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Nephrology, Hypertension, Dialysis, Transplantation, Nephropathology

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Hypertension in Systemic Diseases

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Hypertension in Systemic Diseases

Hypertension in patients with:

- Rheumatic diseases
- Psoriasis
- Vasculitis
- Lupus erythemotodes

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- The prevalence of hypertension is substantially (by about 42%) higher in RA than in the average population . **Among patients with RA the prevalence of hypertension is estimated to 52–73%** , and the proportion of well-controlled patients is much lower, at 13.2%, than in the general population, where it is estimated to be around 30%, but large differences were found in different populations

European Society of Hypertension Scientific Newsletter:
Update on Hypertension Management
2013; 14: No. 57

TREATMENT OF HYPERTENSION IN PATIENTS WITH RHEUMATIC DISEASES

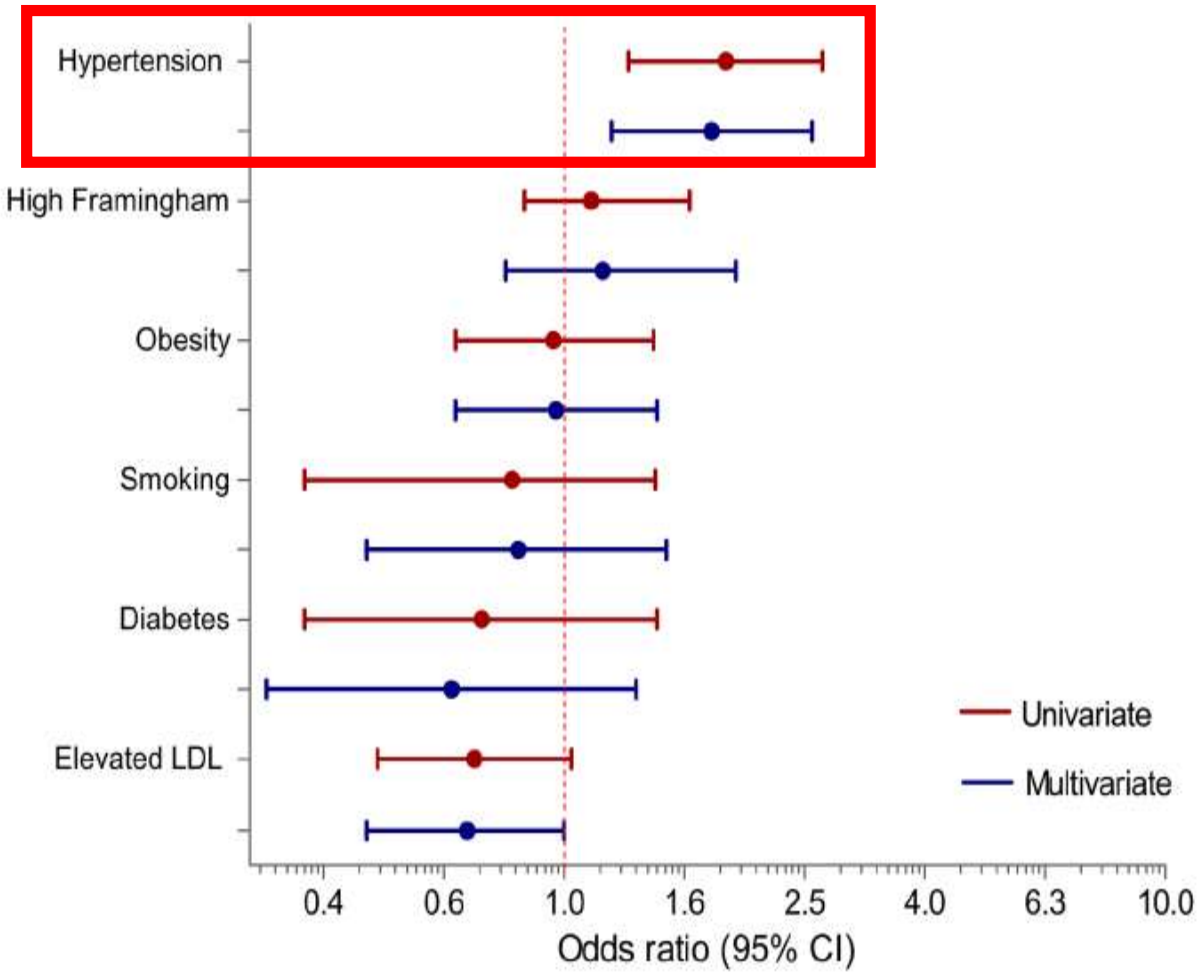
Semin Arthritis Rheum. 2012 February ; 41(4): 535–544. doi:10.1016/j.semarthrit.2011.07.004.

Prevalence of Traditional Modifiable Cardiovascular Risk Factors in Patients with Rheumatoid Arthritis: Comparison with Control Subjects from the Multi-Ethnic Study of Atherosclerosis

Cecilia P. Chung, MD, MPH[*], Jon T. Giles, MD, MPH[†], Michelle Petri, MD, MPH[*], Moyses Szklo, MD, DrPH[‡], Wendy Post, MD, MS[‡,§], Roger S. Blumenthal, MD[§], Allan C. Gelber, MD, MPH, PhD[*,‡], Pamela Ouyang, MD[§], Nancy S. Jenny, PhD[¶], and Joan M. Bathon, MD[†]

Conclusions—Hypertension is more common in RA than in controls. Other traditional cardiovascular risk factors are highly prevalent, underdiagnosed, and poorly controlled in patients with RA, as well as controls.

Risk of hypertension in patients with Rheumatoid Artritis

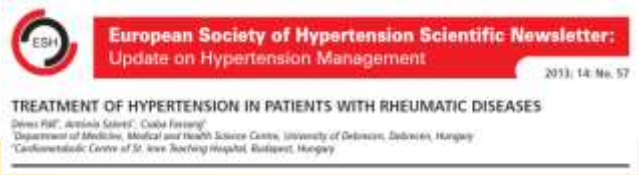


Observational study in 194 patients with RA and 274 subjects from general population

Chung C.P. et al., Seminar Arthr. Rheum., 2012; 41: 535-544

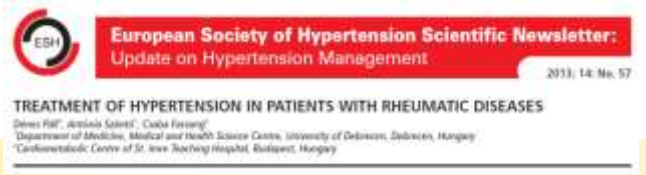
- **Both cardiovascular (CV) morbidity and mortality are increased in RA compared to controls**, which is only partially attributable to traditional CV risk factors, so RA can be characterized as a disease with high CV risk, similarly to diabetes mellitus and chronic kidney diseases

- This increased prevalence of hypertension in patients with RA can be explained by several factors: **systemic and low-grade inflammation, physical inactivity and medication** (e.g. corticosteroids and non-steroidal anti-inflammatory drugs (NSAID) used for the control of disease activity and its symptoms



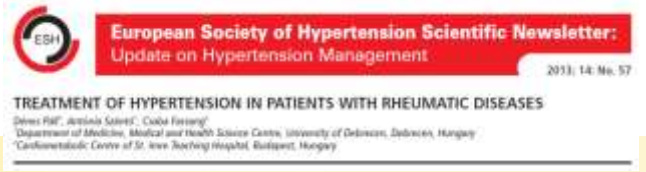
- Inflammatory burden plays a pivotal role in the observed excess CV risk. Increased high-sensitivity C-reactive protein (hsCRP) levels representing systemic inflammation are characteristic for patients with RA. **Low-grade systemic inflammation can lead to hypertension via several mechanisms**:
- reduction of nitric oxide production in endothelial cells leads to vasoconstriction,
- increased production of endothelin-1,
- and platelet activation

- Moreover, **CRP is able to up-regulate the expression of angiotensin type-I (AT1) receptors** thus activating the renin-angiotensin system (RAS)



- As a consequence, **systemic vascular resistance is increased** in RA while **elasticity of small and large arteries is reduced**

- These processes together with the **increased arterial stiffness**, also observed in RA, may lead to blood pressure elevation, **increased shear stress and activation of inflammatory cascade**



Arthritis Rheumatol. 2015 Jun;67(6):1449-55. doi: 10.1002/art.39098.

Disease activity in rheumatoid arthritis and the risk of cardiovascular events.

Solomon DH[1], Reed GW[2], Kremer JM[3], Curtis JR[4], Farkouh ME[5], Harrold LR[2], Hochberg MC[6], Tsao P[1], Greenberg JD[7].

Author information

Abstract

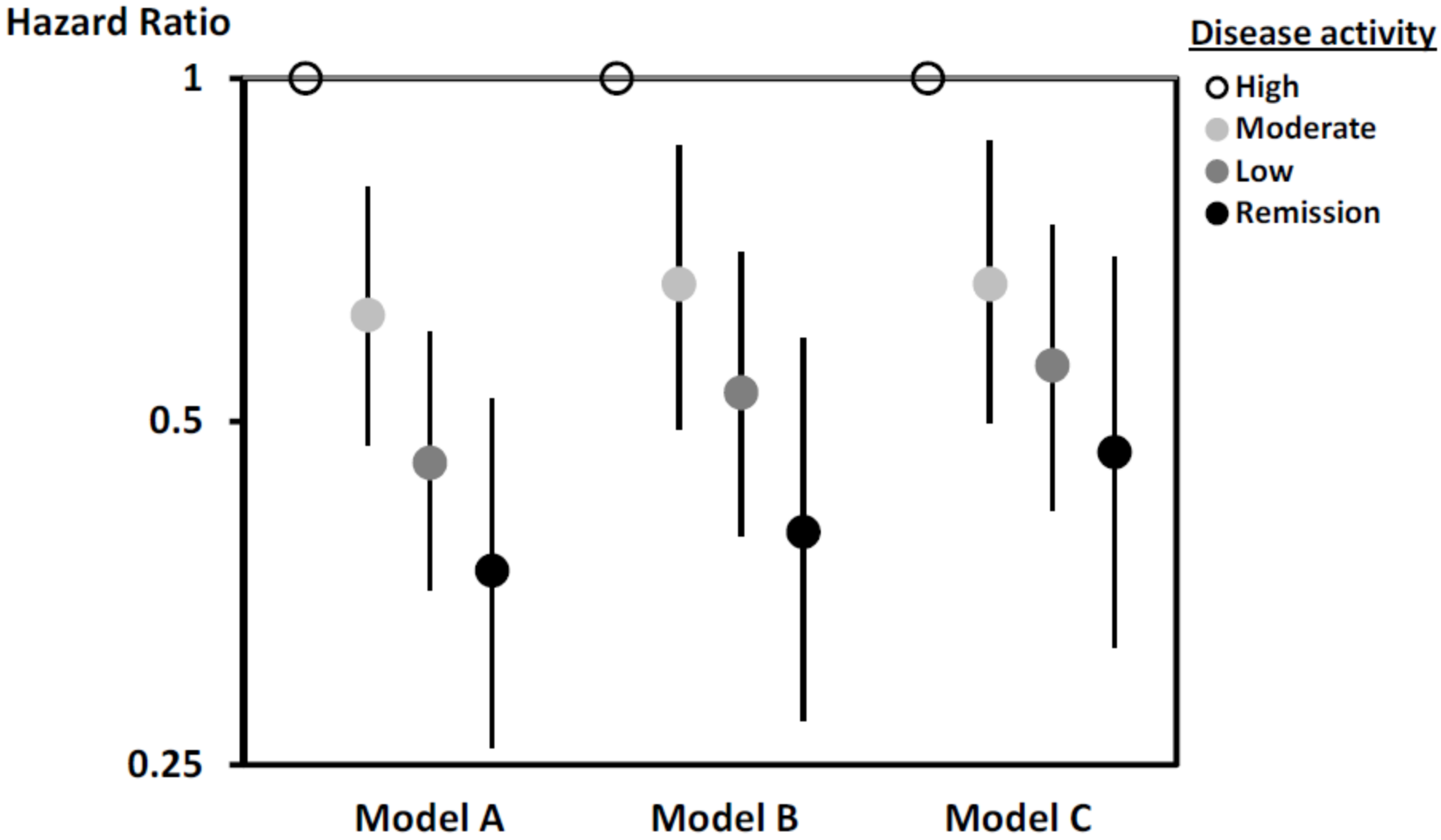
OBJECTIVE: Use of several immunomodulatory agents has been associated with reduced numbers of cardiovascular (CV) events in epidemiologic studies of rheumatoid arthritis (RA). However, it is unknown whether time-averaged disease activity in RA correlates with CV events.

METHODS: We studied patients with RA whose cases were followed in a longitudinal US-based registry. Time-averaged disease activity was assessed during followup using the area under the curve of the Clinical Disease Activity Index (CDAI), a validated measure of RA disease activity. Age, sex, presence of diabetes mellitus, hypertension, or hyperlipidemia, body mass index, family history of myocardial infarction (MI), use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs), presence of CV disease, and baseline use of an immunomodulator were assessed at baseline. Cox proportional hazards regression models were examined to determine the risk of a composite CV end point that included MI, stroke, and death from CV causes.

RESULTS: A total of 24,989 patients who had been followed up for a median of 2.7 years were included in these analyses. During followup, we observed 534 confirmed CV end points, for an incidence rate of 7.8 per 1,000 person-years (95% confidence interval [95% CI] 6.7-8.9). In models adjusted for variables noted above, a 10-point reduction in the time-averaged CDAI was associated with a 21% reduction in CV risk (95% CI 13-29). These results were robust in subgroup analyses stratified by the presence of CV disease, use of corticosteroids, use of NSAIDs or selective cyclooxygenase 2 inhibitors, and change in RA treatment, as well as when restricted to events adjudicated as definite or probable.

CONCLUSION: Our findings showed that reduced time-averaged disease activity in RA is associated with fewer CV events.

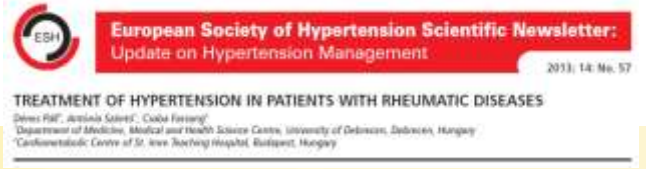
Disease activity and risk of hypertension and CV complications



Solomon D.H. et al.,Arthritis & Rheumatology, 2015 in press

- Patients with RA are limited in physical activity, which can be explained by chronic pain and joint damage. **Lack of exercise may lead to overweight** in some patients, and subsequently, hypertension

- In addition to these pathophysiological processes **numerous drugs used in RA (NSAIDs, glucocorticoids) can also increase blood pressure and inhibit the antihypertensive effect of drugs**, such as diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB)



The impact of antirheumatic drugs on blood pressure:
Non-steroidal anti-inflammatory drugs (NSAIDs)and cyclooxigenase-2 inhibitors (coxibs)

- Non-selective NSAIDs and coxibs are commonly used both in RA and in OA.
- In an earlier meta-analysis, including 50 trials, **NSAIDs caused an average of 5 mm Hg elevation in systolic blood pressure**
- The most pronounced increase in blood pressure was observed during **treatment with piroxicam, indomethacin and naproxen**

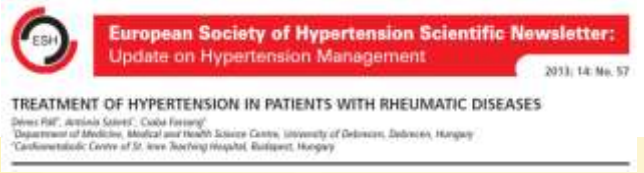


Table 2 Relative risk of developing hypertension for acetaminophen, NSAIDs, and cyclooxygenase 2 inhibitors vs. placebo

Drug (study sample size)	RR (95% CI)	Reference
Acetaminophen ($n = 1903$)	1.93 (1.30–2.88)	[12]
Acetaminophen ($n = 3220$)	1.99 (1.39–2.85)	[12]
NSAIDs ($n = 1903$)	1.78 (1.21–2.61)	[12]
NSAIDs ($n = 3220$)	1.60 (1.10–2.32)	[12]
Rofecoxib ($n = 16512$)	1.87 (1.63–2.14)	[13]
Celecoxib ($n = 20987$)	1.24 (0.80–1.93)	[13]
Etoricoxib ($n = 15728$)	1.1 (0.7–1.75)	[13]
Valdecoxib ($n = 2553$)	4.13 (0.75–22.8)	[13]
Lumiracoxib ($n = 11930$)	1.12 (0.64–1.95)	[13]

Rossi G.P. et al., J. Hypertens., 2011; 29: 2295-2309

Table 3 Changes in blood pressure in hypertensive patients and in normotensive individuals with different anti-inflammatory drugs

	Hypertensive patients (mmHg)	Normotensive individuals (mmHg)
NSAIDs (pooled)	3.6–5.4	1.0–1.1
Indomethacin	4.8–6.0	1.0
Naproxen	3.1–6.1	ND
Piroxicam	2.9–6.2	ND
Sulindac	−1.6 to 2.2	−1.6
Aspirin	−1.8 to 1.0	0.6
COXIBs		
Rofecoxib	2.6–4.7	3.4
Celecoxib	−0.4	4.3

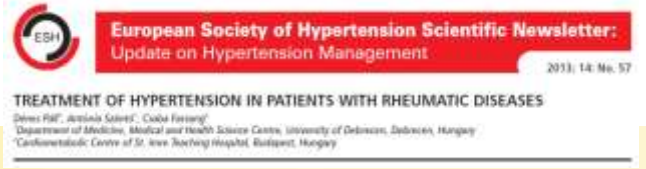
COXIBs, cyclooxygenase-2 inhibitors. Adapted from [27].

Rossi G.P. et al. J. Hypertens., 2011; 29: 2295-2309

- The blood pressure increasing effect of non-selective NSAIDs was **more obvious in hypertensive than in normotensive patients.**

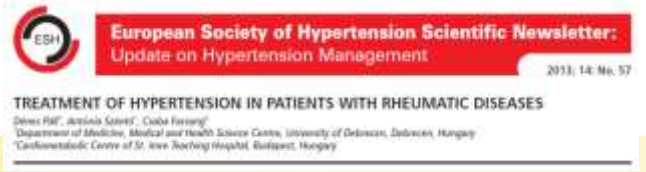
- **Possible mechanisms** in the background can be:

- **salt and water retention by decreased prostaglandin production** in the renal arteries and subsequently increased antinatriuretic effect in the macula densa,
- increased peripheral vascular resistance by **promoting endothelin-1**
- and **inhibiting vasodilatory prostaglandin** synthesis

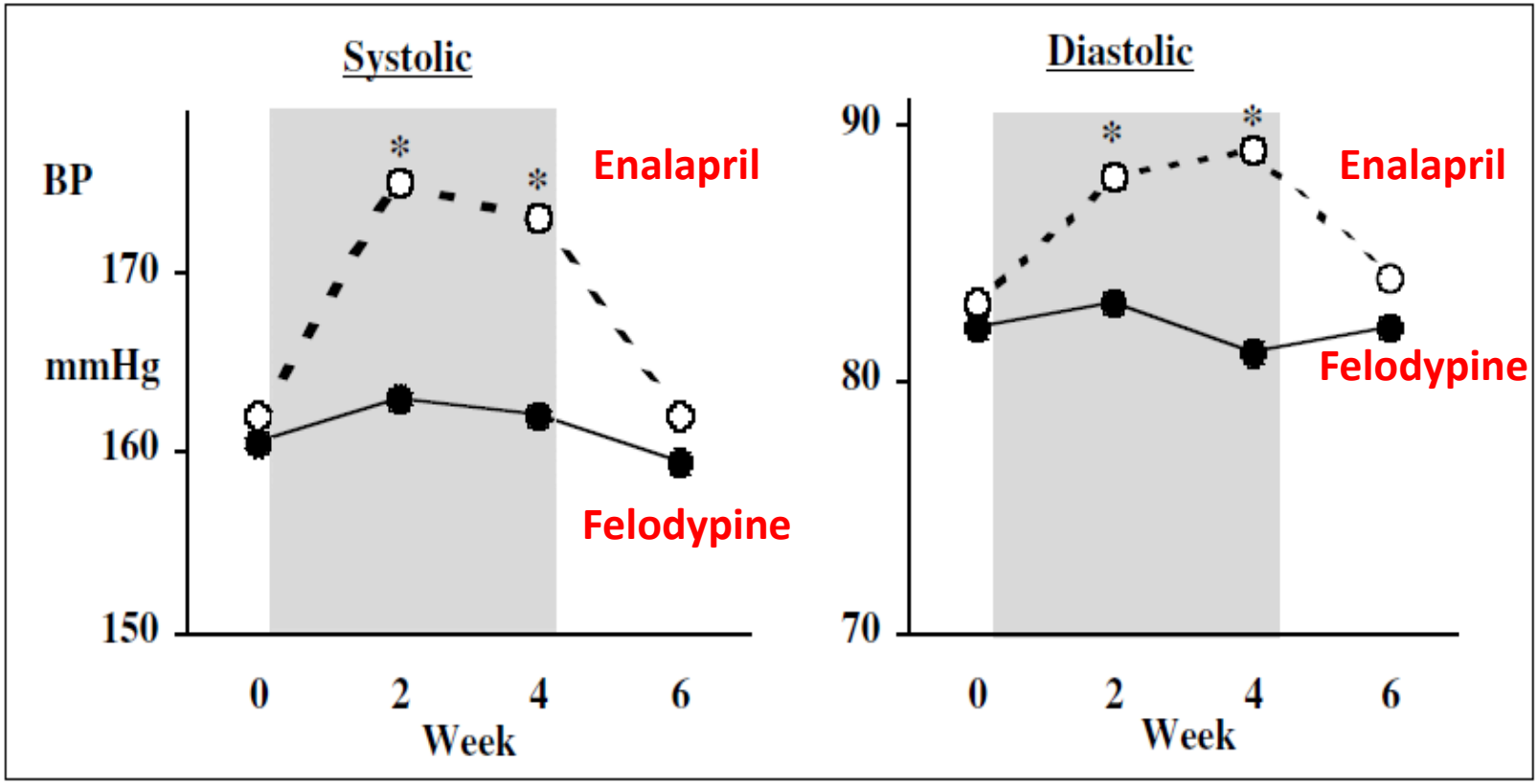


- Several studies have revealed that co-administration of non-selective NSAIDs with diuretics, beta-receptor blockers, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) **result in attenuation of the anti-hypertensive effect**

- Interestingly, this effect **cannot be observed with calcium channel blockers (CCBs)**

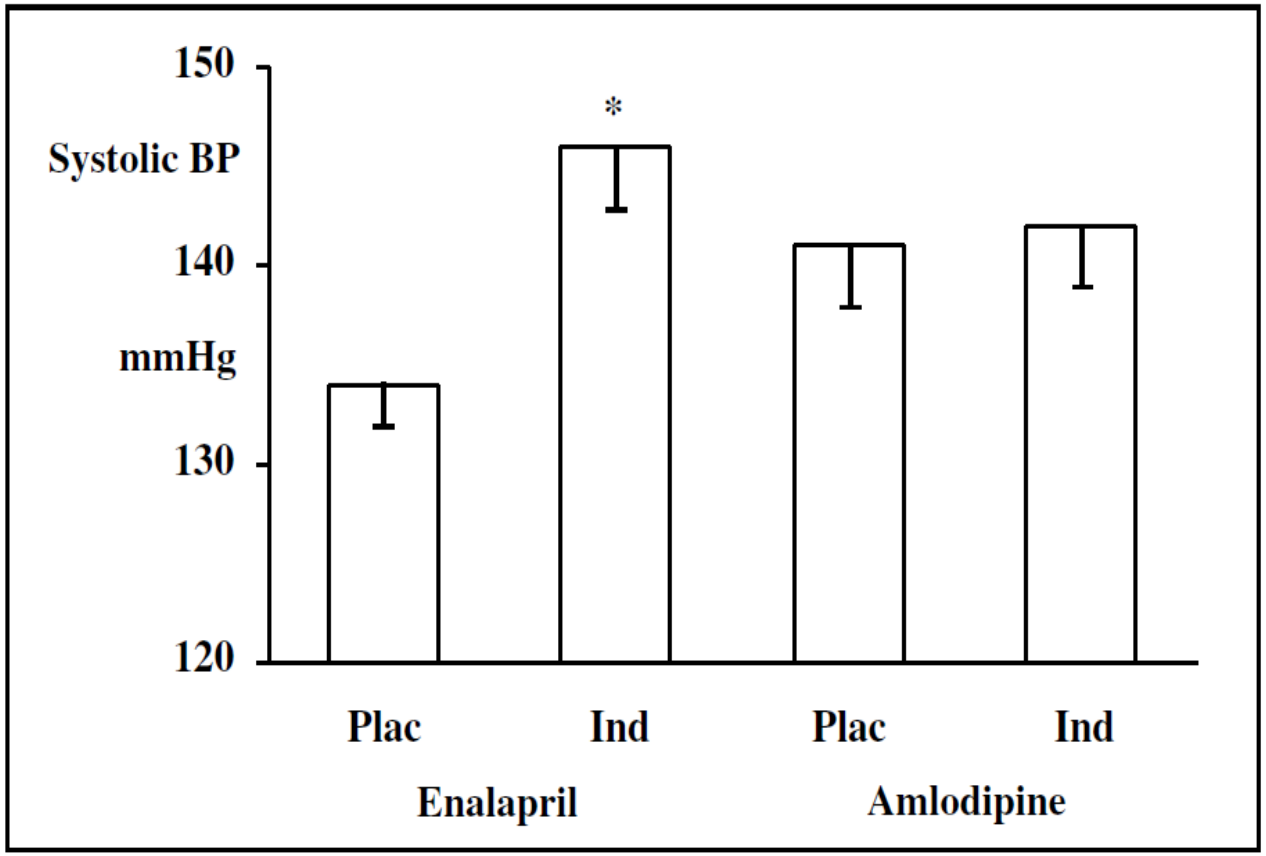


Influence of indomethacin on BP i patients treated with Enalapril or Felodipine



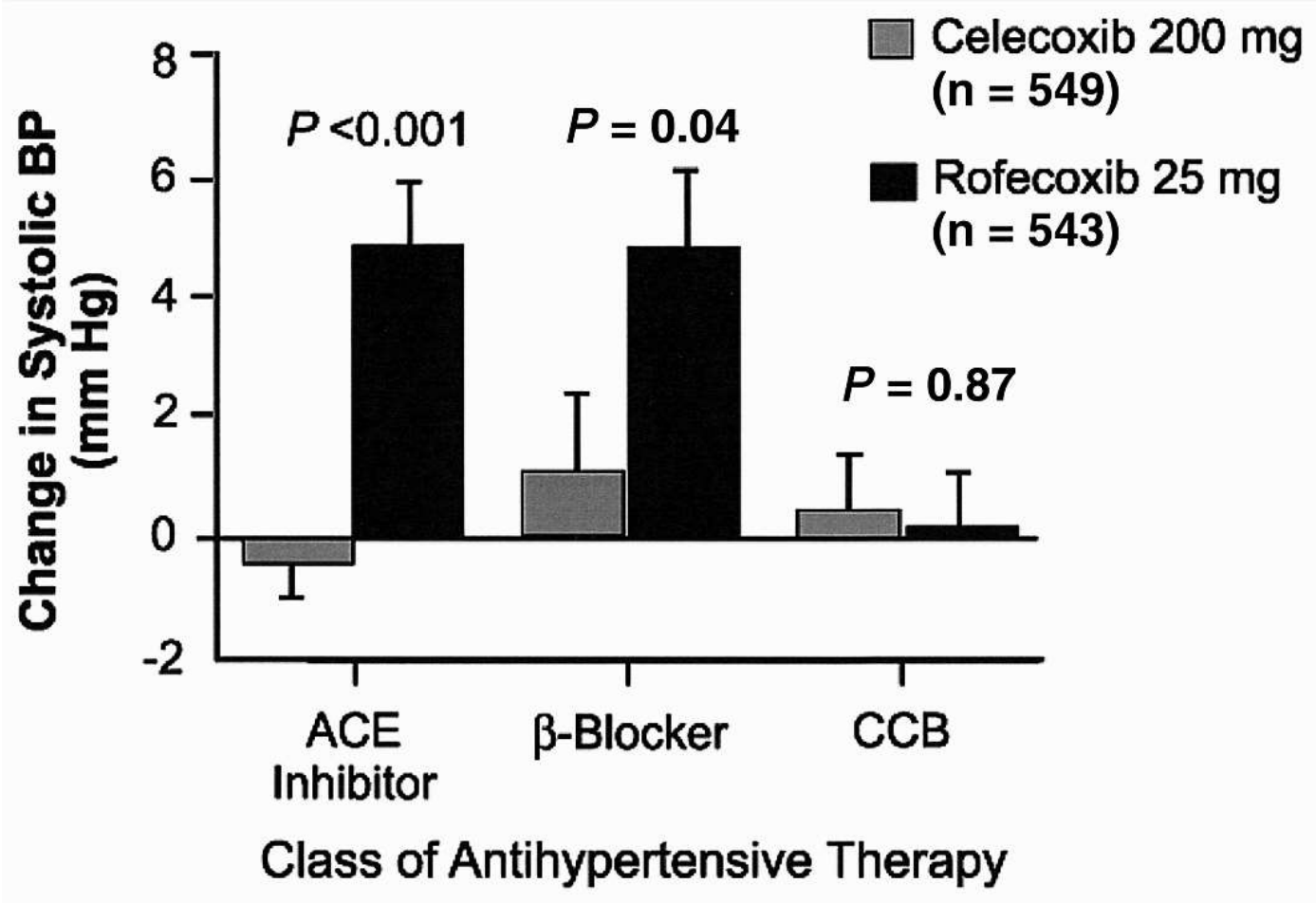
Morgan T. et al., J. Clin. Invest., 2003; 5: 53–57

Influence of indomethacin on BP i patients treated with Enalapril or Amlodipine



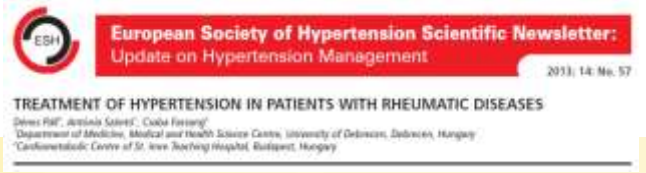
Morgan T. et al., J. Clin. Invest., 2003; 5: 53–57

Influence of coxibes on BP during antihypetensive treatment

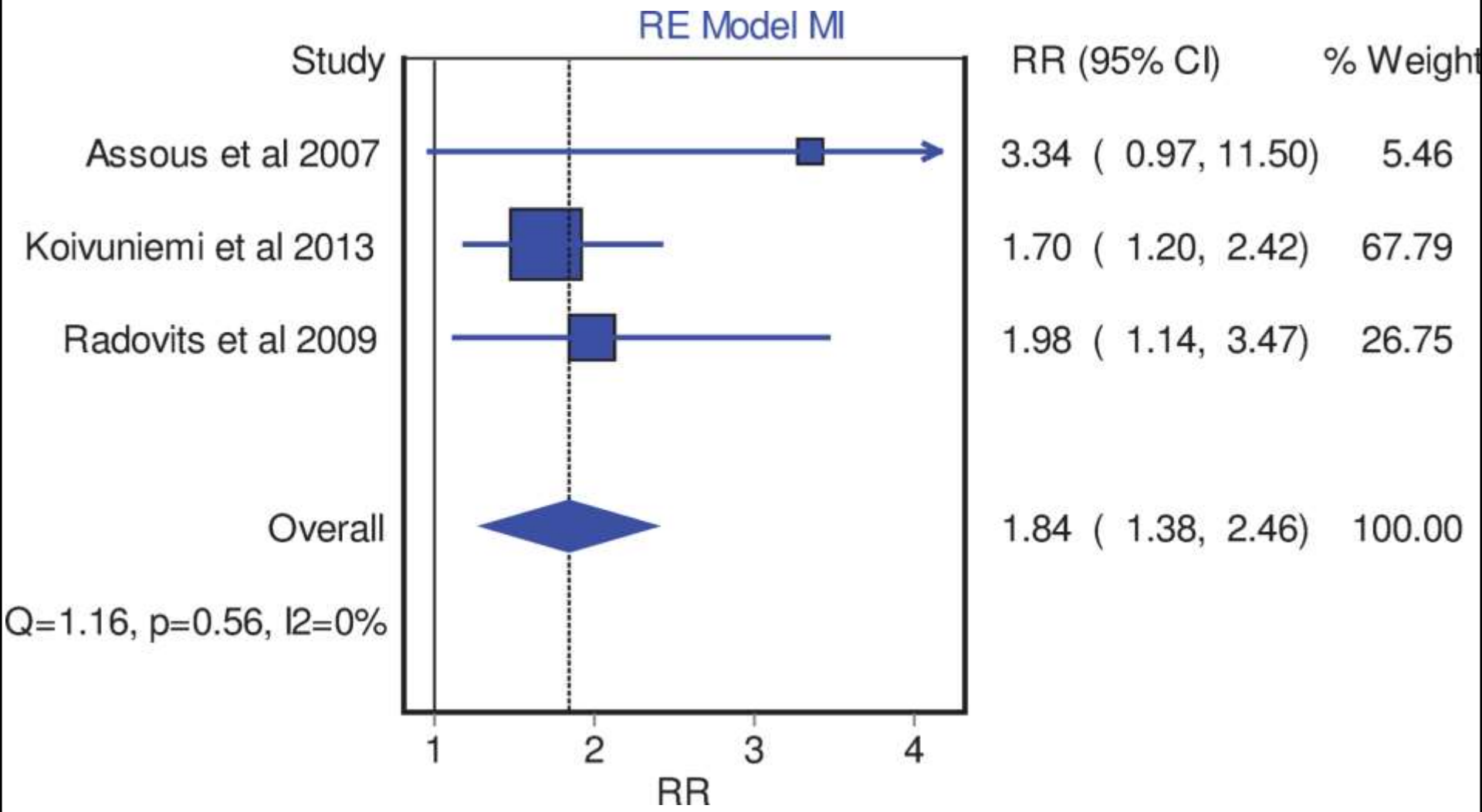


White W.B. et al., Am J Med 2009; 122: S3–S9

- Selective cyclooxygenase-2 inhibitors (coxibs) were developed to decrease the risk of gastrointestinal bleeding in patients who require NSAIDs. However, after a few years it became obvious that **coxibs shift the antithrombotic-prothrombotic balance in the direction of the prothrombotic** way by inhibiting the synthesis of prostacyclin and thereby changing the balance between vasodilatory/vasoconstrictor (thromboxane) synthesis in endothelial cells.
- They markedly **increase systolic more than diastolic** blood pressure.
- As a consequence of these processes, **they are associated with increased cardiovascular and renal risk** (acute coronary syndrome, stroke, CKD).

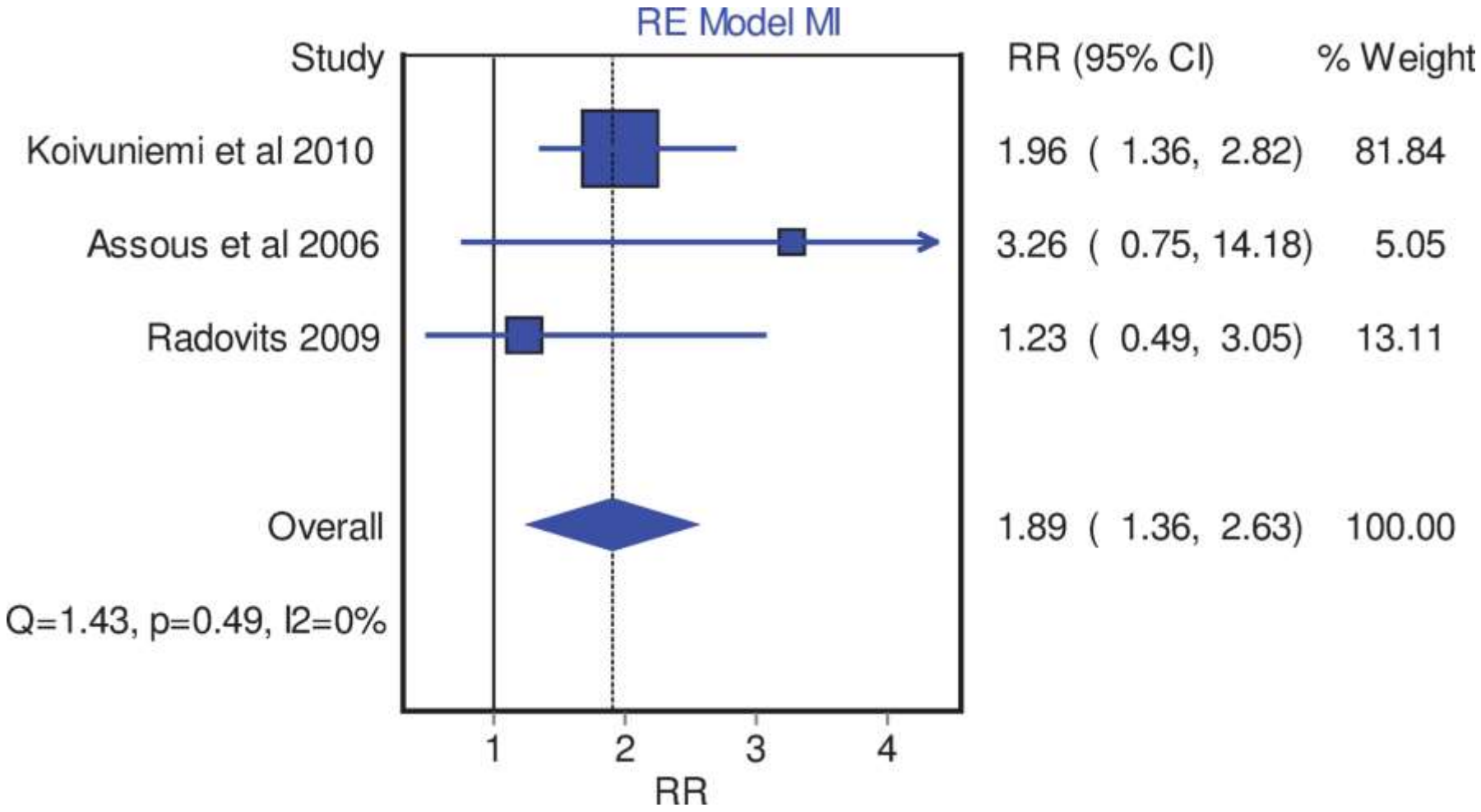


Forest plot depicting the relative risk of MI in hypertensive RA patients versus those without hypertension using random effect model.



Baghdadi R.L. et al., PLOS ONE | 2015,DOI:10.1371/journal.pone.0117952

Forest plot depicting the relative risk of MI in diabetic RA patients versus those without T2D using random effect model

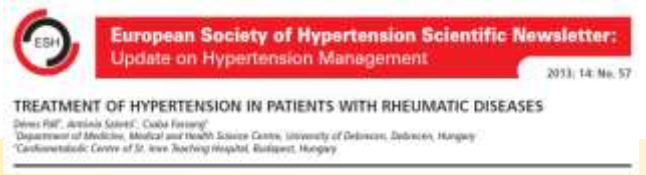


Baghdadi R.L. et al., PLOS ONE | 2015 DOI:10.1371/journal.pone.0117952

Glucocorticoids (GC):

- Although GCs can be administered intra-articularly in OA patients with severe and treatment-resistant pain, their **main application area is the systemic route** in inflammatory rheumatic diseases such as RA.

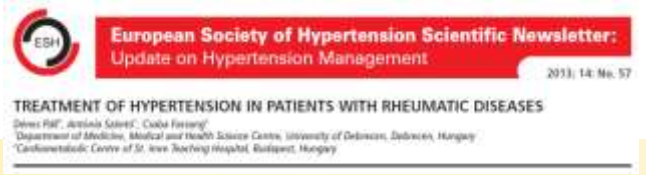
- The blood pressure elevating effect of sustained GC treatment has been known for a long time. **Use of even a moderate dose of prednisolon (> 7.5 mg/day) over more than 6 months elevates blood pressure** and increases the incidence of hypertension



- In the latest EULAR recommendations, **two opposite ways** are mentioned about how GCs influence CV risk in patients with RA:

- at first, due to their well-known **harmful effects on lipids, glucose tolerance and obesity**, corticosteroids could elevate CV risk,

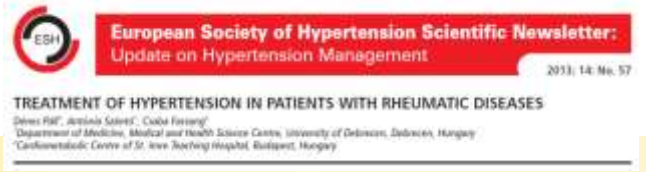
- and secondly, they can even **decrease it by suppressing inflammation and decreasing pain**



Disease-modifying antirheumatic drugs (DMARDs):

- **Leflunomide** induces hypertension in 2-4.7% of patients, presumably by increasing sympathetic tone

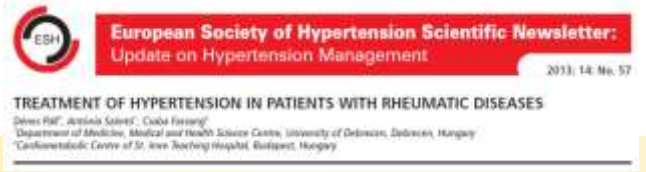
- **Cyclosporin** is known to trigger hypertension, and it is contraindicated in patients with uncontrolled hypertension



- There are several hypotheses for the explanation of **cyclosporin-induced hypertension:**

- by **enhancing endothelin-related vasoconstriction, by reducing nitric oxide and suppressing prostacyclin** production,
- and by **reducing the glomerular filtration rate and causing sodium retention**

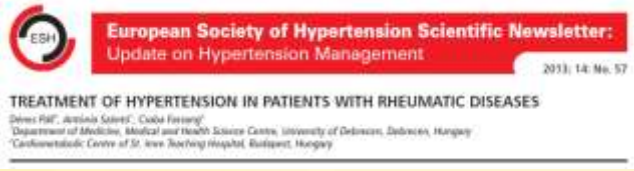
- Cyclosporine-induced hypertension **should be treated with CCBs** (diltiazem and verapamil are preferred because they increase plasma cyclosporin levels).
- **Reduction of the dose or withdrawal of cyclosporin** may be possible if hypertension becomes treatment-resistant



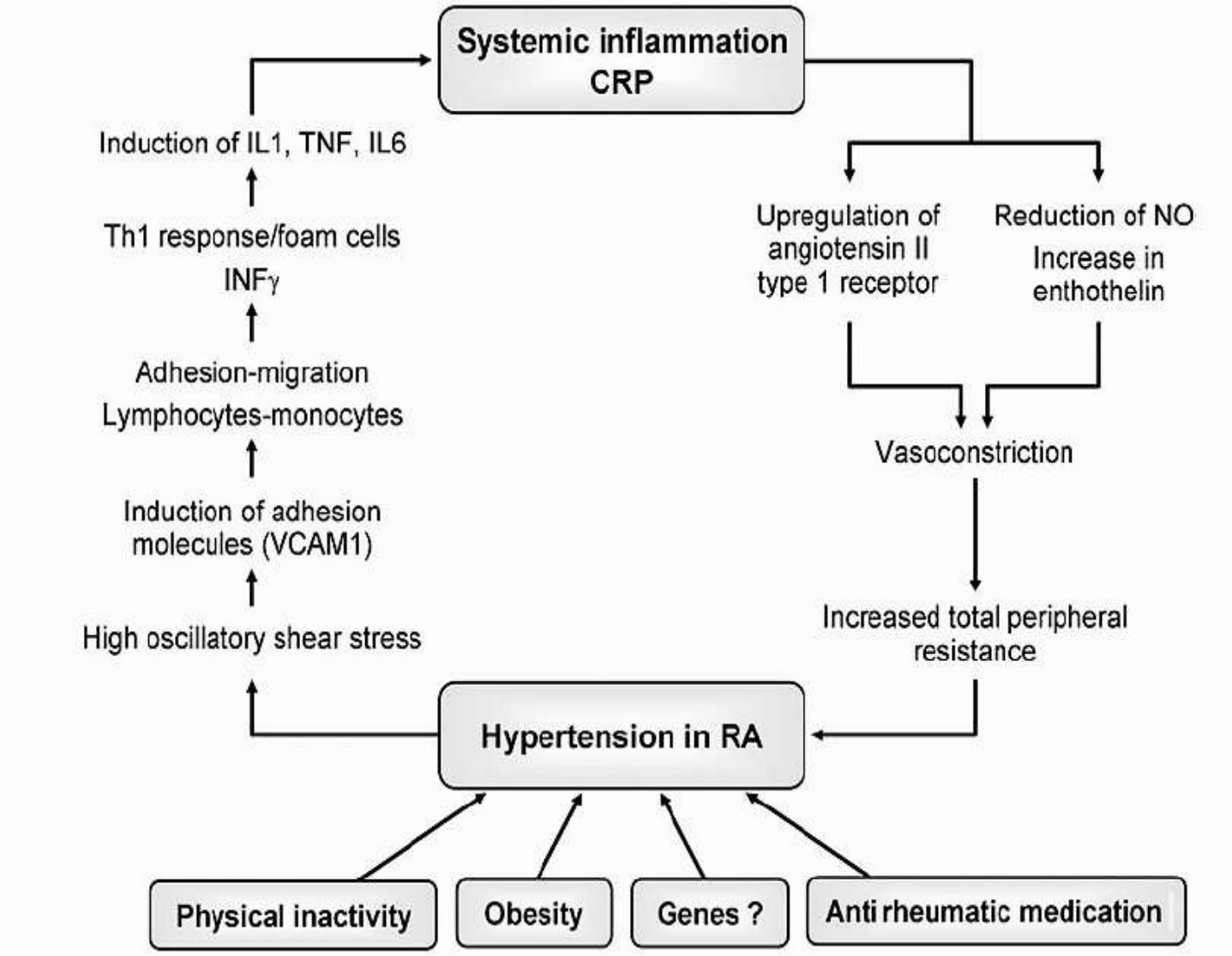
Biological therapies:

- Although there are few observations so far, **no evidence exists to suggest any impact on hypertension, o**r on the effects of antihypertensive medication during treatment with such agents (**TNF-alpha inhibitors, rituximab, anakinra, abatacept**).

- Moreover, the potential future use of **the anti-human IL-6 receptor antibody tocilizumab** has been suggested to treat resistant hypertension



Pathogenesis of hypertension in patients with RA

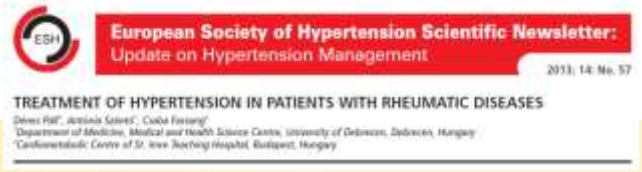


Kitas G.D. et al., Ann. Rhem. Dis., 2011; 70: 8-14

The impact of antihypertensive drugs on rheumatic diseases:

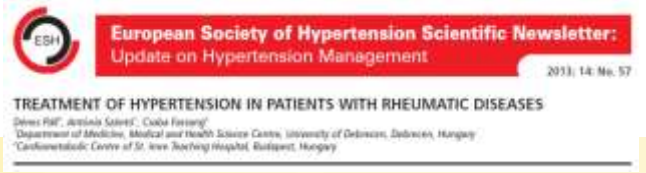
- Concomitant medication of patients must be carefully assessed before the initiation of any antihypertensive treatment. Patients with RA have increased sympathetic activity, which may result in high plasma renin activity. **Therefore, antihypertensive treatment with ACEIs seems to be reasonable**

- Moreover, **ACEIs suppress proinflammatory** mediators such as reactive oxygen species (ROS) and CRP, and promote the expression of some anti-inflammatory factors



- Since insulin resistance — especially under sustained GC treatment - is frequent, **use of conventional non-cardioselective beta-blockers and thiazides should be avoided**

- If Raynaud's phenomenon is associated with RA, selective beta-blockers should be avoided while **ACEIs, ARBs, CCBs, carvedilol or nebivolol might be preferred**

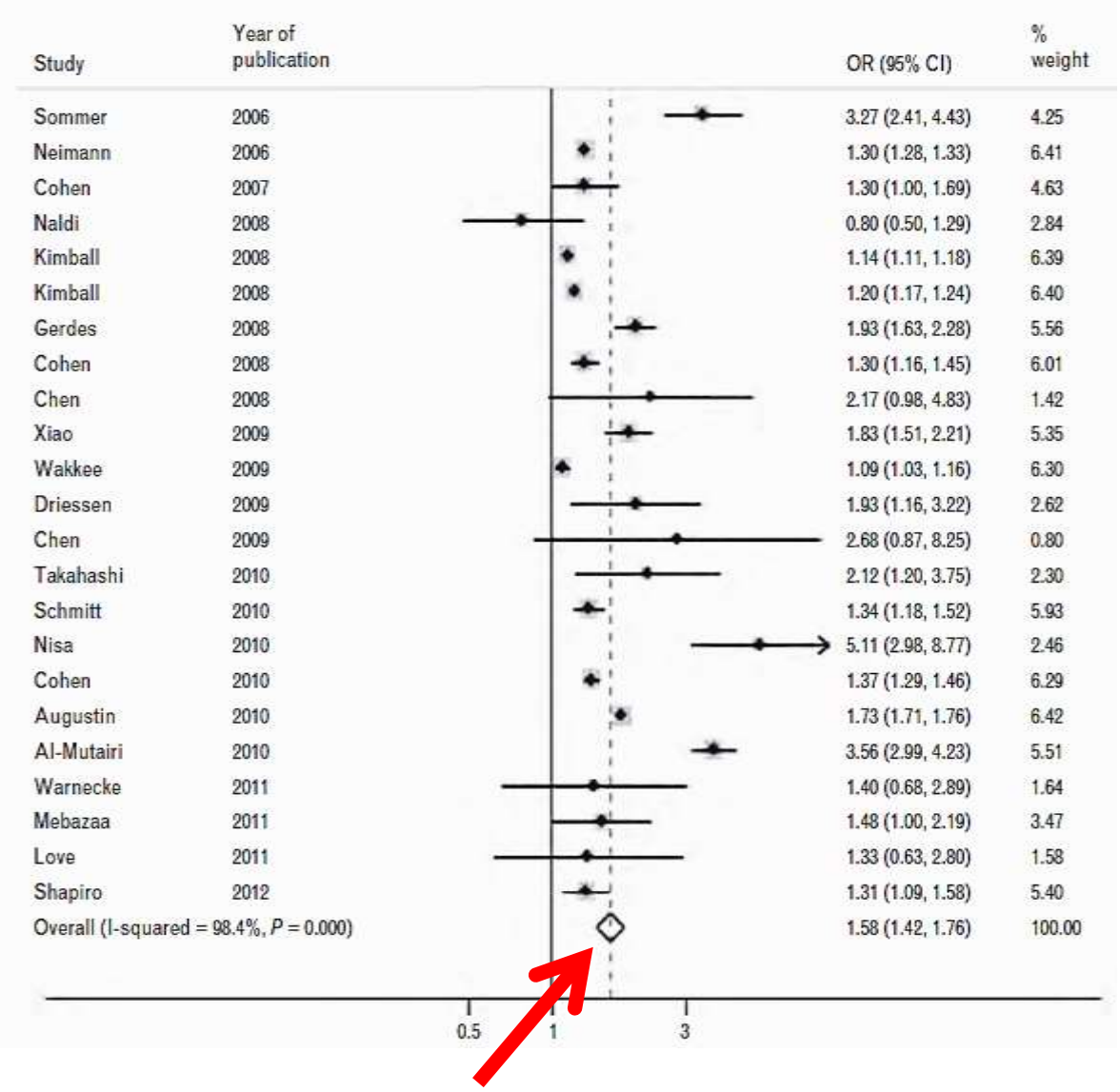


Conclusions:

- Patients with chronic rheumatic diseases **are considered to be at high CV risk**, and this condition is frequently associated with hypertension
- Treatment with **NSAIDs further increases CV risk** (acute coronary syndromes, stroke); therefore, this type of therapy should be carried out with close observation of patients and for the shortest possible duration
- In patients with **hyperuricaemia**, uricosuric antihypertensives such as losartan and CCBs are preferred and thiazides or beta-blockers should be avoided

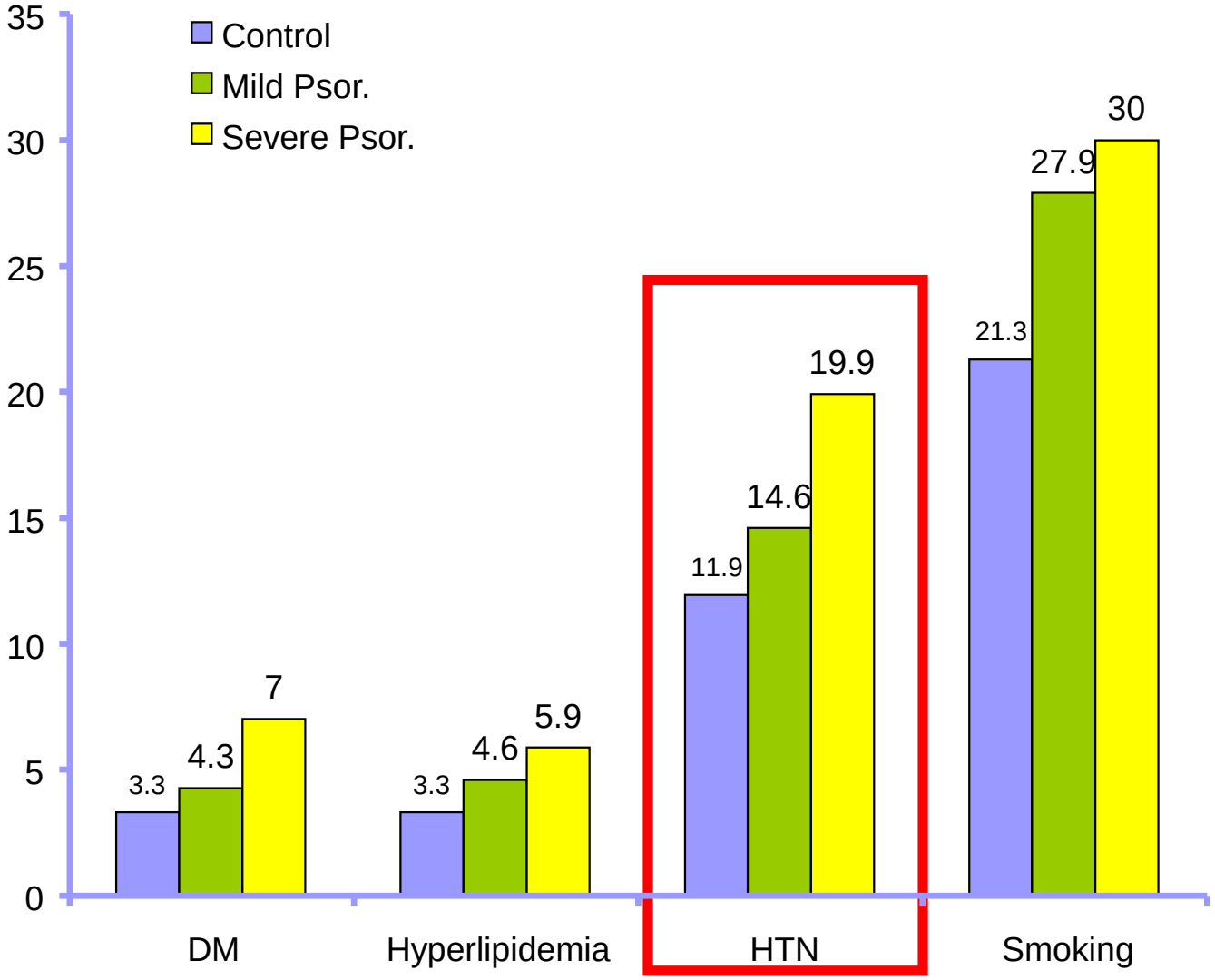
Hypertension in patients with psoriasis

- 24 observational studies
- (2,4 mln subjects including 309 469 patients with psoriais)
- OR **1,58** (95% CI 1,20-1,86)



Armstrong A.W. at al., J Hypertens 2013; 31: 441-443

Hypertension in patients with psoriasis



Gelfand J.M. et al., JAMA 2006; 14: 1735-1741

Cause and relative risk of death by treatment group

	Control		Psoriasis			Cox Model**	
	N	%^	N	%^	p-value*	HR	(95% CI)
Accidents	7	1%	2	1%	1.000	1.03	(0.21–4.96)
Cardiovascular Disease	301	35%	108	34%	0.002	**1.57**	**(1.26–1.96)**
Chronic lower respiratory disease	44	5%	22	7%	0.013	**2.08**	**(1.24–3.48)**
Dementia	10	1%	7	2%	0.060	**3.64**	**(1.36–9.72)**
Diabetes	10	1%	7	2%	0.060	**2.86**	**(1.08–7.59)**
Infection	195	23%	71	22%	0.009	**1.65**	**(1.26–2.18)**
Kidney disease	17	2%	18	6%	0.000	**4.37**	**(2.24–8.53)**
Liver disease	4	0%	2	1%	0.347	2.03	(0.37–11.12)
Malignant neoplasms	190	22%	67	21%	0.019	**1.41**	**(1.07–1.86)**
Other	33	4%	17	5%	0.020	**2.12**	**(1.19–3.88)**
Suicide	1	0%	1	0%	0.361	3.35	(0.21–53.77)
Unknown/ Missing	218	25%	70	22%	0.075	**1.43**	**(1.09–1.89)**
Total Deaths	**862**		**321**				

Notes:

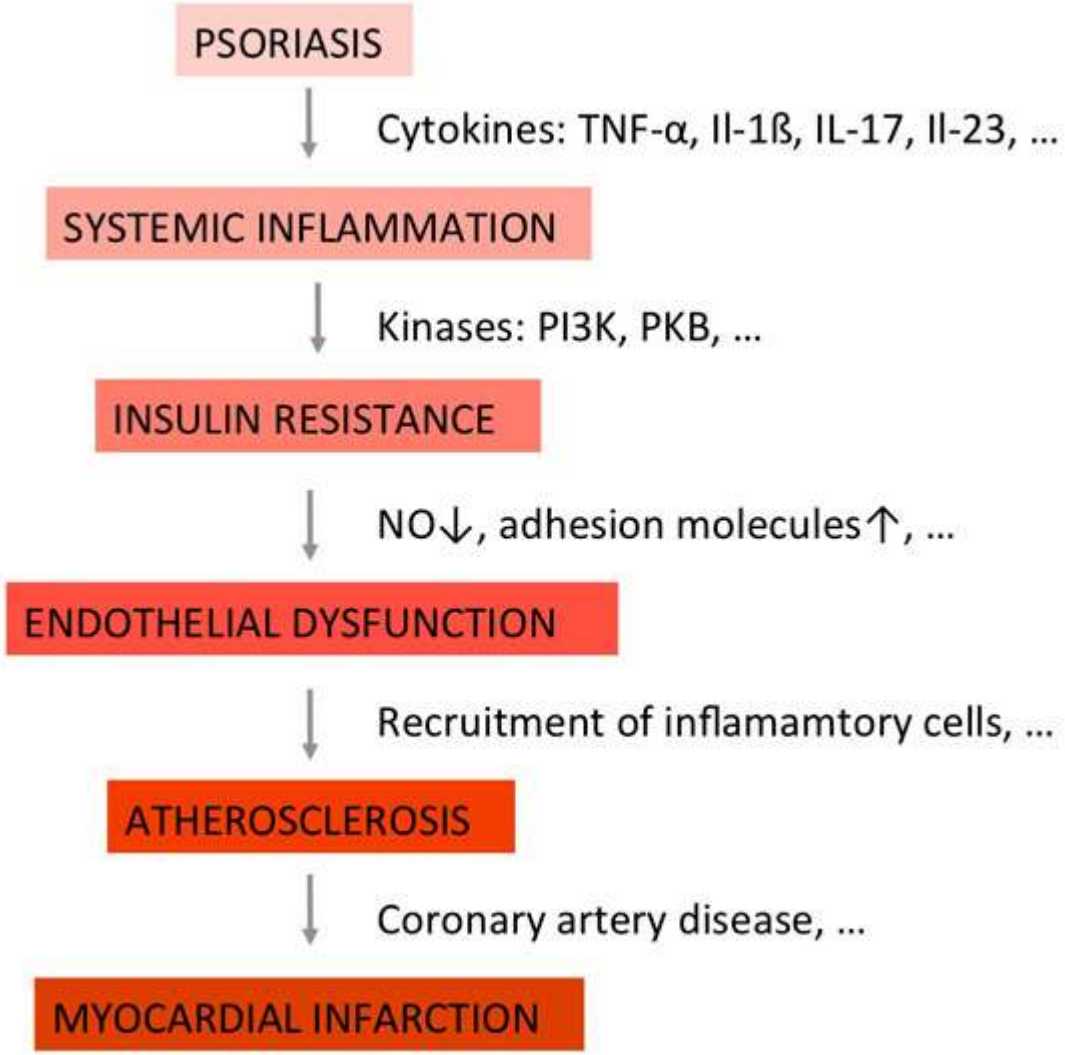
^ Percentages may not sum to 100 because each subject may have had more than one cause of death.

* Two-sided fisher's exact test.

** Adjusted for age and sex

Abuabara K. et al.. Br J Dermatol 2010; 163: 586-592

The concept of the “psoriatic march”



Conclusions:

- Hypertension is frequently present in patients with RA, psoriasis and other systemic diseases
- Inflammation plays an important role in the pathogenesis of hypertension and metabolic disorders in these patients
- Cardiovascular mortality is higher in these patients than in general population
- Antiinflammtory drugs may interfere with the treatment of hyperetension
- Patients with systemic diseases should be consider as a hight risk patients and therefore should remain under the special control both by cardilogist and nephrologists


Thank you very much for your attention !
Andrzej Wiecek
Katowice
Poland
CENTRUM