Hypertenze u žen – má skutečně jiná specifika?

Renata Cífková

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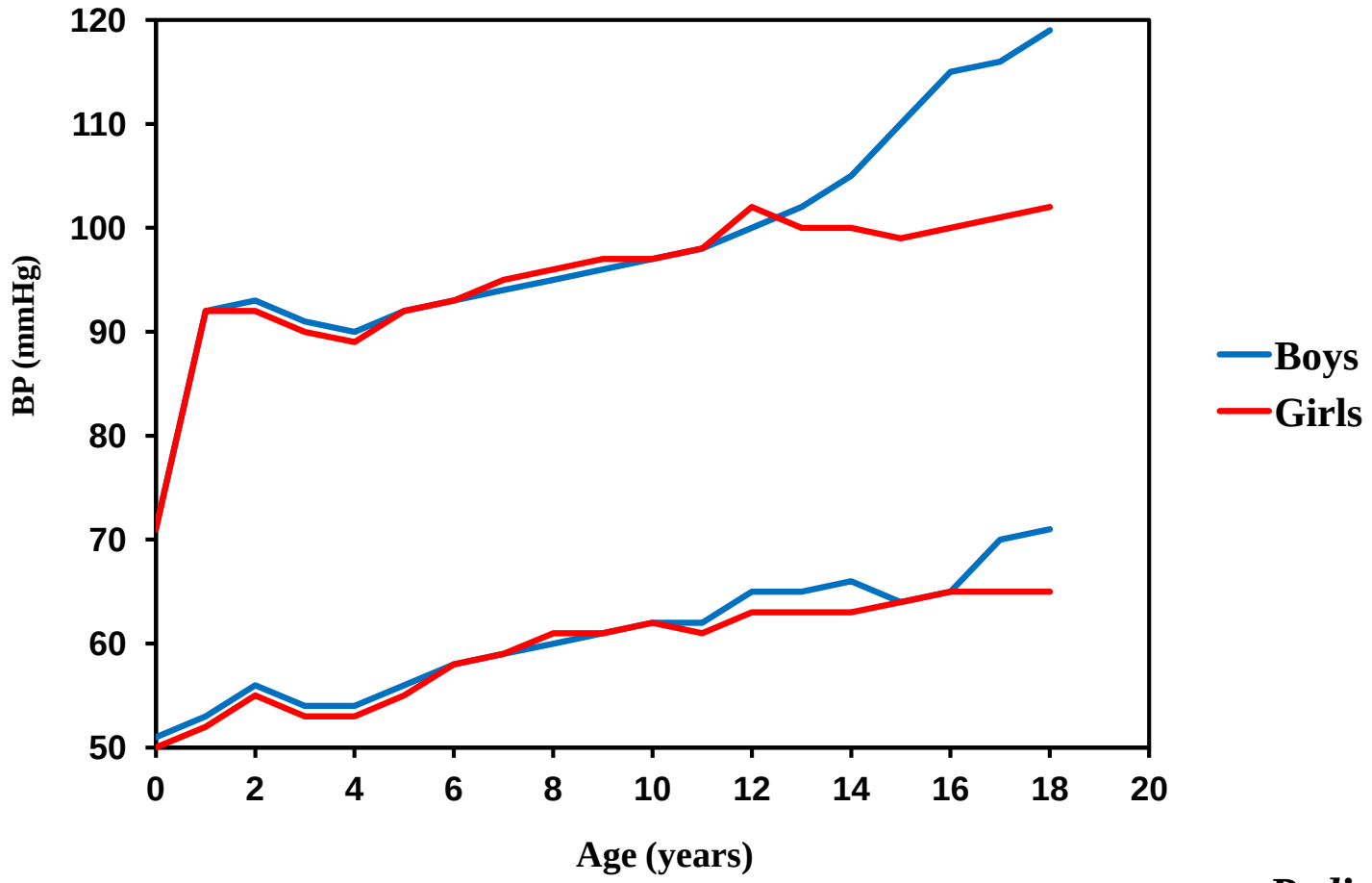
II. interní klinika 1. LF UK a VFN
Praha

XXXI. VÝROČNÍ SJEZD ČESKÉ KARDIOLOGICKÉ SPOLEČNOSTI

- **Epidemiologie hypertenze**
- **TK kolem menopauzy**
- **Velké klinické studie u hypertenze**
- **Nežádoucí účinky léků**

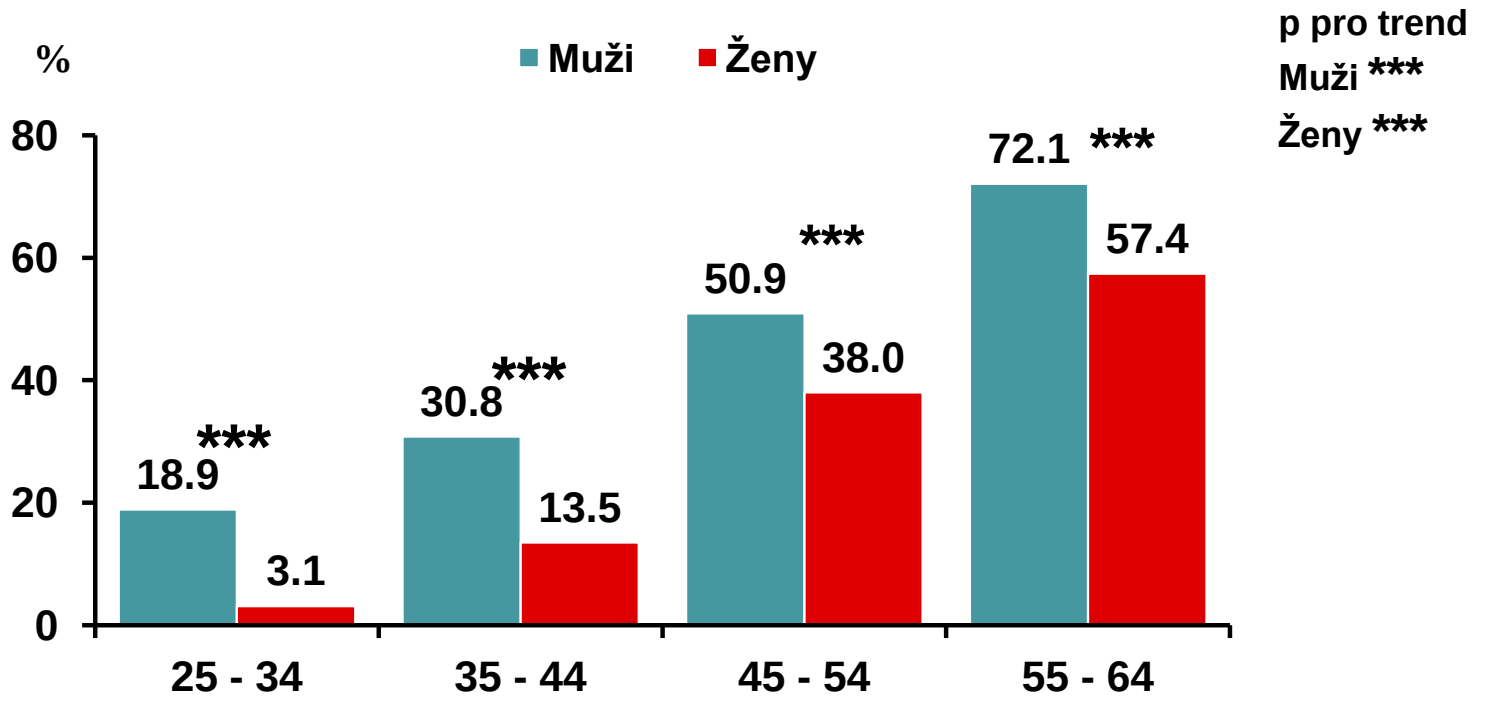
Průměrný STK a DTK u chlapců a dívek, od narození do 18 let věku, USA



Pediatrics 1987;79:1-25

Prevalence hypertenze podle věkových skupin

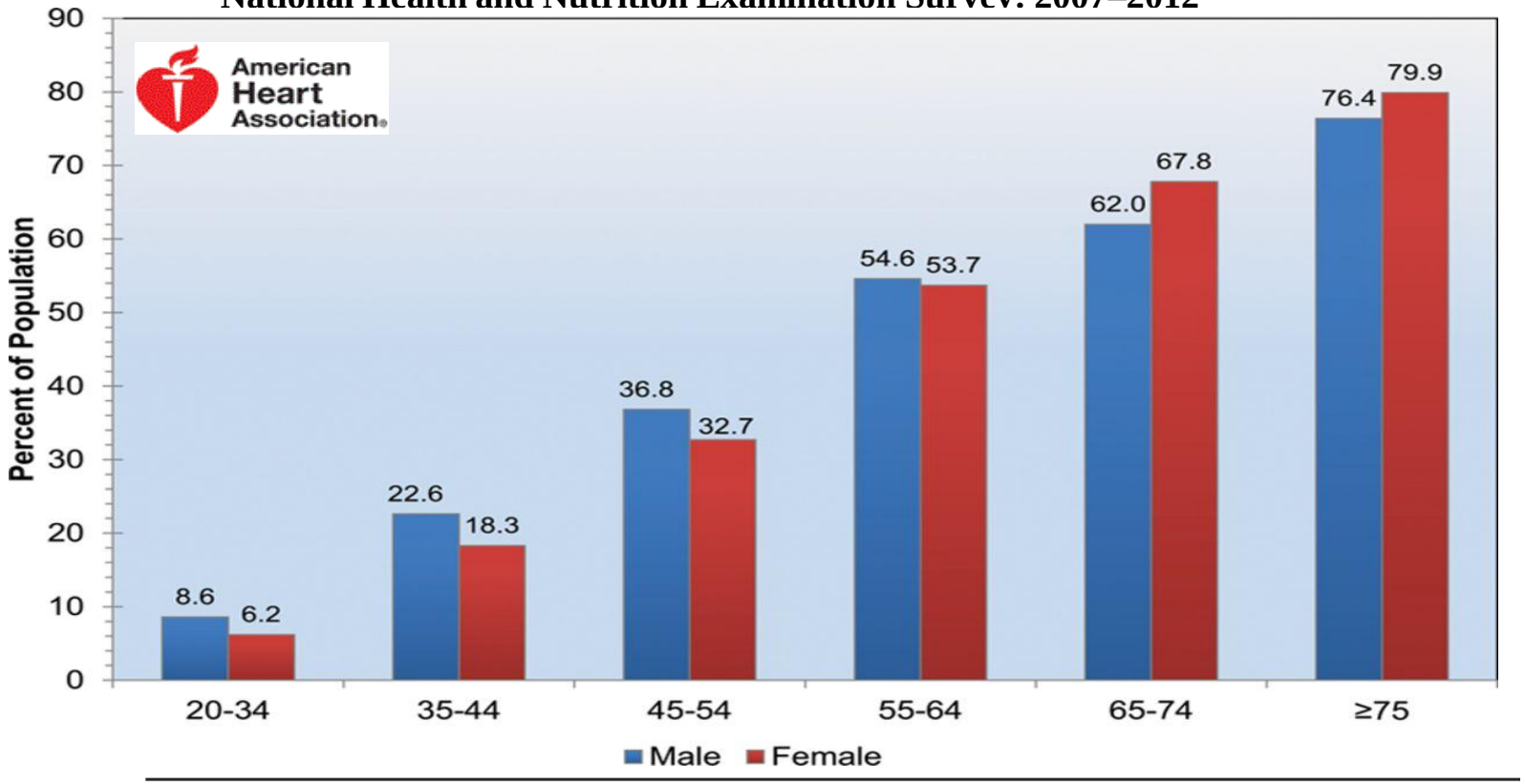
Česká republika, 2016-2018



Cífková et al., Cor Vasa 2020;62:6–15

Prevalence of high BP in adults ≥20 years of age by age and sex

National Health and Nutrition Examination Survey: 2007–2012

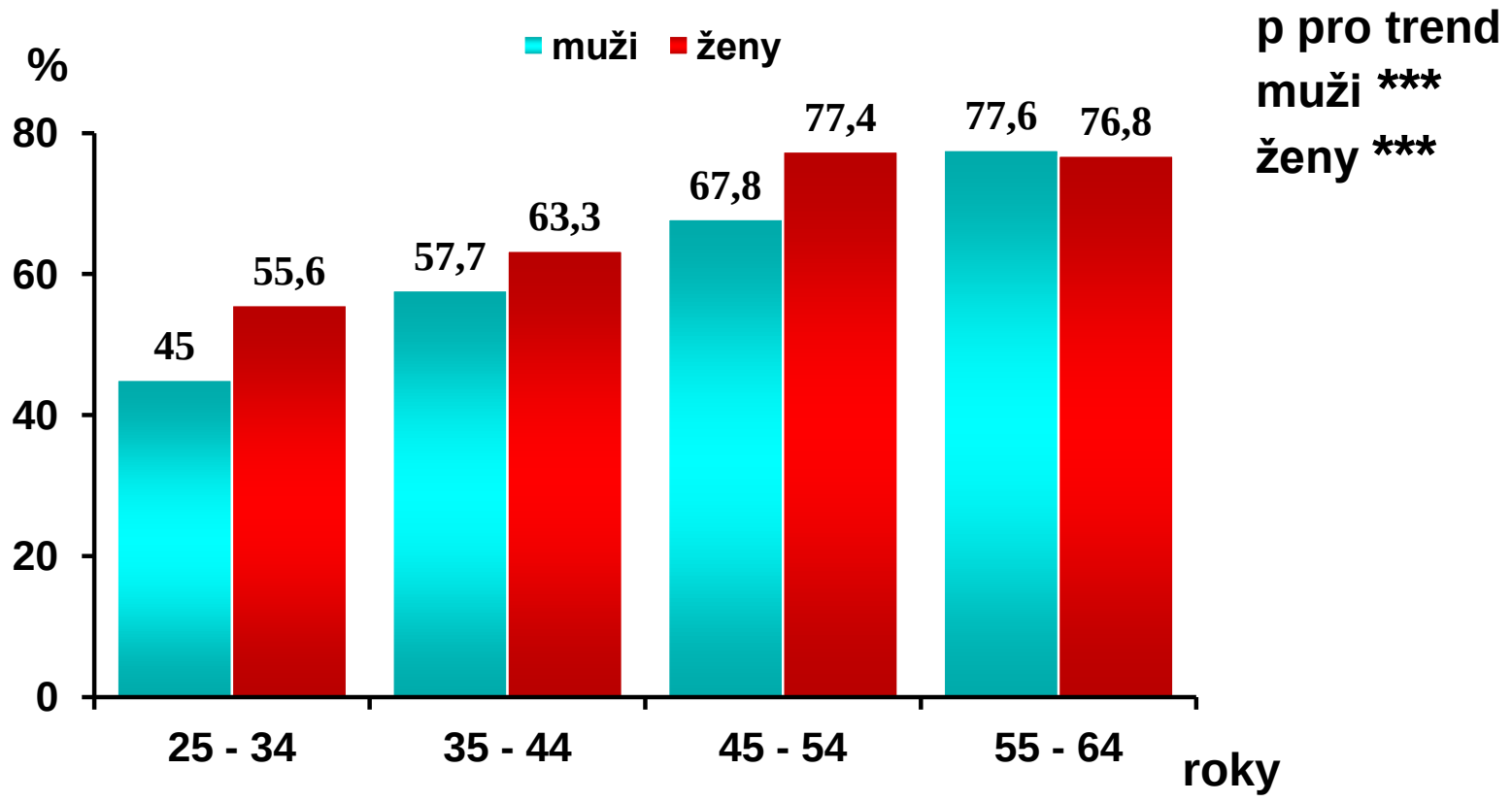


Population Group	Prevalence, 2012, Age ≥20 y	Mortality,* 2013, All Ages	Hospital Discharges, 2010, All Ages
Both sexes	80 000 000 (32.6%)	71 942	488 000
Males	38 300 000 (33.5%)	33 563 (46.7%)†	216 000
Females	41 700 000 (31.7%)	38 379 (53.3%)†	272 000

Circulation. 2016;133:e38-e360

Znalost hypertenze podle věkových skupin

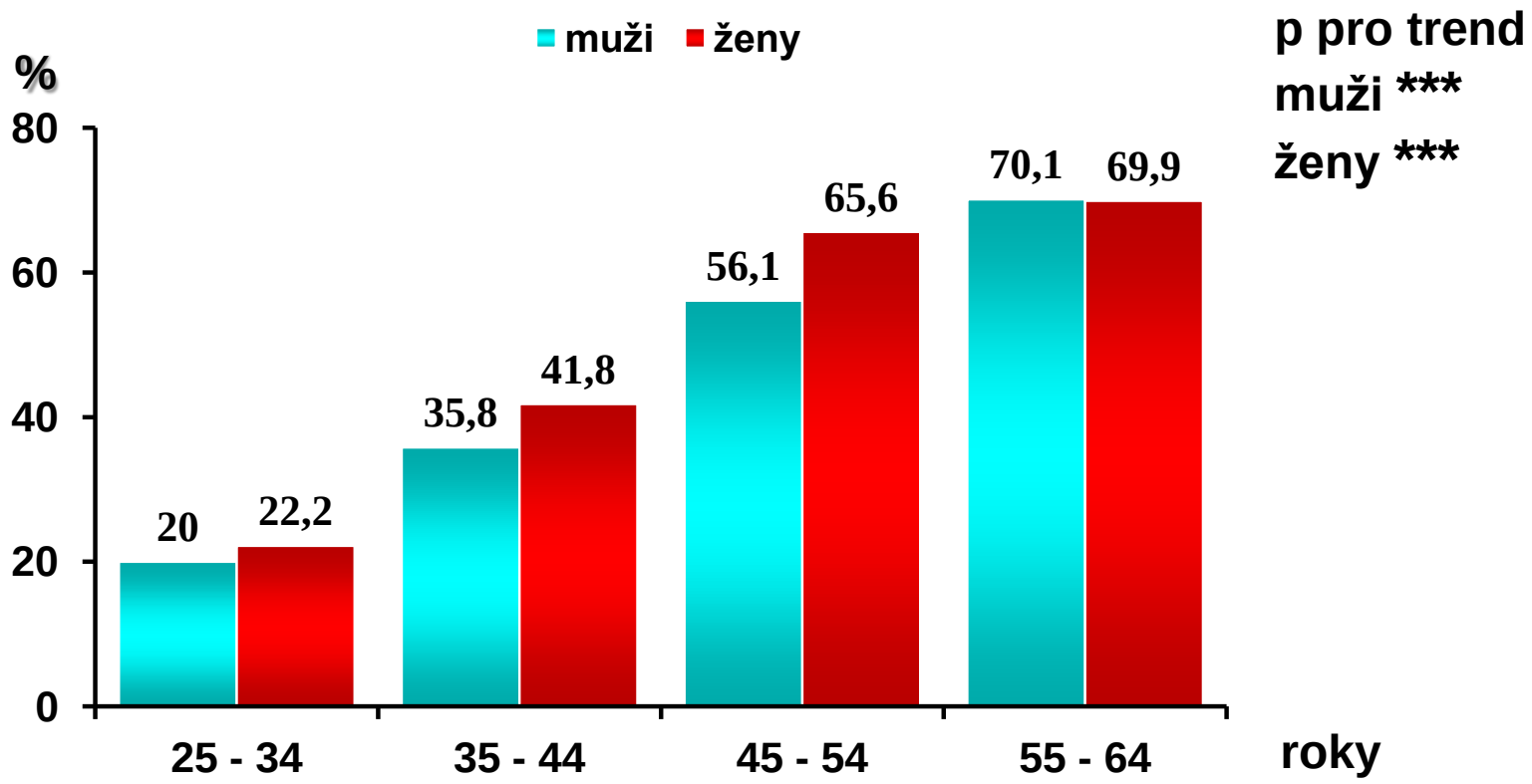
Česká republika 2016-2019



Cífková et al., Cor Vasa 2020;62:6–15

Léčba hypertenze podle věkových skupin

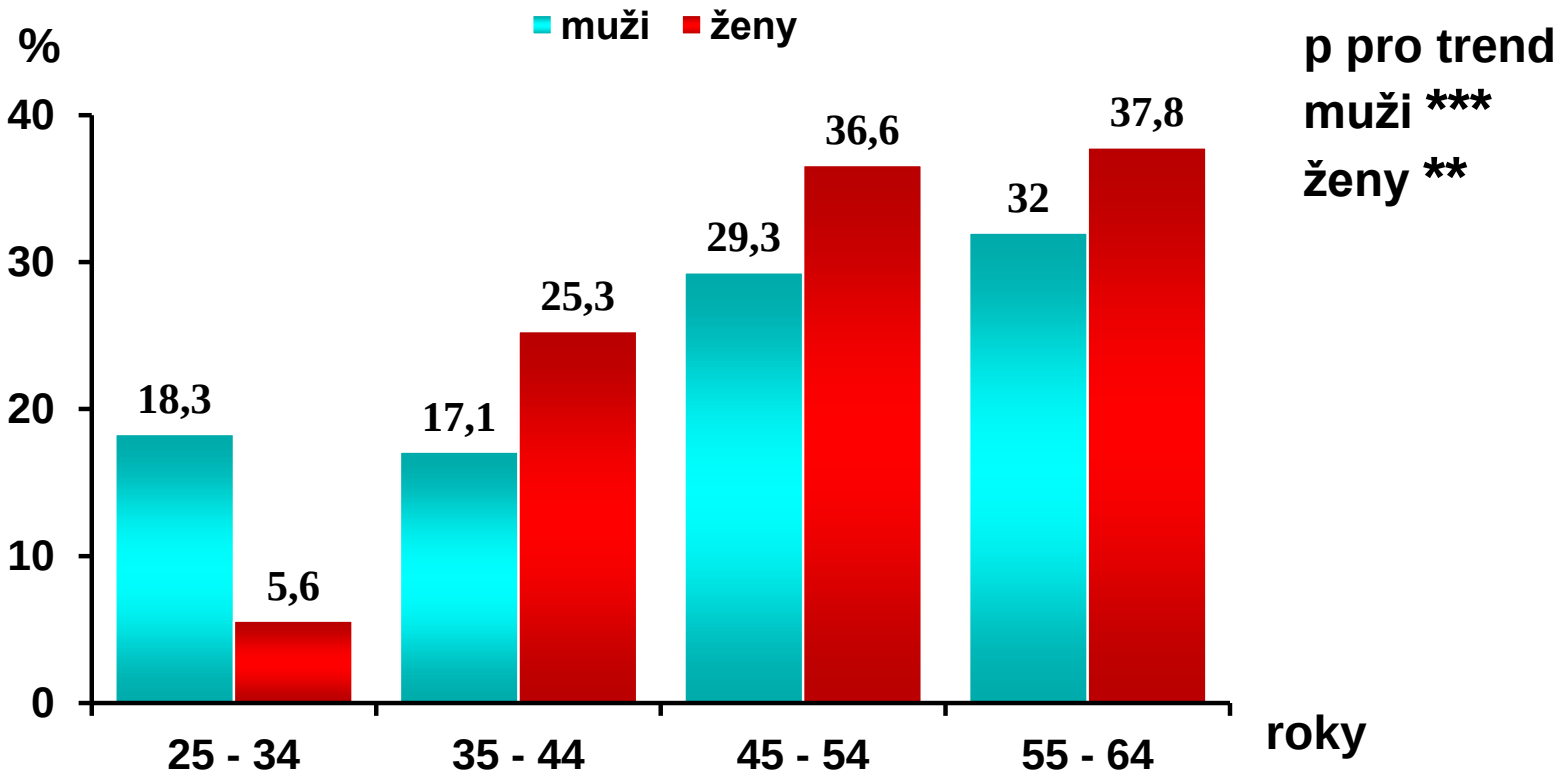
Česká republika 2016-2019



Cífková et al., Cor Vasa 2020;62:6–15

Kontrola hypertenze podle věkových skupin

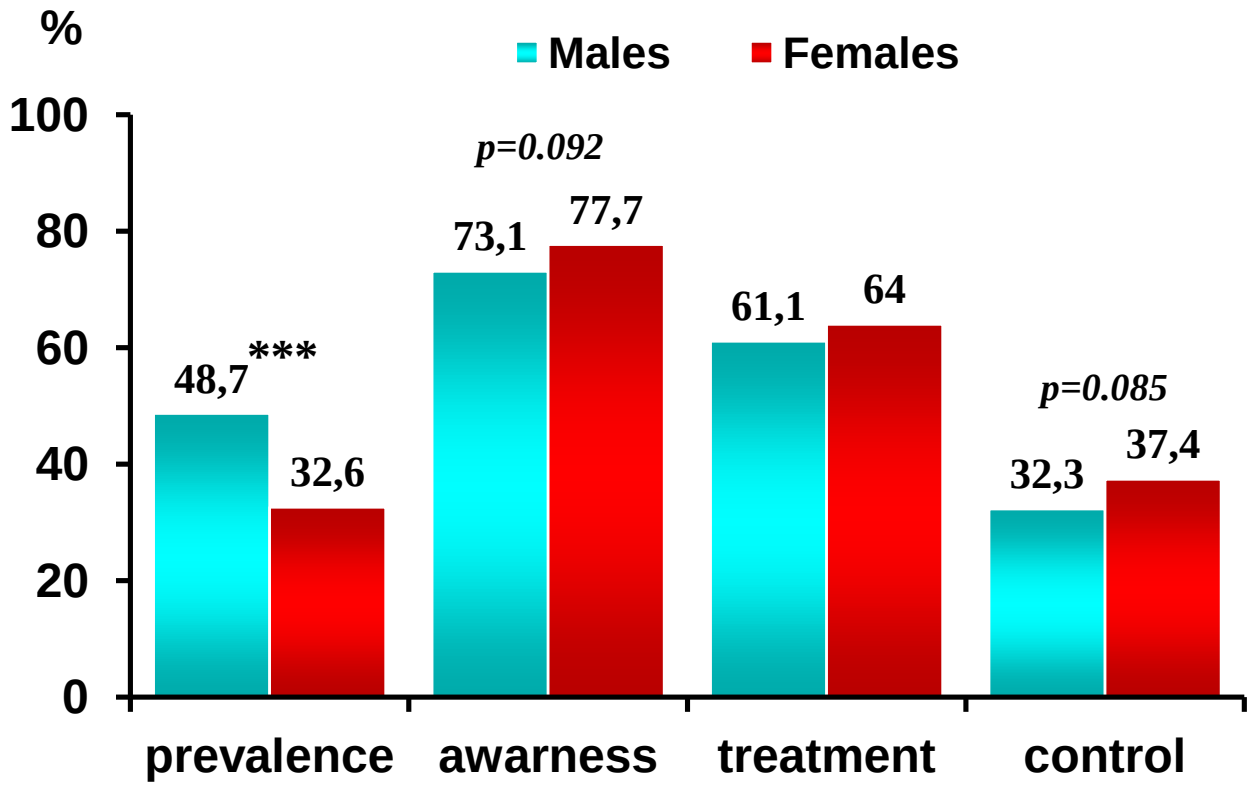
Česká republika 2016-2019



Cífková et al., Cor Vasa 2020;62:6–15

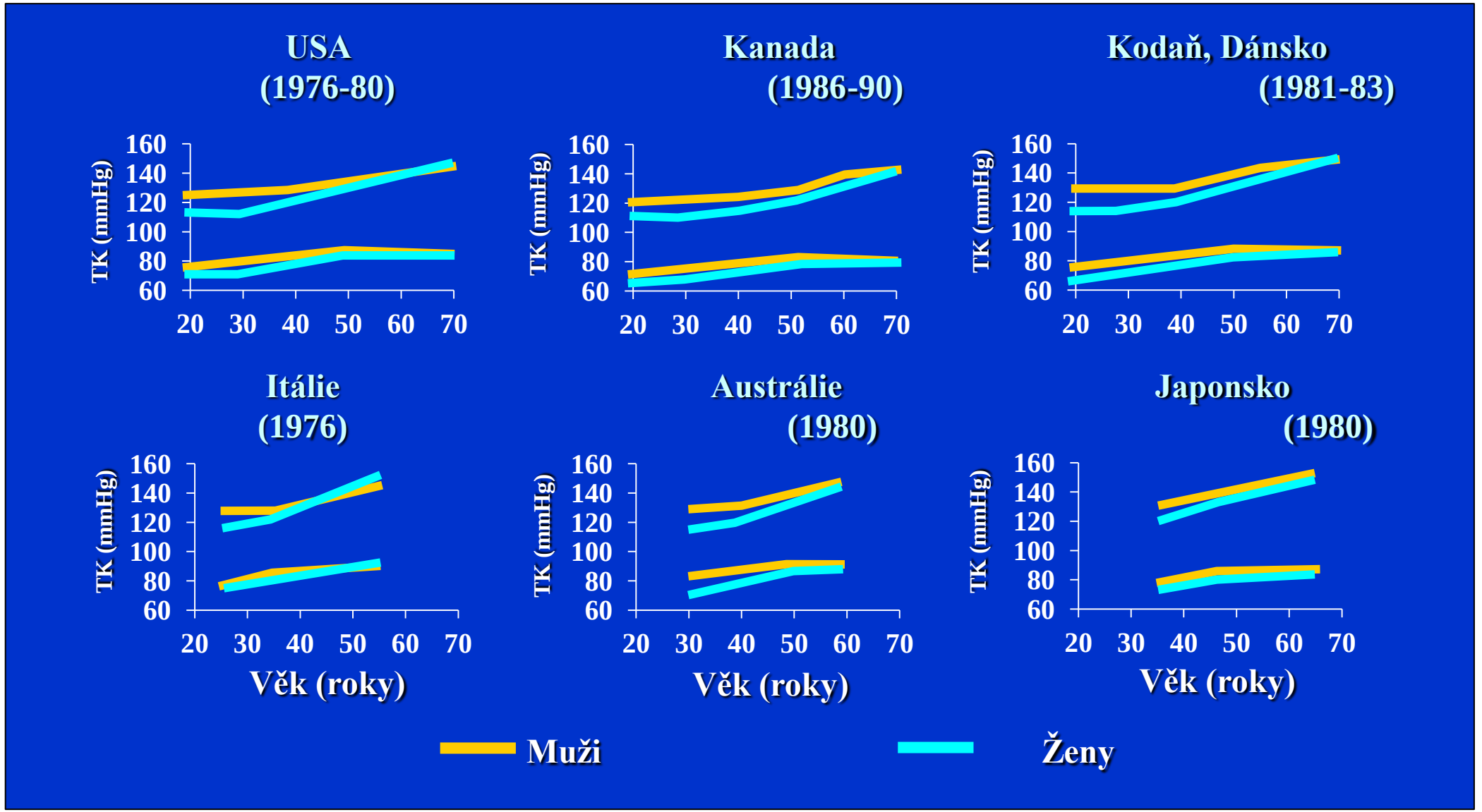
Prevalence, znalost, léčba a kontrola hypertenze

Česká republika, 2015-2018



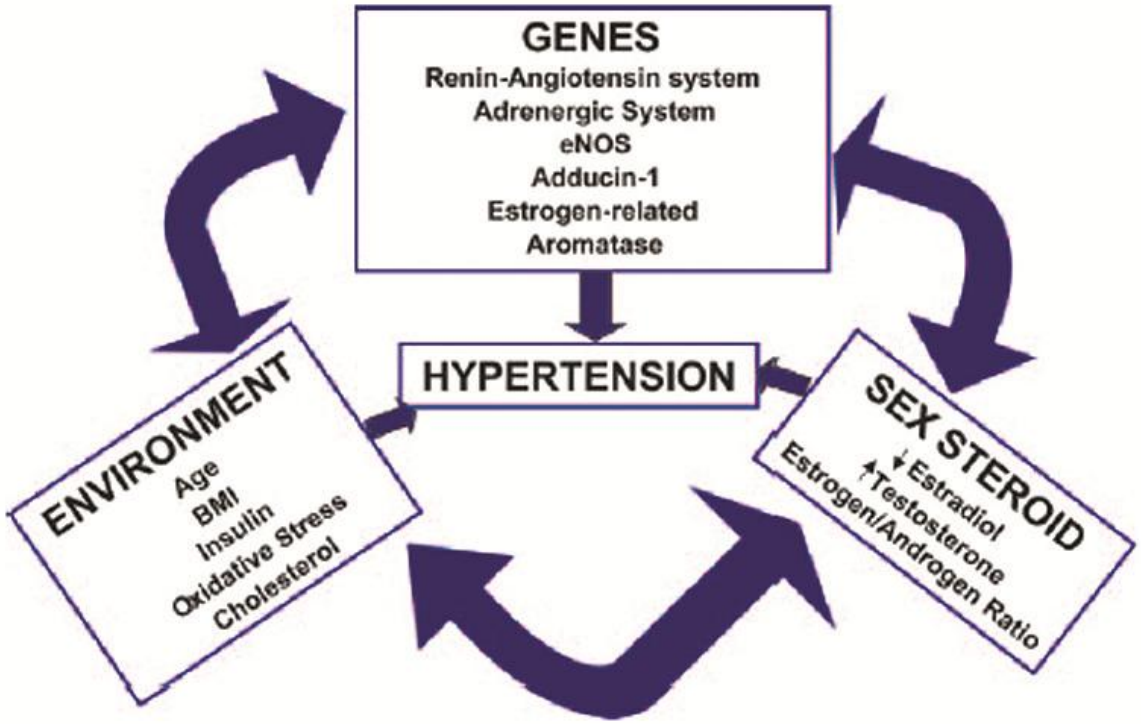
*** p < 0.001

Krevní tlak


USA
(1976-80)
Kanada
(1986-90)
Kodaň, Dánsko
(1981-83)
Itálie
(1976)
Austrálie
(1980)
Japonsko
(1980)
TK (mmHg)
160
140
120
100
80
60
20
30
40
50
60
70
Věk (roky)
Muži
Ženy

Hypertension in postmenopausal women

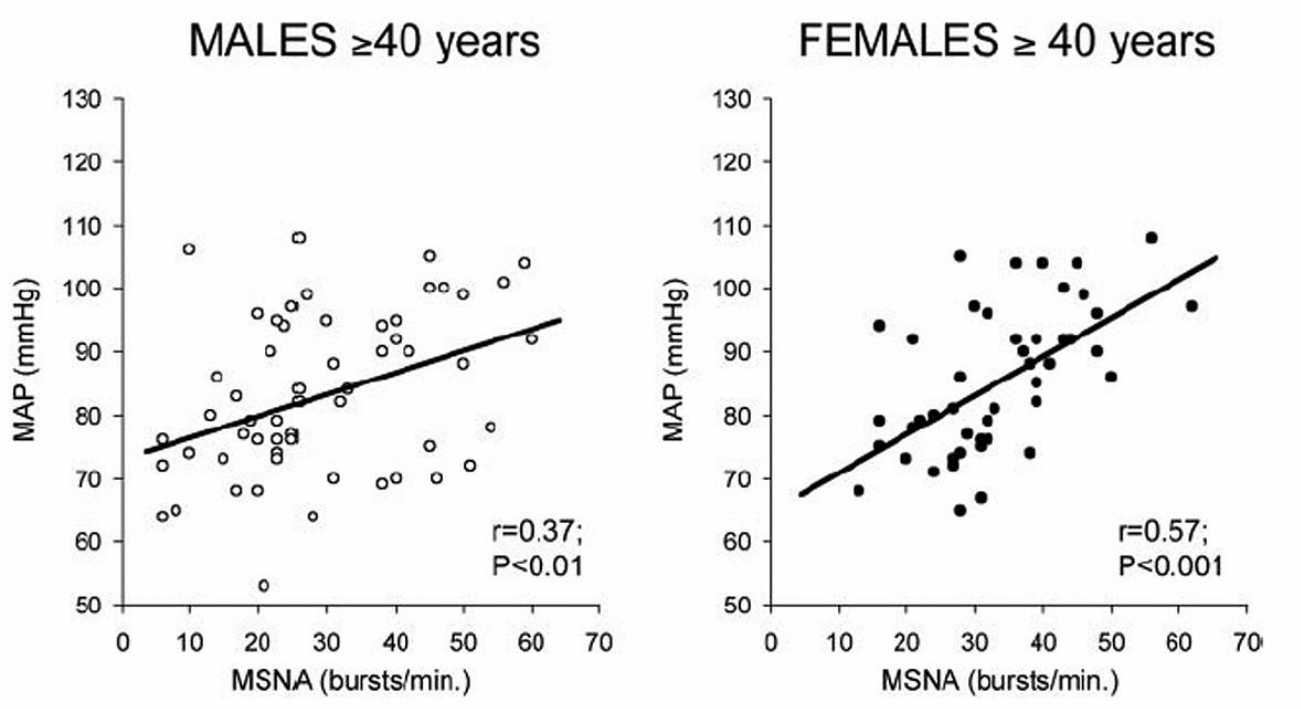
Contributing factors



Hypertension 2008;51:952-959

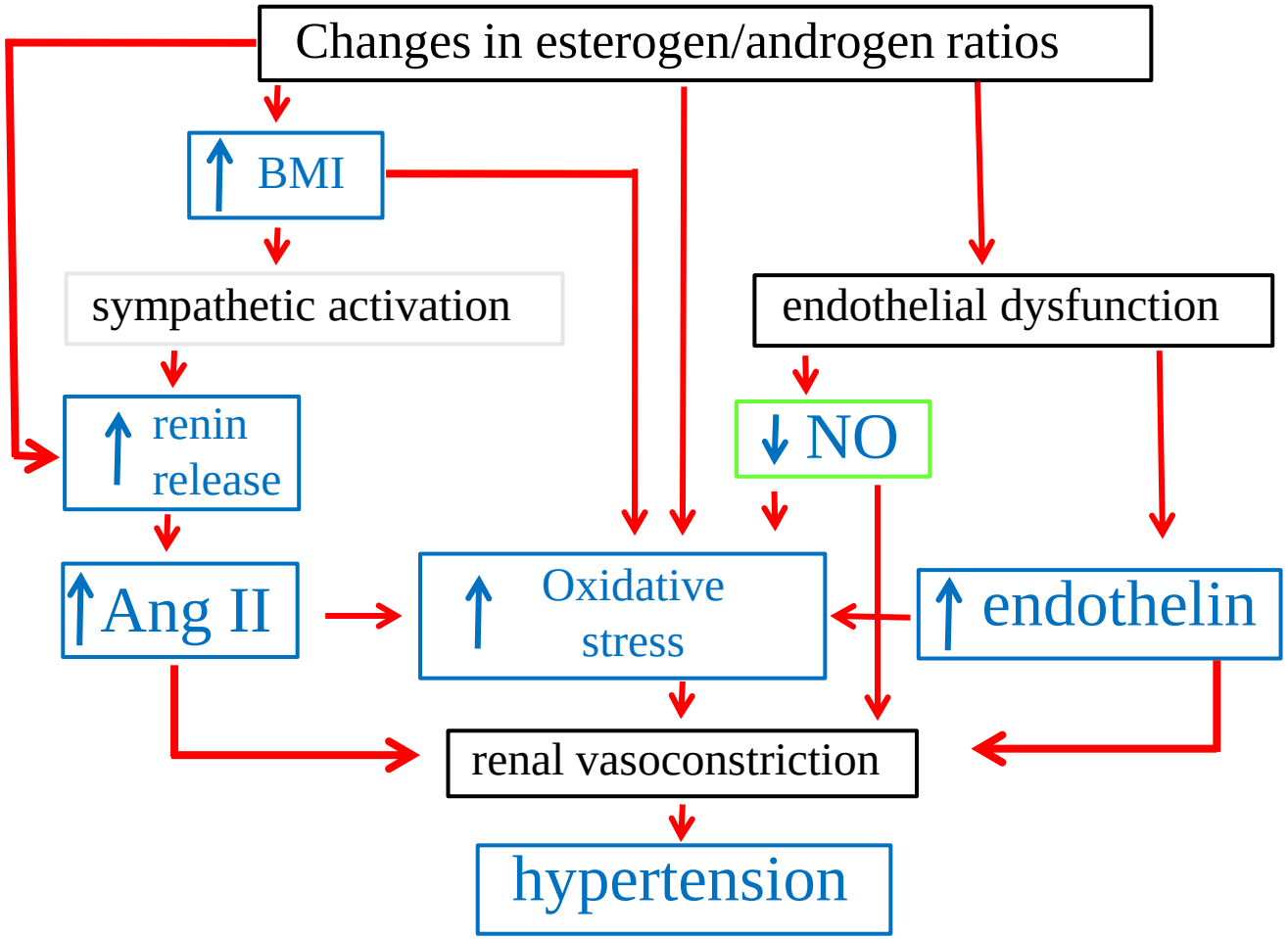
Relationship between MSNA and MAP

Gender differences



Hypertension 2005;45:522-525

Postmenopausal hypertension



Hypertension 2008;51:952-959

Menopauza a krevní tlak

- ***Vzestup***

Weiss NS, 1972; Eferakeya AE, Imasuen JE, 1986; Staessen JA et al., 1989; Bunker CH et al., 1991; Owens JF et al., 1993; Casiglia E et al., 1996; Portaluppi F et al., 1997; Staessen JA et al., 1997; Grobbee DE et al., 1988; Poehlman ET, 1997; Shelley JM et al., 1998; Zanchetti A et al., 2005

- ***Žádná změna***

Casiglia E et al., 1996; Wu ZY et al., 1990; Armellini F et al., 1990; Zamboni M, 1992; Hjortland MC et al., 1976; Lindqvist O, Bengtsson C, 1980; van Beresteyn ECH et al., 1989; Matthews KA et al., 1989; Akahoshi M et al., 1996; Peters HW et al., 1999; Luoto R et al., 2000; Torng PL et al., 2002

- ***Pokles***

Lindqvist O, Bengtsson C, 1980; van Beresteijn EC et al., 1992

Krevní tlak v období menopauzy

Nezodpovězené otázky

1. **Je vzestup TK skutečně ve vztahu k menopause?**

2. **Je vzestup TK způsoben spíše současně stárnutím a vzestupem BMI?**

Cíle práce

Objasnit vliv menopauzy na hodnoty TK u náhodně vybraného populačního vzorku žen z Prahy 4

Populace

- **908 žen, s trvalým bydlištěm v Praze 4**

  respondence 63,9 %
- **873 žen s úplnými daty**
- **věkové rozmezí 45 - 55 let**
- **průměrný věk 50,1 ± 2,70 let**

Definice menopauzy

1. Podle FSH

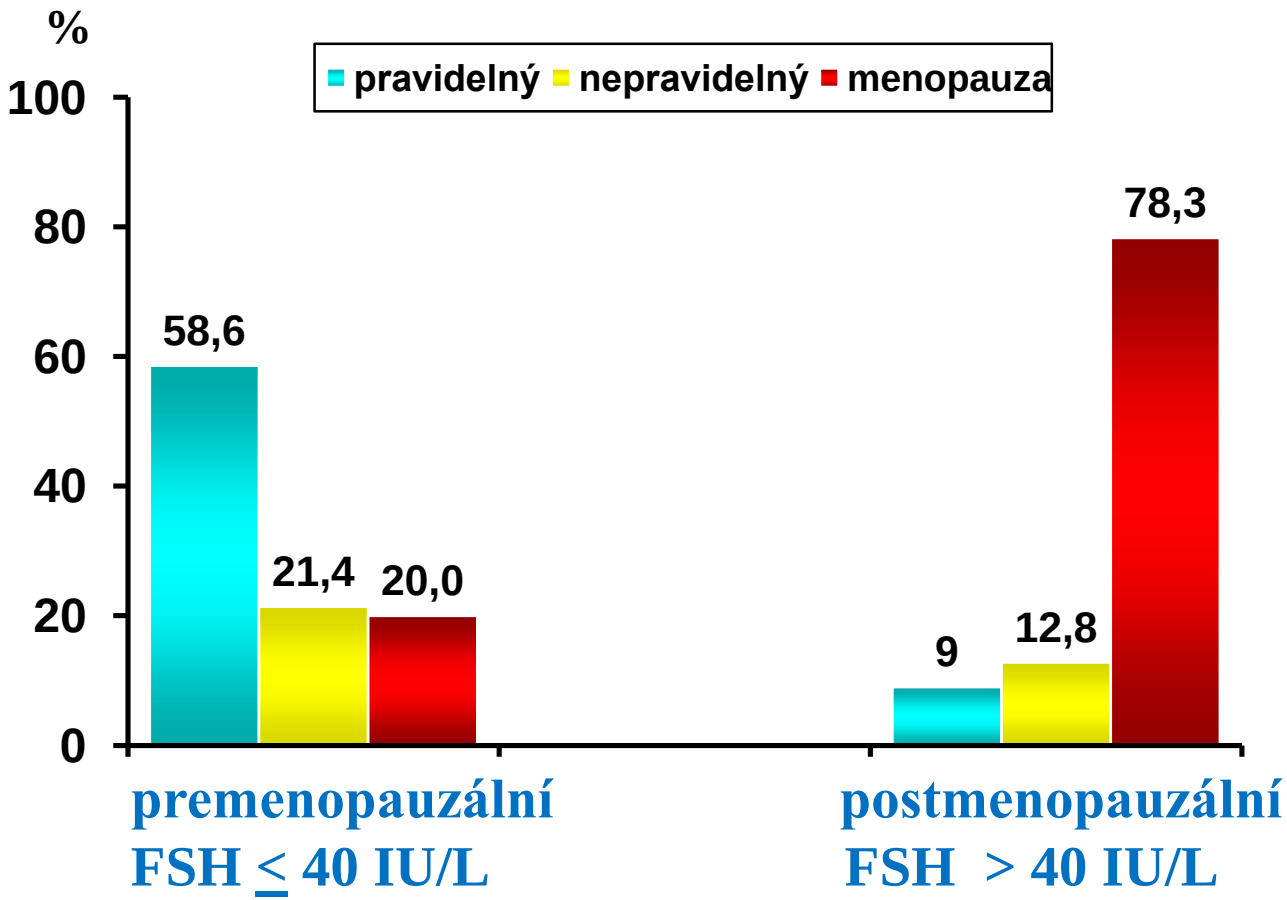
- **premenopauzální FSH ≤ 40 IU/l**
- **postmenopauzální FSH > 40 IU/l**

2. Podle menstruačního cyklu

- **premenopauzální PM < 60 dní**
- **perimenopauzální PM 60-365 dní**
- **postmenopauzální PM > 365 dní**

3. Podle FSH i menstruačního cyklu

Menstruační cyklus



Základní charakteristiky žen

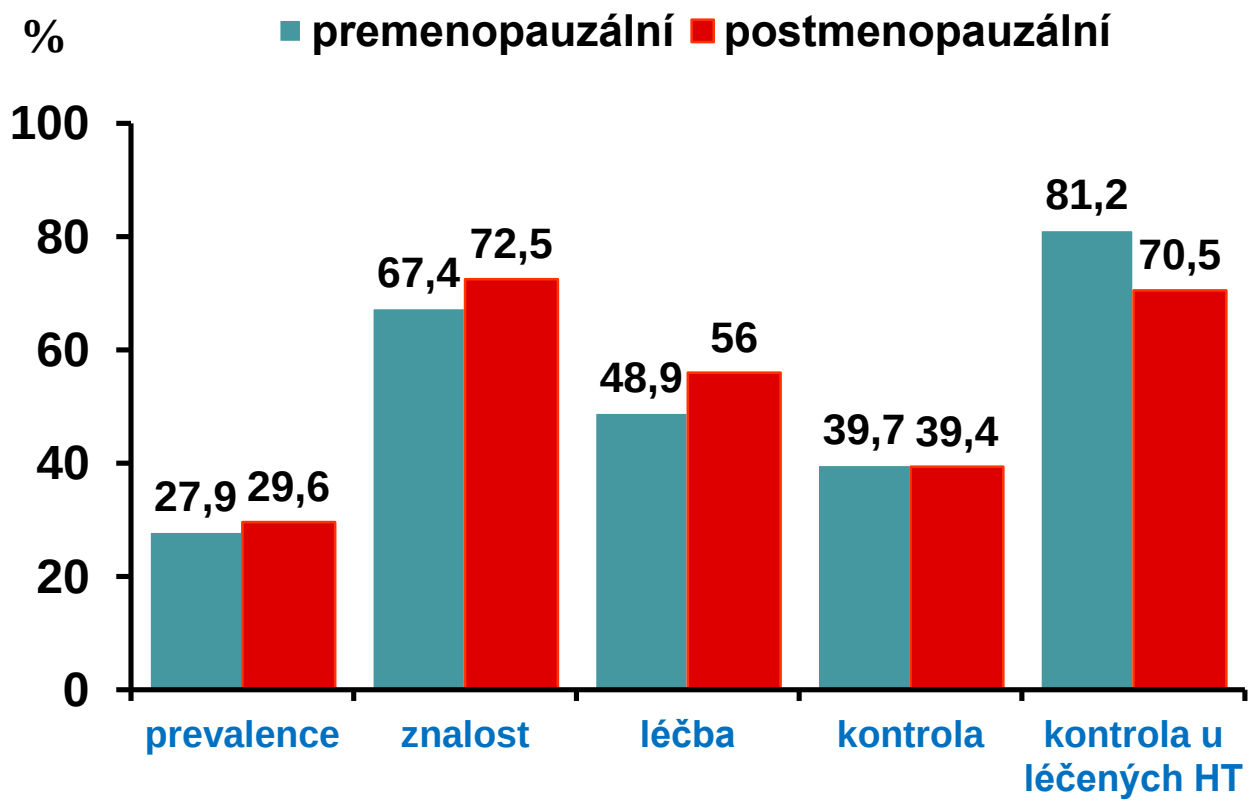
Dělení podle FSH

	Premenopauzální	Postmenopauzální	p
počet	505	368	
věk, roky	49,0 ± 0,11	51,6 ± 0,11	< 0,001
BMI*, kg/m^2	26,3 ± 0,22	25,4 ± 0,27	0,021
STK**, mmHg	118,7 ± 0,71	119,0 ± 0,85	ns
DTK**, mmHg	78,7 ± 0,43	79,2 ± 0,51	ns
TF**, tepů/min	71,2 ± 0,42	69,9 ± 0,51	0,052

* adj. na věk, **adj. na věk a BMI Průměr ± SE

J Hypertens 2008; 26:1976-1982

Prevalence, znalost, léčba a kontrola hypertenze



Regresní koeficienty

(SE; mnohorozměrná regresní analýza)

	Systolický TK		Diastolický TK	
	Premenopauzální Postmenopauzální ženy	ženy	Premenopauzální ženy	Postmenopauzání ženy
Věk	0,33 (0,27)	0,049 (0,38)	-0,01 (0.16)	-0,15 (0,23)
BMI	0,77 (0,15)***	1,01 (0,17)***	0,64 (0,09)* **	0,59 (0,10)***
TF	0,22 (0,08)***	0,21 (0,09)*	0,21 (0.04)***	0,23 (0,05)***
Kouření	-1.20 (1,43)	-3,29 (1,66)*	-0,54 (0,84)	1,97 (0,99)*
Medikace pro hypertenzi	5.02 (2,01)**	7,47 (2,28)***	2,73 (1,19)*	4,59 (1,37)***
R^2 (%)	10,7	16,8	17,5	18,2

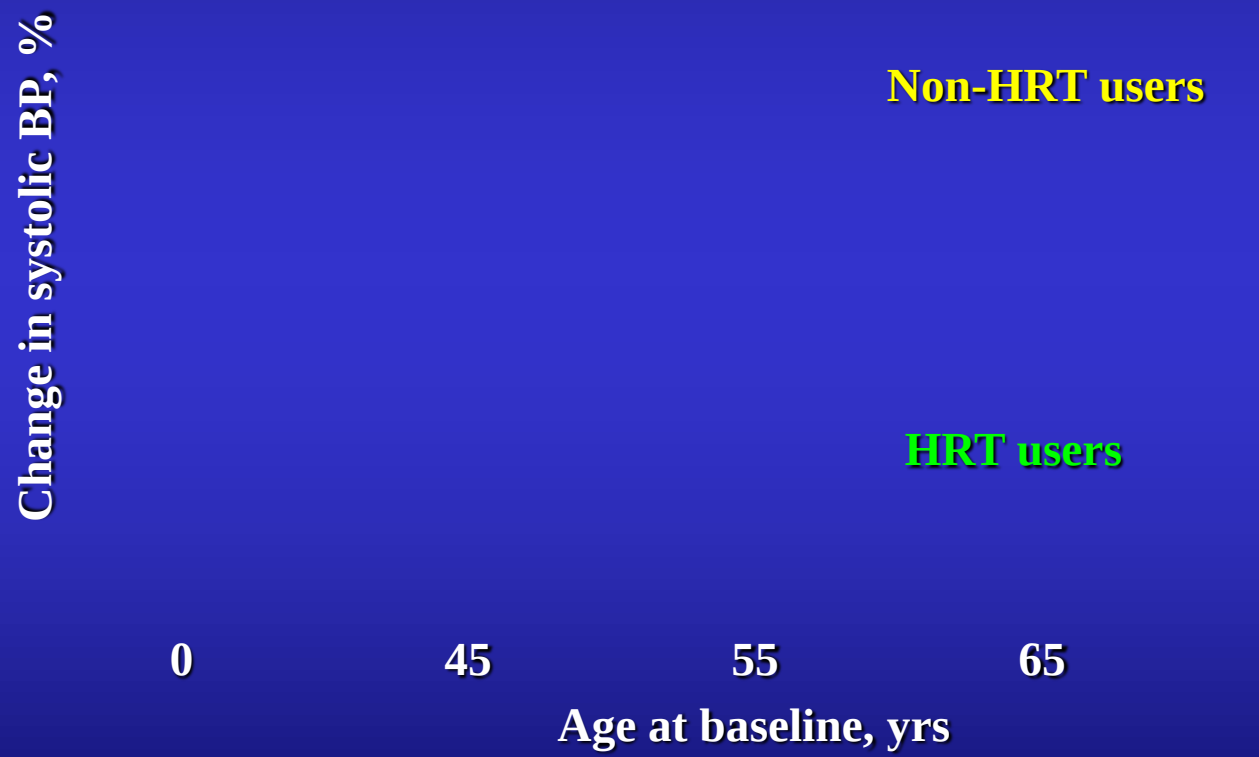
*p < 0,05 **p < 0,01 *** p < 0,001

RR vybraných onemocnění u 50leté bělošky užívající HRT

	RR	
	Estrogeny	*Estrogeny + progesteron*
ICHS	**0,65**	**0,65 – 0,80**
CMP	**0,96**	**0,96**
Fraktura krčku femuru	**0,75**	**0,75**
Ca prsu	**1,25**	**1,25 – 2,0**
Ca endometria	**8,22**	**1,0**

Ann Intern Med 1992;117:1016-1037

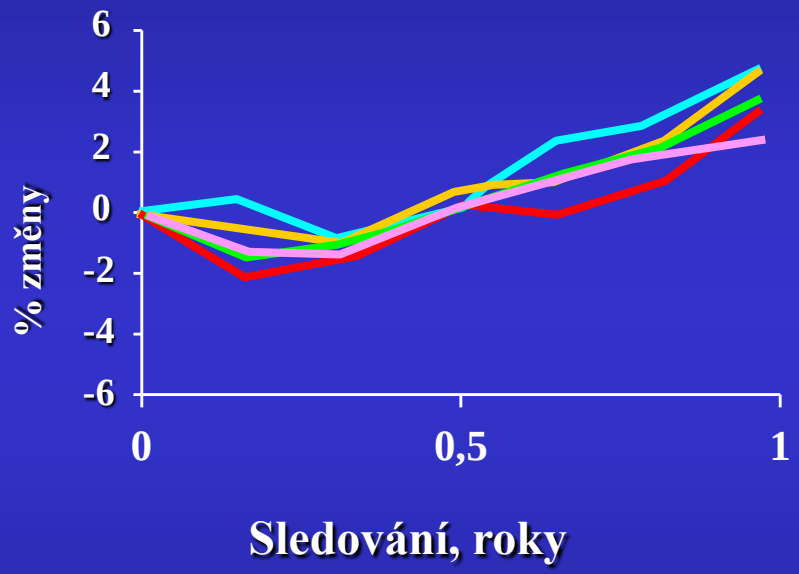
Baltimore Longitudinal Study of Aging



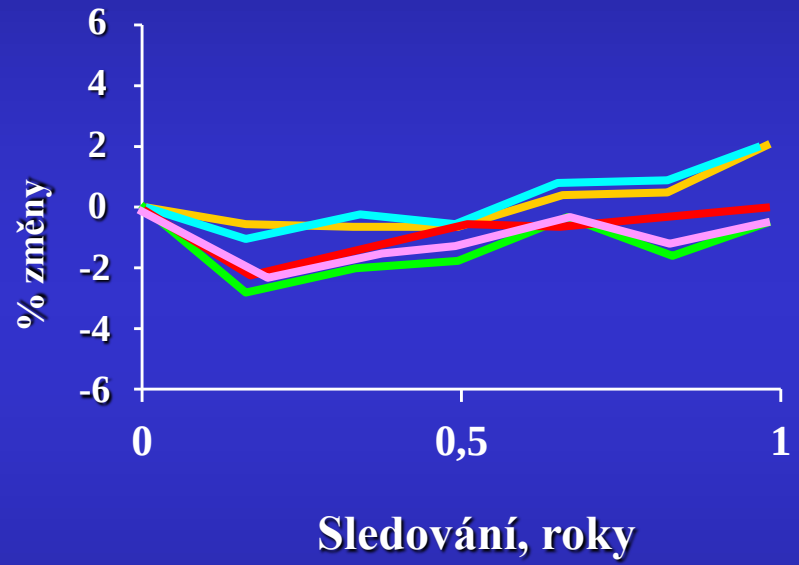
Ann Intern Med 2001; 135:229-238

PEPI TRIAL

STK



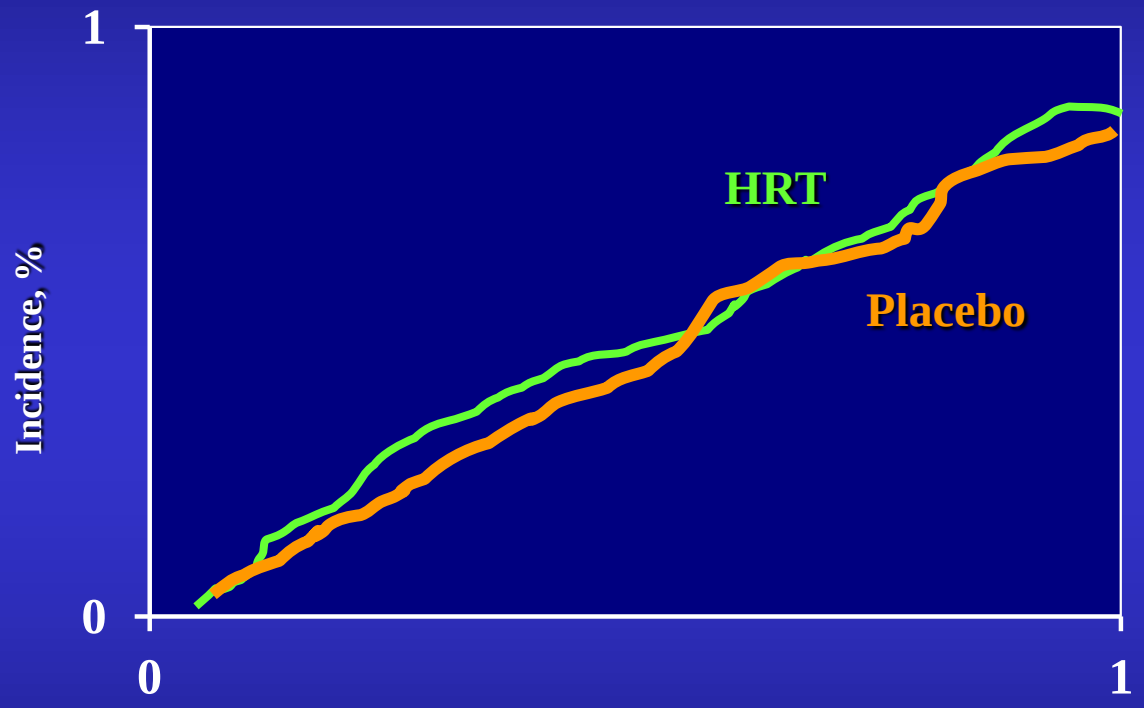
DTK



Placebo
CEE
CEE+MPA (cykl)
CEE+MPA (kont)
CEE+MP (cykl)

JAMA 1995; 273:199-208

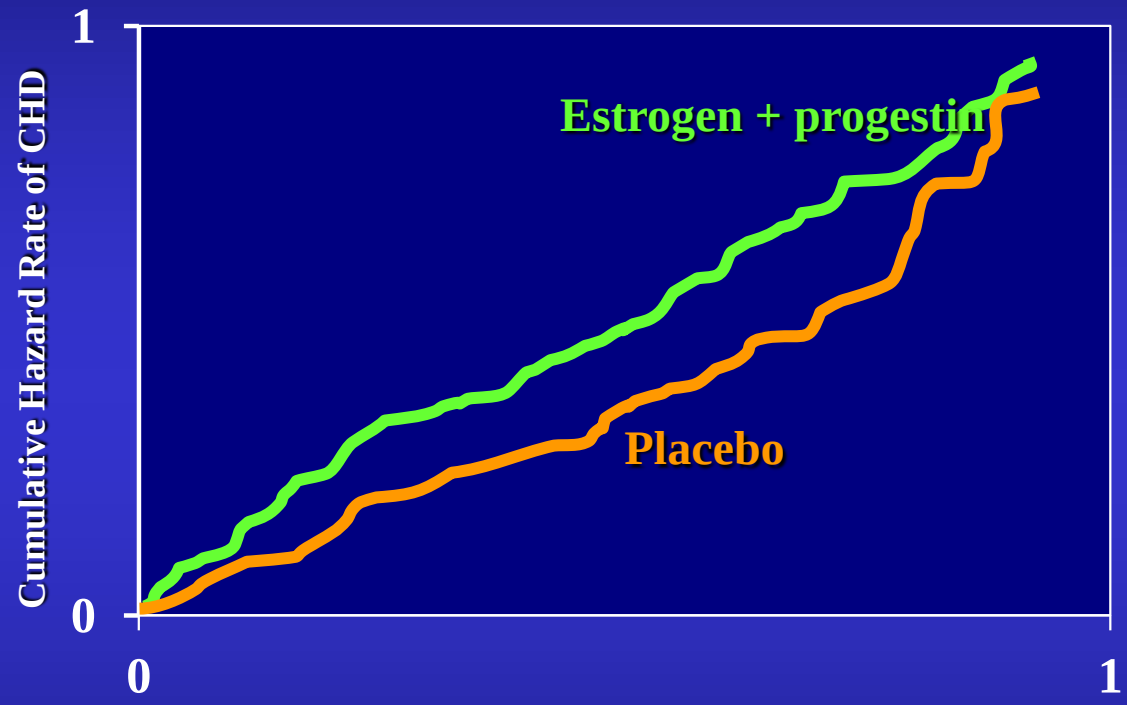
Kumulativní incidence koronárních příhod
HERS II



Počty								
HRT	1380	1303	1247	1196	1133	1043	984	354
Placebo	1383	1334	1269	1209	1122	1039	976	336

JAMA 2002; 288:49-57

Kaplan-Meierovy křivky, ICHS
WHI



Počty								
Estrogen plus progestin	8506	8375	8281	8196	7971	5794	3062	1339
Placebo	8102	8007	7920	7835	7636	5481	2725	988

NEJM 2003; 349:523-34

Diskrepance mezi observačními a randomizovanými studiemi

Diskrepance mezi observačními a randomizovanými studiemi

“Healthy users effect“

- vyšší socioekonomický status
- lepší rizikový profil

Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women

Expert Panel/Writing Group*

Lori Mosca, MD, PhD (Chair)[†]; Lawrence J. Appel, MD[†]; Emelia J. Benjamin, MD[†]; Kathy Berra, MSN, ANP[†§]; Nisha Chandra-Strobos, MD[†]; Rosalind P. Fabunmi, PhD[†]; Deborah Grady, MD, MPH[¶]; Constance K. Haan, MD[‖]; Sharonne N. Hayes, MD[‡]; Debra R. Judelson, MD[#]; Nora L. Keenan, PhD[††]; Patrick McBride, MD, MPH[†]; Suzanne Oparil, MD[†]; Pamela Ouyang, MD[†]; Mehmet C. Oz, MD[†]; Michael E. Mendelsohn, MD[†]; Richard C. Pasternak, MD[†]; Vivian W. Pinn, MD[§§]; Rose Marie Robertson, MD[†]; Karin Schenck-Gustafsson, MD, PhD[†]; Cathy A. Sila, MD[†]; Sidney C. Smith, Jr, MD[¶¶]; George Sopko, MD, MPH[‡‡]; Anne L. Taylor, MD[**]; Brian W. Walsh, MD[‖]; Nanette K. Wenger, MD[†]; Christine L. Williams, MD, MPH[†]

*Representing the following participating organizations and major cosponsors: the American Heart Association†; American College of Cardiology‡; American College of Nurse Practitioners§; American College of Obstetricians and Gynecologists‖; American College of Physicians¶; American Medical Women's Association#; Association of Black Cardiologists**; Centers for Disease Control and Prevention††; National Heart, Lung and Blood Institute‡‡; Office of Research on Women's Health§§; Society of Thoracic Surgeons‖‖; and World Heart Federation¶¶.

In addition, endorsed by: American Academy of Physician Assistants; American Association for Clinical Chemistry; American Association of Cardiovascular and Pulmonary Rehabilitation; American Diabetes Association; American Geriatrics Society; American Society for Preventive Cardiology; American Society of Echocardiography; American Society of Nuclear Cardiology; Association of Women's Health, Obstetric and Neonatal Nurses; Canadian Women's Health Network; Jacobs Institute for Women's Health; Black Women's Health Imperative; National Women's Health Resource Center; The North American Menopause Society; Partnership for Gender-Specific Medicine; Preventive Cardiovascular Nurses Association; Sister to Sister: Everyone Has a Heart Foundation, Inc.; Society for Women's Health Research; Society of Geriatric Cardiology; The Mended Hearts Inc; WomenHeart the National Coalition for Women With Heart Disease; and Women's Health Research Center.

Circulation 2004; 109:672-693

Doporučení pro prevenci KVO u žen

Intervence III. třídy *(intervence není užitečná/je neúčinná a může být dokonce škodlivá)*

HRT

Kombinace estrogenu plus progesteronu *nemá být zahajována* v prevenci KVO u postmenopauzálních žen (třída III, úroveň A)

V kombinaci estrogenu plus progesteronu *nemá být pokračováno* v prevenci KVO u postmenopauzálních žen (třída III, úroveň C)

Jiné formy HRT (např. samotný estrogen) *nemají být zahajovány ani nemají být dále podávány* v prevenci KVO u postmenopauzálních žen až do publikování výsledků probíhajících studií (třída III, úroveň C)

Human Reproduction, Vol.31, No.5 pp. 926–937, 2016
Advanced Access publication on March 22, 2016 doi:10.1093/humrep/dew027

human reproduction

ESHRE PAGES

ESHRE Guideline: management of women with premature ovarian insufficiency†

The ESHRE Guideline Group on POI, L. Webber[1,*], M. Davies[1], R. Anderson[2], J. Bartlett[3], D. Braat[4], B. Cartwright[5], R. Cifkova[6], S. de Muinck Keizer-Schrama[7], E. Hogervorst[8], F. Janse[9], L. Liao[1], V. Vlaisavljevic[10], C. Zillikens[11], and N. Vermeulen[12]

Human Reproduction 2016;31:926–937

Premature ovarian insufficiency

Definition

Clinical syndrome defined by loss of ovarian activity before the age of 40

- Menstrual disturbance (amenorrhea/oligomenorrhea)
- -----↑ gonadotropins
- ↓ estradiol

Prevalence

- **Approx. 1 %** (ethnicity may affect the prevalence; higher in African Americans and Hispanics; lower in Chinese and Japanese populations)

Consequences of POI for the CV system

- **Increased risk of CVD; women with POI should be advised to modify their risk factors**

Recommendation

- **Early HRT initiation is strongly recommended** (despite lack of longitudinal outcome data) **and should be continued until the average age of natural menopause**

Human Reproduction 2016;31:926–937

ESC European Society of Cardiology

European Heart Journal (2021) **42**, 967–984
doi:10.1093/eurheartj/ehaa1044

ESC REPORT

Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists

Angela H.E.M. Maas [1]*, Giuseppe Rosano [2,3], Renata Cifkova [4,5], Alaide Chieffo [6], Dorenda van Dijken [7], Haitham Hamoda [8], Vijay Kunadian [9], Ellen Laan [10], Irene Lambrinoudaki [11], Kate Maclaran[12], Nick Panay [13], John C. Stevenson [14], Mick van Trotsenburg[15], and Peter Collins[14]

[1]Department of Cardiology, Director Women's Cardiac Health Program, Radboud University Medical Center, Geert Grooteplein-Zuid 10, Route 616, 6525GA Nijmegen, The Netherlands; [2] St George's Hospitals NHS Trust University of London, Cranmer Terrace, London SW17 0RE, UK; [3]Department of Medical Sciences, Centre for Clinical and Basic Research, IRCCS San Raffaele Pisana, via della Pisana, 235 Rome, Italy; [4]Center for Cardiovascular Prevention, Charles University in Prague, First Faculty of Medicine and Thomayer Hospital, Vídeňská 800, 140 59 Prague 4, Czech Republic; [5]Department of Internal Cardiovascular Medicine, First Medical Faculty, Charles University in Prague and General University Hospital in Prague, U Nemocnice 2, 128 08 Prague 2, Czech Republic; [6]Interventional Cardiology Unit, IRCCS San Raffaele Hospital, Olgettina Street, 60 - 20132 Milan (Milan), Italy; [7]Department of Obstetrics and Gynaecology, OLVG location West, Jan Tooropstraat 164, 1061 AE Amsterdam, The Netherlands; [8]Department Gynaecology, King's College Hospital, Denmark Hill, London SE5 9RS, UK; [9]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University and Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne NHS Foundation Trust, M4:146 4th Floor William Leech Building, Newcastle upon Tyne NE2 4HH, UK; [10]Department of Sexology and Psychosomatic Gynaecology, Amsterdam University Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands; [11]Menopause Clinic, 2nd Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Aretaieio Hospital, 30 Panepistimiou Str., 10679 Athens, Greece; [12]Department Gynaecology, Chelsea and Westminster Hospital, NHS Foundation Trust, 69 Fulham Road London SW10 9NH, UK; [13]Department of Gynaecology, Queen Charlotte's & Chelsea and Westminster Hospitals, Imperial College, Du Cane Road, London W12 0HS, UK; [14]Department of Cardiology, National Heart & Lung Institute, Imperial College London, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; and [15]Bureau Gender PRO Vienna and Department of Obstetrics and Gynaecology, University Hospital St. Poelten-Lilienfeld, Probst Führer Straße 4 - 3100 St. Pölten, Austria

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Eur Heart J 2021; 42:967-984

Přínos a riziko hormonální léčby

Ženy s menopauzou ve věku > 45 let a ženy užívající HRT pro předčasnou menopauzu a POI

Přínos HT	Riziko HT
HT je nejúčinnější léčbou menopauzálních symptomů	Estrogeny podávané samotné zvyšují riziko ca endometria.
Systémové a lokální (vaginální) podávání účinně ovlivňuje gynekologické a urologické obtíže spojené s menopauzou	Perorální, ale nikoliv transdermální HT zvyšuje riziko hluboké žilní trombózy
HT zabraňuje osteoporóze	HT je spojena s mírným zvýšením rizika CMP, méně v transdermální něž p.o. formě
HT může příznivě ovlivnit špatnou náladu spojenou s menopauzou	HT, zvl. pokud obsahuje gestageny, může být spojena s vyšším rizikem ca mammy, navýšení rizika mizí přerušením HT

Přínos a riziko hormonální léčby

Ženy s menopauzou ve věku > 45 let a ženy užívající HRT pro předčasnou menopauzu a POI

Přínos HT	Riziko HT
HT může snížit celkovou a KV mortalitu u žen < 60 let věku a do 10 let od menopauzy	HT léčba není doporučována ženám s vysokým KV rizikem a ženám po prodělané KV příhodě
Časná iniciace HT po menopauze je spojena s největším přínosem pro KV zdraví	
U žen s POI je HRT doporučována do průměrného věku menopauzy: ovlivňuje menopauzální symptomy, KVO, osteoporózu a kognitivní funkce	
Krátkodobá HRT (do 4 let) u žen po oboustranné salpingo-oophorektomii nezvyšuje riziko ca mammy a snižuje dlouhodobé účinky časné menopauzy	

Etiologie hypertenze u žen

- **esenciální**
- **stenóza renální tepny**

  fibromuskulární dysplasie

  M:Ž = 1:8

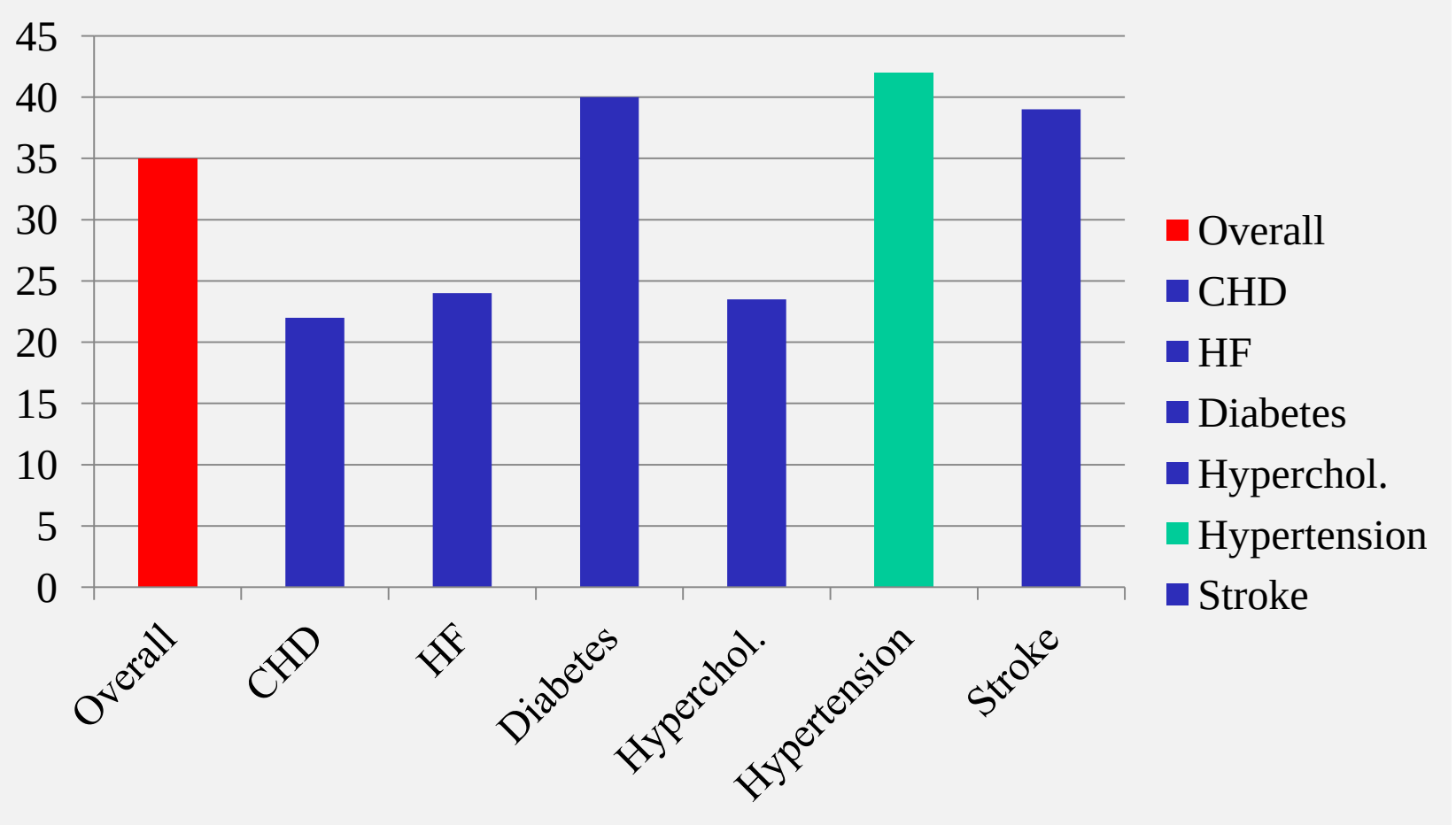
Velké klinické studie u hypertenze

Velké klinické studie u hypertenze
úskalí

- *dřívější studie nezahrnovaly ženy*

- **ženy mají nižší KV riziko a v důsledku toho i nižší incidenci sledovaných příhod**

Women in RCTs



Circ Cardiovasc Qual Outcomes 2010; 3:135 - 142

Representation of Women in Randomized Clinical Trials of Cardiovascular Disease Prevention

Chiara Melloni, MD, MHS; Jeffrey S. Berger, MD, MS; Tracy Y. Wang, MD, MS; Funda Gunes, MS; Amanda Stebbins, MS; Karen S. Pieper, MS; Rowena J. Dolor, MD, MHS; Pamela S. Douglas, MD; Daniel B. Mark, MD, MPH; L. Kristin Newby, MD, MHS

Sex-specific results were discussed in only 31% of primary trial publications.

Conclusions **— Enrollment of women in randomized clinical trials has increased over time but remains low relative to their overall representation in disease populations. Efforts are needed to reach a level of representation that is adequate to ensure evidence-based sex-specific recommendations.**

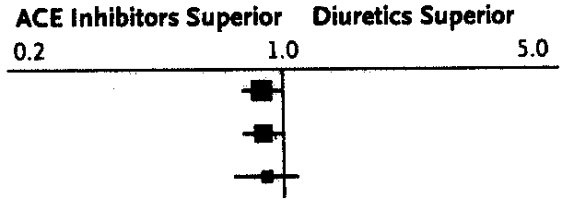
Circ Cardiovasc Qual Outcomes 2010;3:135-142

ANBP 2 Trial

Primary End Points

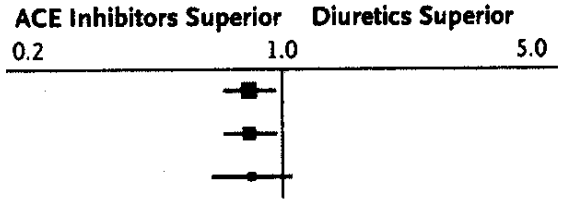
All Subjects

End Point	Hazard Ratio (95% CI)	P Value
All cardiovascular events or death from any cause	0.89 (0.79–1.00)	0.05
First cardiovascular event or death from any cause	0.89 (0.79–1.01)	0.06
Death from any cause	0.90 (0.75–1.09)	0.27



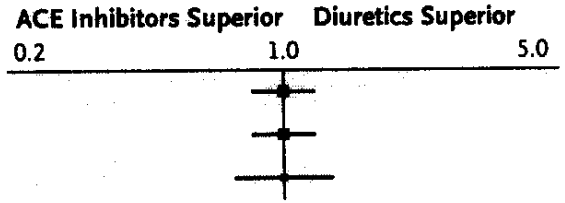
Male Subjects

End Point	Hazard Ratio (95% CI)	P Value
All cardiovascular events or death from any cause	0.83 (0.71–0.97)	0.02
First cardiovascular event or death from any cause	0.83 (0.71–0.97)	0.02
Death from any cause	0.83 (0.66–1.06)	0.14



Female Subjects

End Point	Hazard Ratio (95% CI)	P Value
All cardiovascular events or death from any cause	1.00 (0.83–1.21)	0.98
First cardiovascular event or death from any cause	1.00 (0.83–1.20)	0.98
Death from any cause	1.01 (0.76–1.35)	0.94



NEJM 2003;348:583-92

Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial

Alberto Zanchetti[a], Stevo Julius[b], Sverre Kjeldsen[b,c], Gordon T. McInnes[d], Tsushung Hua[e], Michael Weber[f], John H. Laragh[g], Francis Plat[h], Edouard Battegay[i], Cesar Calvo-Vargas[j], Andrzej Cieśliński[k], Jean Paul Degaute[l], Nicolaas J. Holwerda[m], Janna Kobalava[n], Ole Lederballe Pedersen[o], Faustinus P. Rudyatmoko[p], Kostas C. Siamopoulos[q] and Öyvind Störset[r]

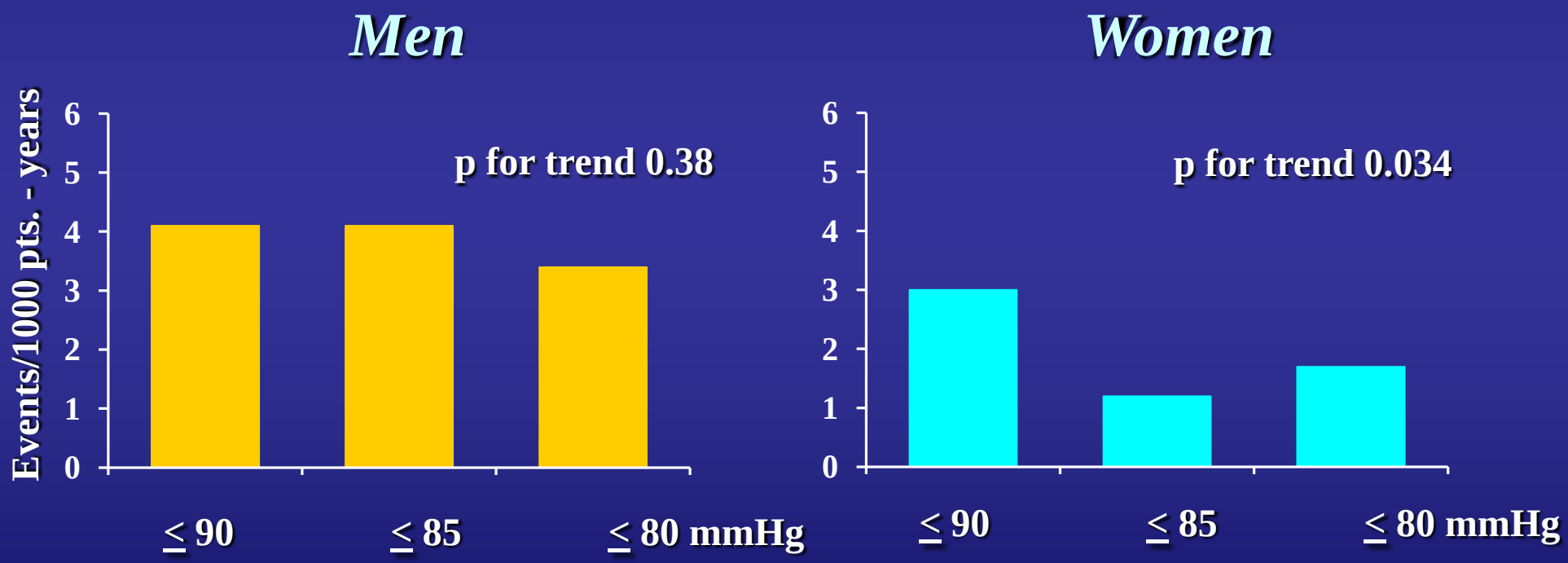
Conclusions

No differences were found in the incidence of composite cardiac endpoints between valsartan- and amlodipine-based treatments; the amlodipine-based regimen was more effective in women whereas the valsartan regimen was more effective in preventing cardiac failure in men.

J Hypertens 2006;24:2163-2168

HOT Study

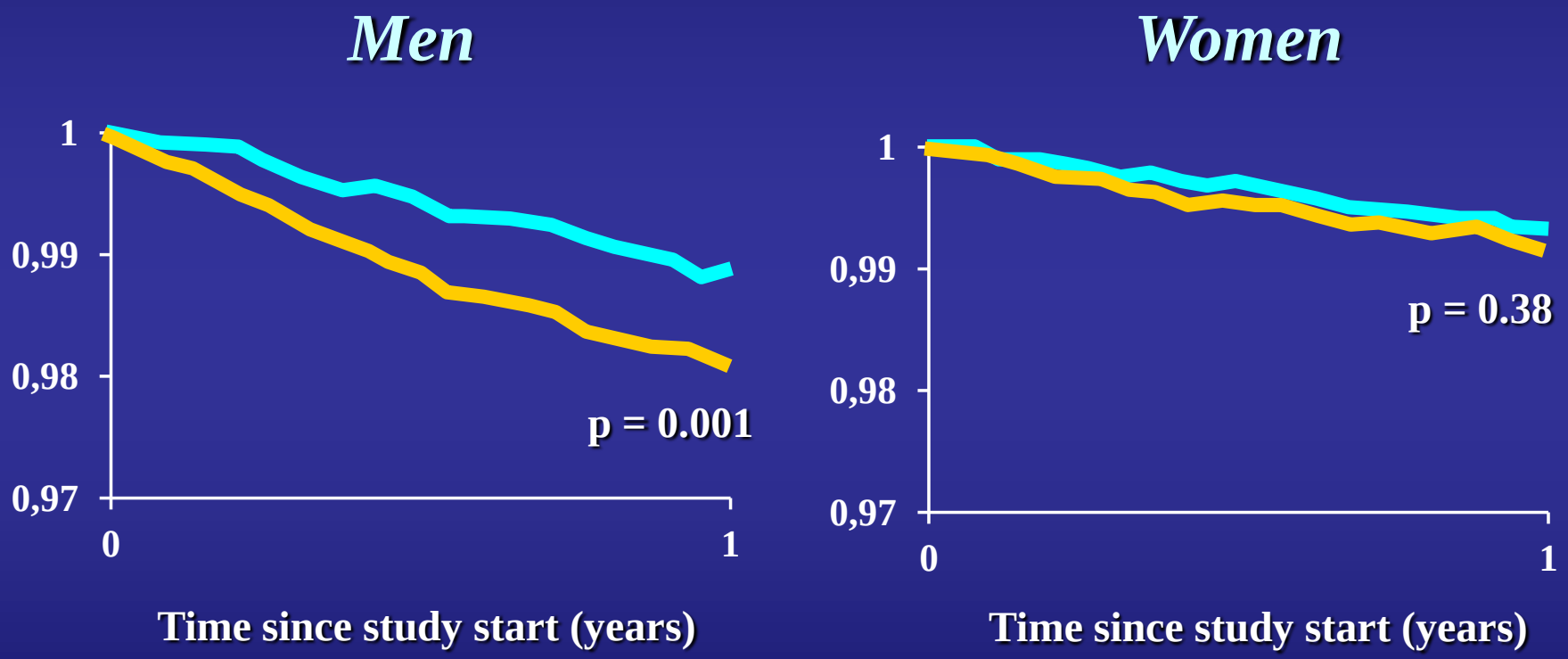
Major CV events by target DBP



J Hypertens 2000; 18:629-642

HOT Study

Probability of follow-up without MI



J Hypertens 2000; 18:629-642

European Heart Journal (2008) **29**, 2669–2680
doi:10.1093/eurheartj/ehn427

CLINICAL RESEARCH
Hypertension

Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials

Fiona Turnbull*, Mark Woodward, Bruce Neal, Federica Barzi, Toshiharu Ninomiya, John Chalmers, Vlado Perkovic, Nicole Li, S MacMahon and the Blood Pressure Lowering Treatment Trialists' Collaboration†

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Received 13 March 2008; revised 31 July 2008; accepted 29 August 2008; online publish-ahead-of-print 13 October 2008

This paper was guest edited by Prof. Gregory Y.H. Lip, University Department of Medicine, City Hospital, Birmingham, UK.

See page 2585 for the editorial comment on this article (doi:10.1093/eurheartj/ehn451)

Eur Heart J 2008;29:2669-2680

European Heart Journal (2016) 37, 24–34
doi:10.1093/eurheartj/ehv598

CURRENT OPINION
Disease management

Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes

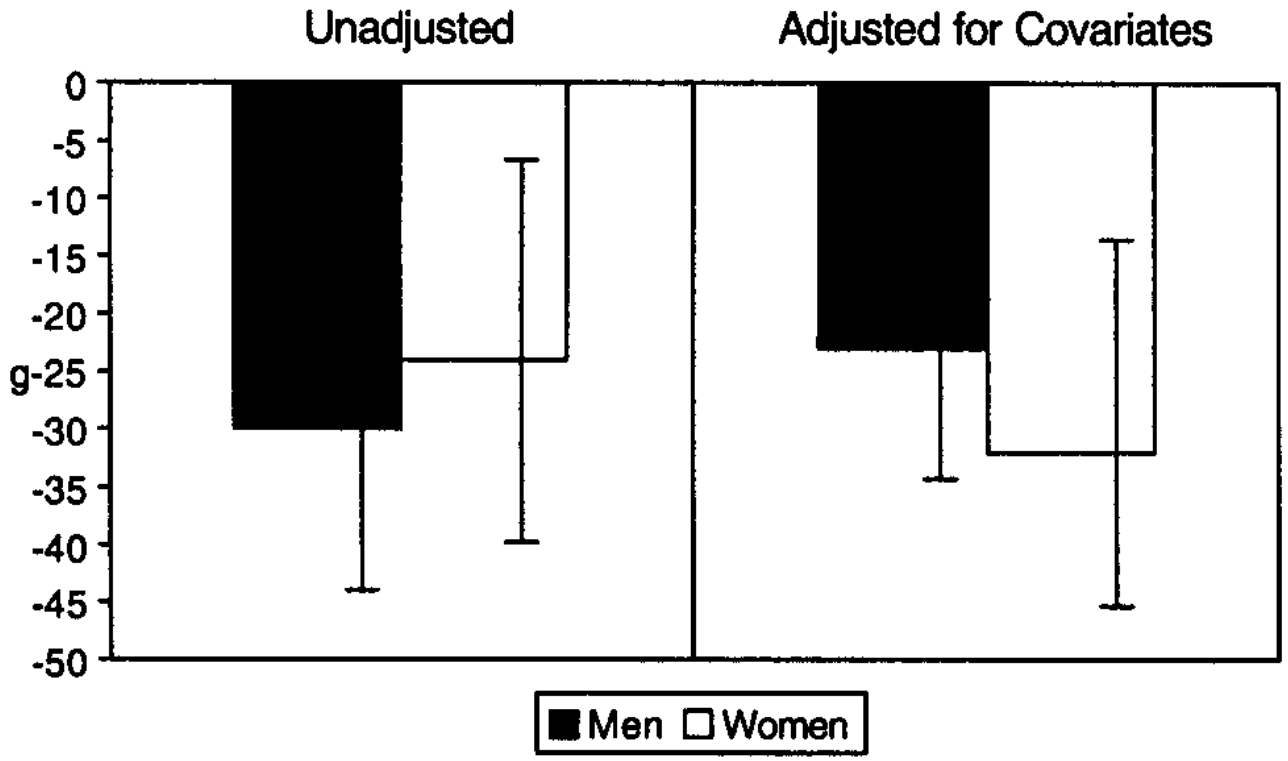
The EUGenMed†, Cardiovascular Clinical Study Group, Vera Regitz-Zagrosek[1,2,3]*, Sabine Oertelt-Prigione[1,2,3], Eva Prescott[4], Flavia Franconi[2,5], Eva Gerdts[6], Anna Foryst-Ludwig[3,7], Angela H.E.M. Maas[8], Alexandra Kautzky-Willer[2,9], Dorit Knappe-Wegner[2,10], Ulrich Kintscher[3,7], Karl Heinz Ladwig[11], Karin Schenck-Gustafsson[2,12], and Verena Stangl[3,13]

Hypertension

A number of sex and gender (S&G) differences in the pathophysiology of hypertension have been reported, mainly related to S&G differences in the renin-angiotensin system and in the bradykinin and NO system. However, none of those have had consequences for medical therapy so far.

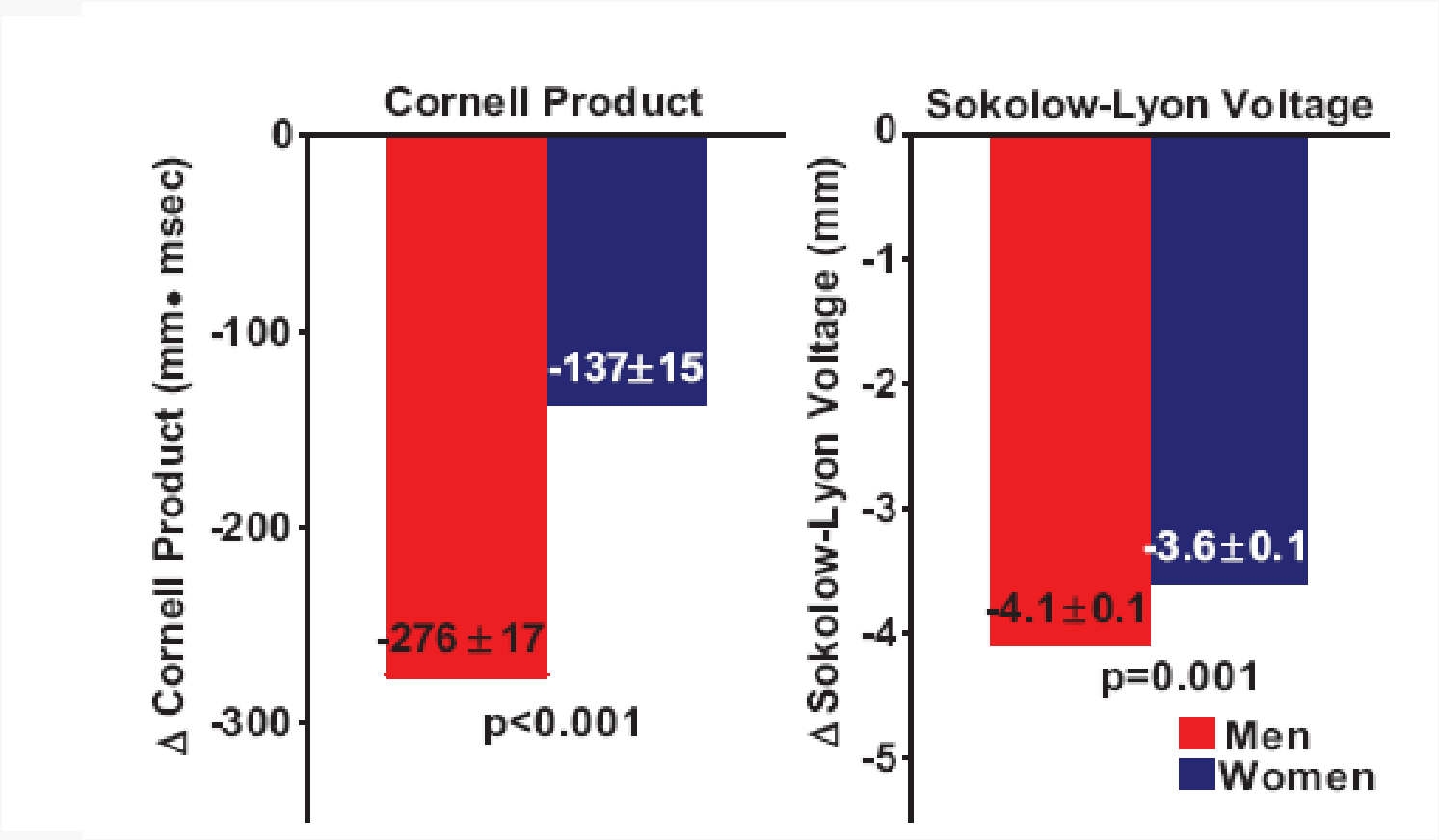
Eur Heart J 2016;37:24–34

Gender differences in LVH regression
LIFE Study



J Hum Hypertens 2004;18:411-416

Gender Differences in Regression of Electrocardiographic LVH During Antihypertensive Therapy



Okin et al. Hypertension 2008;52:100-106.

Má se hypertenze

u mužů a žen léčit odlišně ?

Gender-related differences in adverse effects

Calcium antagonists	↑ **Peripheral edema in women**
ACE inhibitors	↑ **Cough in women**

Rozdíly v NÚ mezi pohlavími

Léková skupina	Nežádoucí účinky
Inhibitory ACE	Suchý kašel 2 – 3x častější u žen, 0 rozdíly angioedem/urticaria
Betablokátory - metoprolol	Výraznější pokles TK u žen Výraznější bradykardizující účinek u žen
Blokátory CA kanálů	Vyšší riziko otoků u žen
Diuretika - thiazidy	Častější hospitalizace pro hyposmolaritu, hypokalemii a hyponatremii a vyšší riziko arytmie u žen Častější hyponatremie a hypokalemie u žen
Statiny	Myopatie častější u starších žen s nízkou hmotností

Eur Heart J-Cardiovasc Pharmacotherapy 2017;3:160-182

Hypertenze v těhotenství

Antihypertenziva užívaná v těhotenství

Ženám s preexistující hypertenzí je doporučováno pokračovat v zavedené medikaci s výjimkou ACEI, AIIA a přímých inhibitorů reninu

Why is RAS important in pregnancy?

- Regulation of renal hemodynamics
  (by maintaining GFR and urine production under conditions of low renal perfusion pressure, which are characteristic of the fetal and neonatal periods)
- Regulation of umbilical and placental circulation
- Regulation of fetal BP
- Kidney development (growth factors)
- Angiogenesis (angiotensin II)
- Regulation of fetal renal growth, function and development (ACE gene)

Administration of AT_1-blockers in pregnancy

- **Fetal arterial hypotension**
- **Decreased glomerular perfusion pressure**
- **Impaired renal tubular development**
- **Reduced fetal urine output, oligohydramnios**
  Sequelae: limb contractures
  pulmonary hypoplasia
  cranio-facial deformation and neonatal anuria
- **Decreased placental and umbilical perfusion:**
  intrauterine growth restriction
- **Action on skull bones angiogenesis:**
  impaired ossification processes

Critical period: second trimester !!

Expozice matky AT_1-blokátorům

Kritické období: druhý trimestr těhotenství

Popsáno 5 případů úmrtí plodu a 1 úmrtí novorozence 4. den po porodu s přetrvávající anurií; expozice na počátku těhotenství, oligohydramnion.

- **Saji H, Yamanaka M, Hagiwara A, Ijiri R. Losartan and fetal toxic effects.** ***Lancet 2001;357:363.***
- **Martinovic J, Benachi A, Laurent N, Daika-Dahmane F, Gubler MC. Fetal toxic effects and angiotensin-II receptor antagonists.** ***Lancet 2001;358:241-8.***
- **Briggs GG, Nageotte MP. Fatal fetal outcome with the combined use of valsartan and atenolol.** ***Ann Pharmacoth 2001;35:859-61.***

Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

William O. Cooper, M.D., M.P.H., Sonia Hernandez-Diaz, M.D., Dr.P.H., Patrick G. Arbogast, Ph.D., Judith A. Dudley, B.S., Shannon Dyer, B.S., Patricia S. Gideon, R.N., Kathi Hall, B.S., and Wayne A. Ray, Ph.D.

RESULTS

Infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations (risk ratio, 2.71; 95 percent confidence interval, 1.72 to 4.27) as compared with infants who had no exposure to antihypertensive medications. In contrast, fetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk (risk ratio, 0.66; 95 percent confidence interval, 0.25 to 1.75). Infants exposed to ACE inhibitors were at increased risk for malformations of the cardiovascular system (risk ratio, 3.72; 95 percent confidence interval, 1.89 to 7.30) and the central nervous system (risk ratio, 4.39; 95 percent confidence interval, 1.37 to 14.02).

N Engl J Med 2006;354:2443-2451

Antihypertenziva užívaná v těhotenství

Centrální alfa agonisté	**Metyldopa je lékem volby.**
Betablokátory	**~~Atenolol~~ a metoprolol jsou bezpečné a účinné v pozdější fázi těhotenství**
Alfa-/beta-blokátory	**Labetalol má srovnatelný účinek jako metyldopa, v případě závažné hypertenze může být podán i.v.**

Atenolol in essential hypertension during pregnancy

Lucy Butters, Susan Kennedy, Peter C Rubin

Abstract

Objective—To determine the effect of atenolol on the outcome of pregnancy in women with essential hypertension.

Design—Prospective, randomised, double blind, placebo controlled study.

Setting—Hospital clinic.

Patients—33 Women with mild essential hypertension (systolic blood pressure 140-170 mm Hg or diastolic pressure 90-110 mm Hg on two occasions at least 24 hours apart) consecutively referred to two obstetric medical clinics. Four patients in the placebo group were withdrawn from the study: control of blood pressure was inadequate in two, one developed breathlessness, and one changed her mind about participating. The mean gestation in the 29 remaining women on entry to the study was 15·9 weeks.

Main outcome measures—Blood pressure and birth weight.

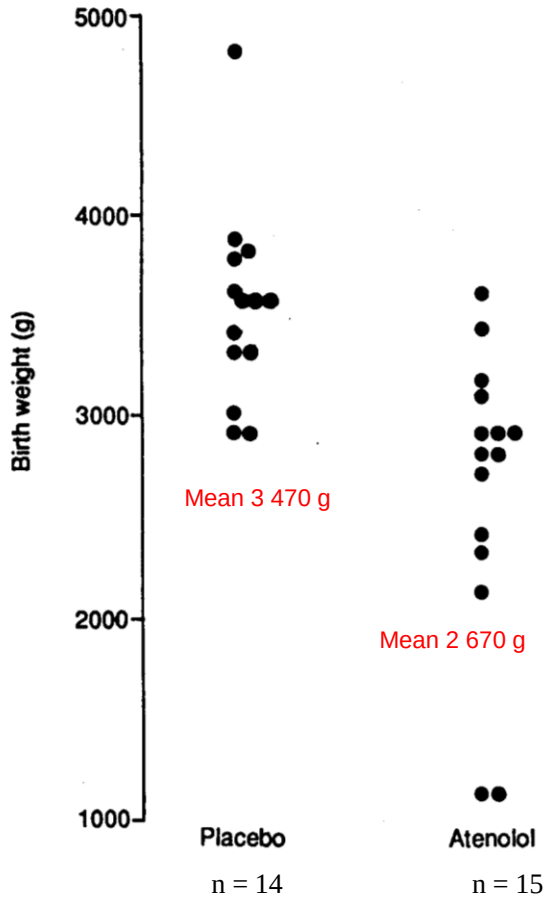
Intervention—14 Women received placebo. 15 Women received atenolol 50 mg daily initially, increasing until either the blood pressure was <140/90 mm Hg or a dose of 200 μg daily was reached.

Results—The mean blood pressure on entry was 148/86 mm Hg in the group given atenolol and 144/86 mm Hg in the group given placebo. During treatment the mean diastolic pressure was significantly reduced by atenolol compared with placebo (to 74 *v* 81 mm Hg; difference in means (95% confidence interval) 7·0 (2·9 to 10·0) mm Hg) but the effect on systolic pressure was marginal (132 *v* 136 mm Hg; 4·0 (−1·4 to 8·6) mm Hg). Babies in the atenolol group had a significantly lower birth weight than those in the placebo group (2620 g *v* 3530 g; 910 (440 to 1380) g).

Conclusion—Atenolol given from the end of the first trimester in patients with mild hypertension is associated with intrauterine growth retardation. When taken in conjunction with the results of a previous study in which methyldopa was given these findings indicate that benefit is unlikely to result from treating mild essential hypertension in pregnancy.

BMJ 1990;301:587-9

Birth weights of babies in atenolol and placebo groups



BMJ 1990;301:587-9

Effect of *Atenolol* on Birth Weight

Gregory Y.H. Lip, MD, Michèle Beevers, SRN, David Churchill, MD, Lara M. Shaffer, MB, and D. Gareth Beevers, MD

A previous small, prospective study from Glasgow reported that babies born to women treated with atenolol in early pregnancy had significantly lower birth weights than those in the placebo group.[1] Beta blockers, while safe in the third trimester of pregnancy, are also considered to cause significant growth restriction when used for longer periods.[2] An antenatal hypertension clinic has been in operation at City Hospital, Birmingham since 1980, where pregnant women with hypertension undergo careful follow-up jointly by an obstetrician and a physician with a special interest in hypertension. Patients were referred to the clinic by obstetricians and general practitioners on the basis of previous hypertension, or raised blood pressures detected for the first time in pregnancy. In many, the blood pressure decreased with no therapy, and where possible antihypertensive drugs were discontinued. After the Glasgow study,[1] the use of atenolol in early pregnancy was discontinued and an audit was conducted of birth weights in relation to drug therapy.

• • •

We conducted an analysis of our own prospectively gathered and computerized database of all women attending our clinic between 1980 and 1995. Information on demographic data, presenting blood pressures, drug therapies, pregnancy complications, and pregnancy outcome were recorded. The mean termine significant predictors for birth weights. A p value <0.05 was considered statistically significant.

We reviewed data from the antenatal records of 398 consecutive pregnancies (137 white, 103 black, 158 Asian women; mean age 30 ± 6 years) attending our antenatal hypertension clinic between 1980 and 1995. Two hundred thirty-five women were not taking any therapy during the first 20 weeks of pregnancy, whereas atenolol was taken by 76 women, labetolol by 7, other β blockers by 12, calcium antagonists by 22, diuretics by 26, methyldopa by 17, and angiotensin-converting enzyme inhibitors by 7 women; 18 women were taking multiple drug combinations.

Blood pressures during antihypertensive therapy are summarized in Table I. When compared with untreated cases, there was a trend toward higher mean systolic (1-way ANOVA, $p = 0.064$) and diastolic blood pressures ($p < 0.001$) in the first 20 weeks of pregnancy among women who were taking antihypertensive drugs (Table I). There were no significant differences in mean gestation period for each patient subgroup of treated and untreated women (1-way ANOVA, p = NS).

Mean birth weights, median placental weights, and ponderal index are also summarized in Table I. Babies born to women taking atenolol were significantly lighter (1-way ANOVA, $F = 5.3$, $p < 0.001$)

AmJ Cardiol 1997;79:1436-1438

Effect of *Atenolol* on Birth Weight

Gregory Y.H. Lip, MD, Michèle Beevers, SRN, David Churchill, MD, Lara M. Shaffer, MB, and D. Gareth Beevers, MD

Závěrem lze konstatovat, že podávání atenololu v časné fázi těhotenství může být škodlivé; tato studie tak potvrzuje výsledky předchozí prospektivní malé randomizované studie. Z našich výsledků lze usuzovat že **atenolol nemá být podáván ženám, které se pokoušejí otěhotnět nebo které jsou v časné fázi těhotenství**.

Am J Cardiol 1997;79:1436-1438

Závěry

- **Existují rozdíly v prevalenci, znalosti o hypertenzi, léčbě a kontrole hypertenze u mužů a žen**

- **V našem poměrně homogenním reprezentativním vzorku populace žen v období kolem menopauzy byl vzestup TK způsoben spíše nárůstem BMI než vlastním vyhasnutím funkce ovárií**

Závěry (pokrač.)

- **HRT nezvyšuje TK, není t.č. indikována v prevenci KVO, vyjma POI**

- **Odpověď na antihypertenzní léčbu a přínos ze snížení TK je stejný u obou pohlaví; *inhibitory ACE, sartany a přímé inhibitory reninu jsou kontraindikovány v těhotenství* a nejsou doporučovány u žen v reprodukčním věku**

- **Atenolol není doporučován u žen, které plánují těhotenství a v časné fázi těhotenství**

frontiers | Frontiers in Cardiovascular Medicine

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SPECIALTY SECTION
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Sex and Gender in Cardiovascular
Medicine,

Sex differences in hypertension. Do we need a sex-specific guideline?

Renata Cífková[1,2]* and Larysa Strilchuk[1,3]

[1]Center for Cardiovascular Prevention, Charles University in Prague, First Faculty of Medicine and Thomayer University Hospital, Prague, Czechia, [2]Department of Medicine II, Charles University in Prague, First Faculty of Medicine, Prague, Czechia, [3]Department of Therapy No 1, Medical Diagnostics, Hematology and Transfusiology, Lviv Danylo Halytsky National Medical University, Lviv, Ukraine

Hypertension is the most prevalent cardiovascular disorder and the leading cause of death worldwide in both sexes. The prevalence of hypertension is lower in premenopausal women than in men of the same age, but sharply increases after the menopause, resulting in higher rates in women

Front Cardiovasc Med 2022 Aug 23;9:960336

European Heart Journal - Cardiovascular Pharmacotherapy (2017) **3**, 163–182
doi:10.1093/ehjcvp/pvw042

REVIEW

Gender differences in the effects of cardiovascular drugs

J. Tamargo[1,2]*, G. Rosano[3,4], T. Walther[5], J. Duarte[2,6], A. Niessner[7], J.C. Kaski[8], C. Ceconi[9], H. Drexel[10], K. Kjeldsen[11,12], G. Savarese[13], C. Torp-Pedersen[14], D. Atar[15], B.S. Lewis[16], and S. Agewall[17]

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Eur Heart J-Cardiovasc Pharmacotherapy 2017;3:160-182

Rozdíly v NÚ mezi pohlavími

Léková skupina	Nežádoucí účinky
Inhibitory ACE	Suchý kašel 2 – 3x častější u žen, 0 rozdíly angioedem/urticaria
Betablokátory - metoprolol	 Výraznější pokles TK u žen Výraznější bradykardizující účinek u žen
Blokátory CA kanálů	Vyšší riziko otoků u žen
Diuretika - thiazidy	Častější hospitalizace pro hyposmolaritu, hypokalemii a hyponatremii a vyšší riziko arytmie u žen Častější hyponatremie a hypokalemie u žen
Statiny	Myopatie častější u starších žen s nízkou hmotností

Eur Heart J-Cardiovasc Pharmacotherapy 2017;3:160-182

ORIGINAL RESEARCH ARTICLE

Association Between Fetal Congenital Heart Defects and Maternal Risk of Hypertensive Disorders of Pregnancy in the Same Pregnancy and Across Pregnancies

Heather Allison Boyd, Saima Basit, Ida Behrens, Elisabeth Leirgul, Henning Bundgaard, Jan Wohlfahrt, Mads Melbye, Nina Øyen

Conclusions: Linked pathophysiological mechanisms may be involved in some congenital heart defects and preterm preeclampsia The strong associations across pregnancies support a predominantly maternal origin of effect.

Circulation 2017; 136:39-48