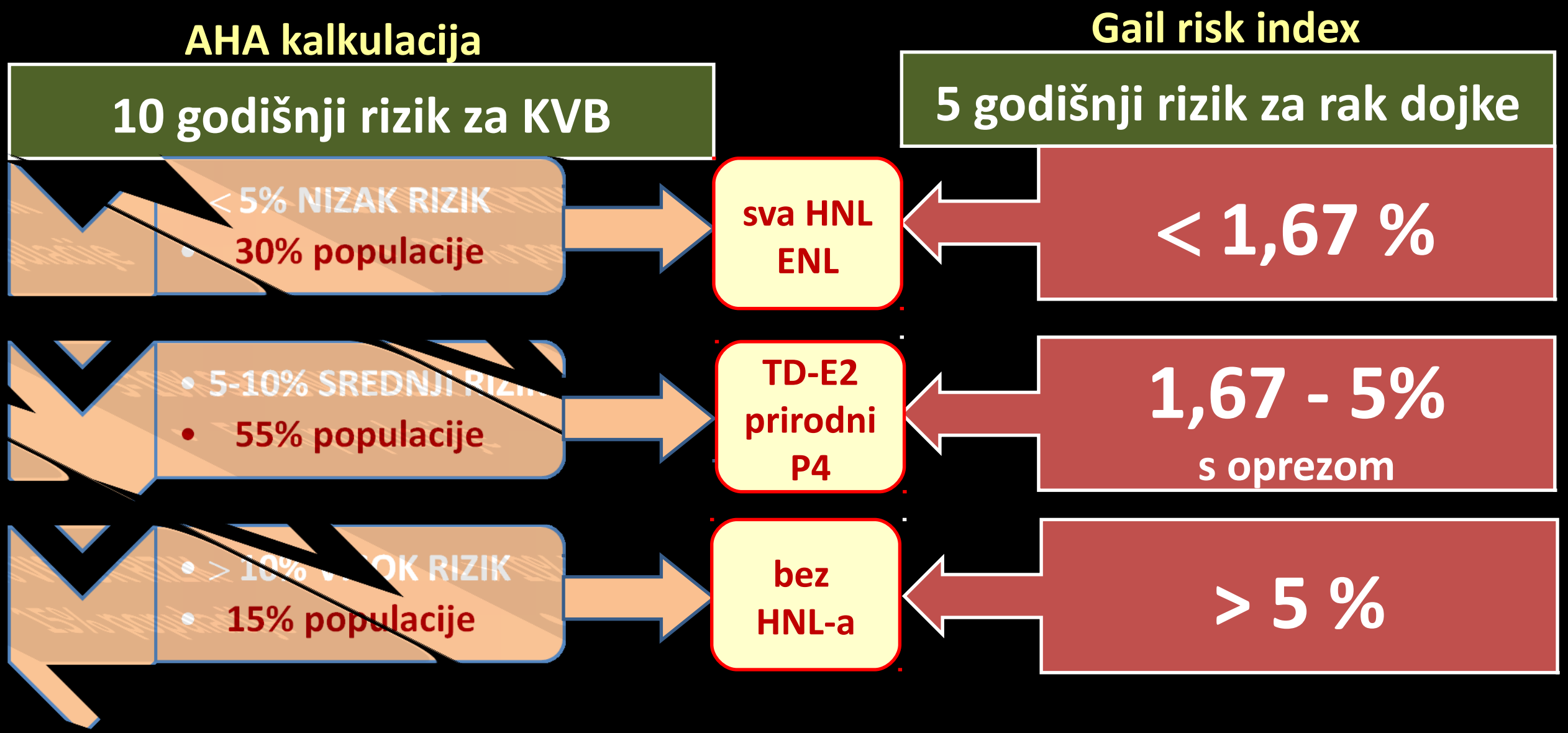
BENEFIT ZNAČAJNO NADMAŠUJE RIZIKE

doza i trajanje MHT sukladno su cilju
liječenja i sigurnosti, individualizirane su

korištenje MHT je personalna odluka

ESHRE POSITION STATEMENT – 2015.

# Odabir HNL-a prema rizicima




Manson, FS, 2014.

Moyar, Ann Int Med, 2013.

# Suvremeni principi hormonskog nadomjesnog liječenja

* Odavno je dokazan i nedavno potvrđen benefit HNL-a za mlađe i zdrave žene u postmenopauzi

* Apsolutni rizik za žene u perimenopauzi, dobi od 50 do 59 godina, je ekstremno nizak

* Primarne indikacije za HNL jesu simptomi menopauze, UGA, niska QoL, te prevencija osteoporoze. HNL ima i sekundarne povoljne učinke

* Transdermalni 17-β estradiol je najpovoljniji izbor za većinu žena.
  - za žene s uterusom neophodan je ciklički dodatak što bezazlenijih progestagena (mikronizirani P, dydrogesteron i sl.)

* Preporučuje se najniža a učinkovita doza, a odabir i trajanje HNL-a trebaju biti individualizirani