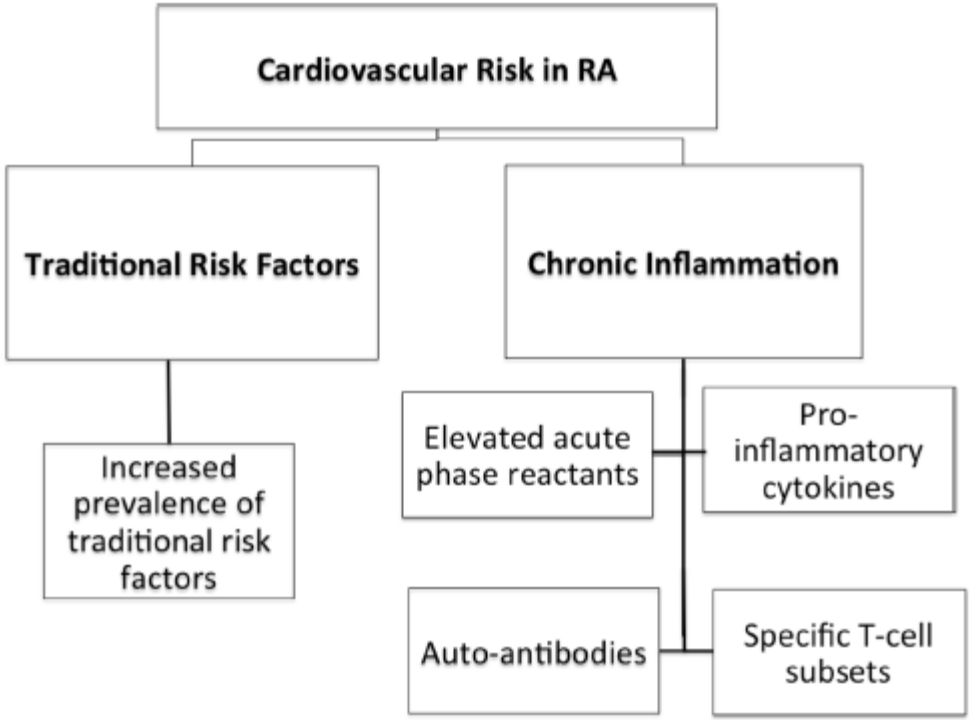
«Φάρμακα που αυξάνουν τον καρδιαγγειακό κίνδυνο στη ΡΑ»

Μαρκολέφα Ιωάννα
Ειδικευόμενη Ρευματολογικής Κλινικής
ΓΝΑ Γ. Γεννηματάς

Καρδιαγγειακός κίνδυνος στη Ρευματοειδή Αρθρίτιδα



(DeMizio and Geraldino-Pardilla 2019)

EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update

Table 1 Overarching principles and recommendations

	Level of evidence	Strength of recommendation	Level of agreement (SD)
Overarching principles A. Clinicians should be aware of the higher risk for CVD in patients with RA compared with the general population. This may also apply to AS and PsA. B. The rheumatologist is responsible for CVD risk management in patients with RA and other IJD. C. The use of NSAIDs and corticosteroids should be in accordance with treatment-specific recommendations from EULAR and ASAS			
Recommendations			
1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA	2b-3	B	9.1 (1.3)
2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy	3–4	C	8.8 (1.1)
3. CVD risk estimation for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available	3–4	C–D	8.7 (2.1)
4. TC and HDLc should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids measurements are also perfectly acceptable	3	C	8.8 (1.2)
5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model	3–4	C	7.5 (2.2)
6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA	3–4	C–D	5.7 (3.9)
7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation for all patients	3	C	9.8 (0.3)
8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population	3–4	C–D	9.2 (1.3)
9. Prescription of NSAIDs in RA and PsA should be with caution, especially for patients with documented CVD or in the presence of CVD risk factors	2a-3	C	8.9 (2.1)
10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked	3–4	C	9.5 (0.7)

Μοντέλα εκτίμησης καρδιαγγειακού κινδύνου σε ασθενείς με Ρευματοειδή Αρθρίτιδα

- SCORE
- Progetto Cuore
- RRS
- QRISK3-2018
- ERS-RA

Cacciapaglia F, Fornaro M, Venerito V, Perniola S, Urso L, Iannone F. Cardiovascular risk estimation with 5 different algorithms before and after 5 years of bDMARD treatment in rheumatoid arthritis. Eur J Clin Invest. 2020;00:e13343. https://doi.org/10.1111/eci.13343

TABLE 1 Variables needed to calculate the different CV risk scores with related outcomes

Variables	10-y Cardiovascular risk scores				
	SCORE charts (age 40-65)	**'Progetto Cuore' (age 35-69)**	**Reynold Risk Score (age 45-80)**	**QRISK3-2018 (age 25-84)**	**ERS-RA (age 20-80)**
Age	✓	✓	✓	✓	✓
Gender	✓	✓	✓	✓	✓
Ethnicity				✓	
Smoking status	✓	✓	✓	✓	✓
Diabetes status		✓	(Exclusion criteria)	✓	✓
Family history of CVD			✓	✓	
Chronic kidney disease				✓	
Atrial fibrillation				✓	
Systolic blood pressure (mm Hg)	✓	✓	✓	✓	
On blood pressure treatment/ hypertension		✓		✓	✓
Rheumatoid arthritis				✓	Validated on RA population
Total cholesterol/ hyperlipidemia	✓	✓	✓		✓
HDL cholesterol		✓	✓		
Cholesterol/HDL ratio				✓	
Height/weight or BMI				✓	
CRP, mg/L			✓		
Disease activity/ mHAQ-DI/RA disease duration/ glucocorticoid					✓
Outcome	Future fatal CV event in the next 10 y	Future heart attack, stroke, or other major heart disease in the next 10 y	Future heart attack, stroke, or other major heart disease in the next 10 y	Stroke, Transient ischaemic attack, Myocardial, infarction or heart attacks, Angina	Myocardial infarction, stroke, or CV-related death

NSAIDS

- Αύξηση του καρδιαγγειακού κινδύνου
- Μελέτες που περιλαμβάνουν ασθενείς με οστεοαρθρίτιδα και ρευματοειδή αρθρίτιδα

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

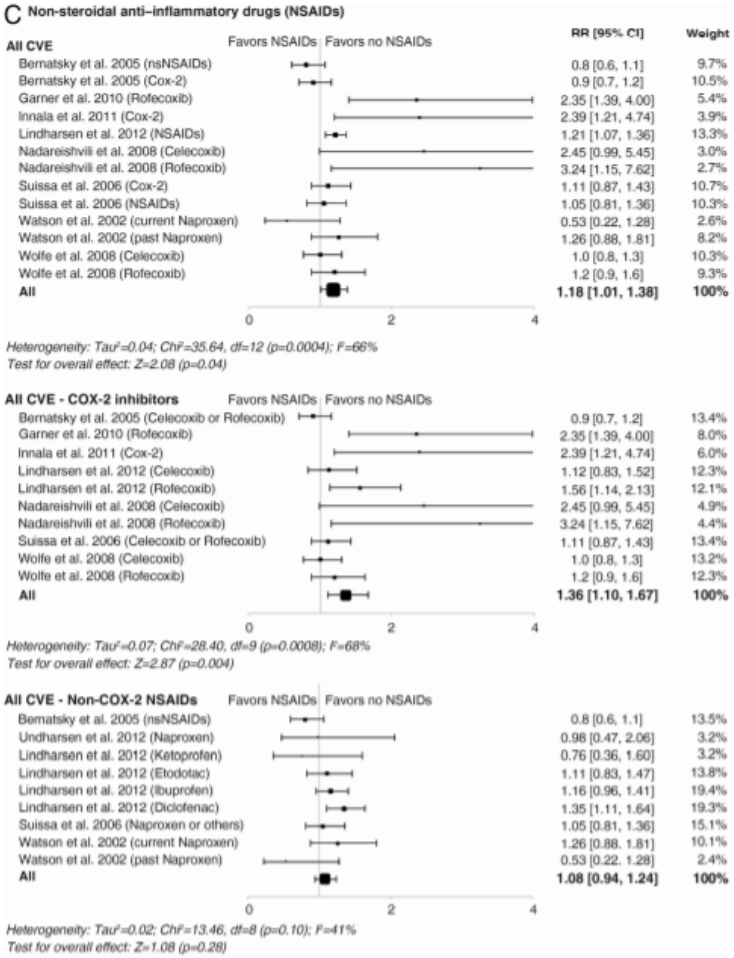
Steven E. Nissen, M.D., Neville D. Yeomans, M.D., Daniel H. Solomon, M.D., M.P.H., Thomas F. Lüscher, M.D., Peter Libby, M.D., M. Elaine Husni, M.D., David Y. Graham, M.D., Jeffrey S. Borer, M.D., Lisa M. Wisniewski, R.N., Katherine E. Wolski, M.P.H., Qiuqing Wang, M.S., Venu Menon, M.D., Frank Ruschitzka, M.D., Michael Gaffney, Ph.D., Bruce Beckerman, M.D., Manuela F. Berger, M.D., Weihang Bao, Ph.D., and A. Michael Lincoff, M.D., for the PRECISION Trial Investigators*

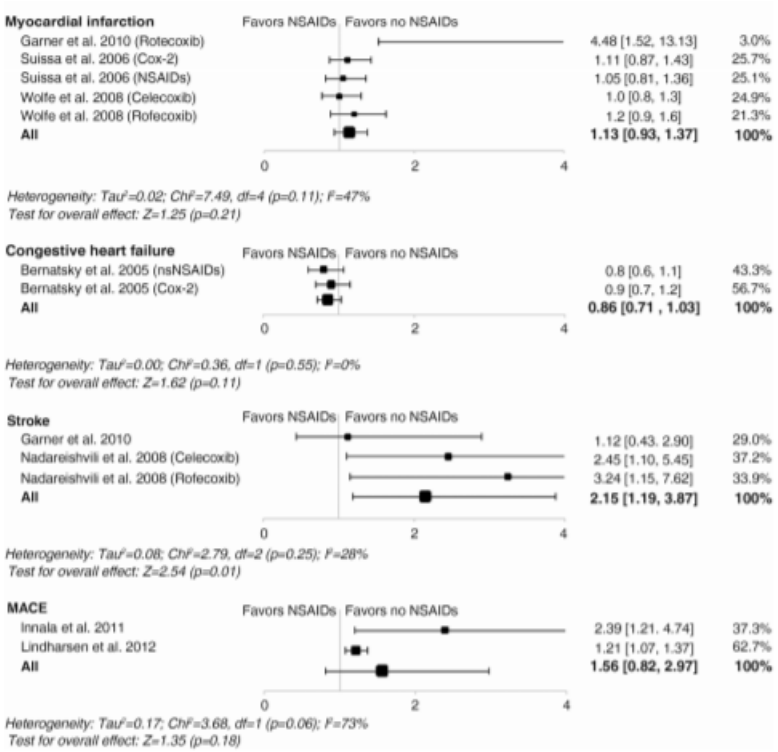
doi: 10.1056/NEJMoa1611593. Epub 2016 Nov 13.

Table 3. Adjudicated Outcomes in the On-Treatment Population.

Outcome	Celecoxib (N=8030)	Naproxen (N=7933)	Ibuprofen (N=7990)	Celecoxib vs. Naproxen Adjusted Hazard Ratio (95% CI)*	Celecoxib vs. Ibuprofen Adjusted Hazard Ratio (95% CI)*
	number of patients (percent)				
Primary APTC outcome†	134 (1.7)	144 (1.8)	155 (1.9)	0.90 (0.71–1.15)	0.81 (0.65–1.02)
Major adverse cardiovascular events‡	247 (3.1)	253 (3.2)	284 (3.6)	0.95 (0.80–1.13)	0.82 (0.69–0.97)
Composite of serious gastrointestinal events	54 (0.7)	115 (1.4)	115 (1.4)	0.45 (0.33–0.63)	0.44 (0.32–0.61)
Clinically significant gastrointestinal events§	27 (0.3)	52 (0.7)	59 (0.7)	0.51 (0.32–0.81)	0.43 (0.27–0.68)
Iron-deficiency anemia of gastrointestinal origin§	27 (0.3)	66 (0.8)	58 (0.7)	0.40 (0.25–0.62)	0.43 (0.27–0.68)
Renal events	42 (0.5)	62 (0.8)	73 (0.9)	0.66 (0.44–0.97)	0.54 (0.37–0.80)
Hospitalization for congestive heart failure	28 (0.3)	35 (0.4)	38 (0.5)	0.78 (0.47–1.27)	0.70 (0.43–1.13)
Hospitalization for hypertension	25 (0.3)	32 (0.4)	37 (0.5)	0.76 (0.45–1.28)	0.64 (0.39–1.07)
Death from any cause	53 (0.7)	79 (1.0)	73 (0.9)	0.65 (0.46–0.92)	0.68 (0.48–0.97)
Components of composite outcomes					
Death from cardiovascular causes	35 (0.4)	49 (0.6)	51 (0.6)	0.69 (0.45–1.07)	0.64 (0.42–0.99)
Nonfatal myocardial infarction	58 (0.7)	53 (0.7)	76 (1.0)	1.06 (0.73–1.54)	0.72 (0.51–1.01)
Nonfatal stroke	43 (0.5)	45 (0.6)	32 (0.4)	0.93 (0.61–1.42)	1.26 (0.80–1.99)
Hospitalization for unstable angina	46 (0.6)	44 (0.6)	49 (0.6)	1.02 (0.68–1.54)	0.89 (0.59–1.33)
Revascularization	132 (1.6)	122 (1.5)	158 (2.0)	1.06 (0.83–1.35)	0.79 (0.62–0.99)
Hospitalization for TIA	12 (0.1)	16 (0.2)	21 (0.3)	0.73 (0.35–1.55)	0.54 (0.27–1.10)

18% αύξηση καρδιαγγειακών συμβαμάτων (RR1.18, 1.01-1.38)





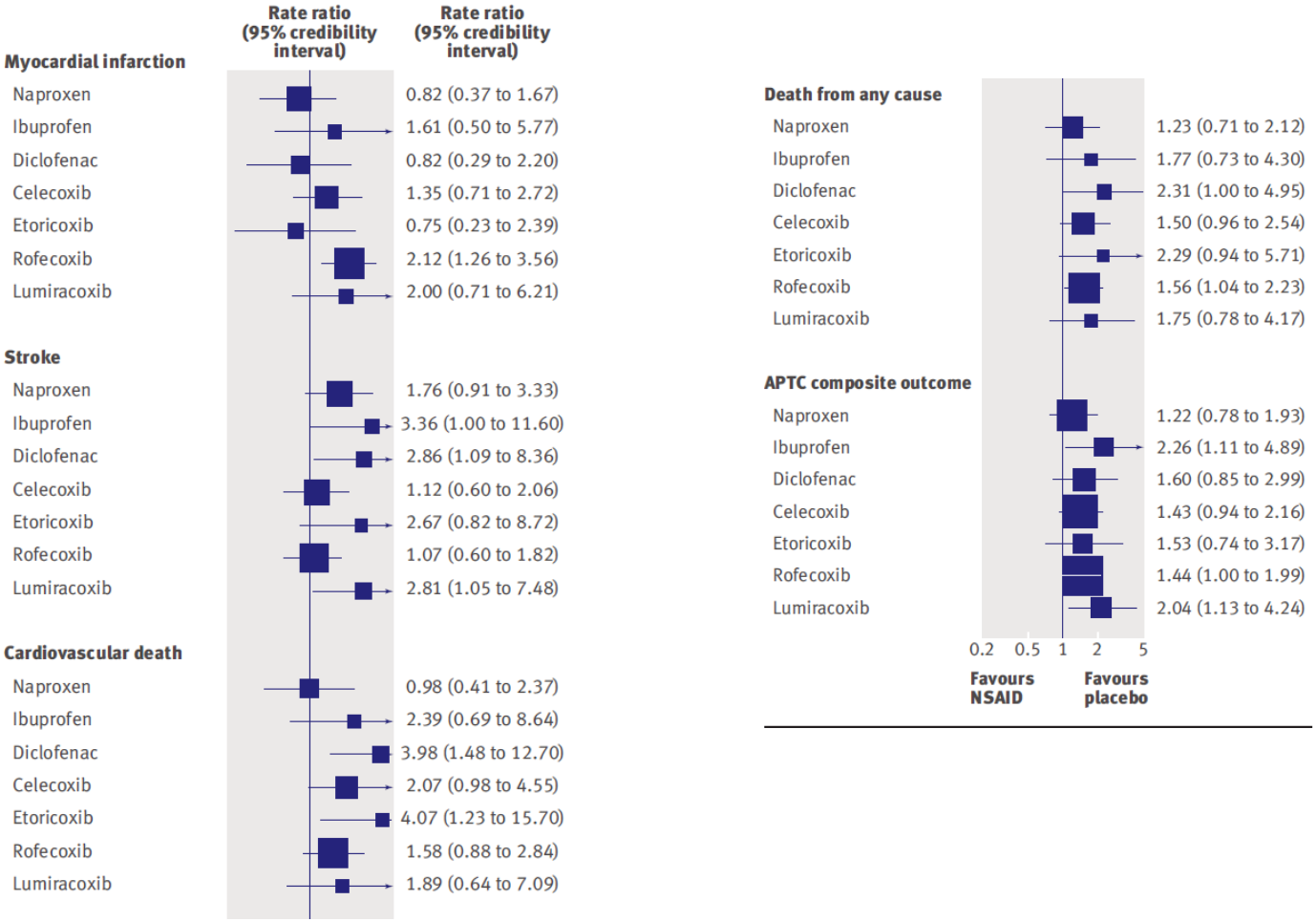
Roubille C, *et al. Ann Rheum Dis* 2015;**74**:480–489. doi:10.1136/annrheumdis-2014-206624

BMJ

RESEARCH

Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis

Sven Trelle, senior research fellow,[1,2] Stephan Reichenbach, senior research fellow,[1,4] Simon Wandel, research fellow,[1] Pius Hildebrand, clinical reviewer,[3] Beatrice Tschannen, research fellow,[1] Peter M Villiger, head of department and professor of rheumatology,[4] Matthias Egger, head of department and professor of epidemiology and public health,[1] Peter Jüni, head of division and professor of clinical epidemiology[1,2]



BMJ 2011;342:c7086

› Am J Cardiol. 2018 May 15;121(10):1271-1277. doi: 10.1016/j.amjcard.2018.01.044. Epub 2018 Feb 12.

Effect on Risk of Stroke and Acute Myocardial Infarction of Nonselective Nonsteroidal Anti-Inflammatory Drugs in Patients With Rheumatoid Arthritis

Yih-Ru Chen [1], Fang-I Hsieh [1], Chi-Ching Chang [2], Nai-Fang Chi [3], Hsin-Chiao Wu [1], Hung-Yi Chiou [4]

Table 4
Risk of stroke and acute myocardial infarction in relation to nonsteroidal anti-inflammatory drugs use among patients with rheumatoid arthritis, based on different lengths for case and control periods

	Case Period 1–14 days Control Period 15–28 days				Case Period 1–30 days Control Period 31–60 days				Case Period 1–30 days Control Period 61–90 days			
	Crude OR	(95%CI)	Adjusted OR*	(95%CI)	Crude OR	(95%CI)	Adjusted OR*	(95%CI)	Crude OR	(95%CI)	Adjusted OR*	(95%CI)
Stroke and AMI (n = 5921)												
Overall NSAIDs use	1.46†	(1.33–1.60)	1.44†	(1.30–1.59)	1.51†	(1.37–1.67)	1.41†	(1.27–1.56)	1.42†	(1.29–1.55)	1.30†	(1.18–1.44)
Selective NSAIDs	0.96	(0.79–1.15)	0.88	(0.72–1.09)	1.40†	(1.15–1.70)	1.20	(0.97–1.49)	1.43†	(1.18–1.74)	1.23	(0.99–1.52)
Nonselective NSAIDs	1.62†	(1.46–1.79)	1.54†	(1.39–1.72)	1.50†	(1.36–1.66)	1.41†	(1.27–1.57)	1.41†	(1.29–1.55)	1.31†	(1.19–1.45)
Stroke (n = 5001)												
Overall NSAIDs use	1.45†	(1.31–1.61)	1.45†	(1.29–1.62)	1.50†	(1.35–1.67)	1.43†	(1.28–1.60)	1.42†	(1.28–1.57)	1.32†	(1.19–1.48)
Selective NSAIDs	0.90	(0.73–1.11)	0.84	(0.67–1.06)	1.35†	(1.09–1.68)	1.20	(0.95–1.50)	1.38†	(1.12–1.71)	1.22	(0.97–1.53)
Nonselective NSAIDs	1.61†	(1.44–1.80)	1.56†	(1.39–1.75)	1.49†	(1.33–1.66)	1.42†	(1.27–1.59)	1.40†	(1.27–1.56)	1.31†	(1.18–1.46)
AMI (n = 920)												
Overall NSAIDs use	1.48†	(1.18–1.86)	1.45†	(1.11–1.90)	1.58†	(1.23–2.02)	1.31	(0.99–1.74)	1.39	(1.10–1.75)	1.17	(0.90–1.53)
Selective NSAIDs	1.19	(0.79–1.78)	1.22	(0.71–2.07)	1.65†	(1.02–2.69)	1.10	(0.62–1.96)	1.72†	(1.05–2.82)	1.12	(0.61–2.03)
Nonselective NSAIDs	1.63†	(1.27–2.10)	1.50†	(1.14–1.98)	1.58†	(1.23–2.02)	1.39†	(1.06–1.82)	1.45†	(1.15–1.83)	1.30†	(1.00–1.69)

Adjusted OR = adjusted odds ratio; CI = confidence interval; NSAIDs = nonsteroidal anti-inflammatory drugs.
* Covariates adjusted in the conditional logistic regression models include: antidiabetes agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β blockers, calcium channel blockers, diuretics, antihypertensive agents, lipid-lowering drugs, anticoagulants, antiplatelet, disease-modifying antirheumatic drugs, glucocorticoids, and biologics between case and control periods.
† p Value <0.05.

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Effect of Aspirin Coadministration on the Safety of Celecoxib, Naproxen, or Ibuprofen

Grant W. Reed, MD, MSc,[a,b] Mouin S. Abdallah, MD, MSc,[a,b] Mingyuan Shao, MS,[a] Kathy Wolski, MPH,[a] Lisa Wisniewski, RN,[a] Neville Yeomans, MD,[c] Thomas F. Lüscher, MD,[d] Jeffrey S. Borer, MD,[e] David Y. Graham, MD,[f] M. Elaine Husni, MD, MPH,[g] Daniel H. Solomon, MD, MPH,[h] Peter Libby, MD,[h] Venu Menon, MD,[a,b] A. Michael Lincoff, MD,[a,b] Steven E. Nissen, MD[a,b]

FIGURE 1 Outcomes in Non-Aspirin Users on Naproxen or Ibuprofen Compared With Celecoxib

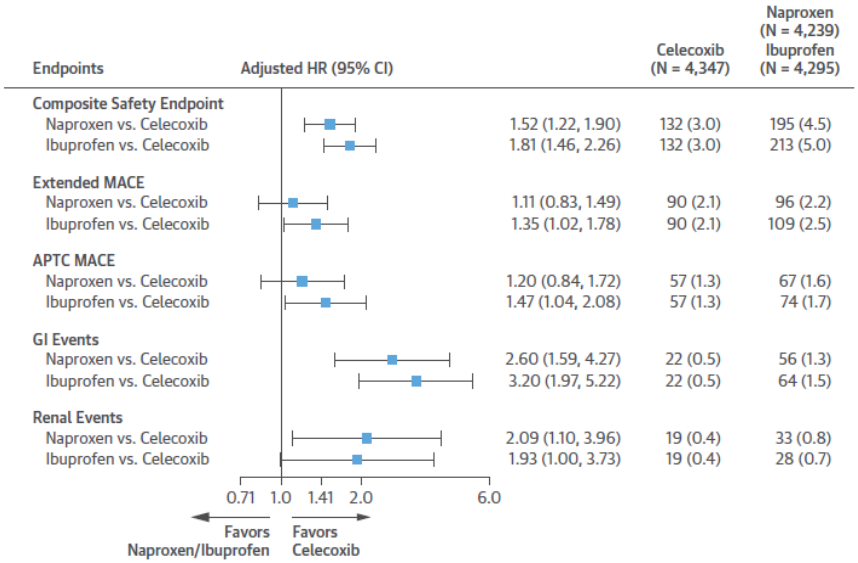
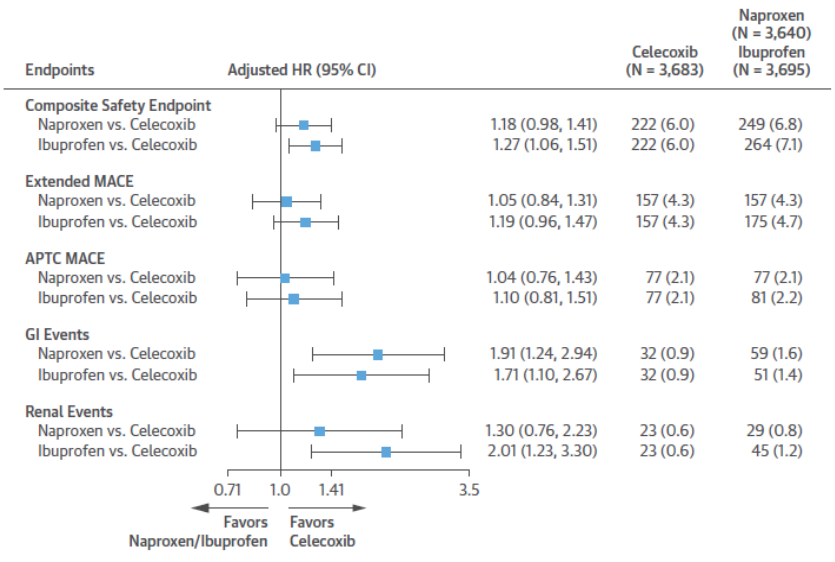


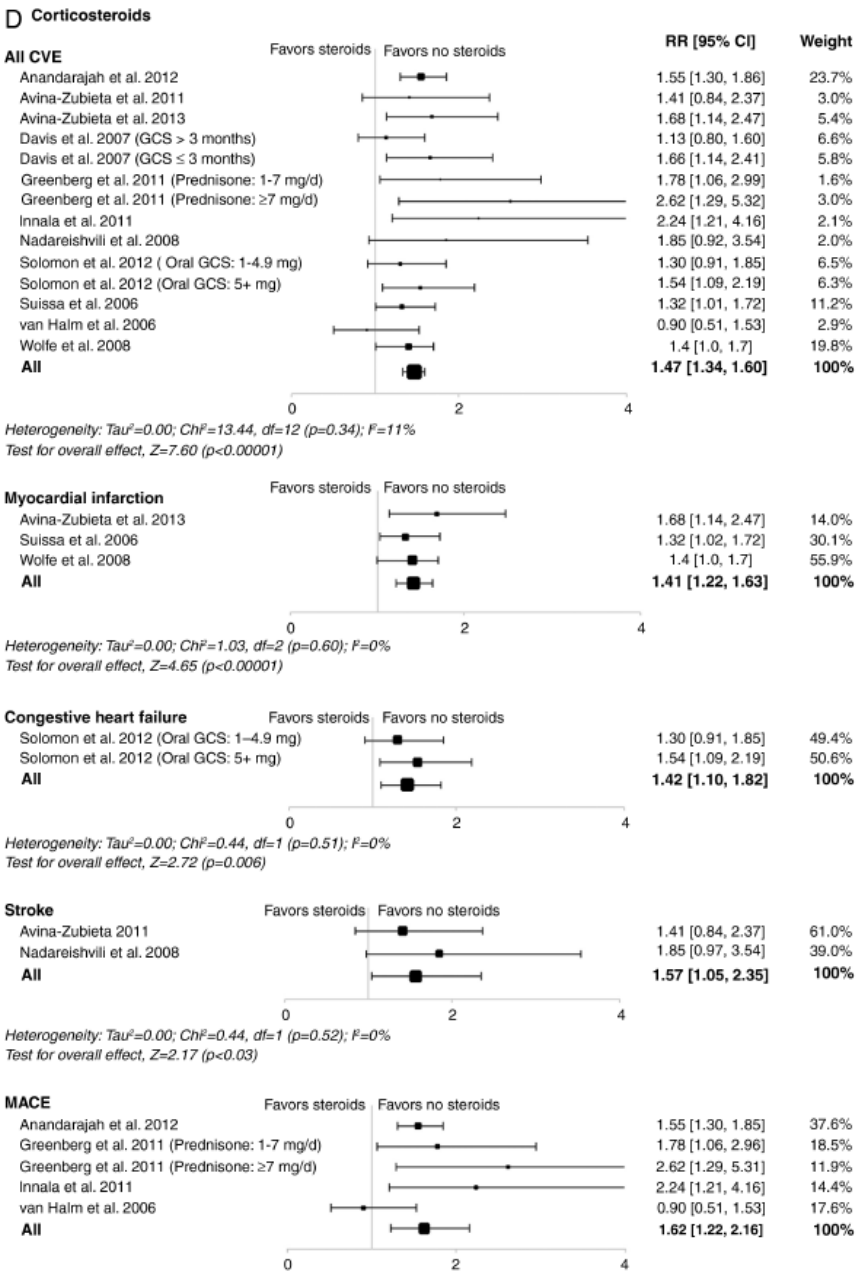
FIGURE 3 Outcomes in Patients on Naproxen or Ibuprofen Compared With Celecoxib, With Combined Aspirin



Κορτικοειδή

- Τα κορτικοστεροειδή μειώνουν τη φλεγμονή στη Ρευματοειδή Αρθρίτιδα ταχέως και αποτελεσματικά

- Αλλά συνολικά αυξάνουν τον καρδιαγγειακό κίνδυνο



Roubille C, *et al. Ann Rheum Dis* 2015;**74**:480–489. doi:10.1136/annrheumdis-2014-206624

Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study

J. Antonio Aviña-Zubieta[1,2,3], Michal Abrahamowicz[4], Mary A. De Vera[2], Hyon K. Choi[2,3], Eric C. Sayre[2], M. Mushfiqur Rahman[2], Marie-Pierre Sylvestre[4,5], Willy Wynant[4], John M. Esdaile[1,2,3,6] and Diane Lacaille[1,2,3]

Model	GC exposure measure	Univariable HR (95% CI)	AIC	Multivariable HR[a] (95% CI)	AIC
1	Current use (yes/no)	1.94 (1.34, 2.80)	5175.4	1.68 (1.14, 2.47)	5114.3
2	Current daily dose (5 mg)	1.17 (1.08, 1.27)	5177.8	1.14 (1.05, 1.24)	5114.9
3	Total cumulative duration of use (year)	1.22 (1.09, 1.37)	5176.4	1.14 (1.00, 1.29)	5116.9
4	Total past cumulative dose (1 g)	1.08 (1.04, 1.11)	5172.9	1.06 (1.02, 1.10)	5113.6
5	Current daily dose (5 mg)	1.14 (1.04, 1.26)	5173.6	1.13 (1.03, 1.24)	5114.9
	+Cumulative duration, year	1.18 (1.04, 1.33)		1.10 (0.97, 1.26)	

Rheumatology 2013;52:68–75
doi:10.1093/rheumatology/kes353

Multicenter Study > Arthritis Rheumatol. 2014 Feb;66(2):264-72. doi: 10.1002/art.38210.

Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis

Inmaculada del Rincón [1], Daniel F Battafarano, Jose F Restrepo, John M Erikson, Agustín Escalante

Table 2. Daily and cumulative glucocorticoid dose thresholds for death from all causes and death from CV causes, adjusted for the propensity to receive glucocorticoids*

Glucocorticoid exposure	All-cause mortality				CV mortality			
	No. of deaths	No. of person-years	HR (95% CI), adjusted for glucocorticoid propensity		No. of deaths	No. of person-years	HR (95% CI), adjusted for glucocorticoid propensity	
			Unadjusted	Adjusted			Unadjusted	Adjusted
Daily dose								
None	95	3,912	1.0 (referent)	1.0 (referent)	48	3,646	1.0 (referent)	1.0 (referent)
<5 mg	22	647	1.38 (0.87–2.20)	1.19 (0.74–1.90)	16	585	2.07 (1.17–3.65)†	1.82 (1.03–3.22)
5–7 mg	69	1,876	1.51 (1.11–2.06)	1.21 (0.88–1.66)	28	1,647	1.28 (0.80–2.05)	1.07 (0.67–1.72)
8–15 mg	42	676	2.58 (1.79–3.71)	1.78 (1.22–2.60)	24	575	3.17 (1.94–5.17)	2.27 (1.36–3.79)
≥15 mg	9	91	3.98 (2.01–7.90)	2.83 (1.41–5.66)	4	72	4.08 (1.47–11.32)	3.21 (1.14–8.97)
Cumulative dose								
None	61	2,535	1.0 (referent)	1.0 (referent)	31	2,372	1.0 (referent)	1.0 (referent)
<9 gm	23	1,498	0.63 (0.39–1.03)	0.59 (0.36–0.95)	14	1,430	0.95 (0.47–1.95)	0.70 (0.37–1.31)
9–39.9 gm	50	1,495	1.38 (0.95–2.01)	1.12 (0.76–1.64)	23	1,323	0.93 (0.45–1.87)	1.08 (0.63–1.88)
≥40 gm	103	1,675	2.46 (1.78–3.39)	1.74 (1.25–2.44)	52	1,398	2.32 (1.36–3.96)	2.05 (1.29–3.27)
Dose/time								
None	61	2,535	1.0 (referent)	1.0 (referent)	31	2,372	1.0 (referent)	1.0 (referent)
<1.98 gm/year	20	1,592	0.51 (0.30–0.85)	0.48 (0.29–0.80)	13	1,529	0.62 (0.32–1.20)	0.60 (0.31–1.16)
1.98–5.08 gm/year	48	1,615	1.23 (0.84–1.80)	0.99 (0.67–1.45)	23	1,405	1.26 (0.73–2.16)	1.04 (0.60–1.81)
≥5.08 gm/year	108	1,460	2.93 (2.14–4.03)	2.11 (1.51–2.94)	53	1,217	3.12 (1.99–4.88)	2.35 (1.48–3.75)

DMARDs

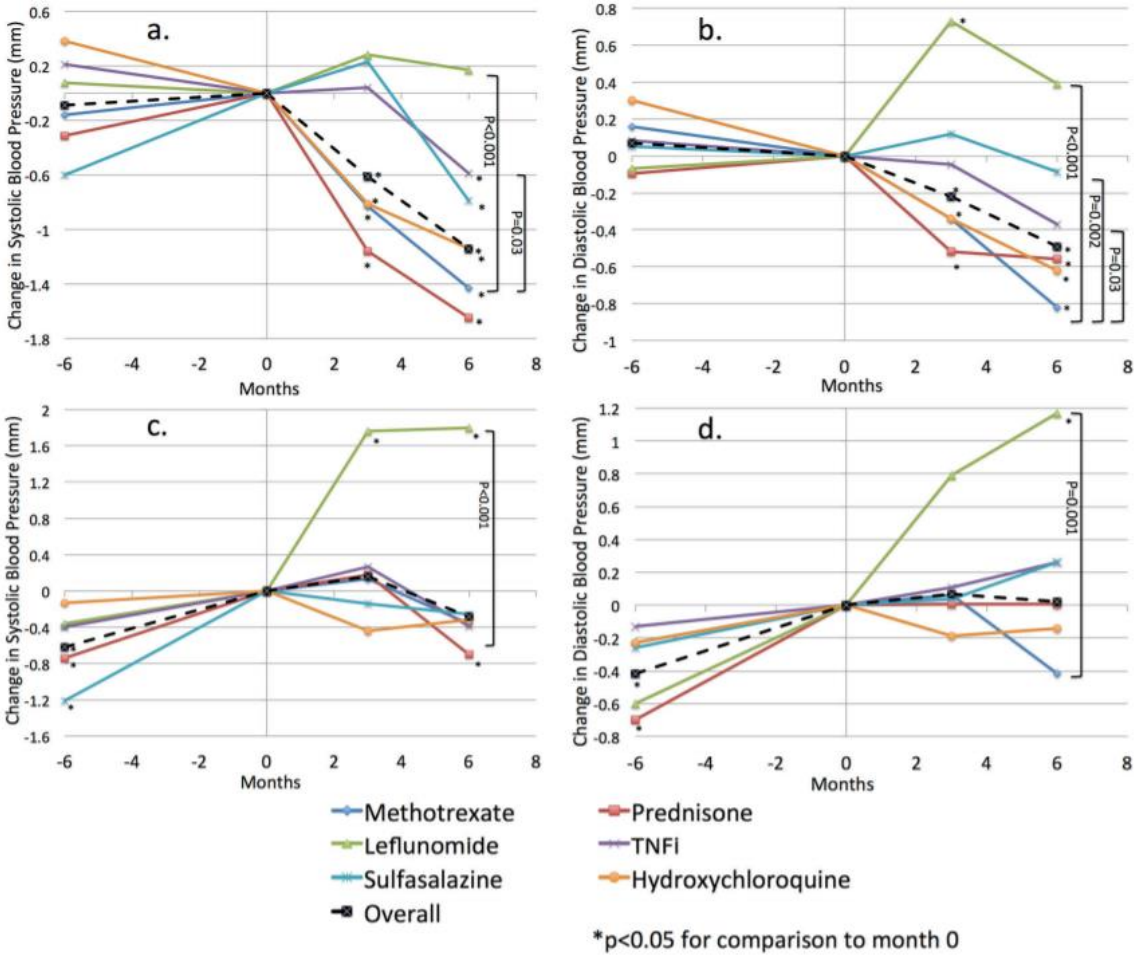
- **Μεθοτρεξάτη**
  - Αυξάνει την παραγωγή ομοκυστεΐνης
- **Λεφλουνομίδη**
  - Αύξηση αρτηριακής πίεσης
- **Κυκλοσπορίνη**
  - Αύξηση αρτηριακής πίεσης

- ***Αλλά….***

J Clin Rheumatol. 2018 Jun;24(4):203-209. doi: 10.1097/RHU.0000000000000736.

Initiation of Disease-Modifying Therapies in Rheumatoid Arthritis Is Associated With Changes in Blood Pressure

Joshua F Baker, Brian Sauer [1], Chia-Chen Teng [1], Michael George [2], Grant W Cannon [1], Said Ibrahim [3], Amy Cannella [4], Bryant R England [4], Kaleb Michaud [5], Liron Caplan [6], Lisa A Davis [6], James O'Dell [7], Ted R Mikuls [7]



- Η κυκλοσπορίνη αυξάνει την αρτηριακή πίεση με δοσοεξαρτώμενο τρόπο

Review > Lupus. 2018 Apr;27(4):591-599. doi: 10.1177/0961203317734922. Epub 2017 Oct 9.

Antimalarial-induced cardiomyopathy: a systematic review of the literature

K Tselios [1], M Deeb [1], D D Gladman [1], P Harvey [2], M B Urowitz [1]

- Σπάνια επιπλοκή μακροχρόνιας χορήγησης ανθελονοσιακών
- Υπερτροφική περιοριστική καρδιομυοπάθεια με ή χωρίς διαταραχές αγωγιμότητας
- Έγκαιρη αναγνώριση και απόσυρση του φαρμάκου οδηγεί σε επιβίωση 55%

«Βιολογικοί» παράγοντες

- bDMARDs
  - Anti-TNF
  - Non- anti-TNF
- tsDMARDs

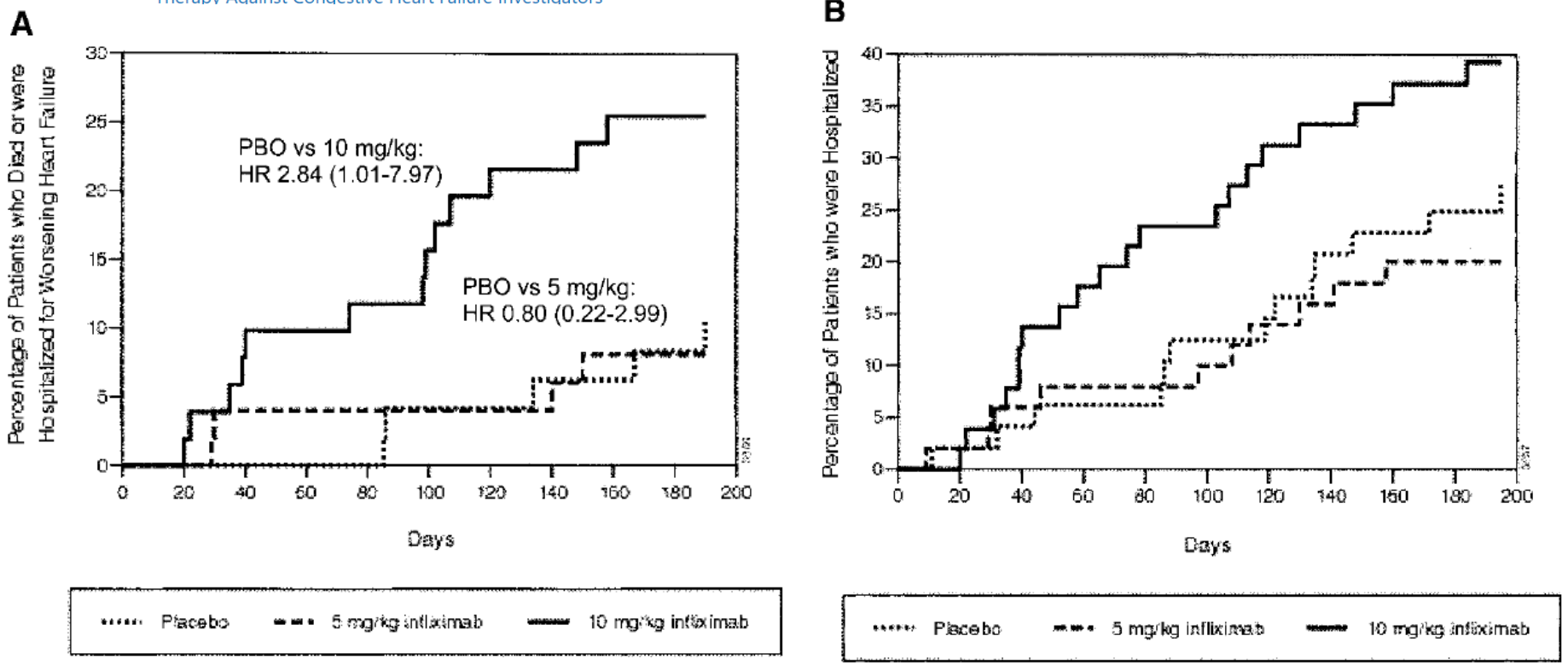
Anti-TNF

- Η καρδιαγγειακή κατάσταση του ασθενούς καθοριστικός παράγοντας για το αποτέλεσμα των anti-TNFα παραγόντων

Clinical Trial > Circulation. 2003 Jul 1;107(25):3133-40. doi: 10.1161/01.CIR.0000077913.60364.D2. Epub 2003 Jun 9.

Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial

Eugene S Chung [1], Milton Packer, Kim Hung Lo, Adedigbo A Fasanmade, James T Willerson, Anti-TNF Therapy Against Congestive Heart Failure Investigators



Clinical Trial > Circulation. 2004 Apr 6;109(13):1594-602.
doi: 10.1161/01.CIR.0000124490.27666.B2. Epub 2004 Mar 15.

Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL)

Douglas L Mann [1], John J V McMurray, Milton Packer, Karl Swedberg, Jeffrey S Borer, Wilson S Colucci, Jacques Djian, Helmut Drexler, Arthur Feldman, Lars Kober, Henry Krum, Peter Liu, Markku Nieminen, Luigi Tavazzi, Dirk Jan van Veldhuisen, Anders Waldenstrom, Marshelle Warren, Arne Westheim, Faiez Zannad, Thomas Fleming

- Χωρίς όφελος στην πιθανότητα θανάτου ή νοσηλείας λόγω απορρύθμισης καρδιακής ανεπάρκειας η χορήγηση Etanercept σε ασθενείς με καρδιακή ανεπάρκεια

American Heart Journal
Volume 156, Issue 2, August 2008, Pages 336-341

Clinical Investigation
Congestive Heart Failure

Tumor necrosis factor-α antagonist use and heart failure in elderly patients with rheumatoid arthritis

Soko Setoguchi MD, DrPH [a], Sebastian Schneeweiss MD, ScD [a], Jerry Avorn MD [a], Jeffrey N. Katz MD, MSc [b], Michael E. Weinblatt MD [b], Raisa Levin MS [a], Daniel H. Solomon MD, MPH [a, b]

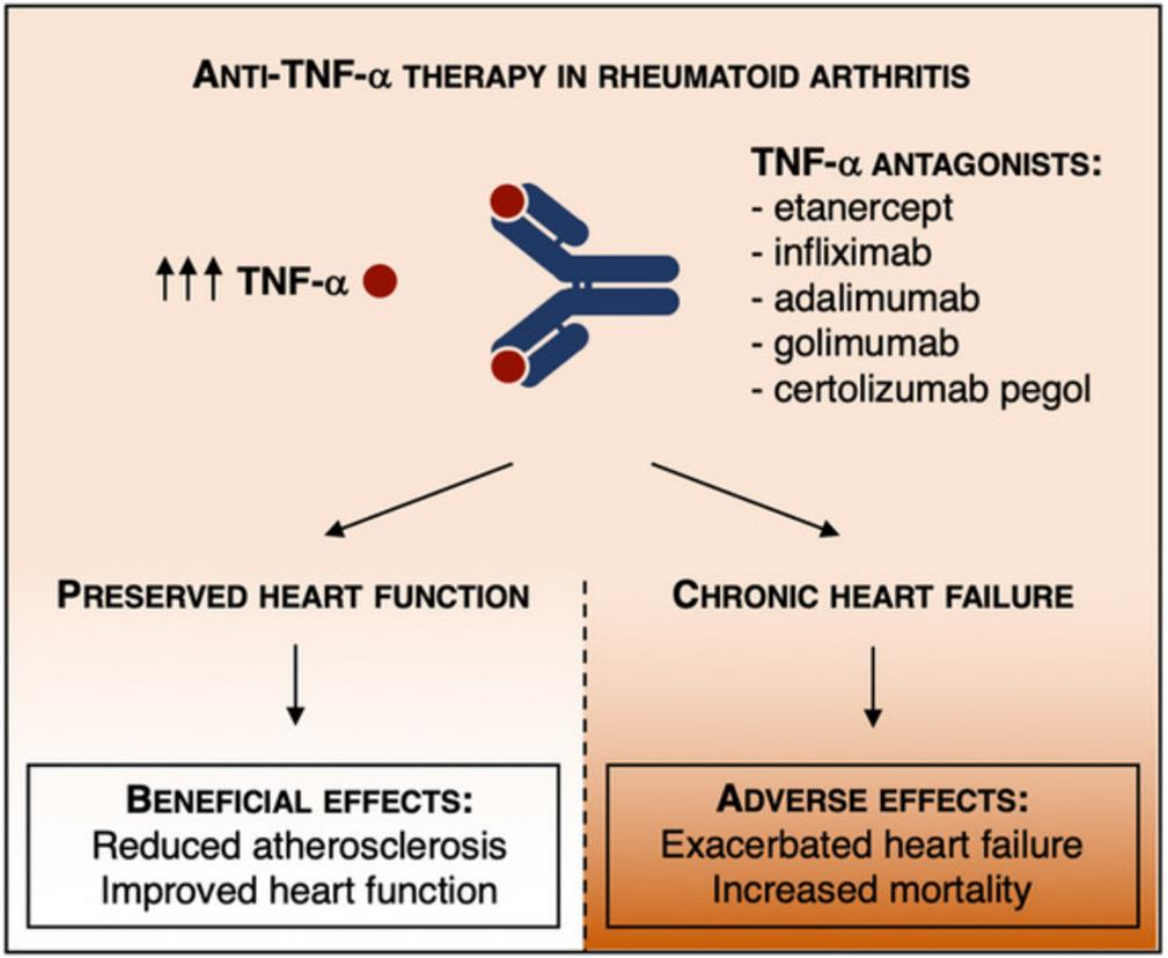
Table II. Number of HF admissions, person-years, and incidence rate of HF admission in study patients with and without previous history of HF (n = 5593)

	TNFA users			MTX users		
	No. of cases	Person-years	Incidence rate	No. of cases	Person-years	Incidence rate
Patients with previous HF (n = 1033)	33	304	108	101	1333	76
Patients with no HF (n = 4560)	26	1375	19	126	9290	14
2 groups combined	59	1680	35	227	10623	21

Incidence rates are per 1,000 person-years.

Table III. Effects of TNFAs compared to MTX on HF and/or death

	With previous HF (n = 1033)			Without previous HF (n = 4560)			2 groups combined (n = 5876)		
	HR	95% CI		HR	95% CI		HR	95% CI	
Unadjusted *	1.33	0.79	2.26	1.67	0.92	3.01	1.73	1.19	2.51
Sex, age, and race adjusted †	1.36	0.80	2.33	1.78	0.98	3.26	1.91	1.31	2.80
Fully adjusted ‡	1.75	0.86	3.56	2.07	1.00	4.25	1.70	1.07	2.69
Fully adjusted ‡ with follow-up ending October 2001(n = 3671)	1.50	0.41	4.79	3.41	0.73	16.05	1.61	0.75	3.49



(Blyszczuk and Szekanecz 2020)

Tocilizumab

- Αύξηση ολικής χοληστερόλης , HDL, LDL και τριγλυκεριδίων

- ***Αλλά…***

JAKinibs

- Tofacitinib και Baricitinib επιδεινώνουν το λιπιδαιμικό προφίλ
- Αναστροφή των μεταβολών αυτών με τη λήψη ατορβαστατίνης σε ασθενείς που έλαβαν tofacitinib
- Δεν αυξάνουν τον καρδιαγγειακό κίνδυνο
- Alert για τον κίνδυνο θρομβοεμβολικών επεισοδίων

Charles-Schoeman C, Wicker P, Gonzalez-Gay MA, Boy M, Zuckerman A, Soma K, et al. Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor. Semin Arthritis Rheum. 2016;46(3):261–71.

Taylor PC, Weinblatt ME, Burmester GR, Rooney TP, Witt S, Walls CD, et al. Cardiovascular safety during treatment with baricitinib in rheumatoid arthritis. Arthritis Rheumatol (Hoboken, NJ). 2019;71(7):1042–55.

Effect of tofacitinib on cardiovascular events and all-cause mortality in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis of randomized controlled trials

Ther Adv Musculoskel Dis

2019, Vol. 11: 1–18

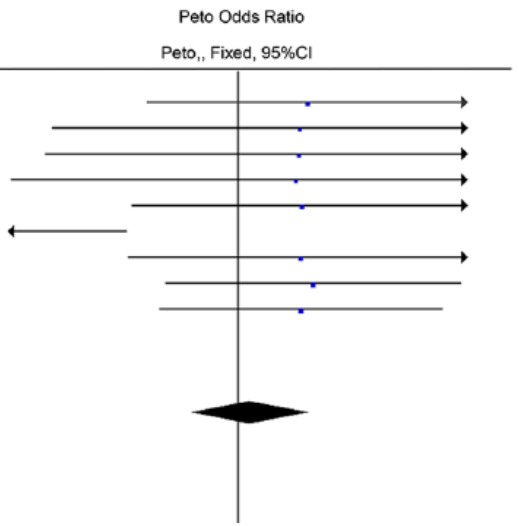
DOI: 10.1177/1759720X19895492

Wenhui Xie, Shiyu Xiao, Yanrong Huang, Xiaoying Sun and Zhuoli Zhang

Tofacitinib vs Placebo

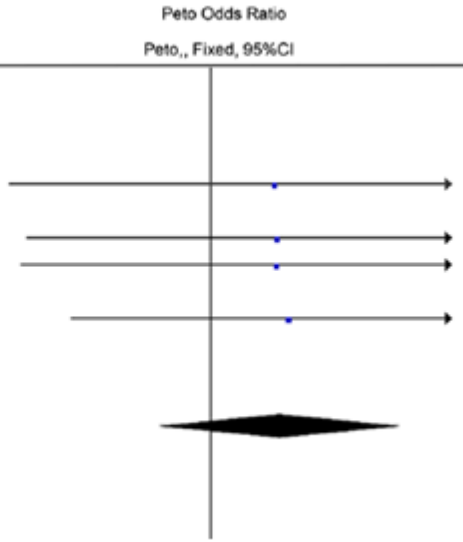
All CVEs	Tofacitinib Events	P-Y	Placebo Events	P-Y	Weight	Peto Odds Ratio Peto,, Fixed, 95%CI	Year
1.1.1 Rheumatoid Arthritis							
Kremer JM 2009	2	23	0	8	5.8%	4.03 [0.16, 101.06]	2009
Tanaka Y 2011	1	25	0	6	2.5%	3.46 [0.02, 493.21]	2011
Fleischmann R 2012	1	63	0	14	2.3%	3.39 [0.02, 546.68]	2012
Kremer JM 2012	1	101	0	16	1.9%	3.18 [0.01, 956.10]	2012
van Vollenhoven RF ORAL Standard 2012	2	93	0	25	5.2%	3.60 [0.12, 108.41]	2012
Fleischmann R ORAL Solo 2012	0	112	3	28	7.5%	0.01 [0.00, 0.11]	2012
Kremer JM ORAL Sync 2013	2	146	0	37	5.1%	3.53 [0.11, 112.23]	2013
Burmester GR ORAL Step 2013	2	61	0	30	6.9%	4.52 [0.23, 87.64]	2013
van der Heijde D ORAL Scan 2013	3	147	0	37	7.5%	3.54 [0.21, 60.60]	2013
Tanaka Y 2015	0	61	0	12		Not estimable	2015
Conaghan PG 2016	0	36	0	37		Not estimable	2016
Winthrop KL 2017	0	13	0	13		Not estimable	2017
Subtotal (95% CI)		**881**		**263**	**44.7%**	**1.29 [0.40, 4.13]**	
Total events	14		3				

Heterogeneity: Chi² = 16.14, df = 8 (P = 0.04); I² = 50%
Test for overall effect: Z = 0.43 (P = 0.67)

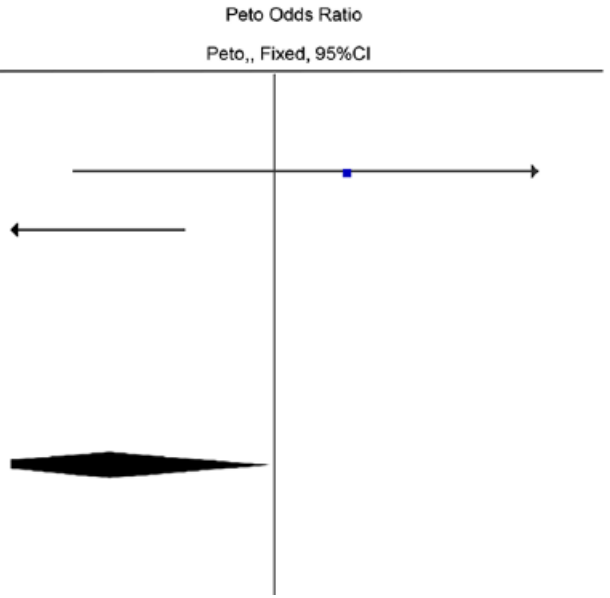


Tofacitinib vs Placebo

MACEs	Tofacitinib Events	Tofacitinib P-Y	Placebo Events	Placebo P-Y	Weight	Peto Odds Ratio Peto,, Fixed, 95%CI	Year
1.2.1 Rheumatoid Arthritis							
Kremer JM 2009	0	23	0	8		Not estimable	2009
Tanaka Y 2011	0	25	0	6		Not estimable	2011
Kremer JM 2012	0	101	0	16		Not estimable	2012
Fleischmann R 2012	1	63	0	14	6.4%	3.39 [0.02, 546.68]	2012
Fleischmann R ORAL Solo 2012	0	112	0	28		Not estimable	2012
van Vollenhoven RF ORAL Standard 2012	1	93	0	25	7.2%	3.56 [0.03, 430.63]	2012
Kremer JM ORAL Sync 2013	1	146	0	37	7.0%	3.50 [0.03, 461.02]	2013
van der Heijde D ORAL Scan 2013	0	147	0	37		Not estimable	2013
Burmester GR ORAL Step 2013	1	61	0	30	9.5%	4.45 [0.07, 287.47]	2013
Tanaka Y 2015	0	61	0	12		Not estimable	2015
Conaghan PG 2016	0	36	0	37		Not estimable	2016
Winthrop KL 2017	0	13	0	13		Not estimable	2017
Subtotal (95% CI)		**881**		**263**	**30.2%**	**3.77 [0.36, 39.32]**	
Total events	4		0				
Heterogeneity: Chi² = 0.01, df = 3 (P = 1.00); I² = 0%							
Test for overall effect: Z = 1.11 (P = 0.27)							



VTEs	Tofacitinib Events	Tofacitinib P-Y	Placebo Events	Placebo P-Y	Weight	Peto Odds Ratio Peto,, Fixed, 95%CI	Year
1.3.1 Rheumatoid Arthritis							
Kremer JM 2009	0	23	0	8		Not estimable	2009
Tanaka Y 2011	0	25	0	6		Not estimable	2011
van Vollenhoven RF ORAL Standard 2012	1	93	0	25	16.0%	3.56 [0.03, 430.63]	2012
Kremer JM 2012	0	101	0	16		Not estimable	2012
Fleischmann R ORAL Solo 2012	0	112	2	28	30.4%	0.01 [0.00, 0.21]	2012
Fleischmann R 2012	0	63	0	14		Not estimable	2012
van der Heijde D ORAL Scan 2013	0	147	0	37		Not estimable	2013
Kremer JM ORAL Sync 2013	0	146	0	37		Not estimable	2013
Burmester GR ORAL Step 2013	0	61	0	30		Not estimable	2013
Tanaka Y 2015	0	61	0	12		Not estimable	2015
Conaghan PG 2016	0	36	0	37		Not estimable	2016
Winthrop KL 2017	0	13	0	13		Not estimable	2017
Subtotal (95% CI)		**881**		**263**	**46.3%**	**0.06 [0.00, 0.95]**	
Total events	1		2				
Heterogeneity: Chi² = 4.35, df = 1 (P = 0.04); I² = 77%							
Test for overall effect: Z = 1.99 (P = 0.05)							

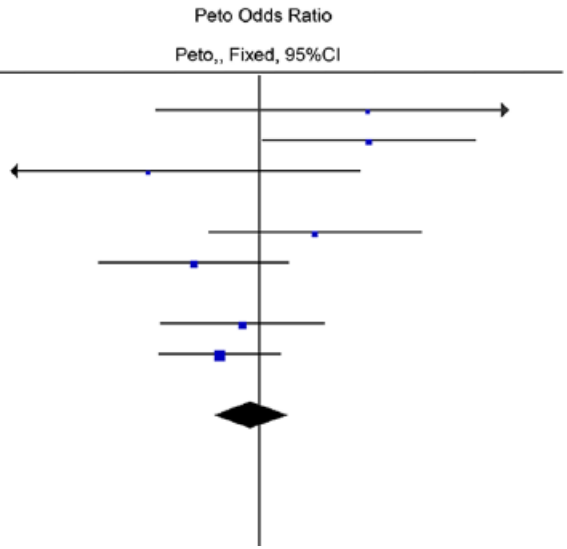


Tofacitinib 10mg vs 5mg

All CVEs	10mg Events	10mg P-Y	5mg Events	5mg P-Y	Weight	Peto Odds Ratio Peto,, Fixed, 95%CI	Year
2.1.1 Rheumatoid Arthritis							
Tanaka Y 2011	1	6	0	6	1.8%	7.39 [0.15, 372.38]	2011
Fleischmann R ORAL Solo 2012	4	113	0	112	7.3%	7.52 [1.05, 54.13]	2012
Kremer JM 2012	0	35	1	33	1.8%	0.13 [0.00, 6.43]	2012
Fleischmann R 2012	0	28	0	23		Not estimable	2012
van Vollenhoven RF ORAL Standard 2012	3	200	1	203	7.3%	2.78 [0.39, 19.88]	2012
Kremer JM ORAL Sync 2013	1	317	4	314	9.2%	0.30 [0.05, 1.72]	2013
van der Heijde D ORAL Scan 2013	0	315	0	320		Not estimable	2013
Burmester GR ORAL Step 2013	3	62	4	61	12.3%	0.73 [0.16, 3.33]	2013
Lee EB 2014	4	792	8	744	22.0%	0.48 [0.15, 1.49]	2014
Tanaka Y 2015	0	12	0	12		Not estimable	2015
Subtotal (95% CI)		**1880**		**1828**	**61.7%**	**0.86 [0.44, 1.70]**	
Total events	16		18				

Heterogeneity: Chi² = 10.55, df = 6 (P = 0.10); I² = 43%

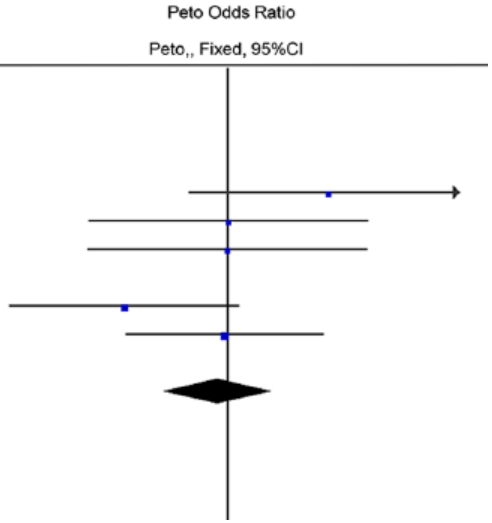
Test for overall effect: Z = 0.43 (P = 0.67)



MACEs	10mg Events	10mg P-Y	5mg Events	5mg P-Y	Weight	Peto Odds Ratio Peto,, Fixed, 95%CI	Year
2.3.1 Rheumatoid Arthritis							
Tanaka Y 2011	0	6	0	6		Not estimable	2011
Fleischmann R 2012	0	28	0	23		Not estimable	2012
Kremer JM 2012	0	35	0	33		Not estimable	2012
Fleischmann R ORAL Solo 2012	2	113	0	112	8.0%	7.39 [0.46, 118.88]	2012
van Vollenhoven RF ORAL Standard 2012	1	200	1	203	8.0%	1.02 [0.06, 16.29]	2012
Kremer JM ORAL Sync 2013	1	317	1	314	8.0%	0.99 [0.06, 15.87]	2013
van der Heijde D ORAL Scan 2013	0	315	0	320		Not estimable	2013
Burmester GR ORAL Step 2013	0	62	3	61	11.9%	0.13 [0.01, 1.26]	2013
Lee EB 2014	2	792	2	744	16.0%	0.94 [0.13, 6.69]	2014
Tanaka Y 2015	0	12	0	12		Not estimable	2015
Subtotal (95% CI)		**1880**		**1828**	**52.0%**	**0.84 [0.28, 2.49]**	
Total events	6		7				

Heterogeneity: Chi² = 4.99, df = 4 (P = 0.29); I² = 20%

Test for overall effect: Z = 0.32 (P = 0.75)

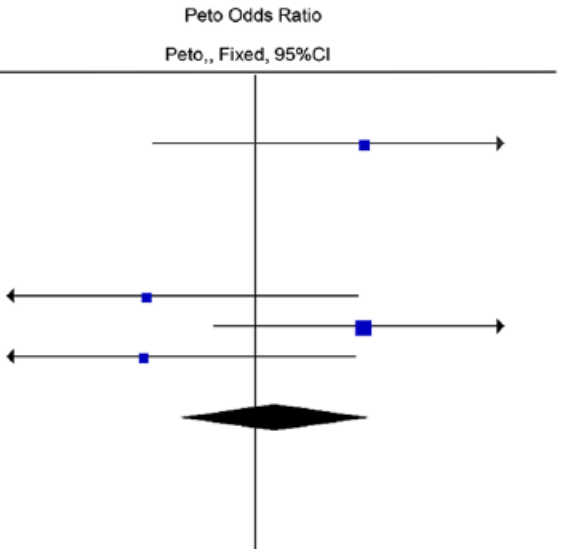


Tofacitinib 10mg vs 5mg

VTEs	10mg Events	10mg P-Y	5mg Events	5mg P-Y	Weight	Peto Odds Ratio Peto,, Fixed, 95%CI	Year
2.4.1 Rheumatoid Arthritis							
Tanaka Y 2011	0	6	0	6		Not estimable	2011
van Vollenhoven RF ORAL Standard 2012	1	200	0	203	20.1%	7.50 [0.15, 378.05]	2012
Fleischmann R ORAL Solo 2012	0	113	0	112		Not estimable	2012
Kremer JM 2012	0	35	0	33		Not estimable	2012
Fleischmann R 2012	0	28	0	23		Not estimable	2012
van der Heijde D ORAL Scan 2013	0	315	0	320		Not estimable	2013
Kremer JM ORAL Sync 2013	0	317	1	314	20.1%	0.13 [0.00, 6.76]	2013
Burmester GR ORAL Step 2013	2	62	0	61	39.8%	7.39 [0.46, 119.53]	2013
Lee EB 2014	0	792	1	744	20.1%	0.13 [0.00, 6.41]	2014
Tanaka Y 2015	0	12	0	12		Not estimable	2015
Subtotal (95% CI)		**1880**		**1828**	**100.0%**	**1.47 [0.25, 8.50]**	
Total events	3		2				

Heterogeneity: Chi² = 4.89, df = 3 (P = 0.18); I² = 39%

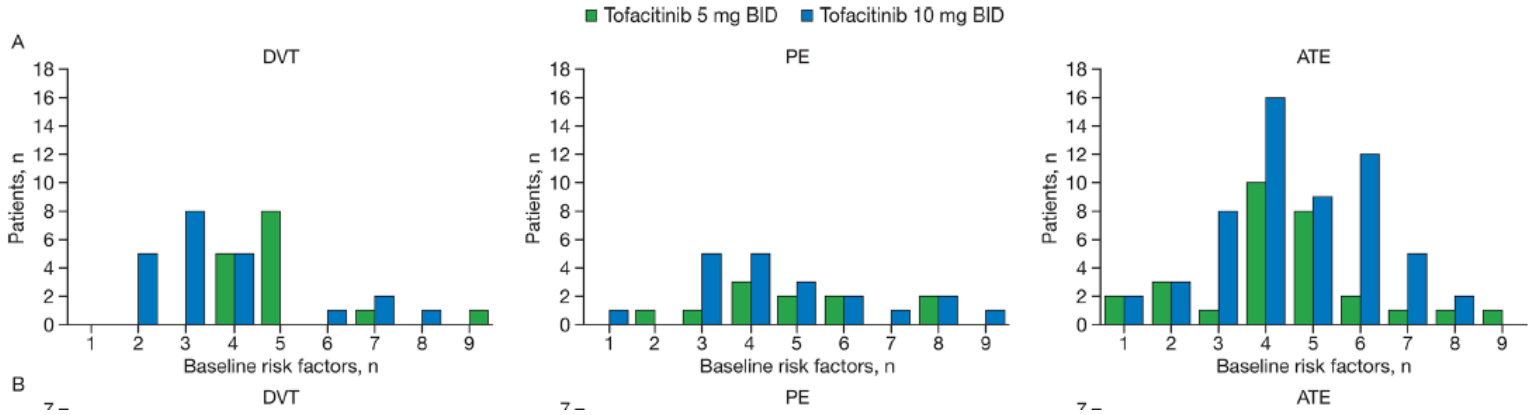
Test for overall effect: Z = 0.43 (P = 0.67)



Ann Rheum Dis. 2020 Nov;79(11):1400-1413. doi: 10.1136/annrheumdis-2019-216761. Epub 2020 Aug 5.

Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data

Philip Mease [1], Christina Charles-Schoeman [2], Stanley Cohen [3], Lara Fallon [4], John Woolcott [5], Huifeng Yun [6], Joel Kremer [7], Jeffrey Greenberg [8], Wendi Malley [8], Alina Onofrei [8], Keith S Kanik [9], Daniela Graham [9], Cunshan Wang [10], Carol Connell [11], Hernan Valdez [12], Manfred Hauben [13] [14], Eric Hung [13], Ann Madsen [15], Thomas V Jones [16], Jeffrey R Curtis [17]

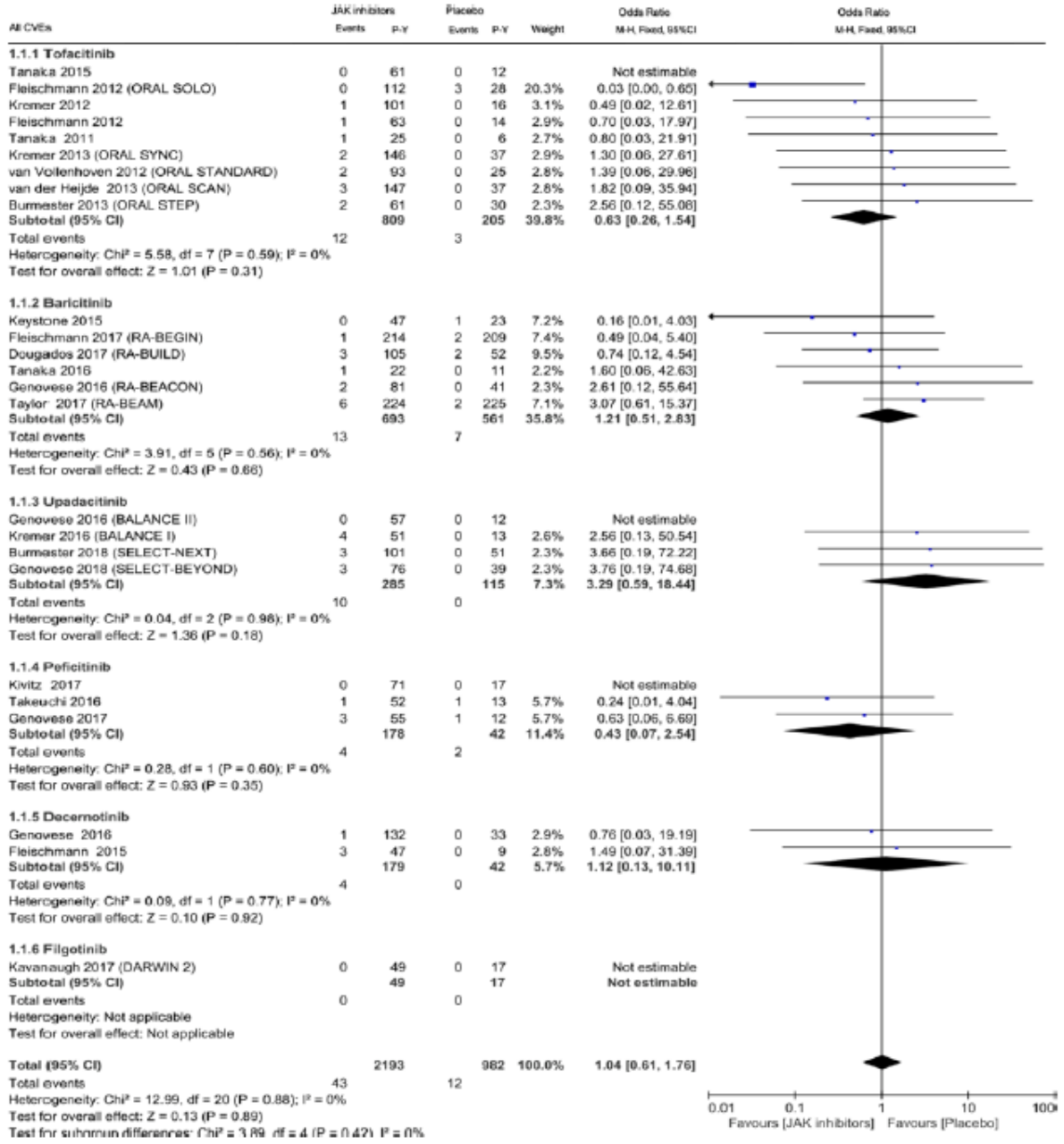


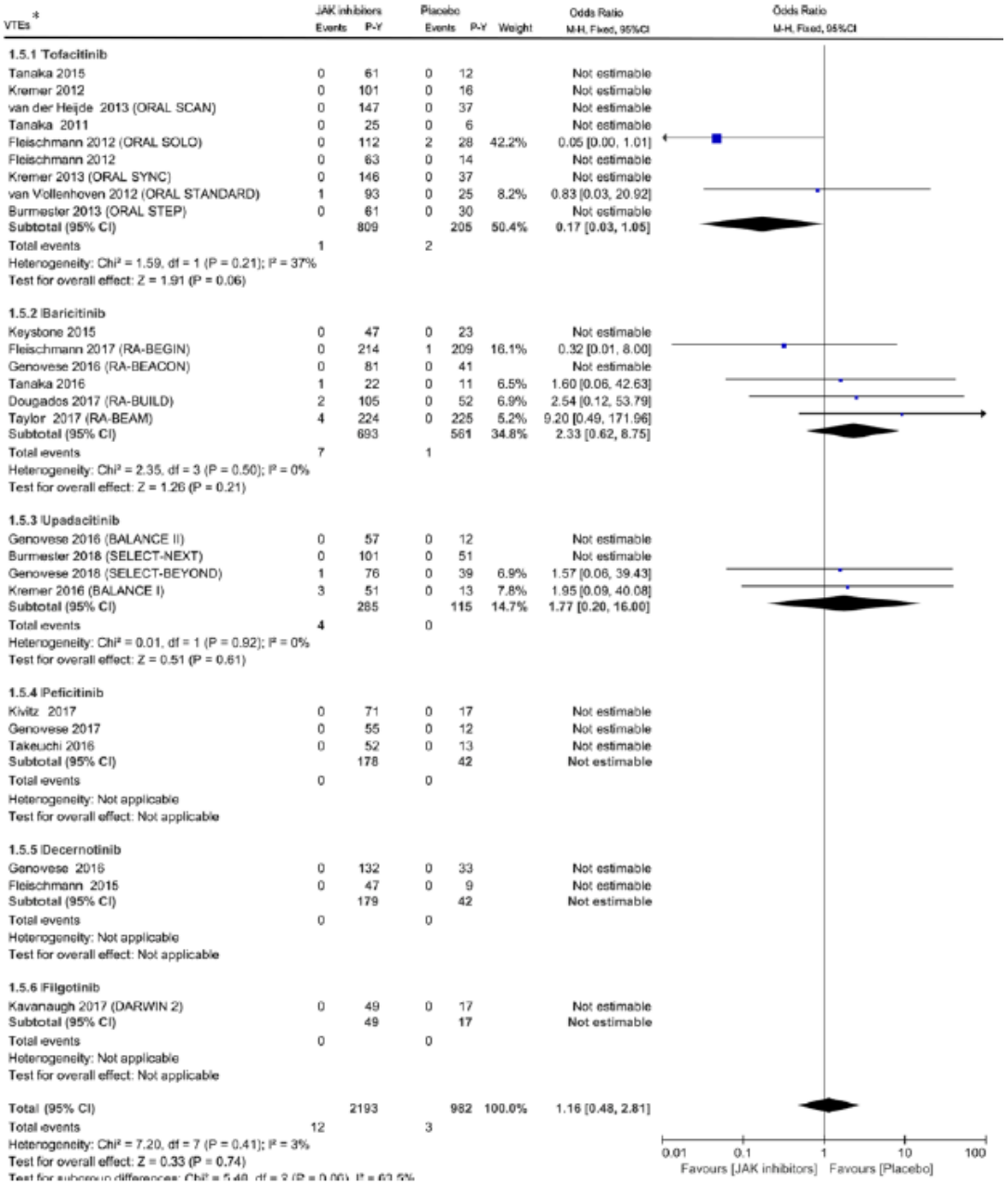
Meta-Analysis > Ann Rheum Dis. 2019 Aug;78(8):1048-1054.
doi: 10.1136/annrheumdis-2018-214846. Epub 2019 May 14.

Impact of Janus kinase inhibitors on risk of cardiovascular events in patients with rheumatoid arthritis: systematic review and meta-analysis of randomised controlled trials

Wenhui Xie [1], Yanrong Huang [1], Shiyu Xiao [2], Xiaoying Sun [1], Yong Fan [1], Zhuoli Zhang [3]

- 26 RCTs -11799 ασθενείς
- Χωρίς στατιστικά σημαντική διαφορά για όλα τα καρδιαγγειακά συμβάντα, τα μείζονα καρδιαγγειακά και τα θρομβοεμβολικά επεισόδια για το σύνολο των αναστολέων JAK, το tofacitinib, το baricitinib, το upadacitinib, το peficotinib, το decernotinib
- Δοσοεξαρτώμενες διαφορές που αφορούν την ασφάλεια του baricitinib: τα 2mg ασφαλέστερα για το σύνολο των καρδιαγγειακών συμβάντων


All CVEs
JAK inhibitors
Events P-Y
Placebo
Events P-Y
Weight
Odds Ratio
M-H, Fixed, 95%CI
Odds Ratio
M-H, Fixed, 95%CI
1.1.1 Tofacitinib
Tanaka 2015 0 61 0 12 Not estimable
Fleischmann 2012 (ORAL SOLO) 0 112 3 28 20.3% 0.03 [0.00, 0.65]
Kremer 2012 1 101 0 16 3.1% 0.49 [0.02, 12.61]
Fleischmann 2012 1 63 0 14 2.9% 0.70 [0.03, 17.97]
Tanaka 2011 1 25 0 6 2.7% 0.80 [0.03, 21.91]
Kremer 2013 (ORAL SYNC) 2 146 0 37 2.9% 1.30 [0.06, 27.61]
van Vollenhoven 2012 (ORAL STANDARD) 2 93 0 25 2.8% 1.39 [0.06, 29.96]
van der Heijde 2013 (ORAL SCAN) 3 147 0 37 2.8% 1.82 [0.09, 35.94]
Burmester 2013 (ORAL STEP) 2 61 0 30 2.3% 2.56 [0.12, 55.08]
Subtotal (95% CI) 809 205 39.8% 0.63 [0.26, 1.54]
Total events 12 3
Heterogeneity: Chi² = 5.58, df = 7 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)
1.1.2 Baricitinib
Keystone 2015 0 47 1 23 7.2% 0.16 [0.01, 4.03]
Fleischmann 2017 (RA-BEGIN) 1 214 2 209 7.4% 0.49 [0.04, 5.40]
Dougados 2017 (RA-BUILD) 3 105 2 52 9.5% 0.74 [0.12, 4.54]
Tanaka 2016 1 22 0 11 2.2% 1.60 [0.06, 42.63]
Genovese 2016 (RA-BEACON) 2 81 0 41 2.3% 2.61 [0.12, 55.64]
Taylor 2017 (RA-BEAM) 6 224 2 225 7.1% 3.07 [0.61, 15.37]
Subtotal (95% CI) 693 561 35.8% 1.21 [0.51, 2.83]
Total events 13 7
Heterogeneity: Chi² = 3.91, df = 5 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.66)
1.1.3 Upadacitinib
Genovese 2016 (BALANCE II) 0 57 0 12 Not estimable
Kremer 2016 (BALANCE I) 4 51 0 13 2.6% 2.56 [0.13, 50.54]
Burmester 2018 (SELECT-NEXT) 3 101 0 51 2.3% 3.66 [0.19, 72.22]
Genovese 2018 (SELECT-BEYOND) 3 76 0 39 2.3% 3.76 [0.19, 74.68]
Subtotal (95% CI) 285 115 7.3% 3.29 [0.59, 18.44]
Total events 10 0
Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.36 (P = 0.18)
1.1.4 Peficitinib
Kivitz 2017 0 71 0 17 Not estimable
Takeuchi 2016 1 52 1 13 5.7% 0.24 [0.01, 4.04]
Genovese 2017 3 55 1 12 5.7% 0.63 [0.06, 6.69]
Subtotal (95% CI) 178 42 11.4% 0.43 [0.07, 2.54]
Total events 4 2
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
1.1.5 Decernotinib
Genovese 2016 1 132 0 33 2.9% 0.76 [0.03, 19.19]
Fleischmann 2015 3 47 0 9 2.8% 1.49 [0.07, 31.39]
Subtotal (95% CI) 179 42 5.7% 1.12 [0.13, 10.11]
Total events 4 0
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
1.1.6 Filgotinib
Kavanaugh 2017 (DARWIN 2) 0 49 0 17 Not estimable
Subtotal (95% CI) 49 17 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Total (95% CI) 2193 982 100.0% 1.04 [0.61, 1.76]
Total events 43 12
Heterogeneity: Chi² = 12.99, df = 20 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.89)
Test for subgroup differences: Chi² = 3.89, df = 4 (P = 0.42), I² = 0%
0.01 0.1 1 10 100
Favours [JAK inhibitors] Favours [Placebo]


VTEs *
JAK inhibitors Events P-Y
Placebo Events P-Y
Weight
Odds Ratio M-H, Fixed, 95%CI
Odds Ratio M-H, Fixed, 95%CI
1.5.1 Tofacitinib
Tanaka 2015 0 61 0 12 Not estimable
Kremer 2012 0 101 0 16 Not estimable
van der Heijde 2013 (ORAL SCAN) 0 147 0 37 Not estimable
Tanaka 2011 0 25 0 6 Not estimable
Fleischmann 2012 (ORAL SOLO) 0 112 2 28 42.2% 0.05 [0.00, 1.01]
Fleischmann 2012 0 63 0 14 Not estimable
Kremer 2013 (ORAL SYNC) 0 146 0 37 Not estimable
van Vollenhoven 2012 (ORAL STANDARD) 1 93 0 25 8.2% 0.83 [0.03, 20.92]
Burmester 2013 (ORAL STEP) 0 61 0 30 Not estimable
Subtotal (95% CI) 809 205 50.4% 0.17 [0.03, 1.05]
Total events 1 2
Heterogeneity: Chi² = 1.59, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 1.91 (P = 0.06)
1.5.2 Baricitinib
Keystone 2015 0 47 0 23 Not estimable
Fleischmann 2017 (RA-BEGIN) 0 214 1 209 16.1% 0.32 [0.01, 8.00]
Genovese 2016 (RA-BEACON) 0 81 0 41 Not estimable
Tanaka 2016 1 22 0 11 6.5% 1.60 [0.06, 42.63]
Dougados 2017 (RA-BUILD) 2 105 0 52 6.9% 2.54 [0.12, 53.79]
Taylor 2017 (RA-BEAM) 4 224 0 225 5.2% 9.20 [0.49, 171.96]
Subtotal (95% CI) 693 561 34.8% 2.33 [0.62, 8.75]
Total events 7 1
Heterogeneity: Chi² = 2.35, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)
1.5.3 Upadacitinib
Genovese 2016 (BALANCE II) 0 57 0 12 Not estimable
Burmester 2018 (SELECT-NEXT) 0 101 0 51 Not estimable
Genovese 2018 (SELECT-BEYOND) 1 76 0 39 6.9% 1.57 [0.06, 39.43]
Kremer 2016 (BALANCE I) 3 51 0 13 7.8% 1.95 [0.09, 40.08]
Subtotal (95% CI) 285 115 14.7% 1.77 [0.20, 16.00]
Total events 4 0
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
1.5.4 Peficitinib
Kivitz 2017 0 71 0 17 Not estimable
Genovese 2017 0 55 0 12 Not estimable
Takeuchi 2016 0 52 0 13 Not estimable
Subtotal (95% CI) 178 42 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
1.5.5 Decernotinib
Genovese 2016 0 132 0 33 Not estimable
Fleischmann 2016 0 47 0 9 Not estimable
Subtotal (95% CI) 179 42 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
1.5.6 Filgotinib
Kavanaugh 2017 (DARWIN 2) 0 49 0 17 Not estimable
Subtotal (95% CI) 49 17 Not estimable
Total events 0 0
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Total (95% CI) 2193 982 100.0% 1.16 [0.48, 2.81]
Total events 12 3
Heterogeneity: Chi² = 7.20, df = 7 (P = 0.41); I² = 3%
Test for overall effect: Z = 0.33 (P = 0.74)
0.01 0.1 1 10 100
Favours [JAK inhibitors] Favours [Placebo]

Συμπεράσματα

- Οι ασθενείς με ρευματοειδή αρθρίτιδα παρουσιάζουν αυξημένο καδιαγγειακό κίνδυνο σε σύγκριση με το γενικό πληθυσμό
- Τα ΜΣΑΦ και τα κορτικοειδή αυξάνουν τον καρδιαγγειακό κίνδυνο, γι' αυτό και η χρήση τους πρέπει να είναι εξορθολογισμένη
- Απαιτείται έγκαιρη αντιμετώπιση υπέρτασης και υπερλιπιδαιμίας που σχετίζονται με τη λήψη DMARDs
- Χρειάζονται περισσότερα δεδομένα για να διευκρινιστεί η επίδραση νεότερων φαρμάκων όπως οι αναστολείς των JAK κινασών στον καρδιαγγειακό κίνδυνο

Ευχαριστώ
για την προσοχή σας!