Con il Patrocinio di

REGIONE PIEMONTE · CONSIGLIO REGIONALE DEL PIEMONTE · CITTA' DI TORINO · CReI · FIMMG · SIR · UNIVERSITÀ DEGLI STUDI DI TORINO

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

6ª Edizione

GERIATRIA E MALATTIE REUMATICHE

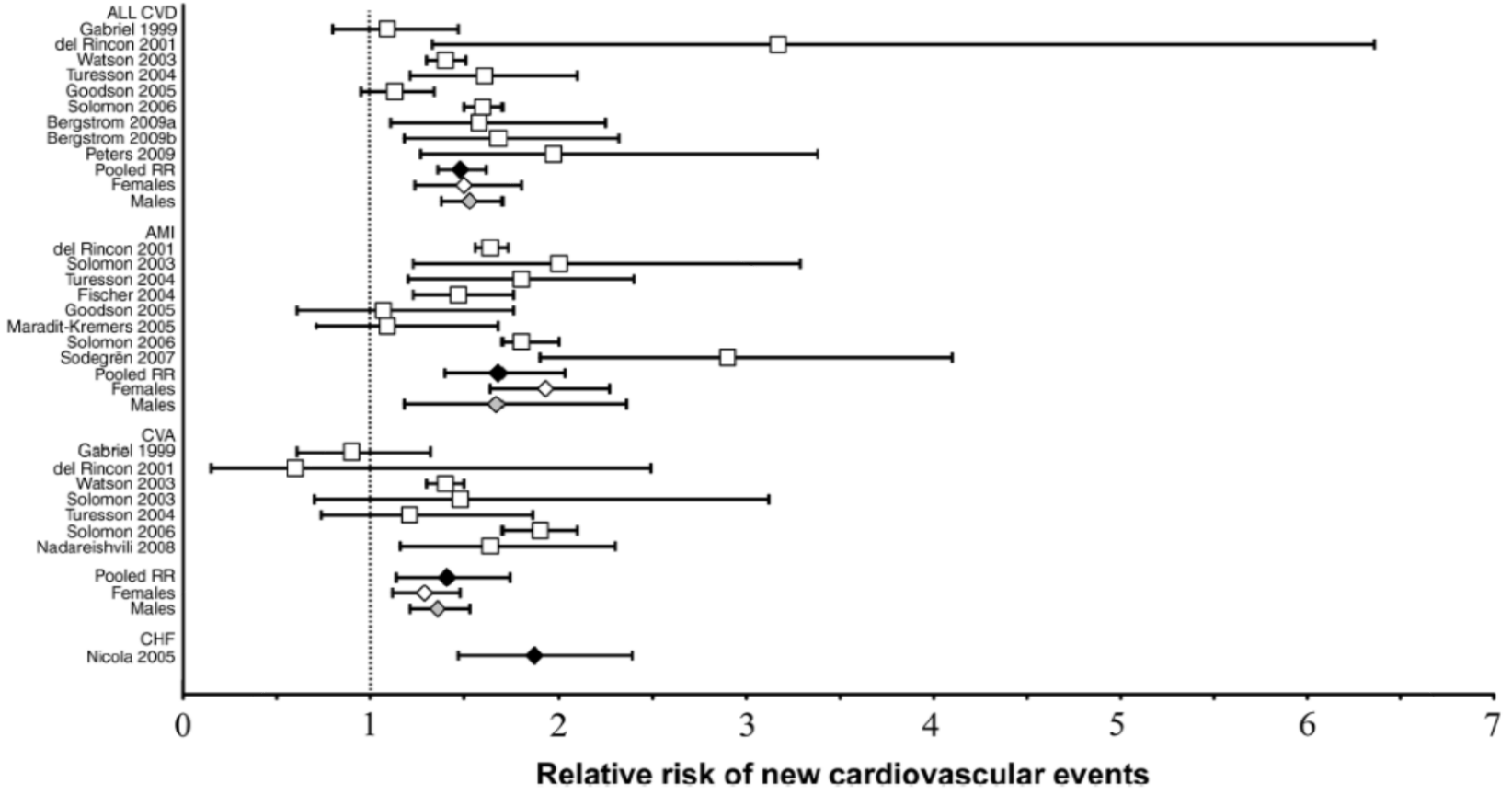
SESSIONE II – MALATTIE REUMATOLOGICHE DELL'ANZIANO I (Moderatori: N. Romeo, C. Pagliolico)

14:00 Rischio cardiovascolare nell'anziano reumatico **(M. Bo)**

Torino, 12-13 ottobre 2018

Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies

Ann Rheum Dis 2012;**71**:1524–1529.



Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies

Ann Rheum Dis 2012;**71**:1524–1529.

Table 2 Overall risk of CVD and sensitivity analysis for the nine studies assessing combined CVDs in patients with rheumatoid arthritis

Study subset*	Studies (n)	Patients (n)	Cardiovascular events (n)	Random effects (pooled RR (95% CI))	p Value
All studies	9	39 901	2047	1.48 (1.36 to 1.62)	
Study population					
Community-based	6	38 799	1545	1.53 (1.44 to 1.62)	NS
Clinic-based	3	1102	502	1.79 (0.96 to 3.32)	
Cohort type					
Inception cohorts	2	965	247	1.12 (0.97 to 1.30)	0.009
Non-inception cohorts	7	38 936	1800	1.56 (1.47 to 1.66)	
Quality score					
Higher quality (score ≥10)	5	1346	224	1.21 (1.06 to 1.39)	NS
Lower quality (score <10)	4	38 555	1823	1.47 (1.35 to 1.61)	

International Journal of Rheumatic Diseases 2015; **18**: 276–286

A qualitative systematic review of the prevalence of coronary artery disease in systemic sclerosis

Hassan ALI,[1] Kiat R. NG[1] and Andrea H. L. LOW[1,2]

Table 3 Coronary artery disease in SSc patients in studies with a control group

Study	Definition of CAD	*n* (%) of SSc with CAD[a]	*n* (%) of controls with CAD	Statistical significance
D'Angelo (1969)[18]	Small coronary arteriosclerosis on autopsy	10/58 (17.2)	1/58 (1.7)	$P < 0.01$
Youssef (1995)[19]	Physician diagnosis of infarct/ischemia[b]	12/31 (38.7)	7/31 (22.6)	RR 1.7 95% CI (0.8–3.7)
Khurma (2008)[16]	Coronary artery calcification on CT	9/17 (52.9)	3/17 (17.6)	$P = 0.03$
Mok (2011)[20]	CT coronary artery calcium score ≥ 101 (moderate to severe CAD)	13/23 (56.5)	10/23 (43.5)	OR 10.9[c] 95% CI (2.2–53.8)
Ngian (2012)[23]	Patient reported infarct/ ischemia[d]	88/850 (10.4)	642/8802 (7.3)	OR 3.2[e] 95% CI (2.3–4.5)
			774/15 787 (4.9)	OR 2.0[e] 95% CI (1.5–2.5)
Man (2012)[9]	Physician diagnosis of infarct/ischemia[f]	20/865 (2.3) [a]Incidence rate 4.4	129/8643 (1.5) [a]Incidence rate 2.5	HR 1.8[g] 95% CI (1.1–3.1)
Nordin (2013)[21]	Physician diagnosis of Ischemic heart disease[h]	13/111 (11.7)	4/105 (3.8)	OR 3.3 95% CI (1.1–10.6)
Chu (2013)[22]	Physician diagnosis of myocardial infarct	31/1344 (2.3) [a]Incidence rate 5.4	203/134 40 (1.5) [a]Incidence rate 3.1	HR 2.5[i] 95% CI (1.6–3.8)

Association Between Polymyalgia Rheumatica and Vascular Disease: A Systematic Review

ADAM T. HANCOCK, CHRISTIAN D. MALLEN, JOHN BELCHER, AND SAMANTHA L. HIDER

Table 2. Sample size and results of studies reporting on vascular mortality*

Author, year (ref.)	PMR group size	Reported outcome
Bengtsson and Malmvall, 1981 (14)	49	"total incidence of myocardial infarction and cerebrovascular disease . . . seems not to be higher than expected"
Andersson et al, 1986 (15)	49	25 vascular deaths vs. 26 expected
Schaufelberger et al, 1995 (16)	220	29 vascular deaths vs. 17 expected ($P < 0.05$)
Uddhammar et al, 2002 (17)	35	
Female		SMR 1.49 (95% CI 1.18–1.89)
Male		SMR 1.58 (95% CI 1.12–2.24)
Myklebust et al, 2003 (18)	315	RR 0.78 (95% CI 0.52–1.18)

* PMR = polymyalgia rheumatica; SMR = standardized mortality rate; 95% CI = 95% confidence interval; RR = relative risk.

Table 3. Sample size and results of studies reporting on other vascular outcomes*

Author, year (ref.)	PMR group size	Outcome	Result
Kremers et al, 2005 (19)	193	MI	OR 1.78 (95% CI 1.13–2.82)
		CVE	OR 1.60 (95% CI 1.08–2.39)
		PVD	OR 2.21 (95% CI 1.37–3.60)
Pfadenhauer et al, 2005 (21)	34	Vertebral narrowing	2.9% of PMR subjects vs. 3.0% of controls
Warrington et al, 2009 (20)	353	PVD	HR 2.50 (95% CI 1.53–4.08)

* PMR = polymyalgia rheumatica; MI = myocardial infarction; OR = odds ratio; 95% CI = 95% confidence interval; CVE = cerebrovascular event; PVD = peripheral vascular disease; HR = hazard ratio.

Arthritis Care & Research
Vol. 64, No. 9, September 2012, pp 1301–1305

Risk of vascular events in patients with polymyalgia rheumatica

CMAJ 2014. DOI: 10.1503/

Methods: We used the General Practice Research Database to identify patients with a diagnosis of incident polymyalgia rheumatica between Jan. 1, 1987, and Dec. 31, 1999. Patients were matched by age, sex and practice with up to 5 patients without polymyalgia rheumatica. Patients were followed until their first vascular event (cardiovascular, cerebrovascular, peripheral vascular) or the end of available records (May 2011). All participants were free of vascular disease before the diagnosis of polymyalgia rheumatica (or matched date). We used Cox regression models to compare time to first vascular event in patients with and without polymyalgia rheumatica.

Table 1: Characteristics of patients with and without a diagnosis of polymyalgia rheumatica

Characteristic	Group; no. (%)* PMR *n* = 3249	No PM *n* = 12
Age at index date, yr, mean ± SD	72.3 ± 8.9	72.0 ±
Female sex	2356 (72.6)	9245 (72.5)
Smoking status (ever smoked)†‡	1308 (43.4)	4496 (41.3)
Hypertension‡	1611 (51.1)	5241 (41.2)
Diabetes‡	438 (13.5)	1266 (9.9)
Hyperlipidemia‡	521 (16.0)	1431 (11.4)
Giant cell arteritis‡	248 (7.6)	67 (0.5)
Follow-up time, yr, median (IQR)	7.8 (3.3–12.4)	7.4 (3.3–12.0)

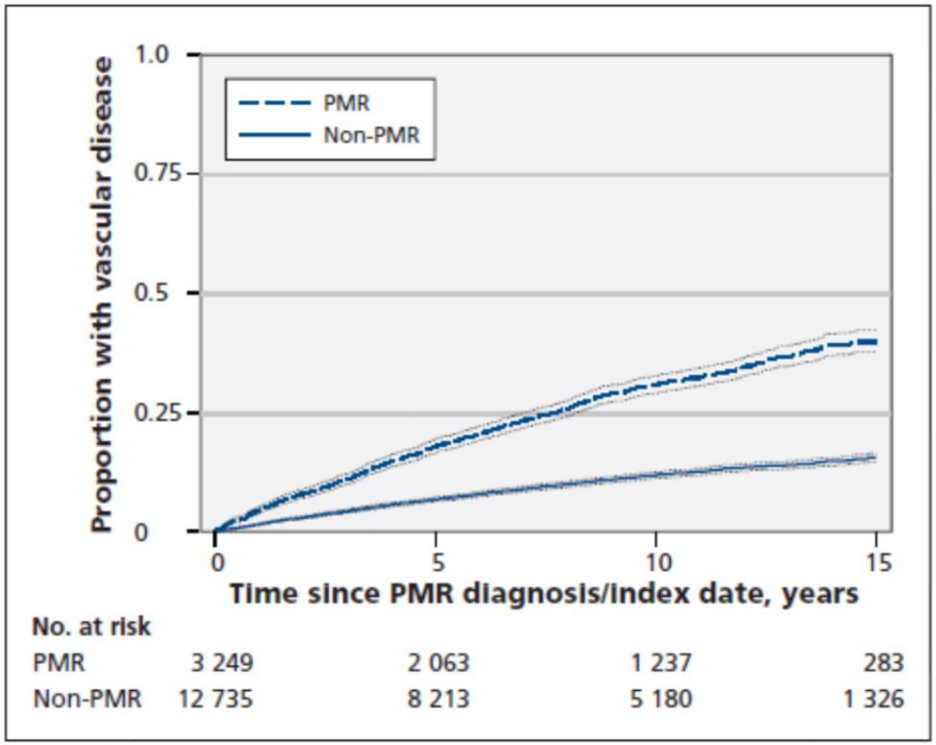


Figure 1: Kaplan–Meier curves for time to first vascular event after the index date among patients with and without a diagnosis of polymyalgia rheumatica (PMR). Dotted lines = 95% confidence intervals.

Risk of vascular events in patients with polymyalgia rheumatica

CMAJ 2014. DOI: 10.1503/

Table 2: Association between diagnosis of polymyalgia rheumatica and all first vascular events, by follow-up period

Follow-up period	No.	All vascular events, rate per 1000 person-years (95% CI)		Hazard ratio (95% CI)	
		PMR	No PMR	Unadjusted	Adjusted*
6 mo	168	47.6 (38.8–60.7)	14.6 (11.9–17.9)	3.3 (2.5–4.5)	3.0 (2.2–4.2)
1 yr	326	45.5 (38.6–53.7)	15.2 (13.2–17.6)	3.0 (2.4–3.7)	2.7 (2.1–3.4)
2 yr	522	41.2 (36.3–46.7)	14.7 (13.2–16.4)	2.8 (2.4–3.3)	2.4 (2.0–2.8)
5 yr	1247	39.6 (36.3–43.1)	14.1 (13.2–15.2)	2.8 (2.5–3.1)	2.4 (2.1–2.7)
10 yr	1892	37.5 (35.0–40.2)	12.9 (12.2–13.8)	2.9 (2.6–3.2)	2.5 (2.3–2.8)
All follow-up periods	2174	36.1 (33.8–38.5)	12.2 (11.6–12.9)	2.9 (2.6–3.2)	2.6 (2.4–2.9)

Table 3: Association between diagnosis of polymyalgia rheumatica and first occurrence of each type of vascular event

Type of vascular event	No.	Specific vascular events, rate per 1000 person-years (95% CI)		Hazard ratio (95% CI)	
		PMR	No PMR	Unadjusted	Adjusted*
Cerebrovascular	1067	15.6 (14.2–17.2)	5.9 (5.5–6.4)	2.6 (2.3–3.0)	2.3 (2.0–2.6)†
Cardiovascular	1134	18.1 (16.6–19.8)	6.1 (5.6–6.6)	3.0 (2.7–3.3)	2.7 (2.4–3.0)
Peripheral	335	5.5 (4.7–6.4)	1.6 (1.4–1.9)	3.3 (2.7–4.1)	2.8 (2.2–3.5)

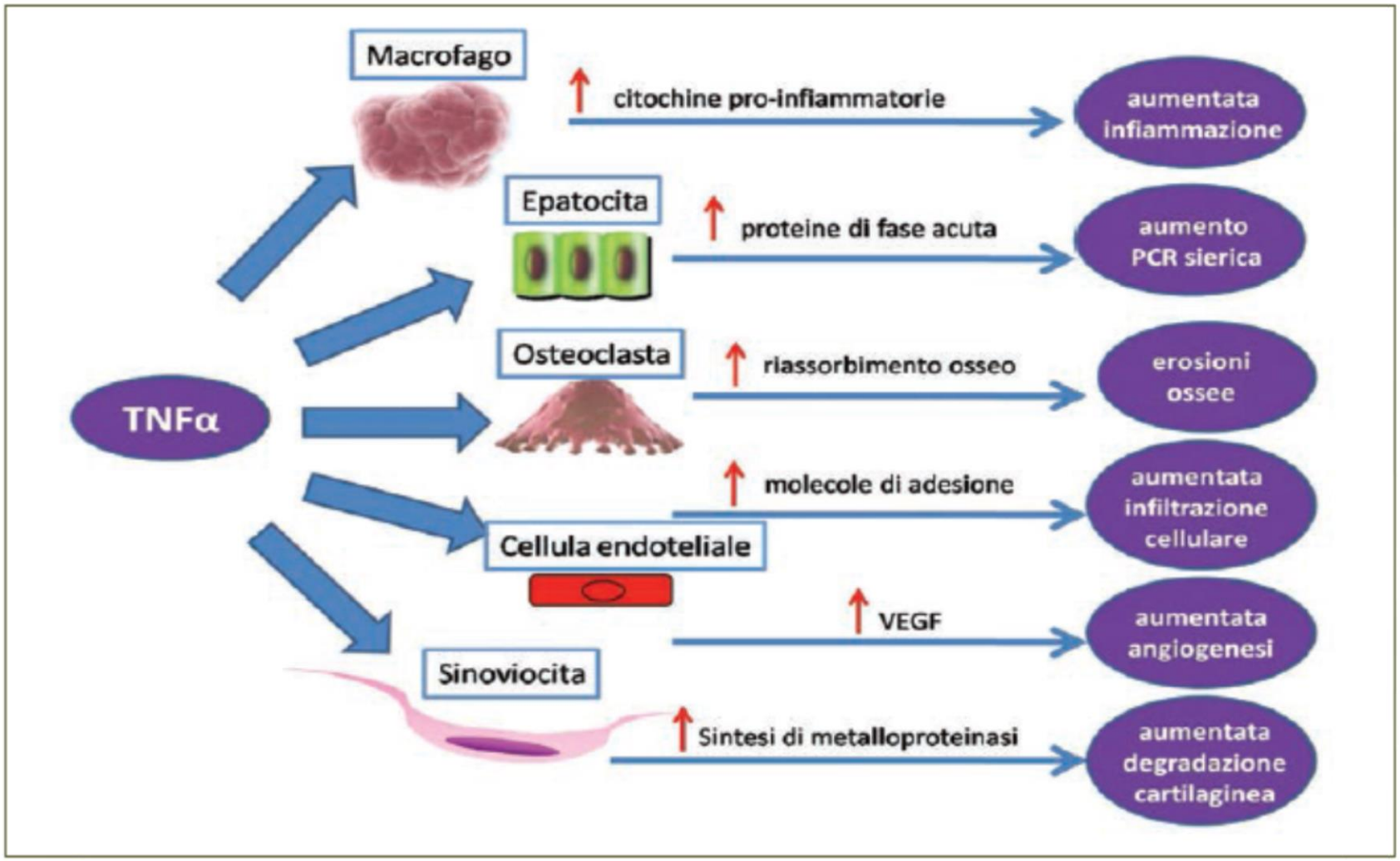


Figura 2 - Ruolo del TNFα nella patogenesi dell'infiammazione e del danno articolare nella AR.

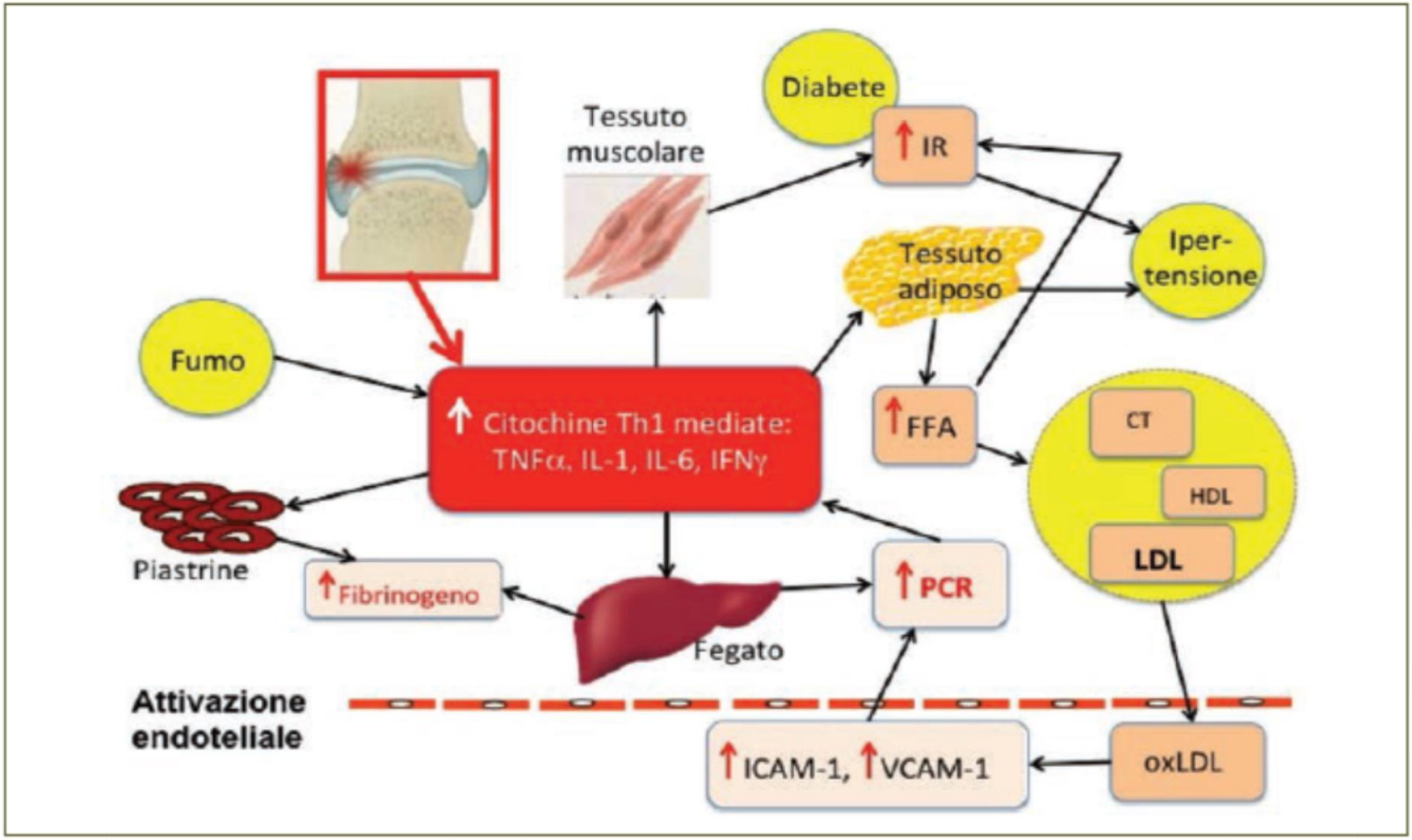


Figura 1 - Meccanismi di *cross talk* tra infiammazione articolare ed aterosclerosi.

STATE-OF-THE-ART PAPER

Inflammation in Atherosclerosis

JACC Vol. 54, No. 23, 2009
December 1, 2009:2129–38

From Pathophysiology to Practice

Peter Libby, MD,* Paul M Ridker, MD, MPH,*† Göran K. Hansson, MD, PHD,‡
for the Leducq Transatlantic Network on Atherothrombosis

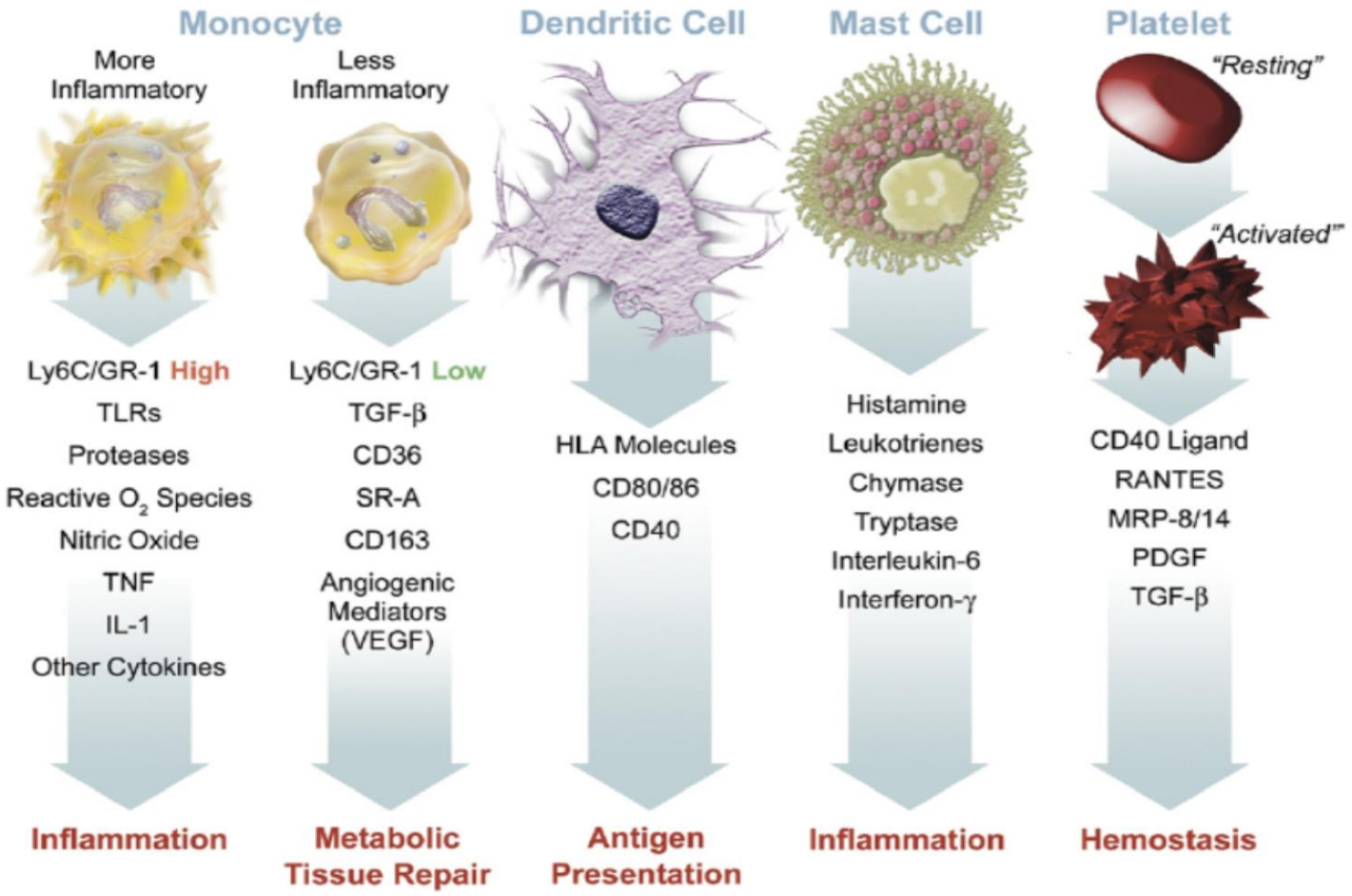


Figure 1 Elements Involved in Innate Immunity

Increased mortality in ankylosing spondylitis is related to disease activity

Ann Rheum Dis 2011;**70**:1921–1925.

Gunnstein Bakland,[1] Jan Tore Gran,[2] Johannes C Nossent[1]

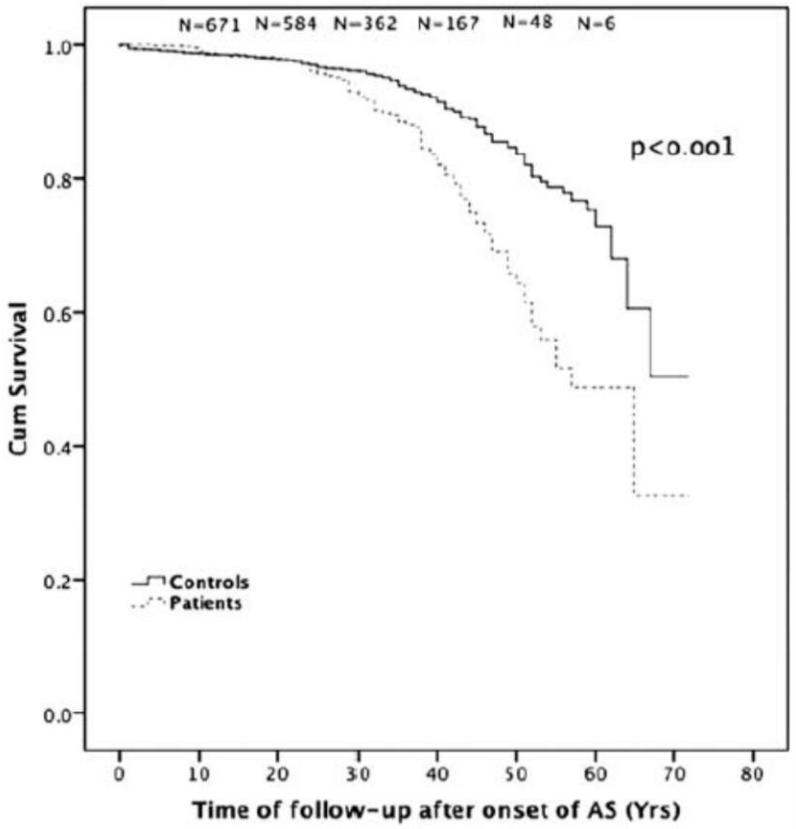


Figure 1 Kaplan–Meier survival curve of men with ankylosing spondylitis (AS) and controls matched for age, gender and area of residency, showing increased mortality among patients with AS.

Table 1 Standardised mortality rate (SMR) and 95% CI in ankylosing spondylitis specified by time of symptom onset

	Overall mortality			
	1.61		1.29–1.93	
	Male		Female	
Time of symptom onset				
–1969	1.34	0.74 to 1.94	2.00	0.04 to 3.96
1970–9	1.89	1.15 to 2.63	1.33	−0.52 to 3.18
1980–9	1.51	0.99 to 2.03	1.20	−0.16 to 2.56
1990–	2.18	0.95 to 3.41	0	
Overall mortality, gender-specified	1.63	1.29 to 1.97	1.38	0.48 to 2.28

Table 2 Causes of death in ankylosing spondylitis

Cause of death	Ascertained	Contributory	Total	(%)*
Circulatory	16	17	33	40.2
Malignancy	22	–	22	26.8
Infection	18	1	19	23.2
Other causes	6	2	8	9.8
Unknown	–	–	16	NA

Table 4 Variables independently associated with increased mortality in ankylosing spondylitis

	OR	p Value	95% CI for OR
CRP, increasing levels	2.68	<0.001	1.774 to 4.048
NSAIDs, infrequent use	4.35	0.002	1.753 to 10.771
Diagnostic delay	1.05	0.026	1.006 to 1.101
Work disability	3.65	0.008	1.400 to 9.506

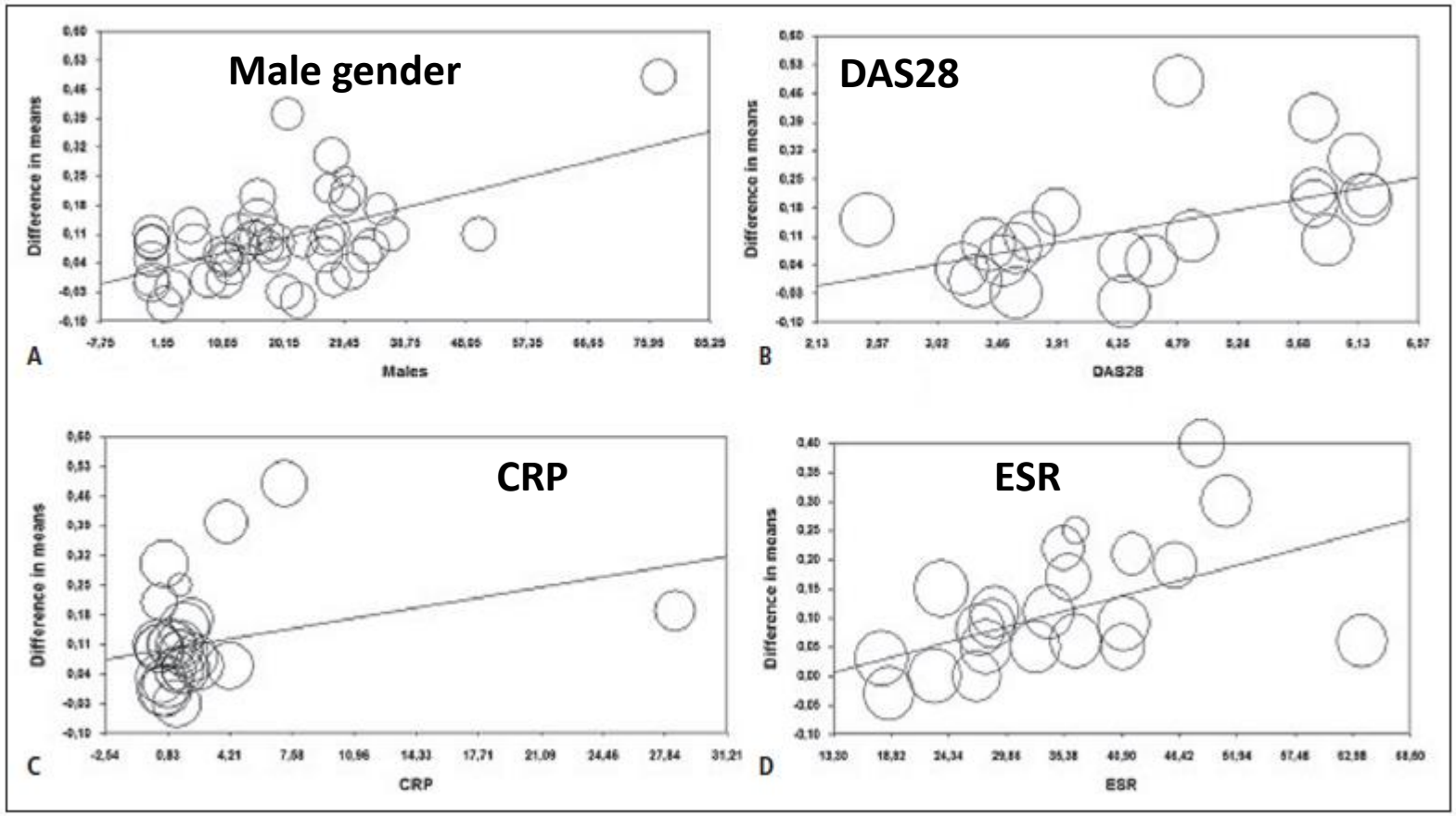
Subclinical atherosclerosis in patients with rheumatoid arthritis

A meta-analysis of literature studies

Thromb Haemost 2015; 113: 916–930

Pasquale Ambrosino[1]; Roberta Lupoli[1]; Alessandro Di Minno[1]; Marco Tasso[1]; Rosario Peluso[1]; Matteo Nicola Dario Di Minno[1,2]

[1]Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy; [2]Unit of Cell and Molecular Biology in Cardiovascular Diseases, Centro Cardiologico Monzino, IRCCS, Milan, Italy



Effect of male gender, DAS28, CRP and ESR on the common carotid IM thickness (IMT) in patients with RA

	N of studies	N of patients	Effect size MD or OR [95 %CI]
Panel A			
CCA-IMT	35 (35 data-sets)	2,725 patients 2,141 controls	MD: 0.09 [0.07, 0.12]; P< 0.00001 I2=94 %; P< 0.00001
Carotid plaques	27 (27 data-sets)	2,428 patients 1,872 controls	OR: 3.60 [2.55, 5.07]; P< 0.00001 I2=63 %; P< 0.00001
Panel B			
CCA-IMT	44 (45 data-sets)	3,228 patients 2,677 controls	MD: 0.09 [0.07, 0.12]; P< 0.00001 I2=95 %; P< 0.00001
Carotid plaques	31 (31 data-sets)	2,625 patients 2,044 controls	OR: 3.78 [2.67, 5.35]; P< 0.00001 I2=61 %; P< 0.00001
Panel C			
CCA-IMT	46 (47 data-sets)	3,156 patients 2,684 controls	MD: 0.10 [0.08, 0.12]; P< 0.00001 I2=95 %; P< 0.00001
Carotid plaques	35 (35 data-sets)	2,859 patients 2,303 controls	OR: 3.61 [2.65, 4.93]; P< 0.00001 I2=60 %; P< 0.00001
Panel D			
CCA-IMT	50 (51 data-sets)	3,500 patients 2,920 controls	MD: 0.09 [0.07, 0.11]; P< 0.00001 I2=94 %; P< 0.00001
Carotid plaques	34 (34 data-sets)	2,824 patients 2,268 controls	OR: 3.69 [2.68, 5.08]; P< 0.00001 I2=61 %; P< 0.00001

N: number; MD: mean difference; OR: odds ratio; 95 %CI: 95 % Confidence Intervals; CCA-IMT: common carotid artery intima-media thickness.

Table 3: Sensitivity analyses. A) "High quality" studies (i. e. Newcastle-Ottowa Scale ≥ 7) included; B) Exclusion of studies potentially reporting on the same population as other included studies; C) Exclusion of studies providing a composite IMT; D) Case-control studies.

European Heart Journal (2016) **37**, 2315–2381
doi:10.1093/eurheartj/ehw106

JOINT ESC GUIDELINES

2016 European Guidelines on cardiovascular disease prevention in clinical practice

Carotid ultrasound IMT screening for CV risk assessment is not recommended **III** **A**

PLOS ONE | DOI:10.1371/journal.pone.0146991 January 12, 2016

Cardiovascular Comorbidities Relate More than Others with Disease Activity in Rheumatoid Arthritis

Gloria Crepaldi[1], Carlo Alberto Scirè[2], Greta Carrara[2], Garifallia Sakellariou[1], Roberto Caporali[1]*, Ihsane Hmamouchi[3], Maxime Dougados[4], Carlomaurizio Montecucco[1]

A total of 3,920 patients were included: age (mean ±SD) 56.27 ±13.03 yrs, female 81.65%, disease duration median 7.08 yrs (IQR 2.97–13.27), DAS28 (mean ±SD) 3.74 ± 1.55.

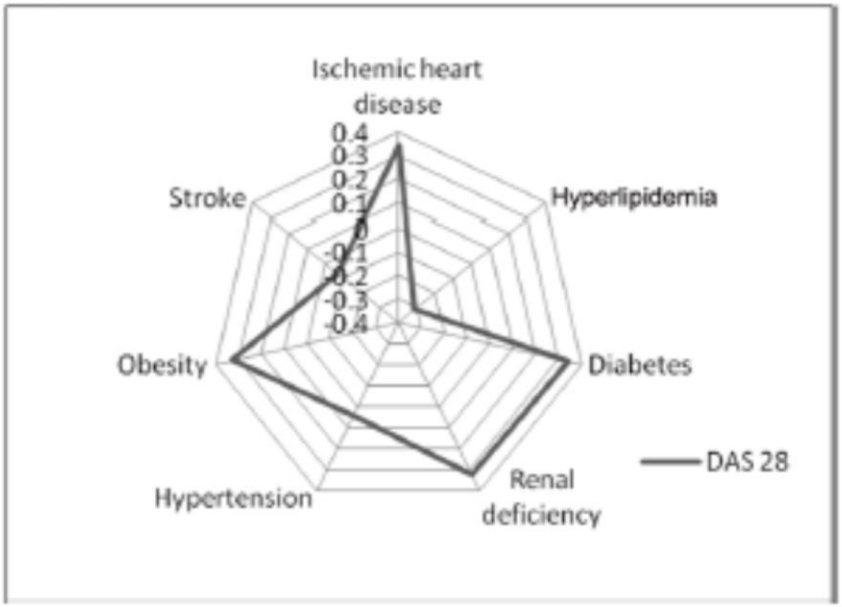


Fig 2. Association between cardiovascular comorbidities and DAS28-ESR. The correlation was statistically significant with concomitant diabetes, hyperlipidemia, ischemic heart disease and obesity. DAS28, Disease Activity Score using 28 joints.

European Heart Journal (2017) **38**, 1717–1727

Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis

Pietro Enea Lazzerini*, Pier Leopoldo Capecchi, and Franco Laghi-Pasini

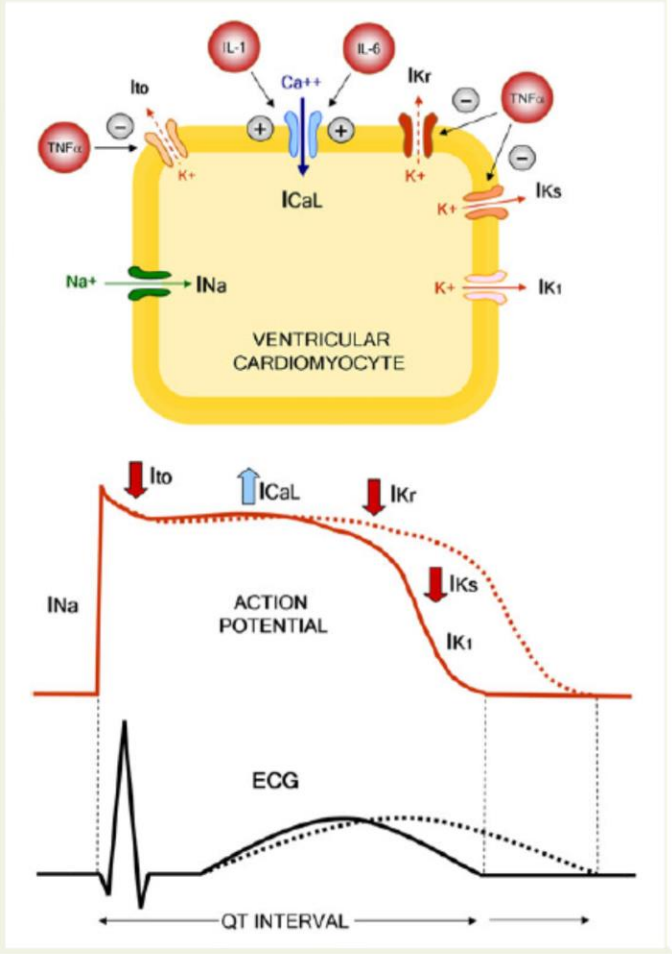
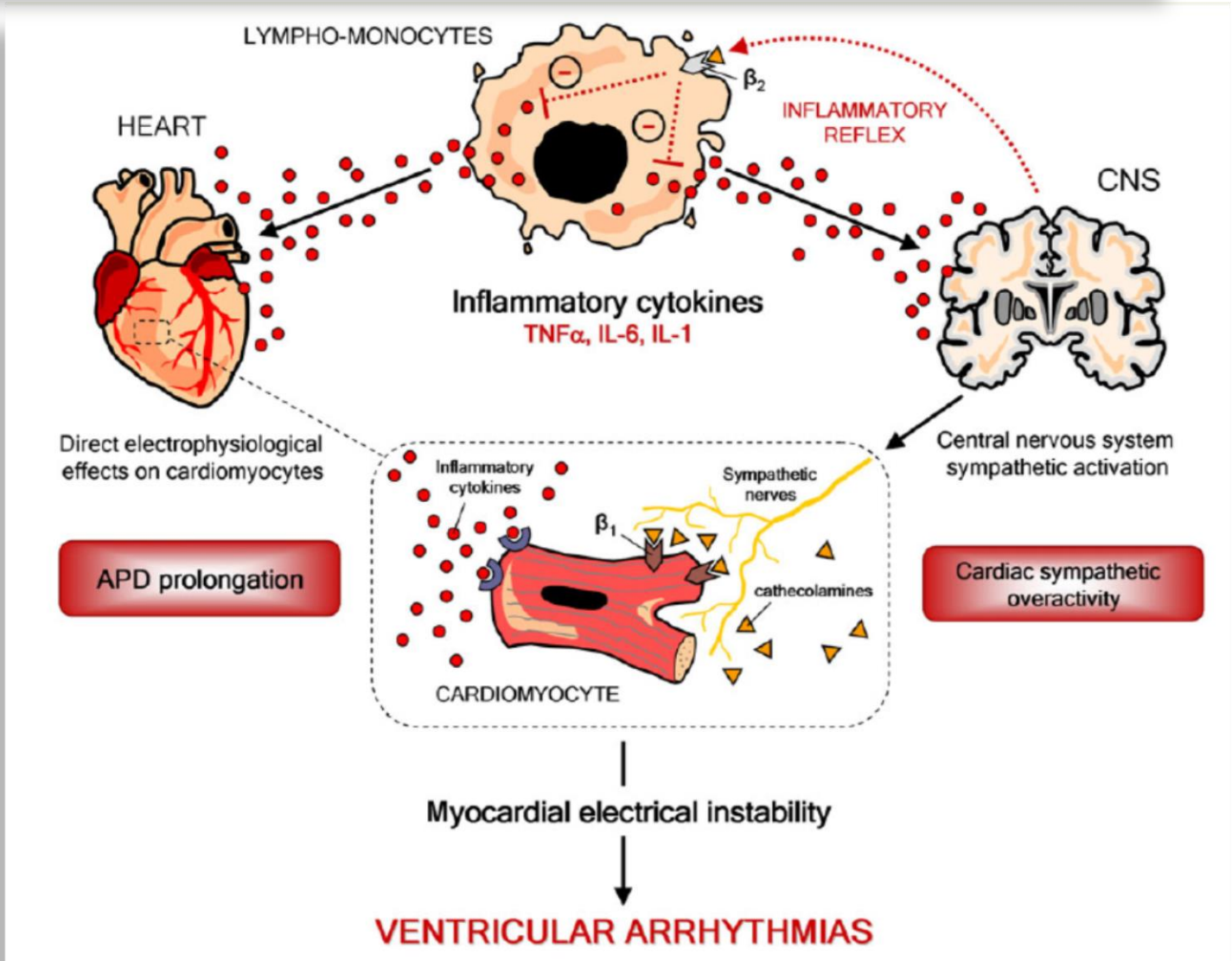


Figure 1 Electrophysiological basis of inflammation-mediated QTc prolongation, from the cell to the surface electrocardiogram. TNFα, tumor necrosis factor alpha; IL-1, interleukin-1; IL-6, interleukin-6; INa, sodium current; Ito, transient outward current; ICaL, L (long-lasting)-type calcium current; IKr, rapid component of the delayed rectifier potassium current; IKs, slow component of the delayed rectifier potassium current; IK1, inward rectifier potassium current. Modified from: Lazzerini *et al.*[63]

European Heart Journal (2017) **38**, 1717–1727

Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis

Pietro Enea Lazzerini*, Pier Leopoldo Capecchi, and Franco Laghi-Pasini



European Heart Journal (2017) **38**, 1717–1727

Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis

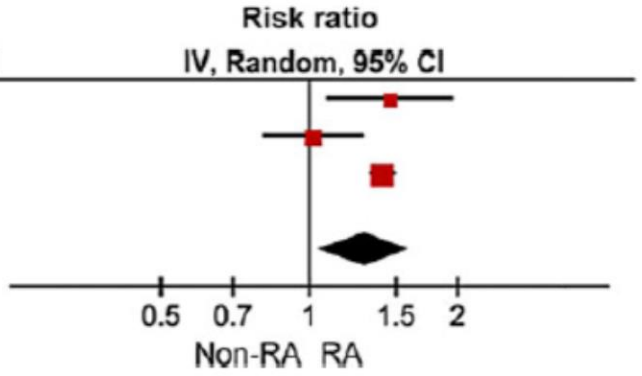
Pietro Enea Lazzerini*, Pier Leopoldo Capecchi, and Franco Laghi-Pasini

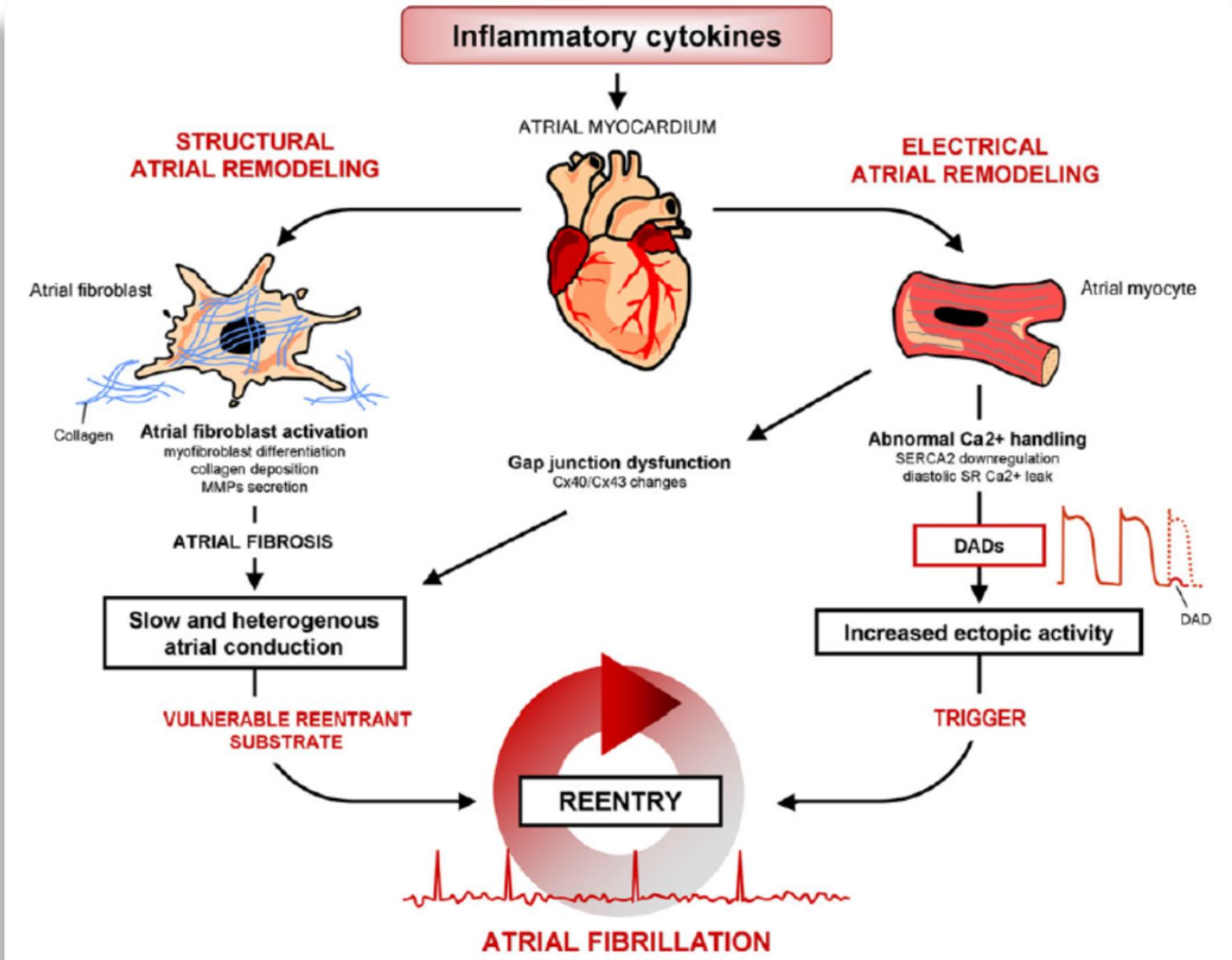
Risk of atrial fibrillation in rheumatoid arthritis patients: a meta-analysis of population-based studies.

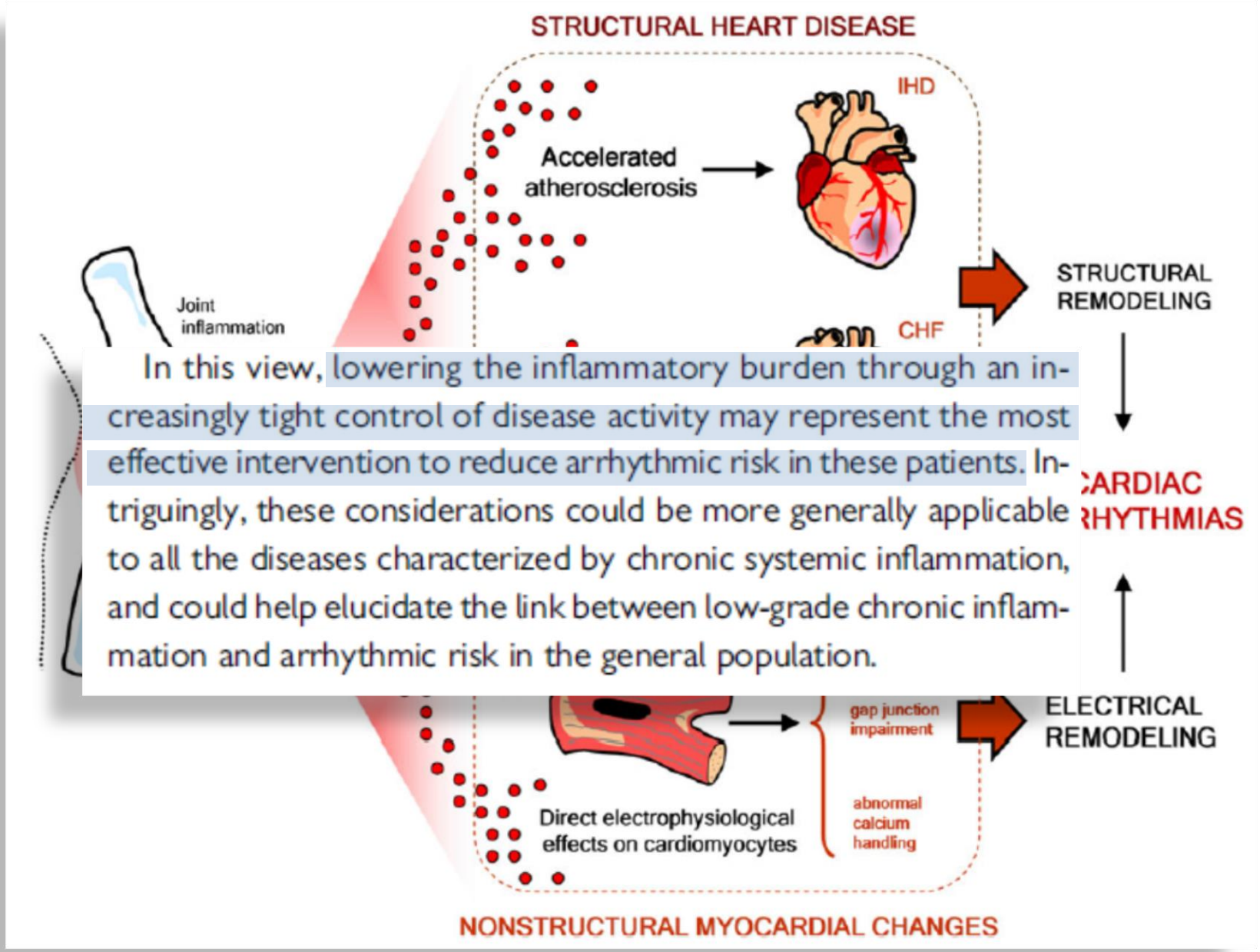
Study or subgroup	Log[Risk ratio]	SE	Weight	Risk ratio IV, Random, 95% CI
Bacani et al.	0.3784	0.15	24.4%	1.46 [1.09, 1.96]
Kim et al.	0.0196	0.12	29.6%	1.02 [0.81, 1.29]
Lindhradsen et al.	0.3436	0.03	46.0%	1.41 [1.33, 1.50]
Total (95% CI)			**100.0%**	**1.29 [1.05, 1.59]**

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 6.99$, df = 2 ($P = 0.03$); $I^2 = 71\%$

Test for overall effect: $Z = 2.42$ ($P = 0.02$)




Inflammatory cytokines
ATRIAL MYOCARDIUM
STRUCTURAL ATRIAL REMODELING
ELECTRICAL ATRIAL REMODELING
Atrial fibroblast
Collagen
Atrial fibroblast activation
myofibroblast differentiation
collagen deposition
MMPs secretion
ATRIAL FIBROSIS
Atrial myocyte
Abnormal Ca2+ handling
SERCA2 downregulation
diastolic SR Ca2+ leak
Gap junction dysfunction
Cx40/Cx43 changes
DADs
DAD
Slow and heterogenous atrial conduction
Increased ectopic activity
VULNERABLE REENTRANT SUBSTRATE
TRIGGER
REENTRY
ATRIAL FIBRILLATION



In this view, lowering the inflammatory burden through an increasingly tight control of disease activity may represent the most effective intervention to reduce arrhythmic risk in these patients. Intriguingly, these considerations could be more generally applicable to all the diseases characterized by chronic systemic inflammation, and could help elucidate the link between low-grade chronic inflammation and arrhythmic risk in the general population.

Rheum Dis Clin N Am 42 (2016) 33–46

Glucocorticoids and Rheumatoid Arthritis

Cardiovascular Risk Factors and Atherosclerosis

Long-term use of prednisone in patients with RA may be associated with a higher risk of hypertension. Baseline blood pressure and age are more important for the development of significant hypertension than are low-dose GCs.[31]

Atherosclerosis seems to be accelerated in patients with RA taking GC therapy. Patients with RA without medications are still at a higher risk of advanced atherosclerosis than the normal population, which suggests that atherosclerosis can be disease related and medication related.[32]

The lipid profile is also influenced by GCs, with an increase in total plasma cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels, in a dose-dependent effect. In low doses, the antiinflammatory effect of GCs results in a favorable lipid profile.[31,33]

The cardiovascular risk in patients with RA is related to the GC dose, disease activity, comorbidities, and cotherapies.[31,33]

Aging and Disease Volume 9, Number 1; 143-150, February 2018

A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly

Thus, all NSAIDs (COX-2 and non-selective) may be associated with increased cardiovascular adverse effects and each medications' risk/benefit profile should be considered before prescribing to individual patients [26].

Can suppression of inflammation by anti-TNF prevent progression of subclinical atherosclerosis in inflammatory arthritis?

Rheumatology 2014;53:1108–1119

Lai-Shan Tam[1], George D. Kitas[2] and Miguel A. González-Gay[3]

Methods. A search of the MEDLINE and Web of Knowledge databases was conducted to identify studies into the effect of TNF-α antagonists on subclinical atherosclerosis and arterial stiffness in patients with RA, AS and PsA. Carotid intima–media thickness (cIMT) was used to assess subclinical atherosclerosis. Two methods were used to assess arterial stiffness: pulse wave velocity (PWV) and aortic augmentation index (AIx). Twenty-three studies matching the search criteria were included for analysis.

Inf: infliximab; Ada: adalimumab; Eta: etanercept; Toci: tocilizumab; Gol: golimumab

Rheumatology key messages

- Uncontrolled inflammation in arthritis patients may accelerate the progression of subclinical atherosclerosis and arterial stiffness.
- TNF-α blockers can prevent progression of intima–media thickness and pulse wave velocity in patients with inflammatory arthritis.

PLOS ONE | DOI:10.1371/journal.pone.0130709 June 26, 2015

The Impact of Newer Biological Disease Modifying Anti-Rheumatic Drugs on Cardiovascular Risk Factors: A 12-Month Longitudinal Study in Rheumatoid Arthritis Patients Treated with Rituximab, Abatacept and Tociliziumab

Results

24 patients on rituximab, 5 on abatacept and 7 on tocilizumab were included. At 3 months PWV was significantly reduced in the tocilizumab group only, but at 12 months rituximab patients showed a significant reduction in PWV. Reduced inflammation at 3 months was associated with increased TC and HDL-c in the entire cohort.

Conclusion

Treatment with tocilizumab and rituximab reduces PWV, a marker of CVD risk, in patients with RA.

Expert Opin. Drug Saf. (2015) **14**(12):1905-1913

Cardiovascular effects of Etanercept in patients with psoriatic arthritis: evidence from the cardiovascular risk in rheumatic diseases database

. Similarly, the anti-inflammatory effect of Etanercept is associated with a significant improvement of hemostatic and fibrinolytic parameters in PsA subjects, maximal changes being documented in patients achieving minimal disease activity. In addition, the treatment with Etanercept seems to be associated with a carotid intima-media thickness significantly lower as compared with matched patients receiving traditional disease-modifying anti-rheumatic drugs.

Mod Rheumatol, 2014; 24(2): 335–339

Effects of infliximab treatment in terms of cardiovascular risk and insulin resistance in ankylosing spondylitis patients

Results. After 12 weeks of infliximab treatment, there was no statistically significant difference in fasting insulin, HOMA-IR, lipid parameters, body–mass index, waist circumference and waist–hip ratio, whereas fasting glucose levels ($p = 0.001$), triglycerides/high-density lipoprotein (HDL) ratio ($p = 0.043$) and total cholesterol/HDL ($p = 0.041$) ratio increased significantly from baseline. A significant decrease was observed for both systolic blood pressures ($p < 0.001$) and diastolic blood pressures ($p = 0.003$) in the 12th-week visit. A significant decrease was also found in terms of Framingham risk scores ($p = 0.028$) after treatment.

The NEW ENGLAND JOURNAL of MEDICINE

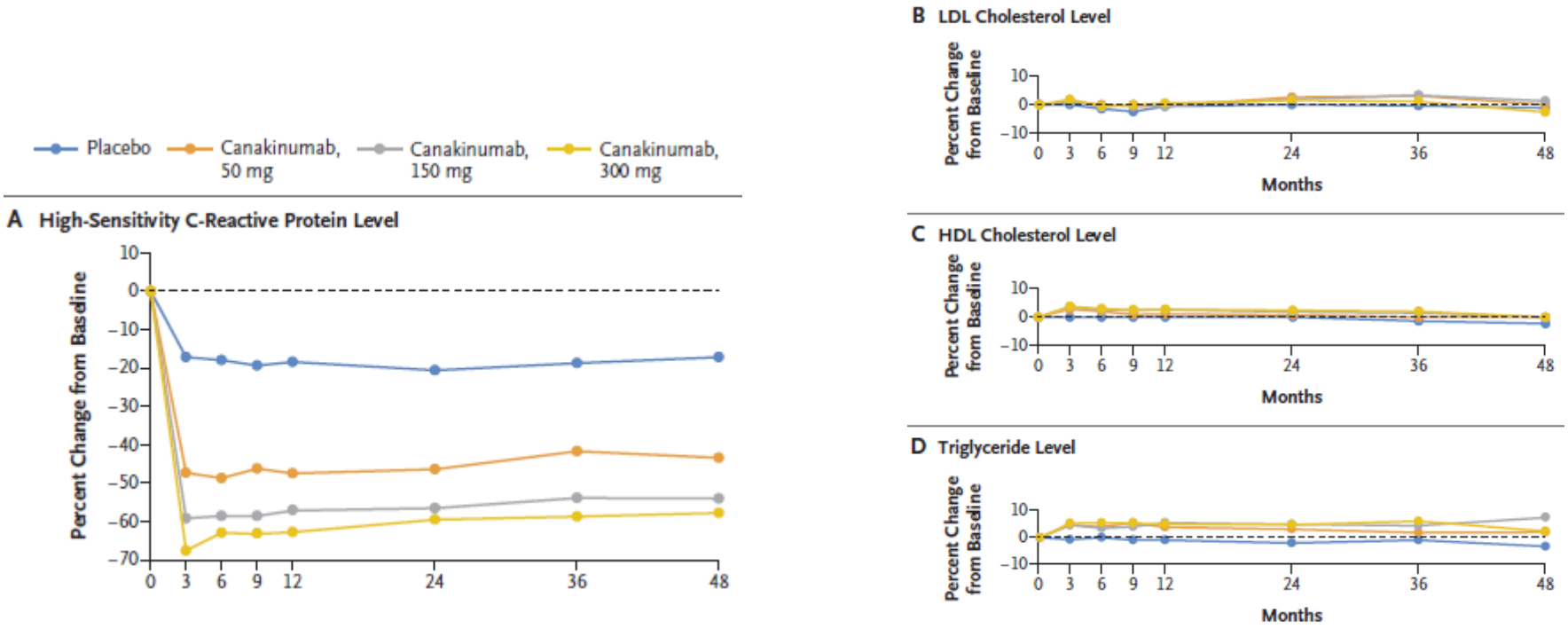
SEPTEMBER 21, 2017

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

CANTOS Trial Group*

We conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter. The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

Age — yr	61.1±10.0
Female sex — no. (%)	865 (25.9)



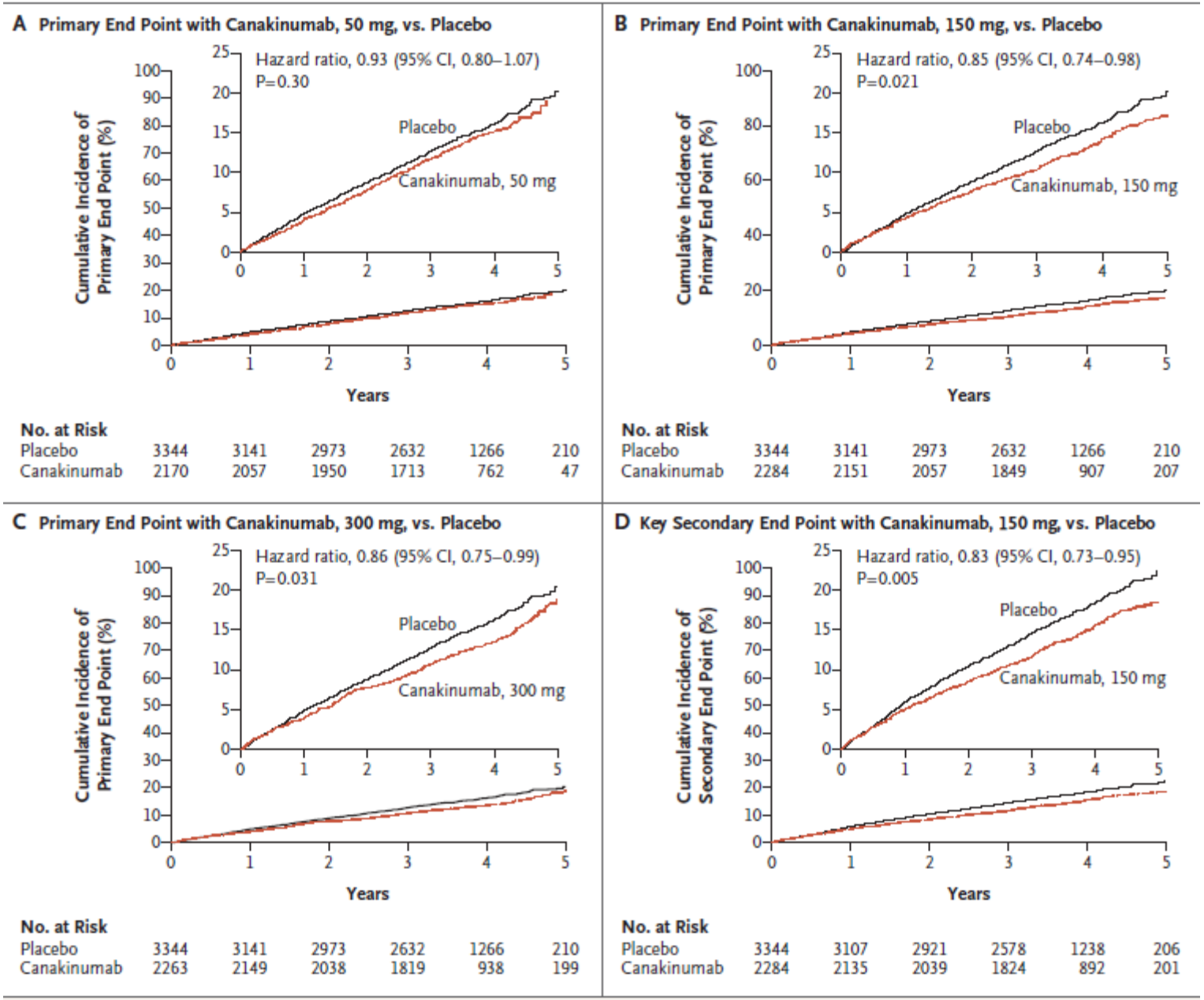


Figure 2. Cumulative Incidence of the Primary End Point and the Key Secondary Cardiovascular End Point.

Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial

Lancet 2018; 391: 319-28

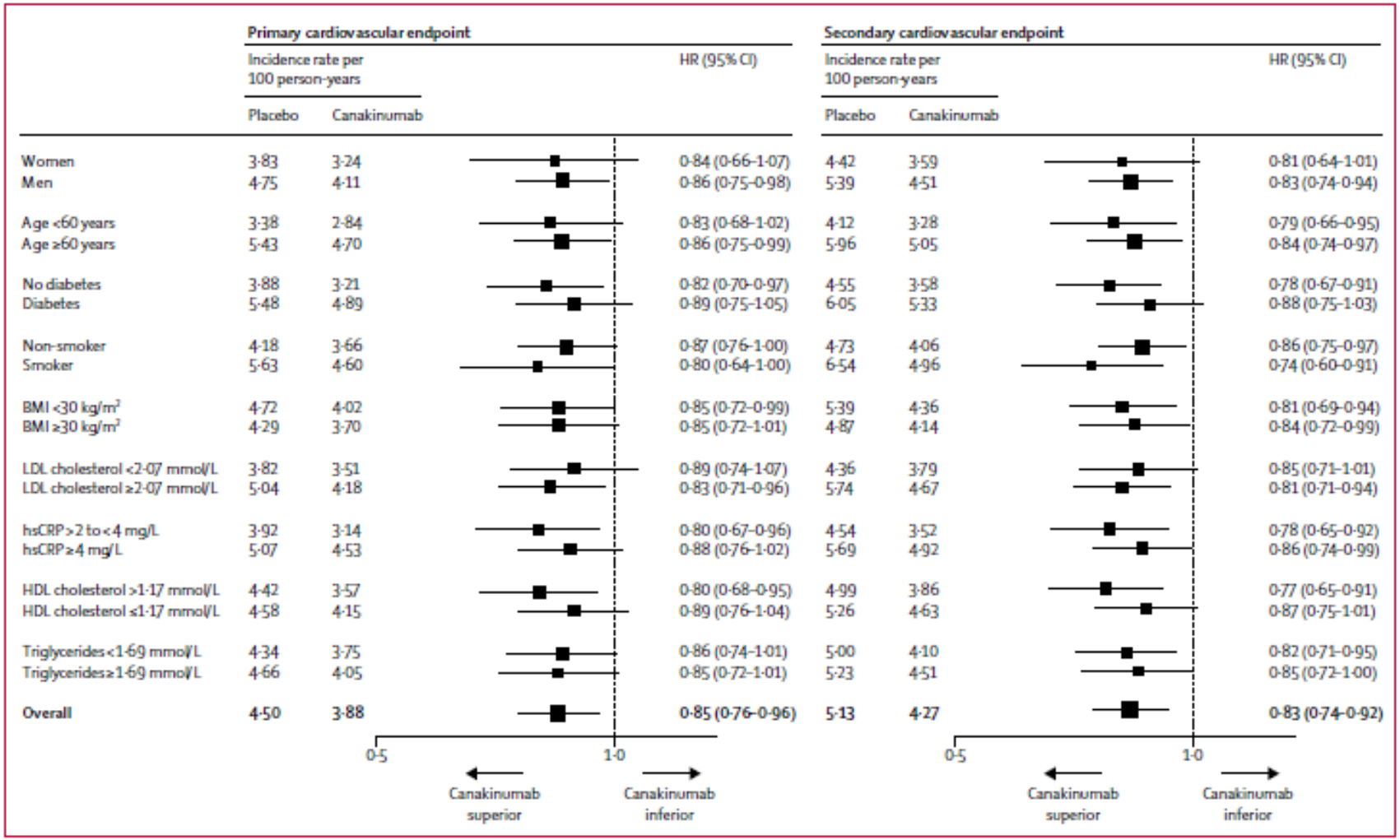
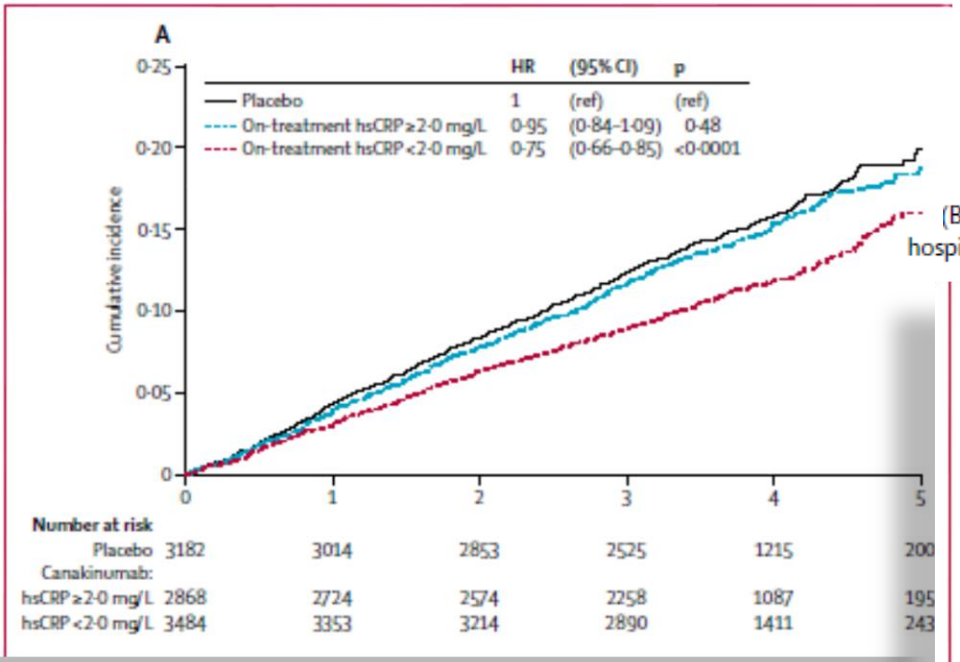


Figure 1: Clinical efficacy of canakinumab as compared with placebo for the trial primary endpoint (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death) and the trial secondary endpoint (non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina requiring unplanned revascularisation, or cardiovascular death) according to subgroups based upon baseline clinical characteristic

Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial

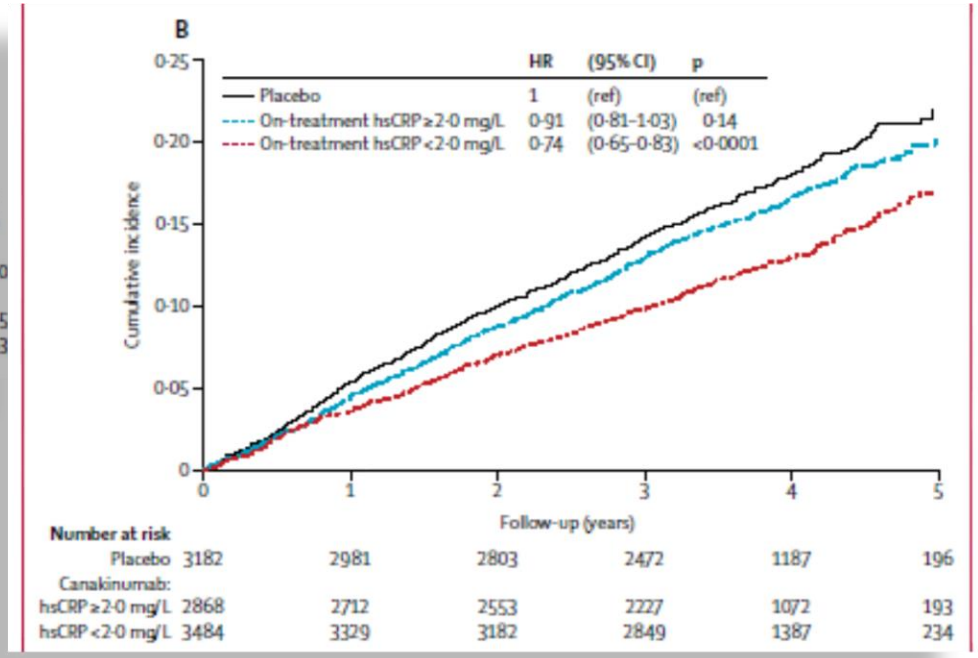
Lancet 2018; 391: 319-28

(A) the primary endpoint (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death)



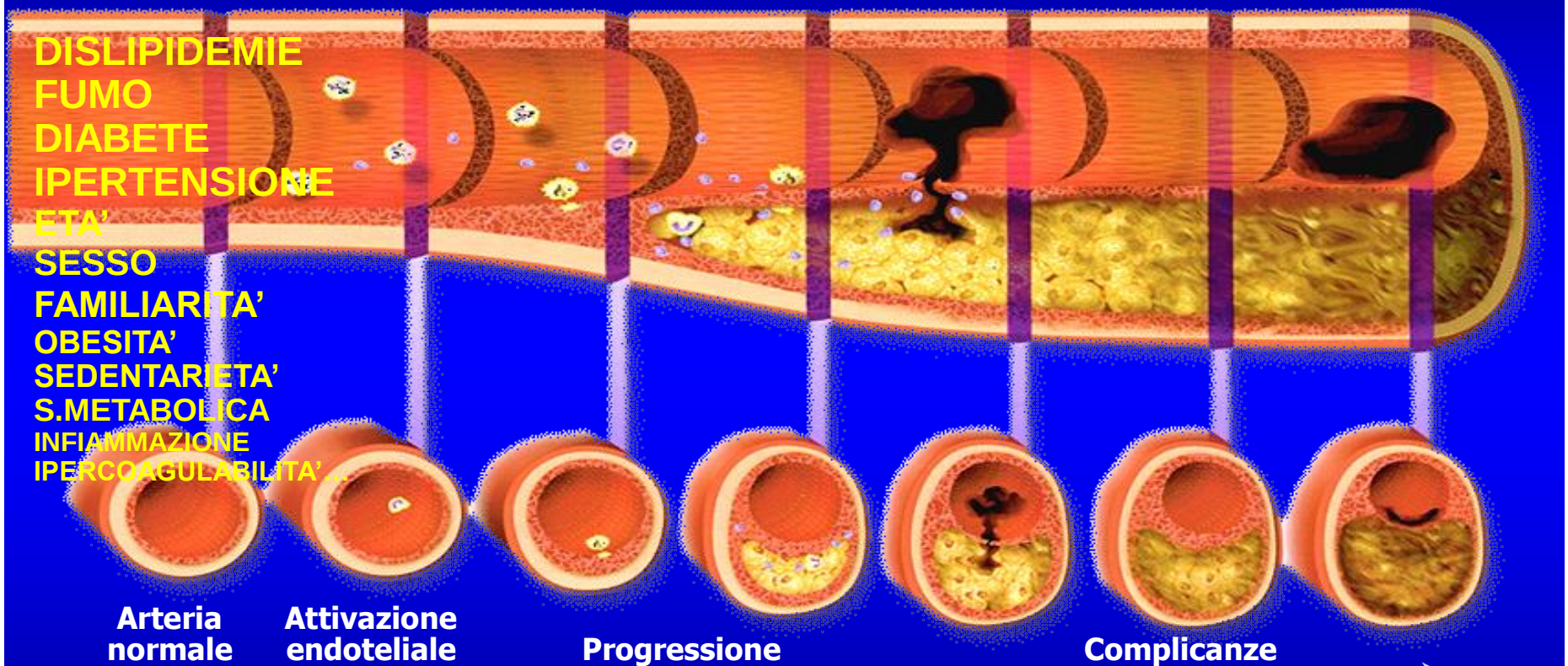
CV events in **Placebo treated, Canakinumab treated** with **CRP >=2.0 mg/l** and **CRP<2.0 mg/L**

(B) the key prespecified secondary endpoint (non-fatal myocardial infarction, non-fatal stroke, hospitalisation for unstable angina requiring unplanned revascularisation, or cardiovascular death).



Interpretation The magnitude of hsCRP reduction following a single dose of canakinumab might provide a simple clinical method to identify individuals most likely to accrue the largest benefit from continued treatment. These data further suggest that lower is better for inflammation reduction with canakinumab.

LA STORIA NATURALE DELL'ATEROSCLEROSI



NEJM, 1999.

Tabella I - Raccomandazioni EULAR sulla gestione del rischio CV nei pazienti con AR, ApS ed SA.

1	AR va considerata come una condizione ad alto rischio di sviluppo di malattie CV. Questo rischio sembrerebbe legato sia all'aumento dei tradizionali fattori di rischio CV che dell'infiammazione
2	Per ridurre il rischio CV è necessario un controllo adeguato dell'attività di malattia
3	È raccomandata una valutazione del rischio CV utilizzando le LG nazionali per tutti i pazienti con AR e va rivalutato ogni anno anche nei pazienti con ApS e SA. Va inoltre ricalcolato qualora si modifichi la terapia con farmaci antireumatici
4	I modelli di rischio vanno adattati ai pazienti con AR tramite l'introduzione di un fattore di moltiplicazione di 1,5 che va utilizzato qualora gli stessi presentino 2 dei seguenti 3 criteri: - durata di malattia da oltre 10 anni - FR o anti-CCP positivi - presenza di manifestazioni extrarticolari
5	Il rapporto Colesterolo Tot/Colesterolo HDL va utilizzato quando si applica il modello SCORE
6	Gli interventi terapeutici devono seguire le linee guida nazionali
7	Sono da preferire trattamenti con: statine, ACE-inibitori e/o antagonisti dell'ATII
8	Non è stato ancora completamente definito il ruolo dei FANS tradizionali e dei COXib sul rischio CV. Si raccomanda cautela nella prescrizione in particolare nei pazienti con rischio CV documentato o in presenza di fattori di rischio CV
9	I corticosteroidi vanno utilizzati al minor dosaggio possibile
10	Si raccomanda la sospensione del fumo

European Heart Journal (2016) 37, 2315–2381
doi:10.1093/eurheartj/ehw106

JOINT ESC GUIDELINES

2016 European Guidelines on cardiovascular disease prevention in clinical practice

2.5.2. Elderly

Age is the dominant driver of cardiovascular risk, and most individuals are already at (very) high risk at the age of 65 years. Especially in the oldest old, CV risk management is controversial…..

2.5.2.1 Hypertension

Most of the elderly specific evidence is avaialble for BP. In general more lenient targets are advocated in the elderly….evidence that biological rather calendar age is important

2.5.2.2 Diabetes mellitus

Evidence supporting more lenient glycaemic control targets in the elderly is also available for DM. The rola of biologcal age/frailty is less well established than for BP, but nonetheless, a Class IIa recommendation is given to relax glycaemic control targets in elderly or frail patients

2.5.2.3 Hyperlipidemia

Few areas in CVD prevention are more controversial than the mass use of statins in the elderly. ..There is no evidence of decreasing effectiveness of statins in patients>75 years of age…also, evidence supportin effectiveness in the oldest old (>80 years of age) is very limited

Primary Prevention With Statins in the Elderly

(J Am Coll Cardiol 2018;71:85-94)

Martin Bødtker Mortensen, MD, PhD, Erling Falk, MD, DMSc

CENTRAL ILLUSTRATION Age-Dependent Implementation of Guidelines in Clinical Practice

Sex: Male	SBP: 135 mm Hg	HDL cholesterol: 37 mg/dL	Race: White
Smoker	Total cholesterol: 232 mg/dL	Diabetes: No	No antihypertensives

	Age 56	Age 66	Age 76	Age 86
PCE:	18%	26%	34%	NA
QRISK2:	17%	28%	43%	NA
Framingham:	31%	49%	NA	NA
SCORE:	4%	NA	NA	NA

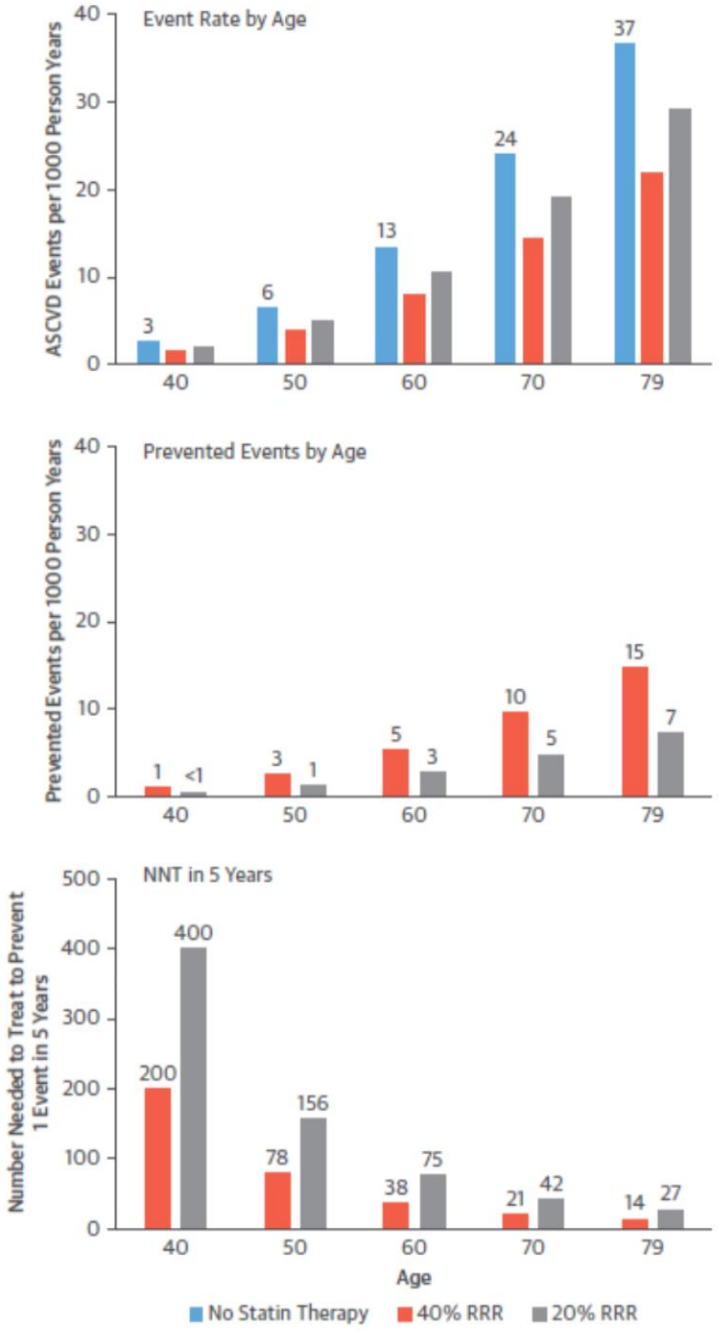
Guideline Recommendation				
ACC/AHA	✓ Class I	✓ Class I	— Class IIb	— Class IIb
NICE	✓ Strong	✓ Strong	✓ Strong	— Specific recommendation for individuals ≥85 years
CCS	✓ Strong	✓ Strong	—	—
USPSTF	✓ Level B	✓ Level B	X	X
ESC/EAS	X	— Class IIa	— Class IIa	— Class IIa

✓ : Strong Statin Recommendation — : Weak Statin Recommendation X : Not Recommended for Statin

Mortensen, M.B. et al. J Am Coll Cardiol. 2018;71(1):85-94.

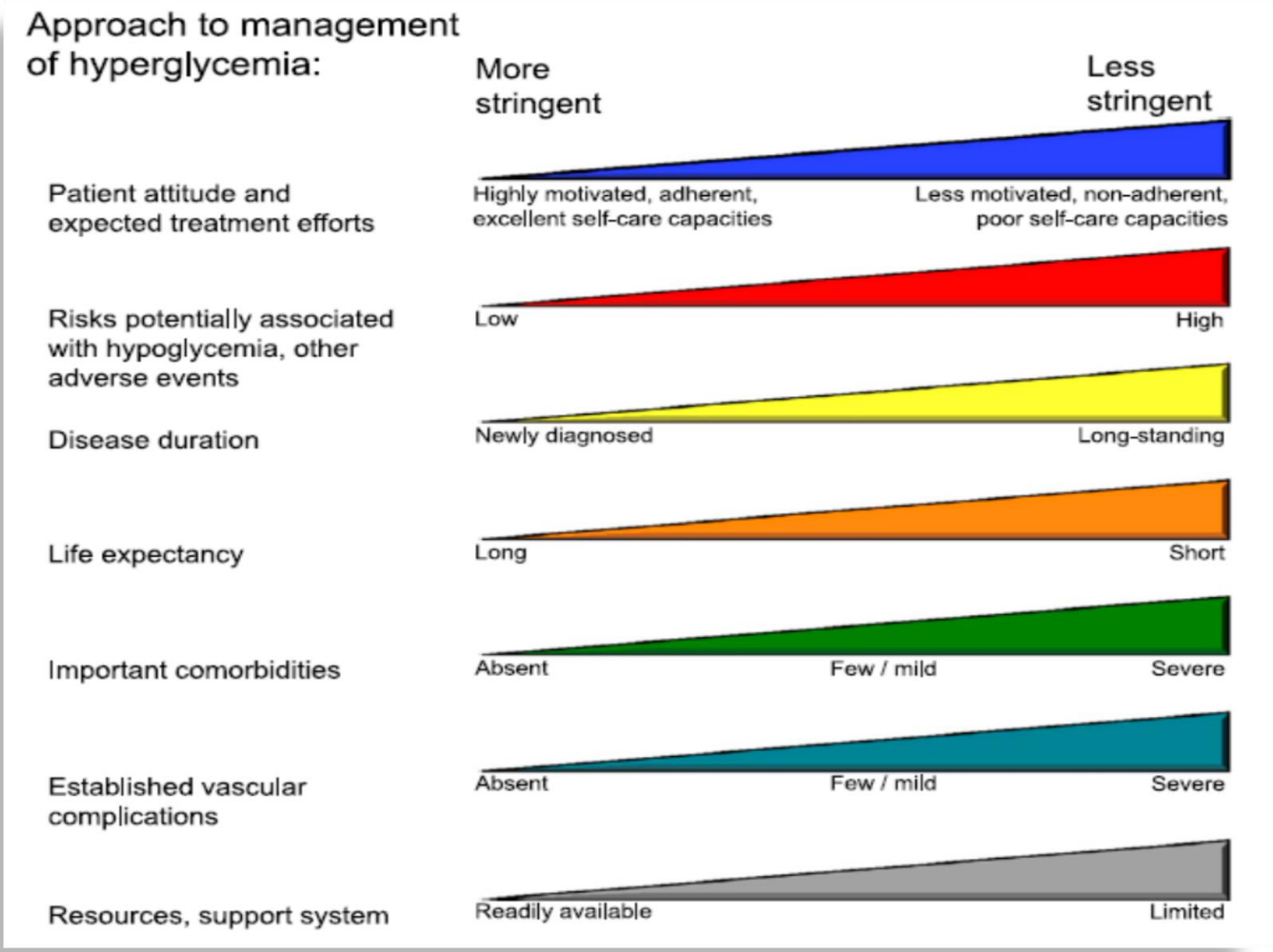
In apparently healthy individuals with risk factors shown in the box, all but the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines provide a strong indication for statin therapy in the range of 56 to 66 years of age. Above 75 years of age, only the National Institute for Health and Care Excellence (NICE) guideline provides a well-defined indication for statin therapy. See Table 1 for risks above which statin therapy is recommended. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; Framingham = Framingham Risk Score for general cardiovascular disease; NA = not applicable; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

FIGURE 4 Conceptual Relationship Between Age and Absolute Benefit of Statin Therapy



Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



Ann Intern Med. 2018;168:569-576. doi:10.7326/M17-0939

Hemoglobin A_{1c} Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians

Guidance Statement 1: *Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.*

Guidance Statement 2: *Clinicians should aim to achieve an HbA_{1c} level between 7% and 8% in most patients with type 2 diabetes.*

Guidance Statement 3: *Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA_{1c} levels less than 6.5%.*

Guidance Statement 4: *Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.*

2013 ESC/ESH TREATMENT THRESHOLDS FOR OLDER PATIENTS

In elderly hypertensive patients drug treatment is recommended when SBP is >=160 mmHg	I	A
Antihypertensive drug treatment may also be considered in the elderly (at least when younger than 80 years) when SBP is in the 140-159 mmHg range, provided that antihypertensive treatment is well tolerated	IIb	C

2018 ESC/ESH TREATMENT THRESHOLDS FOR OLDER PATIENTS

In fit older patients with hypertension (even if aged >80 years), BP lowering drug treatment is recommended when SBP is **>=160 mmHg**	I	A
BP-lowering drug treatment is recommended for fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (**140-159 mmHg**), provided that treatment is well tolerated		
Antihypertensive drug treatment may also be considered in older frail patients if well well tolerated	IIb	B

2013 ESC/ESH TREATMENT TARGETS FOR OLDER PATIENTS

In elderly hypertensives less than 80 years old with SBP >=160 mmHg there is solid evidence to recommend reducing SBP to between **150 and 140 mmHg**	I	A
In fit elderly patients less than 80 years old, target SBP values **< 140 mmHg** may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability	IIb	C
In individual older than 80 years and with initial SBP>=160 mmHg it is recommended to reduce SBP tobetween **150 and 140 mmHg**, if in good physical and mental conditions	I	A

2018 ESC/ESH TREATMENT TARGETS FOR OLDER PATIENTS

In older patients (aged >=65 years) receiving BP lowering drugs: • SBP should be targeted to a BP range of **130-139 mmHg** • Close monitoring of adverse effects is recommended • These BP targets are recommended for patients at any level of CV risk and in patients with and without established CVD	I	A

European Heart Journal (2016) **37**, 2315–2381

2016 European Guidelines on cardiovascular disease prevention in clinical practice

3a.10 Antiplatelet therapy

Key messages

- Antiplatelet therapy is not recommended in individuals free from CVD, due to the increased risk of major bleeding.

Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.	III	B

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

DOI: 10.1056/NEJMoa1805819

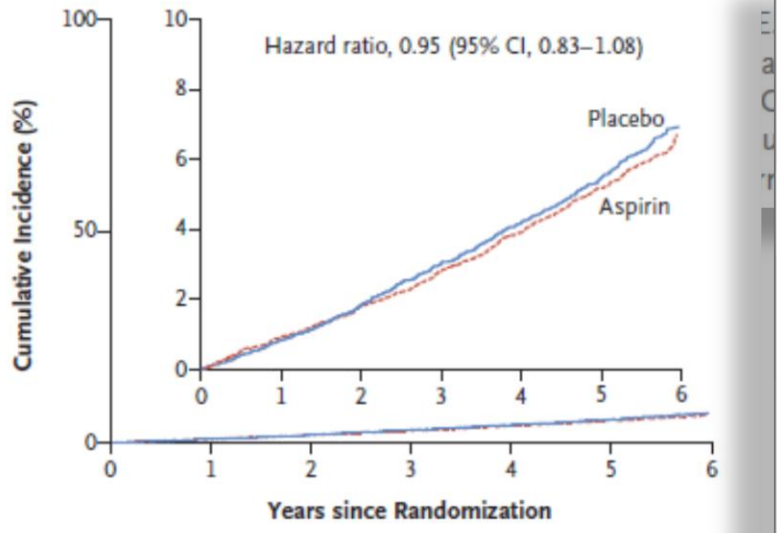


Figure 1. Cumulative Incidence of Cardiovascular Disease.

Shown is the incidence of the prespecified secondary end point of cardiovascular disease (a composite of fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure) according to trial group. The graph stops at year 6 because only a small number of participants (44 in the aspirin group and 43 in the placebo group) reached year 7. The inset shows the same data on an enlarged y axis.

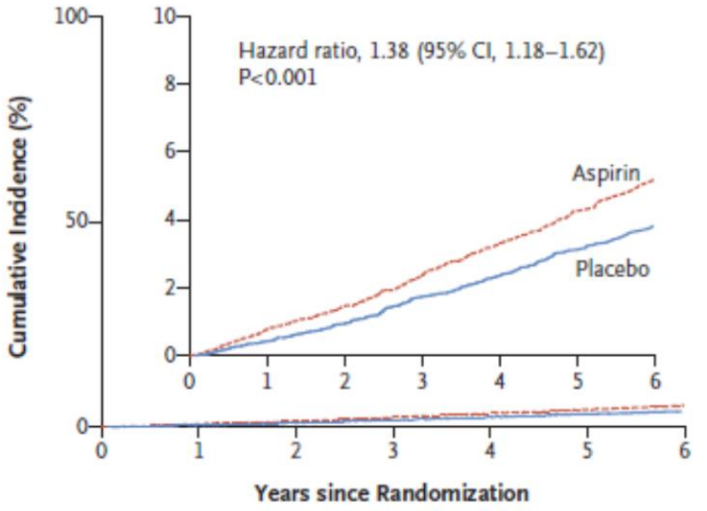


Figure 2. Cumulative Incidence of Major Hemorrhage.

Shown is the incidence of the prespecified secondary end point of major hemorrhage (a composite of hemorrhagic stroke, symptomatic intracranial bleeding, or extracranial bleeding that led to transfusion, hospitalization, prolongation of hospitalization, surgery, or death) according to trial group. The graph stops at year 6 because only a small number of participants (44 in the aspirin group and 43 in the placebo group) reached year 7. The inset shows the same data on an enlarged y axis.

CONCLUSIONS

The use of low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo. (Funded by the

European Heart Journal (2016) **37**, 2315–2381

2016 European Guidelines on cardiovascular disease prevention in clinical practice

3a.10 Antiplatelet therapy

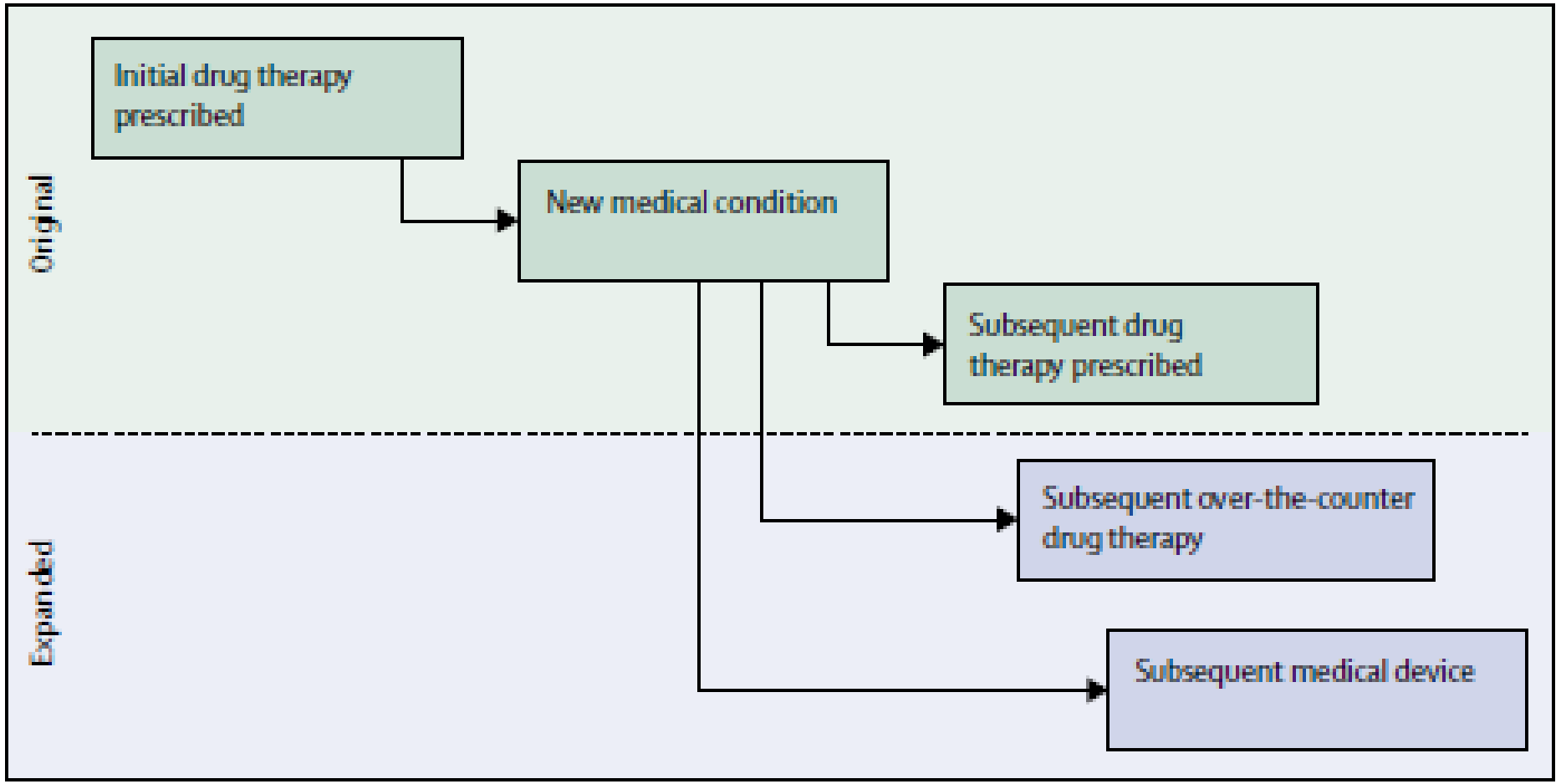
Key messages

- Antiplatelet therapy is not recommended in individuals free from CVD, due to the increased risk of major bleeding.

Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.	III	B

E invece molto spesso l'antiaggregante viene aggiunto, ma si **<u>tutela</u>** il paziente con l'aggiunta di un **inibitore di pompa protonica**

The prescribing cascade revisited



ORIGINAL INVESTIGATION

JAMA Intern Med. 2013;173(7):518-523.

Proton Pump Inhibitors and Risk of 1-Year Mortality and Rehospitalization in Older Patients Discharged From Acute Care Hospitals

Original Investigation | LESS IS MORE

JAMA Intern Med. 2015;175(5):784-791.

Continuous Proton Pump Inhibitor Therapy and the Associated Risk of Recurrent *Clostridium difficile* Infection

Long-term use of proton pump inhibitors, dose–response relationship and associated risk of ischemic stroke and myocardial infarction

JIM Original Article

INAPPROPRIATE PROTON PUMP INHIBITOR PRESCRIPTION IN ELDERLY ADULTS: AS USUAL AS DANGEROUS

JAGS OCTOBER 2015–VOL. 63, NO. 10

poiché l'anziano è estremamente sensibile e vulnerabile agli effetti avversi delle terapie mediche, la prevenzione cardiovascolare nel vecchio non può prescindere dal

- ***Mantenimento e miglioramento dell'autonomia funzionale***
- ***Mantenimento della performance psico-cognitiva***
- ***Prevenzione del danno iatrogeno***
- ***Prevenzione delle cadute***