Torino
4 aprile 2014

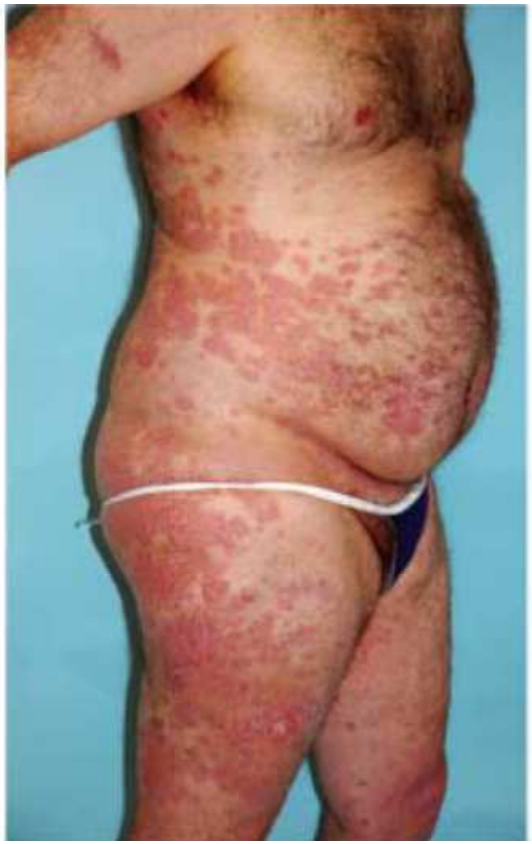
Manifestazioni cardiovascolari e patologie articolari

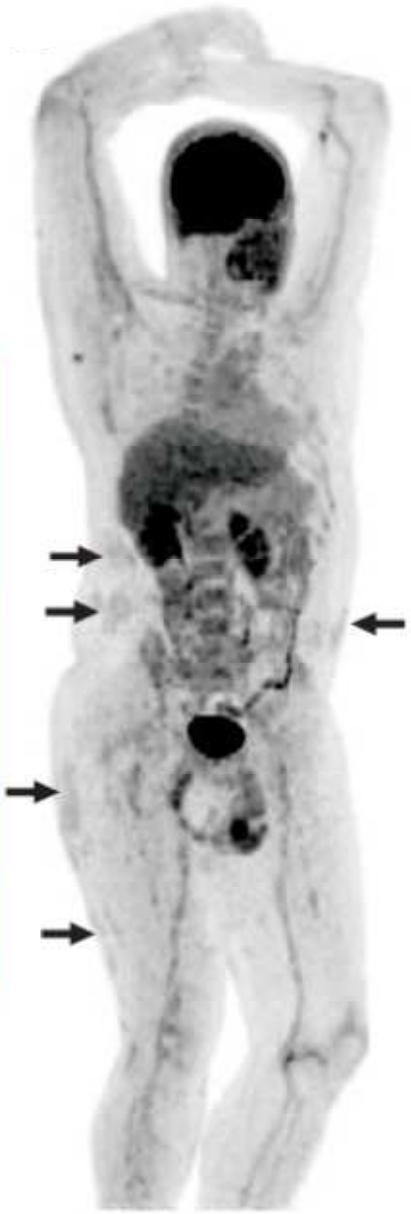
Artrite Psoriasica

A. Marchesoni

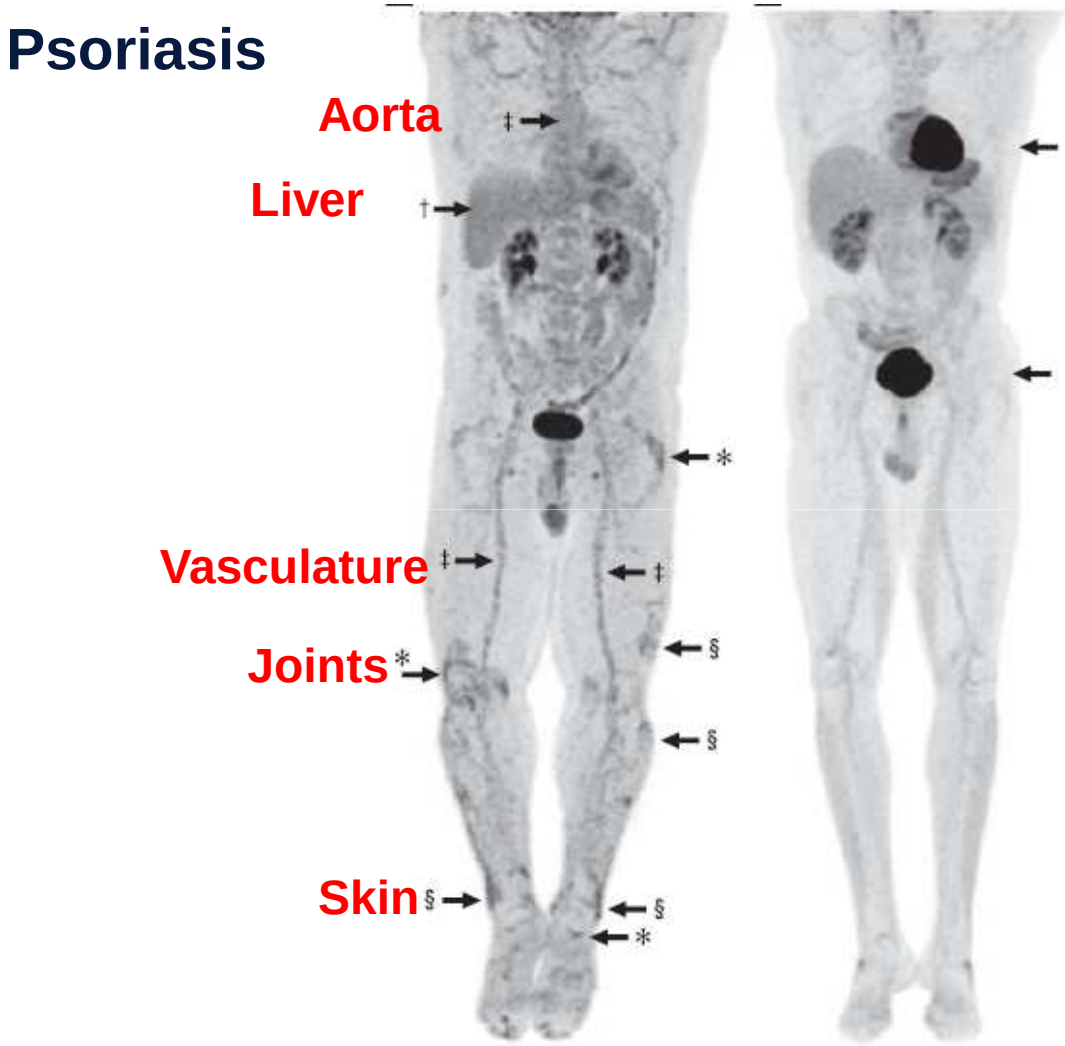
U.O.C. Day Hospital di Reumatologia
Istituto Ortopedico G. Pini, Milano

- **FDG-PET/CT imaging of skin correlates with observed skin inflammation.**
- **Photograph of a patient with psoriasis showing extensive multifocal plaques.**
- **Corresponding PET image from a FDG-PET/CT study in the same patient demonstrates skin inflammation in similar distribution (arrows).**





FDG-PET/CT imaging shows inflammation in skin, liver, vasculature, joints of patients with psoriasis



The systemic, inflammatory nature of psoriasis was recently demonstrated by these positron emission tomography-computed (PET/CT) images

FDG = fluorodeoxyglucose; PET/CT = Positron emission tomography/computed tomography

In the control patient, FDG uptake is noted within the myocardium (top arrow) within the range of normal variation and also seen in the kidneys and bladder (bottom arrow), where FDG is excreted

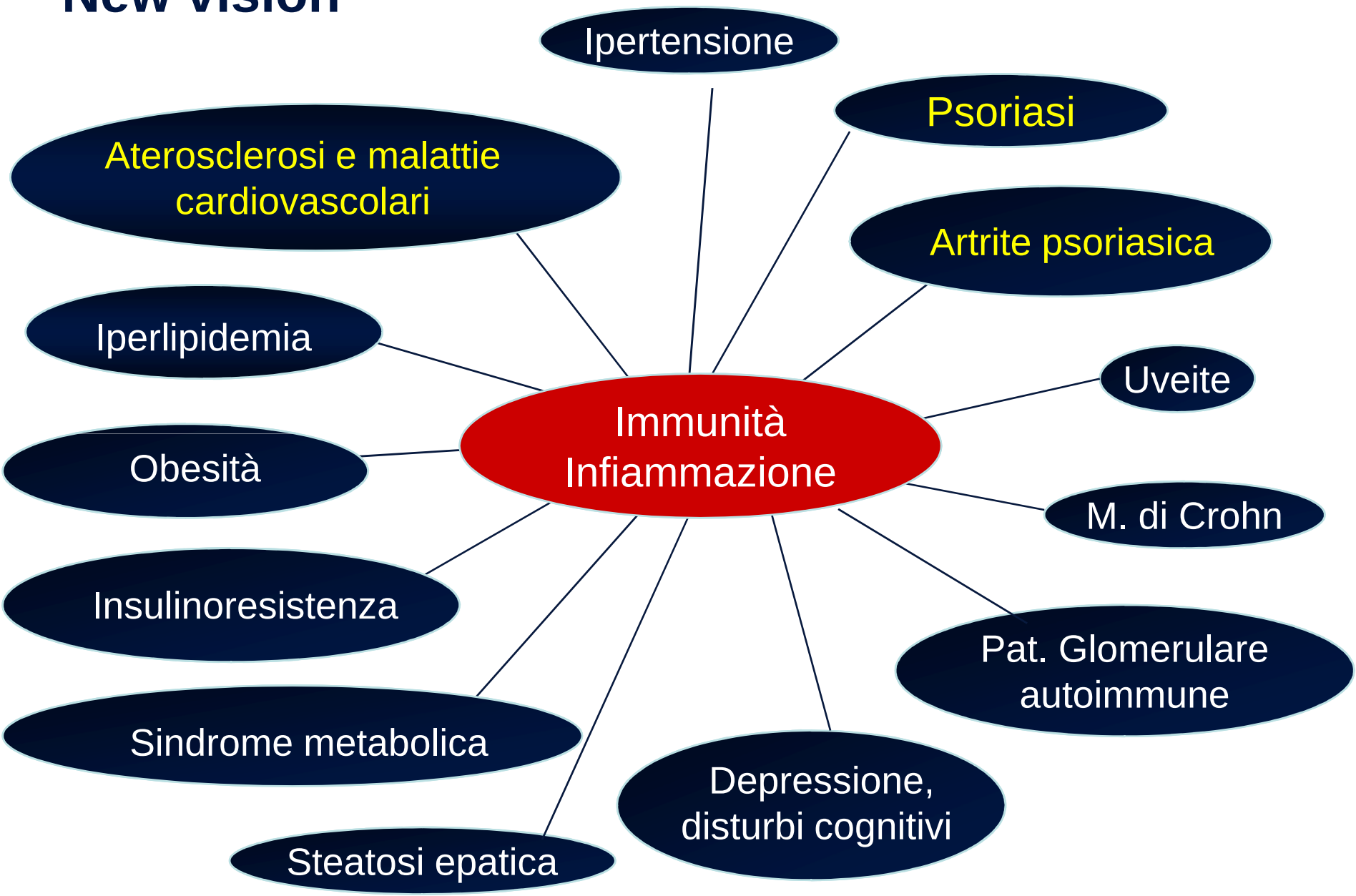
Mehta NN, *et al. Arch Dermatol.* 2011;147:1031–9.

Da malattia della pelle verso un concetto di “malattia sistemica”

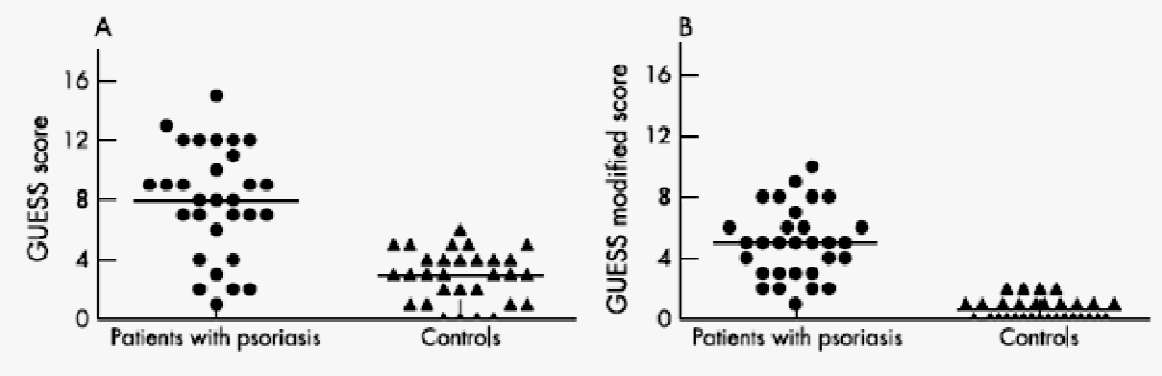
- La psoriasi è stata per lungo tempo considerata una malattia esclusivamente cutanea.
- Più recenti studi indirizzati alla comprensione dei meccanismi fisiopatologici della psoriasi e delle sue co-morbidità hanno evidenziato la **natura sistemica** della malattia.
- Studi di imaging hanno recentemente fornito un significativo contributo alla nuova visione di psoriasi come:

Condizione patologica multi-organo sostenuta da un processo infiammatorio sistemico

New vision


Ipertensione
Psoriasi
Aterosclerosi e malattie cardiovascolari
Artrite psoriasica
Iperlipidemia
Uveite
Immunità Infiammazione
Obesità
M. di Crohn
Insulinoresistenza
Pat. Glomerulare autoimmune
Sindrome metabolica
Depressione, disturbi cognitivi
Steatosi epatica

Sub-clinical or pre-clinical PsA?



Asymptomatic enthesitis in Ps patients

Gisondi P et al, Ann Rheum Dis 2008;67:26

Clinically undetectable arthritis and enthesitis in Ps patients

Naredo E et al, Rheumatol 2011;50:1838

Group	Synovitis	Synovial PD signal	Enthesopathy	Entheseal PD signal
Patients in psoriasis group, *n* (%)	69 (50.7)	13 (9.6)	85 (62.5)	10 (7.4)
Patients in control group, *n* (%)	15 (32.6)	3 (6.5)	18 (39.1)	0 (0)
P-values	0.024	0.529	0.005	0.050
Sites in psoriasis group, *n* (%)	147 (3.2)	18 (0.4)	285 (11.6)	15 (0.6)
Sites in control group, *n* (%)	21 (1.3)	3 (0.2)	44 (5.3)	0 (0)
P-values	<0.0005	0.183	<0.0005	0.013

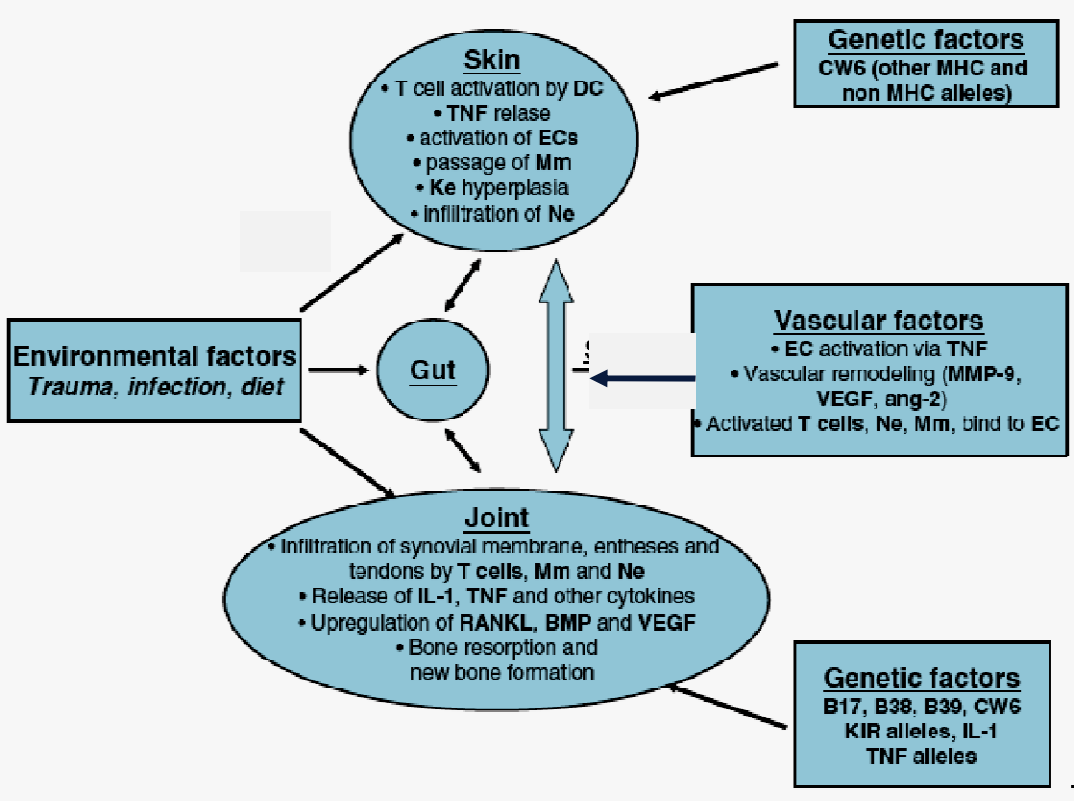
EDITORIAL JADV 2010; 24:627

Psoriatic disease: concepts and implications

R Scarpa,[†,*] G Altomare,[‡] A Marchesoni,[§] N Balato,[¶] M Matucci Cerinic,[**] T Lotti,[††] I Olivieri,[‡‡] GA Vena,[§§] C Salvarani,[¶¶] G Valesini,[***] A Giannetti[‡‡‡]

Psoriatic disease is a disorder that involves several different compartments in the same patient:

- skin
- enthesis-joint-bone
- subcutaneous fat tissue
- gut
- uvea
- liver
- arteries
- heart
- others?



Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review

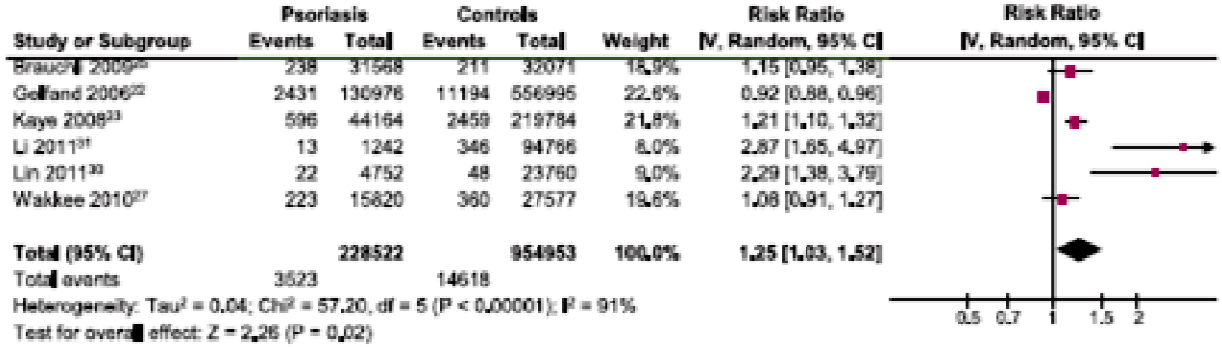


Figure 2 Meta-analysis of cohort studies: risk of myocardial infarction in psoriasis.

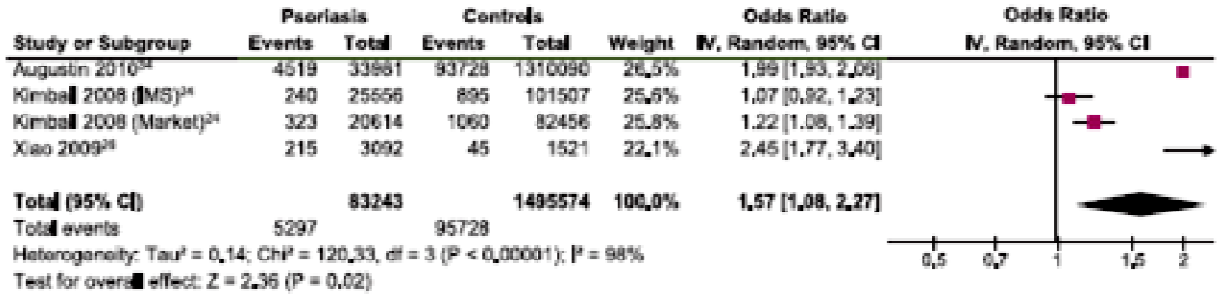


Figure 3 Meta-analysis of cross-sectional studies: risk of myocardial infarction in psoriasis.

Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review

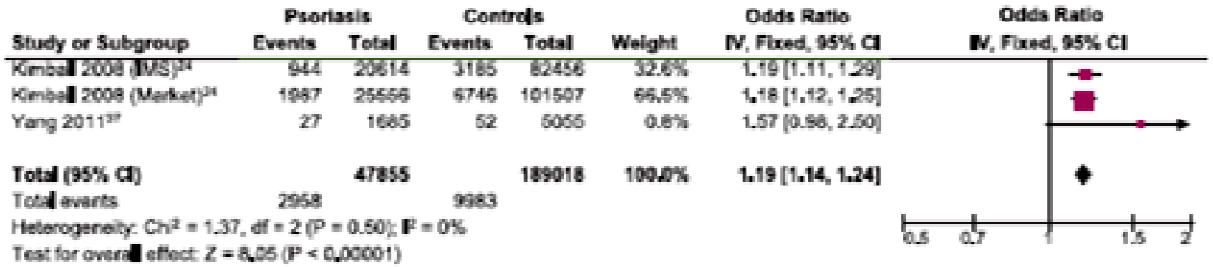


Figure 4 Meta-analysis of cross-sectional studies: risk of coronary artery disease in psoriasis.

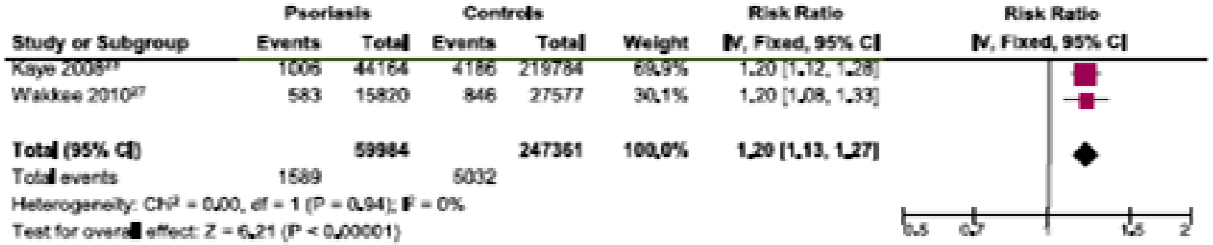


Figure 5 Meta-analysis of cohort studies: risk of coronary artery disease in psoriasis.

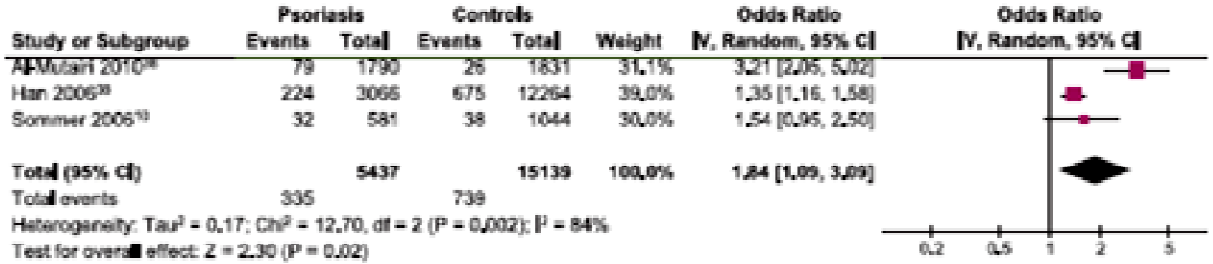
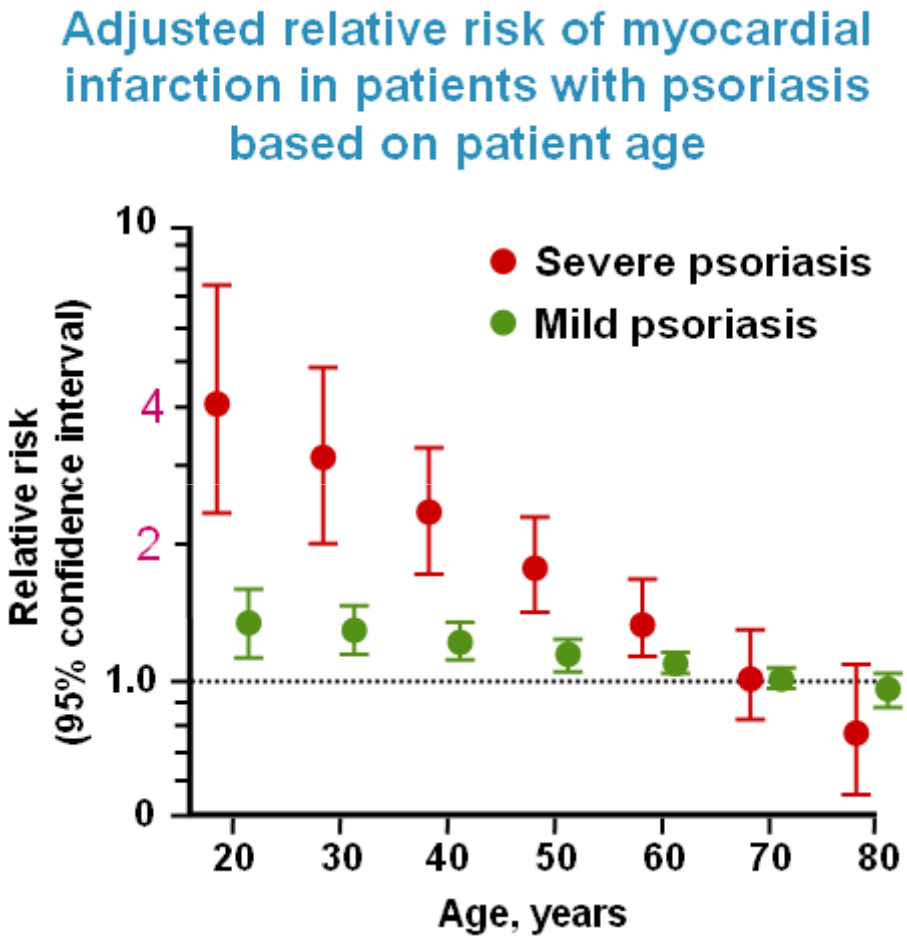


Figure 6 Meta-analysis of case–control studies: risk of coronary artery disease in psoriasis.

Myocardial infarction is common among patients with psoriasis

- Psoriasis patients had a higher incidence of myocardial infarction than controls; highest rate in severe* disease
- Highest relative risk for myocardial infarction occurred in younger patients
  - RR: 1.29 and 3.10 in a 30-year-old patient with mild of severe psoriasis



*Patients with psoriasis were classified as severe if they ever received a systemic therapy.

Gelfand JM, *et al. J Am Med Assoc* 2006;296(14):1735–41.

Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review

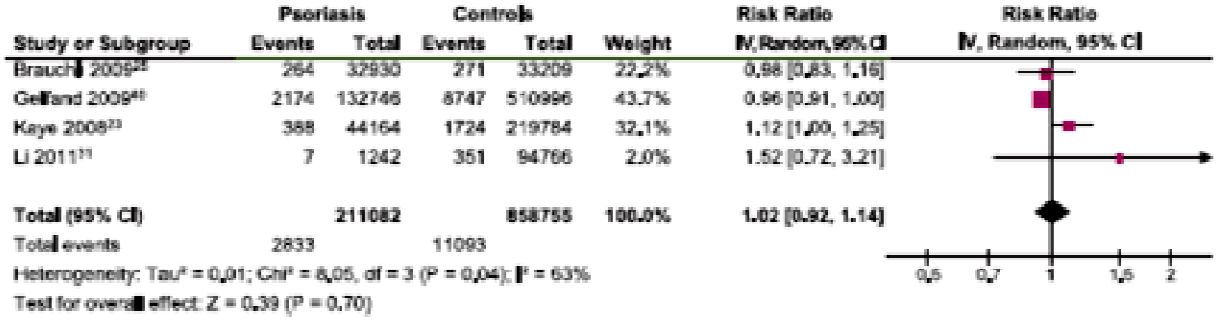


Figure 7 Meta-analysis of cohort studies: risk of stroke in psoriasis.

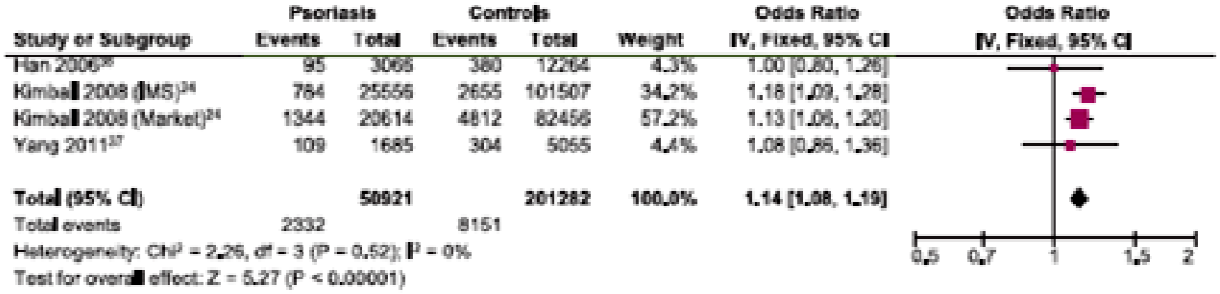
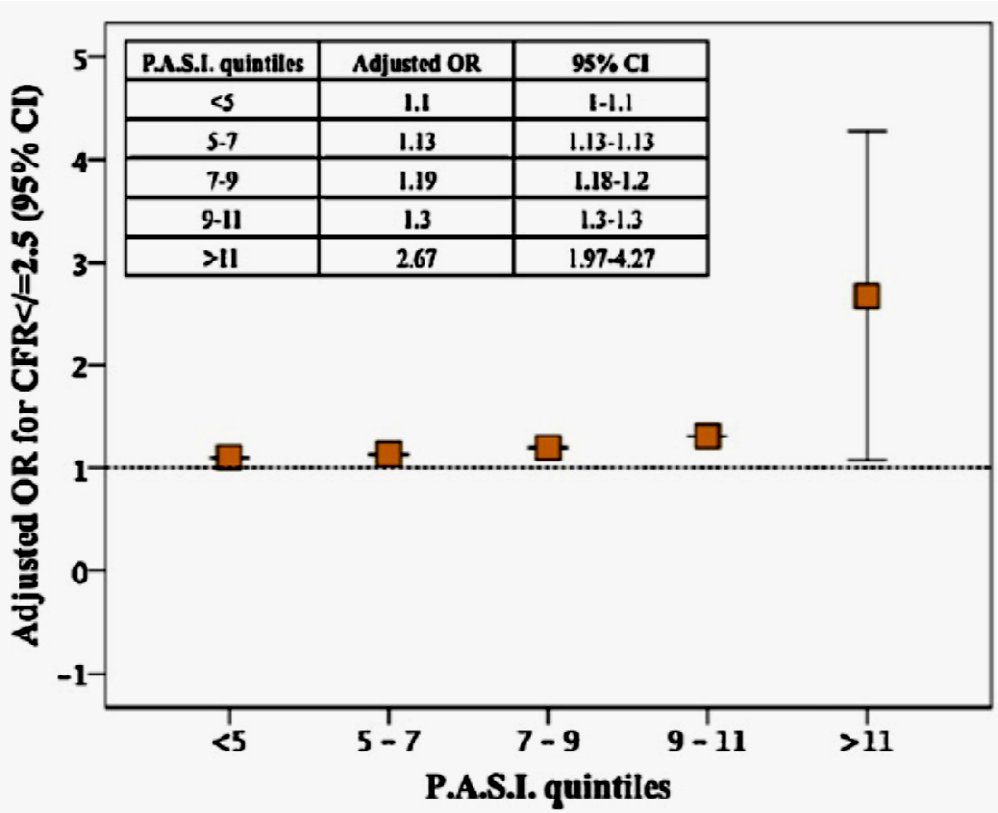


Figure 8 Meta-analysis of cross-sectional studies: risk of stroke in psoriasis.

Impaired coronary flow reserve in young patients affected by severe psoriasis

Elena Osto[a,1], Stefano Piaserico[b,1], Anna Maddalozzo[a], Giulia Forchetti[b], Roberta Montisci[c], Giulia Famoso[a], Andrea Giovagnoni[d], Andrea Peserico[b], Sabino Iliceto[a], Francesco Tona[a,*]



CFR in young pts with severe Pso without coronary disease is reduced suggesting a coronary microvascular dysfunction, independently related to the severity and extension of Pso. This early microvascular impairment might be hypothesized as the consequence of prolonged and sustained systemic inflammation and might explain the increased cardiovascular risk conferred by Pso

Cardiovascular comorbidities in patients with psoriatic arthritis: a systematic review

Type of study	Comparison group	Subjects; total number (ascertainment procedures); gender distribution; age, years	Time period	Statistical analyses	Findings
Cross-sectional study; patient source: PharMetrics Patient-Centric Database, USA	Four matched controls: sex, age, geographical region, previous length of time in plan	3066 PsA patients (ICD-9);49.7±11.2 years	2001–2	Age and sex adjusted prevalences of comorbidities; the prevalence ratios were estimated by Cochran–Mantel–Haenszel method	Increased prevalence of:* ischaemic heart disease (7.3%); peripheral vascular disease (2.9%); congestive heart failure (1.9%); cerebrovascular disease (3.1%)
Prospective cohort	Canadian Community Health Survey	648 PsA patients (inflammatory arthritis associated with psoriasis); 56% male; 43.5 years	1978–2004	Cross-sectional examination with age and gender matched groups; SPR were calculated; Cox relative risk regression analysis	Increased SPR:* angina (SPR 1.97); myocardial infarction (SPR 2.57)
Single-centre study	Comparison with 353 RA patients[43]	489 PsA patients aged between 50 and 75 years (according to Moll and Wright criteria)	2010	Logistic regression analysis	Cardiovascular disease defined as a history of myocardial infarction and/or stroke and/or transient ischaemic attack; prevalence of cardiovascular disease in PsA was 10% compared to 12% in RA; OR 0.78; 95% CI 0.51 to 1.20, p=0.26; also age and sex stratified OR were not different between RA and PsA
Population-based study	General population of Denmark (n=4 003 265)	607 PsA patients (ICD-8 and 10); age and gender distribution of PsA patients are lacking	1997–2006	RR and 95% CI; Poisson regression models; confounders: age, calendar year, concomitant medication use, comorbidity, socioeconomic data, gender	Increased cardiovascular risk in PsA patients; RR 1.79; 95% CI 1.31 to 2.45†

Cardiovascular comorbidities in patients with psoriatic arthritis: a systematic review

Mortality

Two out of three observational cohort studies demonstrated a higher standardised mortality rate (SMR): 1.6 and 1.4, respectively.[11 13] Data from these two studies were derived from the same cohort, but from different time periods, demonstrating an increased overall mortality risk over nearly four decades of follow-up, but the mortality risk declined over time.[11 13] Moreover, increased mortality appeared to be associated with disease severity, as indicated by a high erythrocyte sedimentation rate (ESR) and radiological damage.[16] In contrast, a more recent cohort study following 453 patients with PsA for 22 years did not observe increased mortality with a combined SMR for men and women of 81.82% (95% CI 57.61 to 112.78).[12] However, cardiovascular disease was the leading cause of death (38%).[12]

With regard to the available population-based studies, only one out of three studies reported increased mortality.[7]

Ann Rheum Dis 2013;**72**:211-

Cardiovascular and other comorbidities in patients with psoriatic arthritis: A comparison with patients with psoriasis

Abstract

Objective

To determine whether the presence of psoriatic arthritis (PsA) is associated with greater comorbidity, in particular cardiovascular morbidity, compared to psoriasis without arthritis.

Methods

Six hundred eleven patients with PsA were recruited from the University of Toronto Psoriatic Arthritis Clinic and 449 psoriasis without arthritis patients were recruited from the University of Toronto Psoriasis Cohort. The clinical database was used to identify the prevalence of cardiovascular and other comorbidities in both PsA and psoriasis without arthritis patients. Univariate and multivariate logistic regression analyses were conducted to estimate odds ratios (ORs), comparing the odds of ever having a given comorbid disease in PsA patients with those in psoriasis without arthritis patients. Covariates included age, sex, education, smoking status, severity and duration of psoriasis, medication status, and other comorbidities.

Results

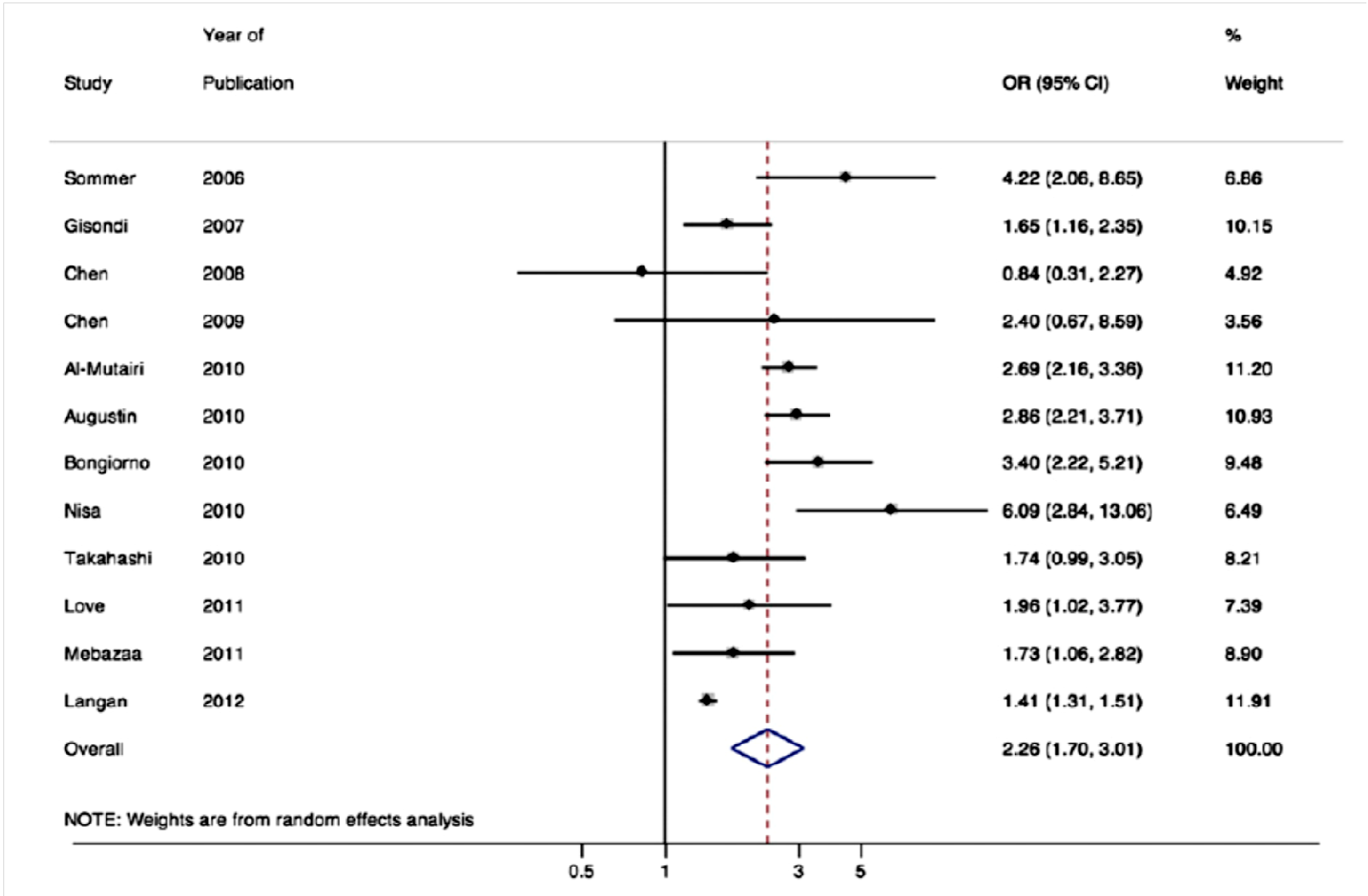
The prevalence of hypertension, obesity, hyperlipidemia, type 2 diabetes mellitus, and at least 1 cardiovascular event in PsA patients was 37.1%, 30.0%, 20.7%, 12.0%, and 8.2%, respectively. This was significantly higher than in psoriasis without arthritis patients, with unadjusted ORs ranging from 1.54 to 2.59. In the multivariate analyses, hypertension remained significantly elevated (adjusted OR 2.17). PsA was also significantly associated with infections not treated with antibiotics (presumably viral), neurologic conditions, gastrointestinal disorders, and liver disease (adjusted ORs 2.83, 4.76, 21.53, and 7.74, respectively). Infections treated with antibiotics and depression/anxiety were relatively common in PsA, with a prevalence of 30.5% and 20.7%, respectively. However, this was not significantly different from psoriasis without arthritis after multivariate adjustments.

Conclusion

The results suggest that inflammatory joint disease may play a role in both cardiovascular and noncardiovascular morbidity in PsA.

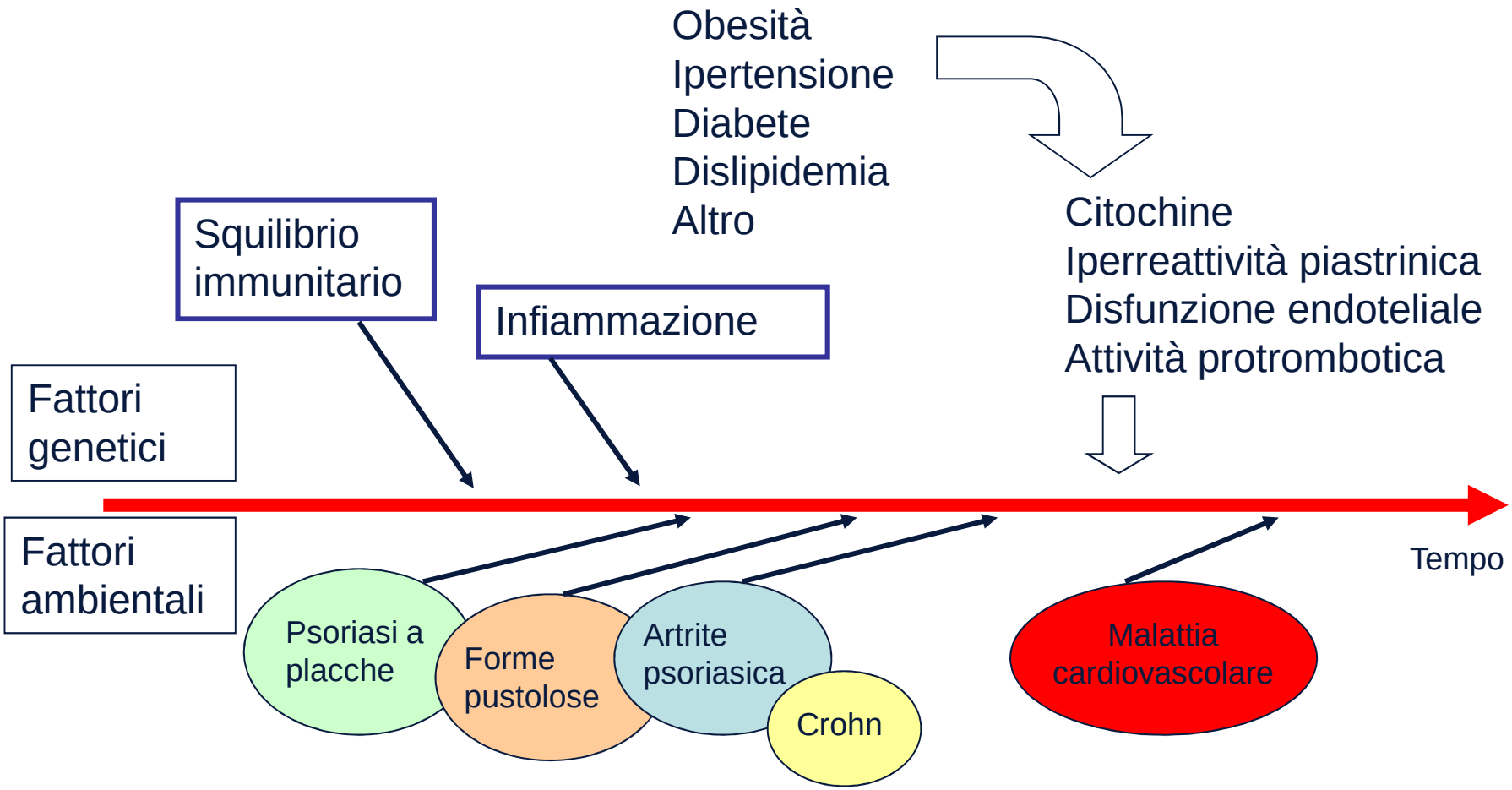
Husted JA et al. Arthritis Care Res 2011;63:1729

Psoriasis and metabolic syndrome: A systematic review and meta-analysis of observational studies



(J Am Acad Dermatol 10.1016/j.jaad.2012.08.015.)

Comorbidities in psoriasis



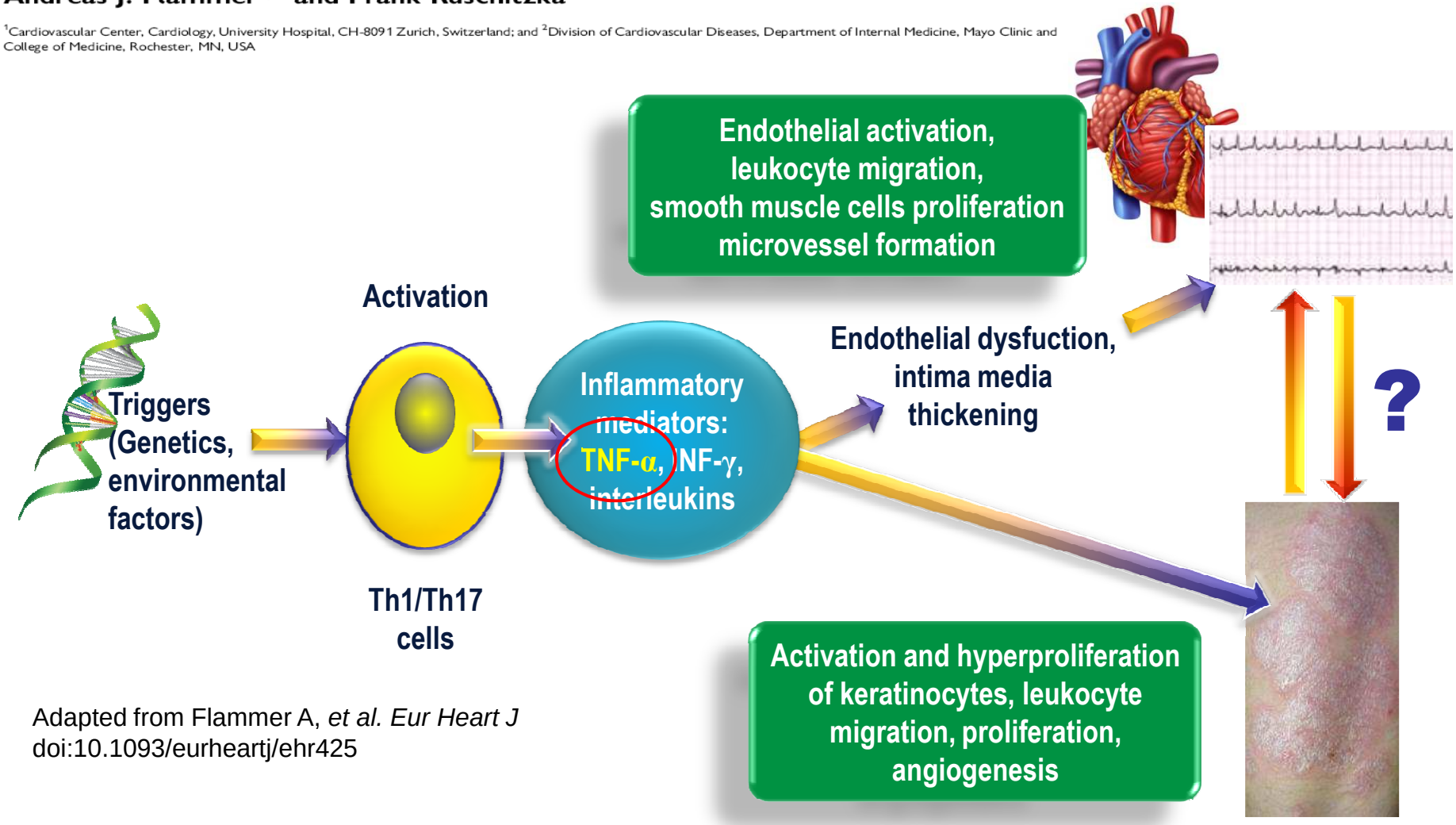
European Heart Journal
doi:10.1093/eurheartj/ehr425

EDITORIAL

Psoriasis and atherosclerosis: two plaques, one syndrome?

Andreas J. Flammer[1,2] and Frank Ruschitzka[1]*

[1]Cardiovascular Center, Cardiology, University Hospital, CH-8091 Zurich, Switzerland; and [2]Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic and College of Medicine, Rochester, MN, USA



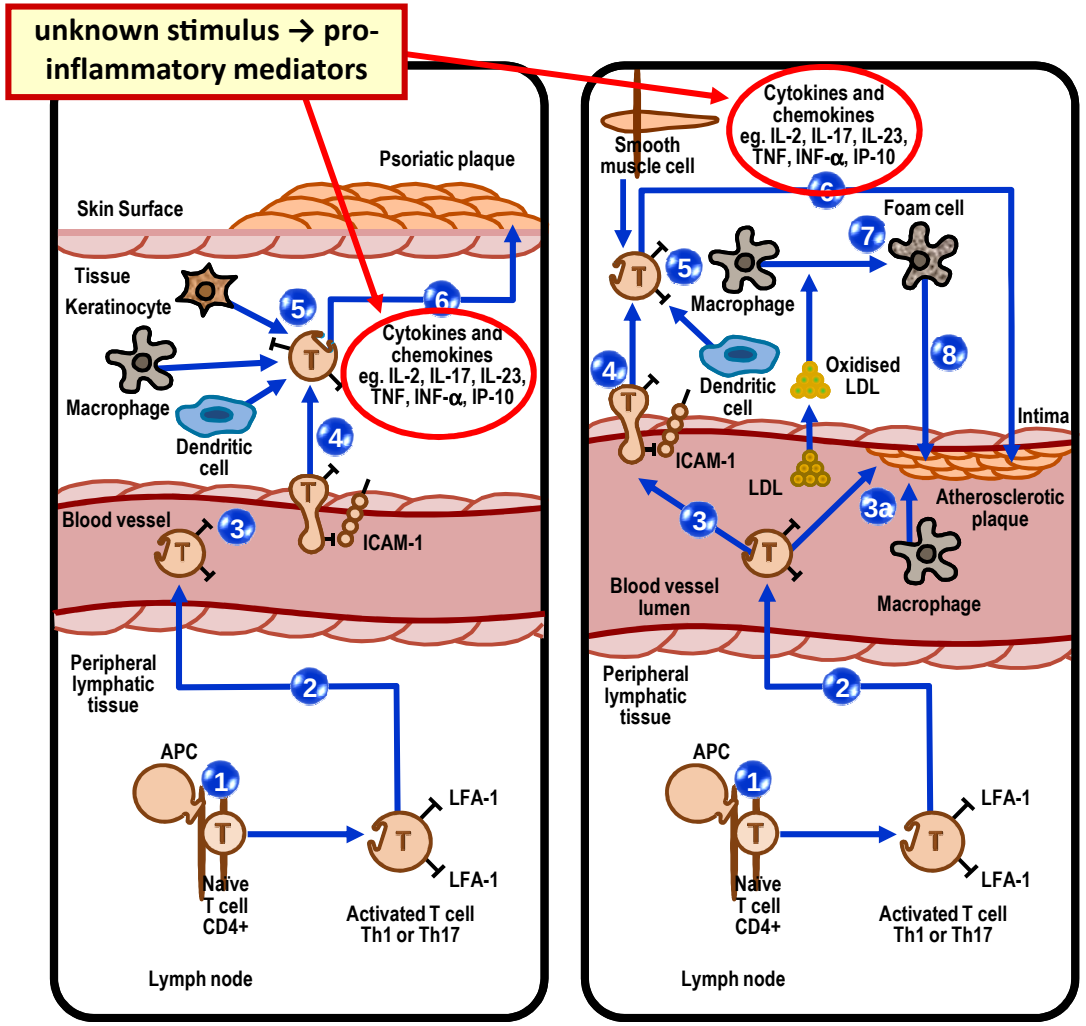
Adapted from Flammer A, *et al. Eur Heart J* doi:10.1093/eurheartj/ehr425

Caratteristiche comuni nella formazione della placca psoriasica e ateromatosa

1. Antigen-presenting cells (APC) activate T cells
   - LFA-1 expression ↑
2. Activated T cells → blood vessel
3. - Adhere to endothelium, and

3a. - Collect on endothelium with macrophages

4. Extravasation of T cells
5. T cell interacts with smooth muscle cells/ keratinocytes, and other cells
6. T cells and macrophages secrete chemokines and cytokines, inducing formation of:
   (a) psoriatic plaque, or
   (b) atherosclerotic plaque
7. Macrophages take up oxidized LDL → foam cells
8. 'Fatty streaks' form (subendothelium) → atherosclerotic plaques



Psoriatic plaque[1] **Atherosclerotic plaque[1]**

Adapted from:
Späh F, *et al. British Journal of Dermatology* 2008;159:10–17

International Journal of Dermatology 2010, **49**, 642–646

Is psoriasis a pre-atherosclerotic disease? Increased insulin resistance and impaired endothelial function in patients with psoriasis

Abstract

Background Several studies have shown an association between psoriasis and atherosclerotic risk factors. In this study, we aimed to evaluate endothelial function by flow-mediated dilation (FMD) and insulin resistance by Homeostasis model assessment-insulin resistance (HOMA-IR).

Methods We examined 75 consecutive psoriasis patients and 50 healthy controls. All subjects underwent transthoracic echocardiography and brachial artery imaging for detecting FMD. Fasting blood samples were drawn from all subjects for measuring insulin, C-peptide, fasting blood glucose. HOMA-IR was calculated.

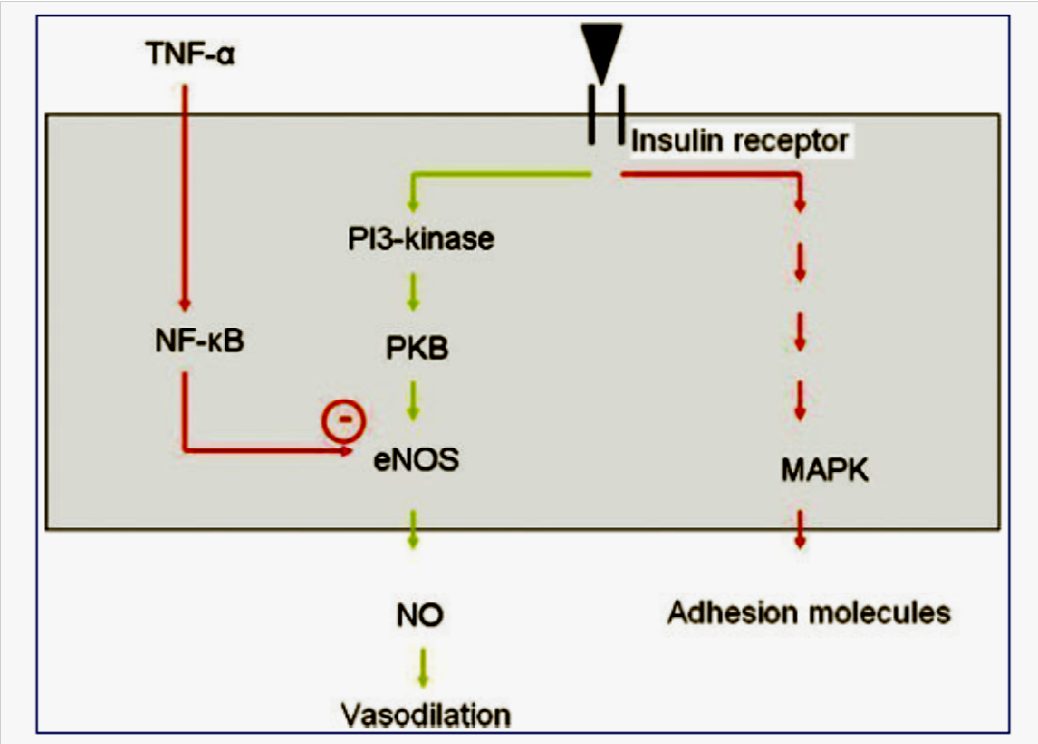
Results Baseline characteristics of both groups were similar. Twenty-four psoriatic patients had arthritis. Insulin [9.3 (4.0–208.1) vs. 8.2 (2.3–16.5) mcIU/ml, $P = 0.016$] and C-peptide [2.5 (0.9–20.0) vs. 2.0 (0.9–3.7) ng/ml, $P = 0.009$] levels were significantly higher in patients with psoriasis than in controls. HOMA-IR [2.1 (0.8–68.9) vs. 1.8 (0.6–8.6), $P = 0.036$] was significantly higher in patients with psoriasis than in controls. FMD was reduced in patients with psoriasis compared with healthy controls (5.6 ± 1.9% vs. 10.9 ± 1.9%, $P < 0.001$).

Conclusions This study demonstrated a significant impairment in endothelial function and increased insulin resistance in patients with psoriasis. This is a comprehensive study for identifying atherosclerotic risk factors in psoriasis. We suggest that psoriatic patients should be paid attention for atherosclerosis and its risk factors.

JDDG Journal of the German Society of Dermatology
Review Article
DOI: 10.1111/j.1610-0387.2009.07083.x

Psoriasis – a systemic inflammatory disorder: clinic, pathogenesis and therapeutic perspectives

Wolf-Henning Boehncke[1], Wolfram Sterry[2]

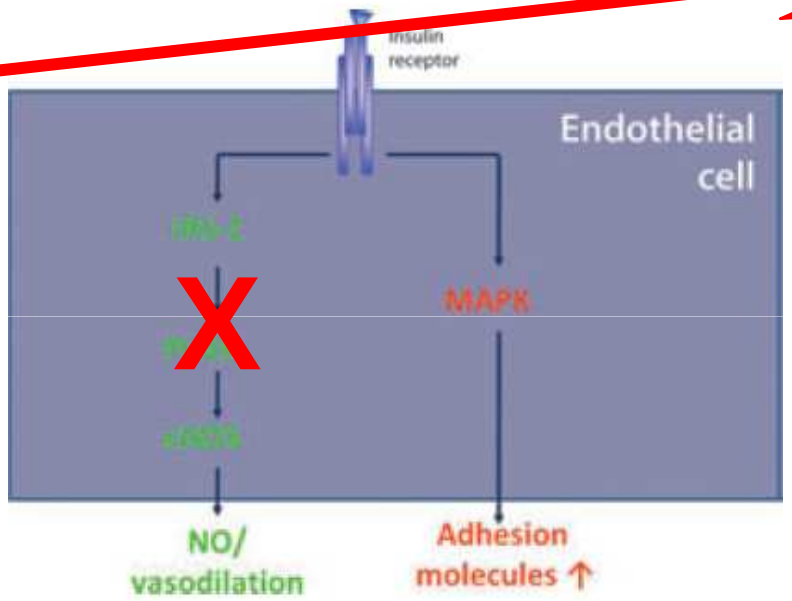


Insulin resistance as the molecular basis for endothelial dysfunction. Physiologically, insulin is a vasodilating hormone through induction of NO production. Inflammation, namely TNF-, blocks the production of NO. Moreover, at the state of insulin resistance, insulin's mitogenic effects are still effectively mediated through the MAPK pathway

L’infiammazione distrugge l’equilibrio endoteliale

Insulino-resistenza

Infiammazione sistemica



Cascata PI(3)K/PKB
- Uptake del glucosio
- Espressione ridotta delle molecole di adesione (adesione ridotta delle piastrine)
- Produzione di prostaglandine (aggregazione ridotta delle piastrine)
- NO produzione (vasodilatazione)

Cascata MAP
- Secrezione di Endotelina-1 (vasocostrizione)
- Espressione delle molecole di adesione

Anti-aterogenico, anti-trombotico

Pro-aterogenico, pro-trombotico

Boehncke WH, *et al. Exp Dermatol* 2011;20(4):303–7; Boehncke WH, et al. Hautarzt 2009;60:116–21.

eNOS, endothelial nitric oxide synthase; IRS-1, insulin receptor substrate 1; MAPK, mitogen-activated protein kinase; NO, nitric oxide; P1(3)K, phosphoinositide-3-kinase.

Ipertesione: pressione arteriosa sistolica ≥160 o diastolica 95 mmHg o trattamento specifico
border line: pressione arteriosa sistolica fra 140 e 159 o pressione arteriosa diastolica fra 90 e 94 mmHg.

Ipercolesterolemia: colesterolemia ≥240 mg/dl o trattamento specifico
border line: colesterolemia fra 200 e 239 mg/dl.

Diabete: glicemia ≥126 mg/dl o trattamento specifico.
border line: glicemia fra 110 e 125 mg/dl.

Sindrome metabolica: presenza di tre o più delle seguenti componenti:

- obesità centrale (circonferenza vita >102 cm negli uomini e >88 cm nelle donne)
- alterata regolazione della glicemia (glicemia a digiuno ≥110 mg/dl) o pregressa diagnosi di diabete
- trigliceridemia elevata (≥150 mg/dl)
- colesterolemia - HDL bassa (<40 mg/dl negli uomini e <50 mg/dl nelle donne)
- pressione arteriosa elevata (≥130/85 mmHg) o in trattamento antipertensivo.

Abitudine al fumo: viene considerato fumatore chi fuma anche solo una sigaretta al giorno, a settimana o al mese; non fumatori ed ex fumatori sono considerate quelle persone che hanno smesso di fumare da almeno un anno.

Sovrappeso: indice di massa corporea 25,0-29,9 Kg/m².

Obesità: indice di massa corporea (IMC) ≥ 30 Kg/m².

Adiposità addominale:

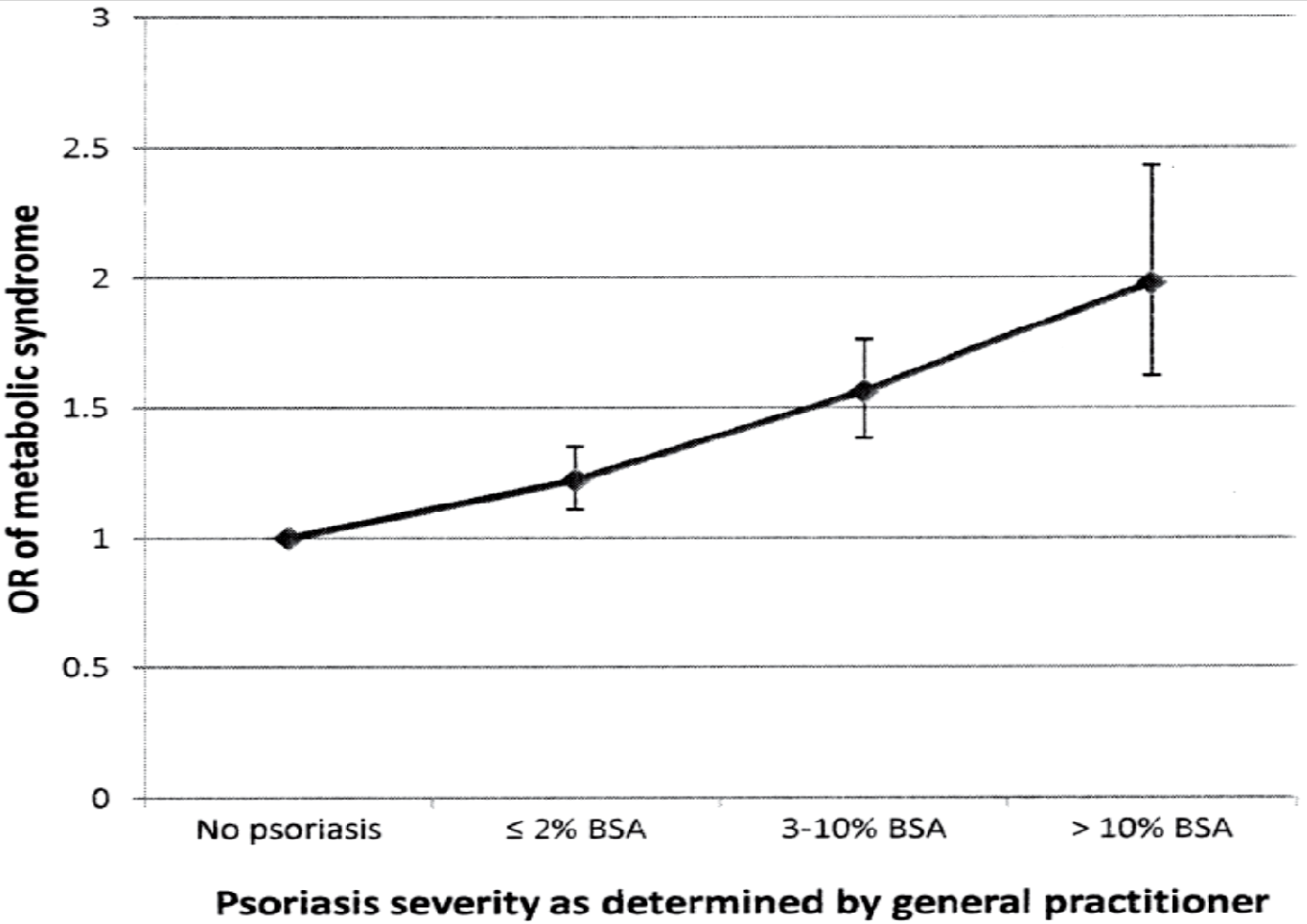
- **circonferenza vita** > 102 cm negli uomini e 88 cm nelle donne
- **rapporto vita/fianchi** > 0,95 negli uomini e 0,85 nelle donne.

Sedentarietà: riguarda la sedentarietà nel tempo libero e nell'attività lavorativa.

Familiarità: la familiarità per malattie cardiovascolari aterosclerotiche viene indagata con domande riguardanti familiari consanguinei di primo grado (genitori, fratelli/sorelle, figli) ammalati o deceduti in età < 55 anni negli uomini e < 65 anni nelle donne a causa di ictus e infarto del miocardio.

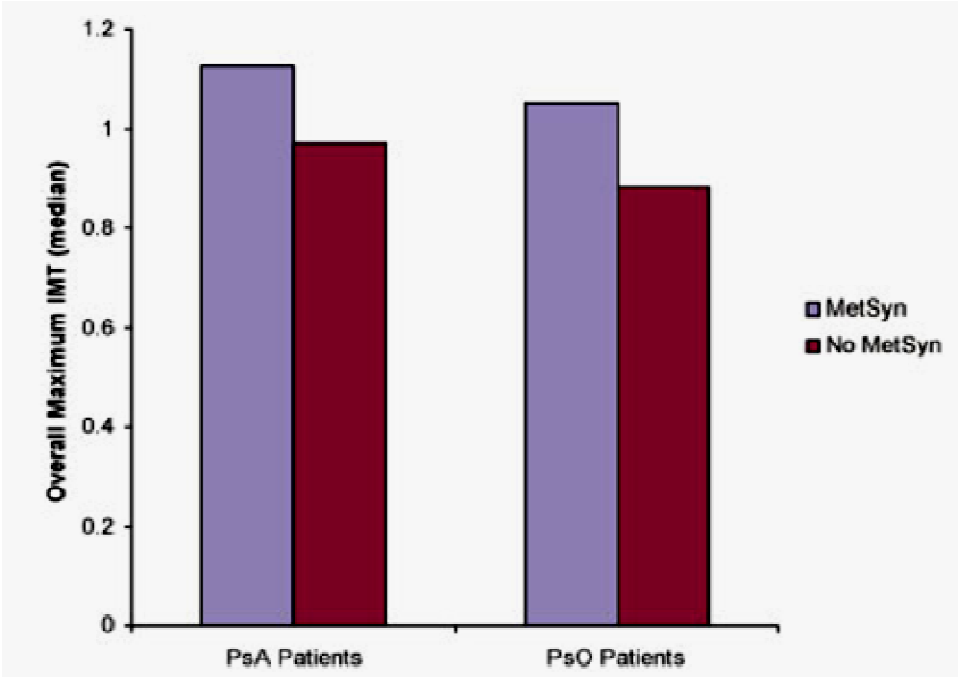
Rischio cardiovascolare globale assoluto: probabilità di essere colpiti da un evento fatale o non fatale coronarico o cerebrovascolare nei successivi 10 anni. È costruito sulla base di otto fattori di rischio (età, sesso, abitudine al fumo, diabete, colesterolemia totale e HDL, pressione sistolica, terapia antipertensiva).

Prevalence of metabolic syndrome in patients with psoriasis: A population-based study in the United Kingdom



J Invest Dermatol. 2012 March ; 132(3): 556–562. doi:10.1038/jid.2011.365.

Relationship between MetSyn and carotid intima-media thickness: comparison between psoriasis and psoriatic arthritis



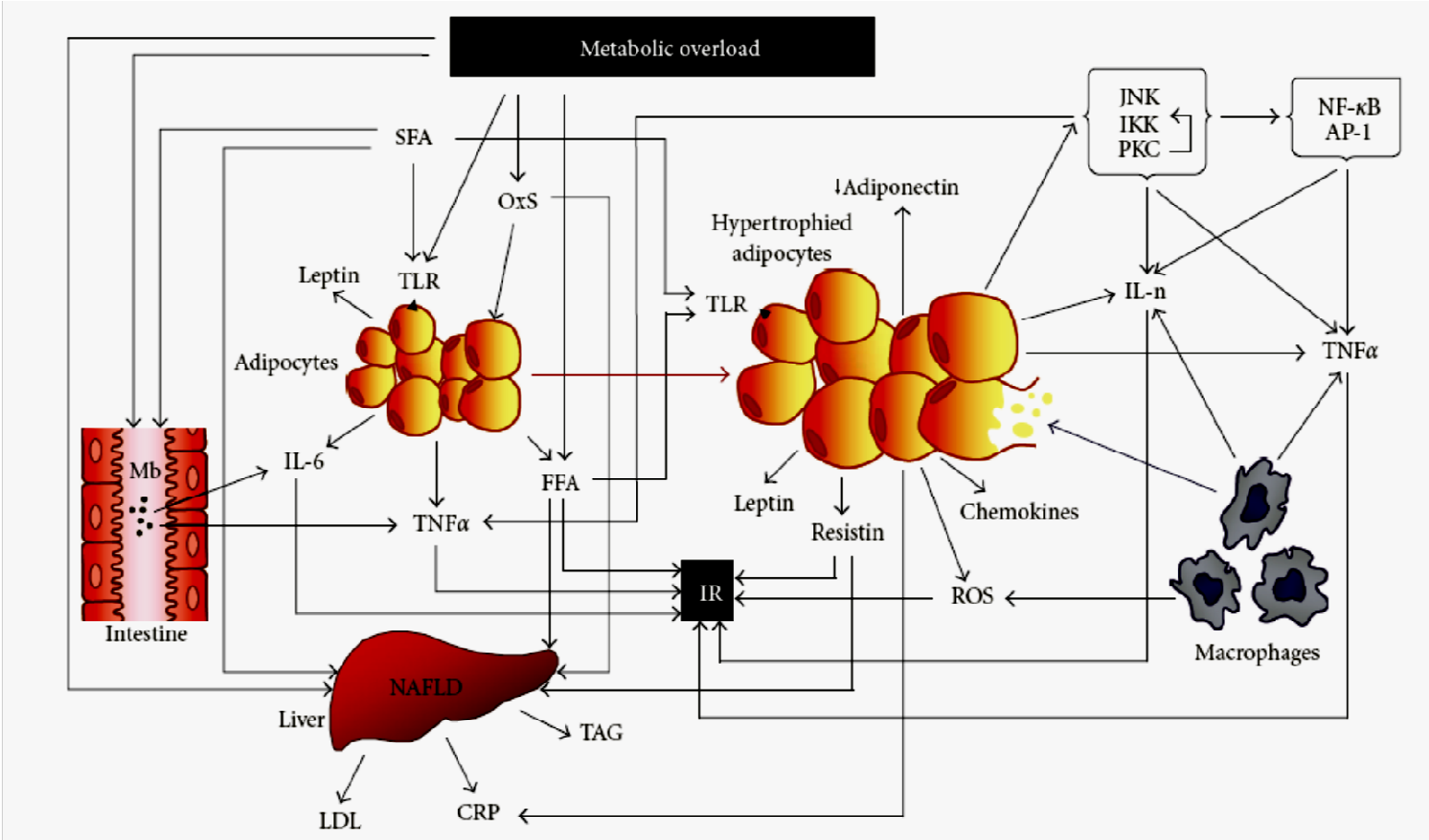
	Psoriasis patients		PsA patients		
	No metabolic syndrome (n = 83)	Metabolic syndrome (n = 34)	No metabolic syndrome (n = 55)	Metabolic syndrome (n = 43)	*P*
Maximum IMT, median (Q1, Q3)	0.88 (0.75, 1.06)	1.05 (0.9, 1.19)	0.98 (0.88, 1.25)	1.13 (0.92, 1.31)	< 0.001
Plaque, no. (%)	28 (33.7)	12 (35.3)	13 (23.6)	22 (51.2)	0.43

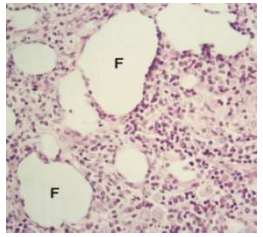
* IMT = intima-media thickness; PsA = psoriatic arthritis.

Lin YH et al. Arthritis Care Res 2014;66:97

Tessuto adiposo ed infiammazione

Adipose tissue functions as an endocrine organ, releasing pro-inflammatory and adipocyte-derived cytokines such as **TNF-α**, leptin, resistin, and adiponectin, which are thought to constitute an important link between obesity and insulin resistance. These cytokines can also contribute to an increased risk for atherosclerotic diseases.

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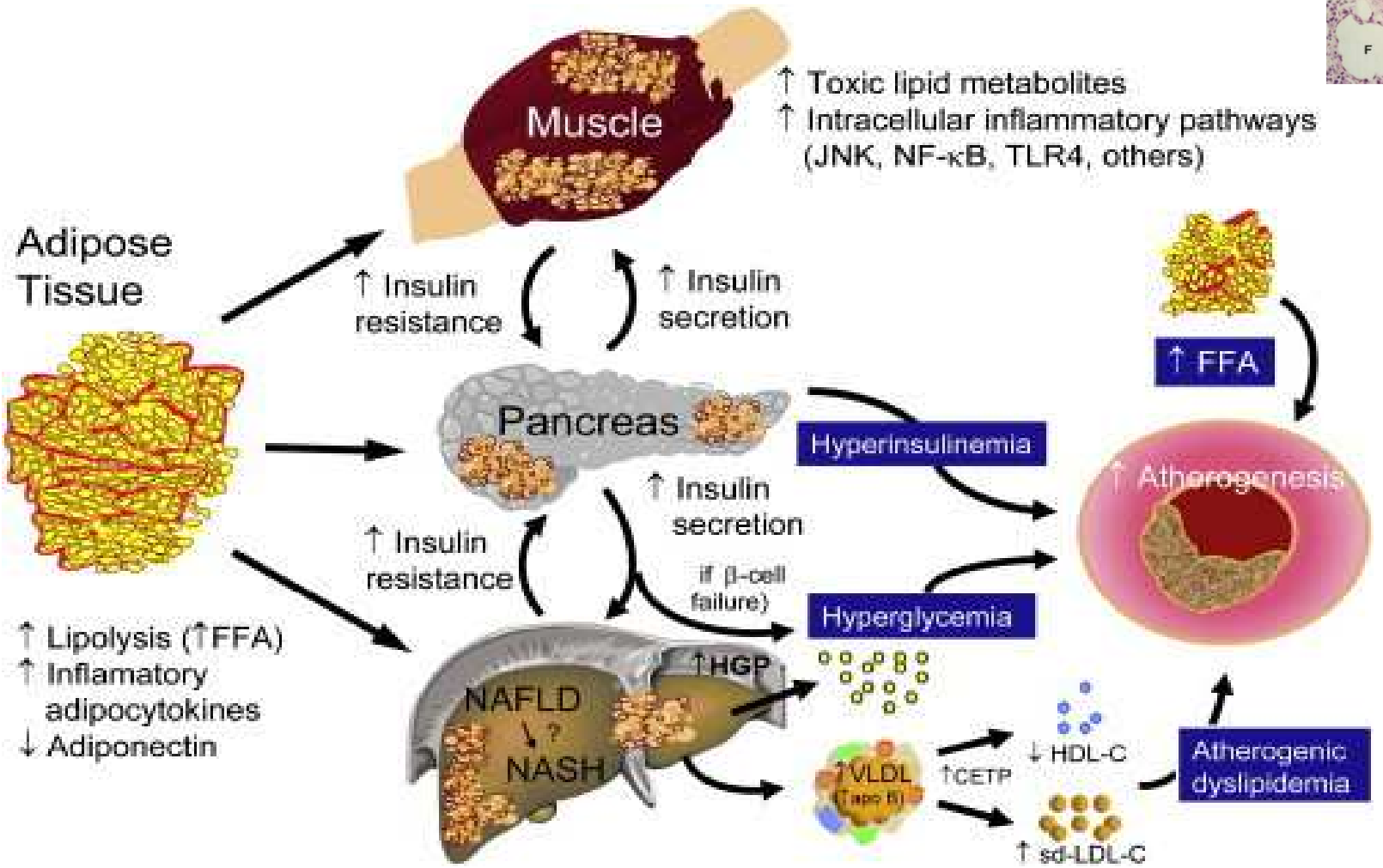

Muscle
↑ Toxic lipid metabolites
↑ Intracellular inflammatory pathways
(JNK, NF-κB, TLR4, others)
Adipose Tissue
↑ Insulin resistance
↑ Insulin secretion
↑ FFA
Pancreas
Hyperinsulinemia
↑ Atherogenesis
↑ Insulin secretion
↑ Insulin resistance
if β-cell failure)
Hyperglycemia
↑ Lipolysis (↑FFA)
↑ Inflamatory adipocytokines
↓ Adiponectin
↑HGP
NAFLD
?
NASH
↑VLDL
(↑apo B)
↑CETP
↓ HDL-C
↑ sd-LDL-C
Atherogenic dyslipidemia

Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis☆

Paolo Gisondi[1,*,#], Giovanni Targher[2,#], Giacomo Zoppini[2], Giampiero Girolomoni[1]

[1]*Section of Dermatology, Department of Biomedical and Surgical Science, University of Verona, Piazzale A. Stefani 1, 37126 Verona, Italy*
[2]*Section of Endocrinology, Department of Biomedical and Surgical Science, University of Verona, Verona, Italy*

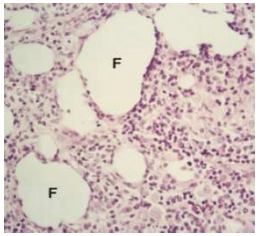
Background/Aims: **Non-alcoholic fatty liver disease (NAFLD) and chronic plaque psoriasis are both associated with metabolic syndrome and increased risk of incident cardiovascular disease. We assessed the frequency and characteristics of NAFLD in patients with chronic plaque psoriasis.**

Methods: **One hundred and thirty consecutive patients with chronic plaque psoriasis and 260 apparently healthy controls matched for age, sex and body mass index were enrolled. NAFLD was diagnosed by abdominal ultrasound after excluding other secondary causes of chronic liver disease.**

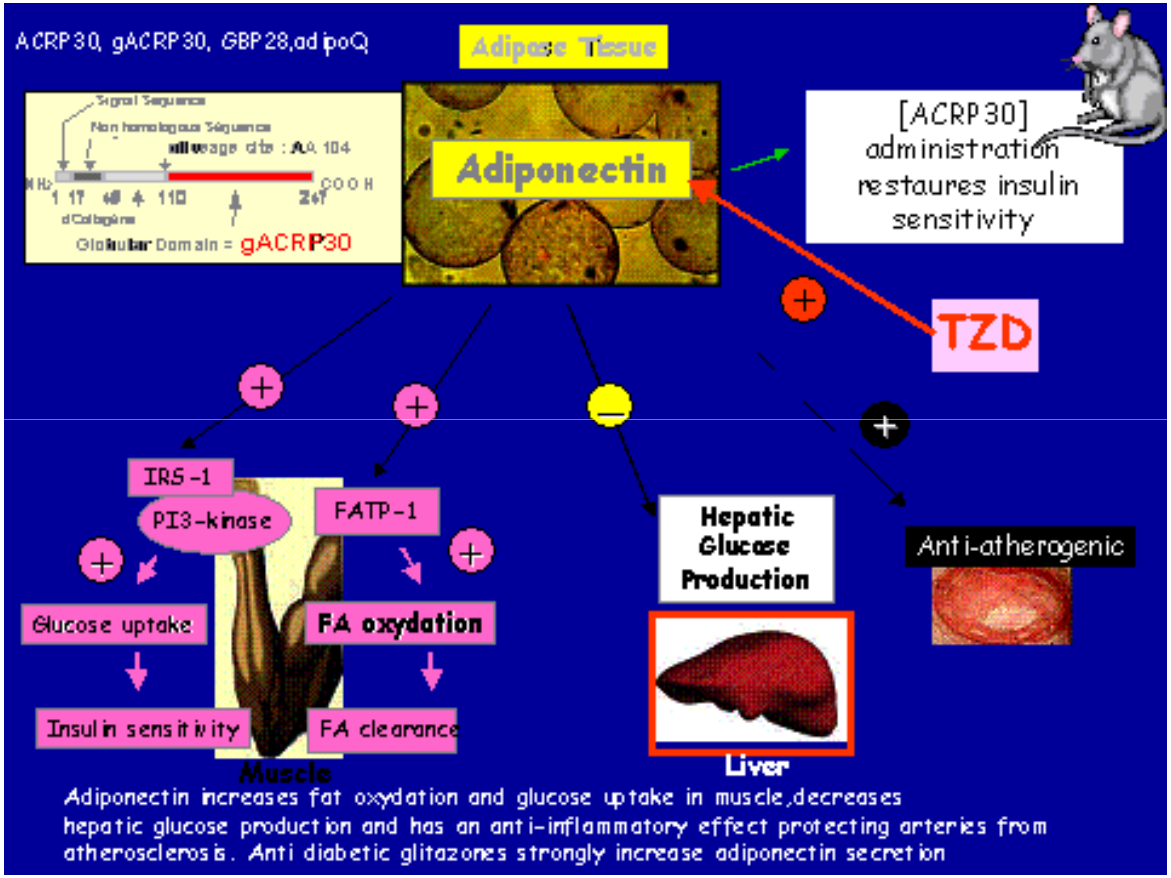
Results: **The frequency of NAFLD was remarkably greater in psoriasis patients than in controls (47% *vs.* 28%; $p < 0.0001$). Patients with psoriasis and NAFLD ($n = 61$) were more likely to have metabolic syndrome and had higher serum C-reactive protein concentrations and greater severity of psoriasis according to the Psoriasis Area and Severity Index (PASI) score (14.2 ± 12.6 *vs.* 9.6 ± 7.4; $p < 0.01$) than those with psoriasis alone ($n = 69$). In a subgroup of psoriasis patients ($n = 43$), those with NAFLD ($n = 21$) also had significantly higher serum interleukin-6 and lower serum adiponectin levels. Notably, in multivariate regression analysis, NAFLD was associated with higher PASI score independently of age, gender, body mass index, psoriasis duration, and alcohol consumption.**

Conclusions: **NAFLD is frequent in patients with chronic plaque psoriasis – affecting up to nearly half of these patients – and is strongly associated with psoriasis severity. Early recognition of NAFLD by radiological imaging tests in this group of patients is warranted.**

Adiponectine....



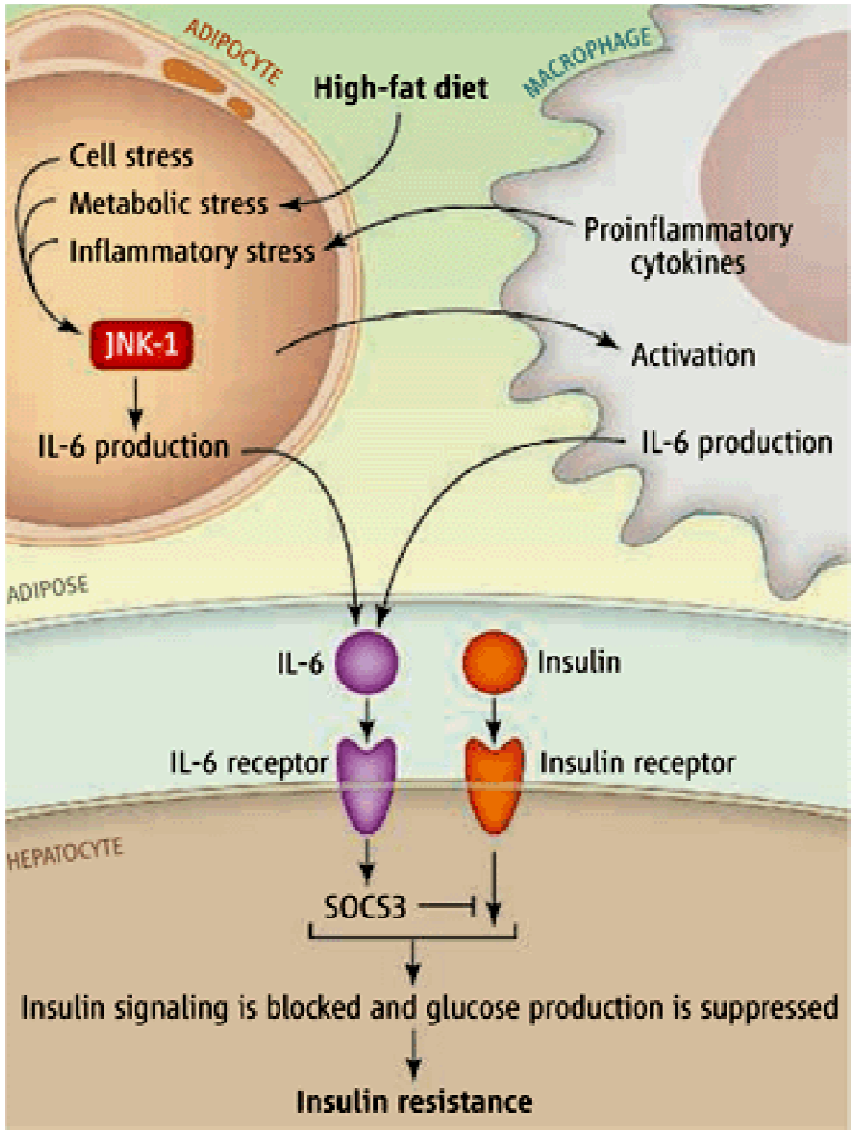
- A negative correlation was demonstrated between plasma adiponectine levels and both the PASI score and TNF-a level in psoriasis patients.
- Adiponectin has anti-inflammatory effects and functions in regulating insulin sensitivity.
- The adiponectin level is decreased in obese subjects, particularly in those viscerally obese. Reduced adiponectin levels have also been found to be associated with metabolic syndrome, atherosclerosis, and insulin resistance.



TNF-α and IL-6

- Similarly, TNF-a and IL-6 are secreted in adipose tissue and have important roles in the pathogenesis of psoriasis. TNF-a and IL-6 promote a chronic inflammatory state, angiogenesis, and oxidative stress, which contribute to the aetiology of insulin resistance, glucose intolerance, dyslipidaemia, hypertension, endothelial dysfunction, and atherogenesis.

- Viscerally obese patients are more susceptible to thrombosis and are more likely to show evidence of a chronic inflammatory state.



Acta Derm Venereol 2010; 90: 23–26

INVESTIGATIVE REPORT

Psoriasis and Hypertension: A Case-Control Study

Arnon D. COHEN[1,2], Dahlia WEITZMAN[3] and Jacob DREIHER[1,2]
[1]Clalit Health Services, [2]Siaal Research Center for Family Medicine and Primary Care, and [3]Department of Epidemiology and Health Services Evaluation, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

In recent years, numerous reports have demonstrated an association between psoriasis and metabolic syndrome. However, some studies failed to demonstrate an association between psoriasis and hypertension. The aim of the present study was to examine the association between psoriasis and hypertension. Psoriasis patients of a health-maintenance organization were compared with enrollees without psoriasis regarding the prevalence of hypertension in a case-control study. The study included 12,502 psoriasis patients over the age of 20 years and 24,285 age- and sex-frequency-matched controls. The prevalence of hypertension was significantly higher in psoriasis patients than controls (38.8%, 29.1%, respectively, $p < 0.001$). In a multivariate analysis, hypertension was associated with psoriasis after controlling for age, sex, smoking status, obesity, diabetes, non-steroidal anti-inflammatory drugs (NSAIDs) and use of Cox-2 inhibitors (odds ratio: 1.37, 95% confidence interval: 1.29–1.46). The results of this

We suggest that patients with psoriasis should be routinely screened for the presence of hypertension

ENDOTELINA-1

- Prodotto dai cheratinociti (fatt. di crescita autocrino)
- ↑ nelle lesioni psoriasiche e nel siero di pz con PsO
- Correla con la gravità della PsO
- Potente VASOCOSTRITTORE

organization in Israel, serving a population of approximately 3,800,000 enrollees. A comprehensive computerized database with continuous real-time input from pharmaceutical, medical and administrative computerized operating systems facilitates epidemiological studies such as the current analysis.

In recent years we have used the CHS database to study the association between psoriasis and metabolic syndrome (6, 7). The methodology of using the CHS database has been described previously (6, 7). Briefly, the CHS database was set up in 1997 and includes registration of 162 chronic conditions. Special field codes are used to describe the patients, who are defined as diagnosed with chronic diseases such as psoriasis or hypertension. Chronic disease registration and definitions were identical in cases and controls. The diagnoses are validated using multiple data sources in community medicine and hospital discharge

More than skin deep: atherosclerosis as a systemic manifestation of psoriasis

British Journal of Dermatology 2009 **161,** pp1–7

A.B. Alexandroff, M. Pauriah,* R.D.R. Camp,† C.C. Lang,* A.D. Struthers* and D.J. Armstrong‡

A meta-analysis of inflammation results from psoriasis and atherosclerosis studies

Adipokines

	Pso	ATH	Both
Resistin	+	+	
Leptin	+	+	
PAI-1	+	+	

Leucocytes

	Pso	ATH	Both
CD4	+	+	
CD8	+	+	
CLA+ T cells	+	-	No
CD103+ T cells	+	-	No
NK cells	+	+	
NK T cells	+	+	
Mast cells	+	+	
Neutrophils	+	+	
Treg downregulation	+	+	
Th1 & Th17 upregulation	+	+	
Monocytes/macrophages	+	+	
Plasmacytoid dendritic cells	+	+	
Myeloid dendritic cells	+	+	

Pso = psoriasis; ATH = atherosclerosis

Other important molecules

	Pso	ATH	Both
LL-37	+	+	
CRP	+	+	
Endothelin-1	+	+	
iNOS	+	+	
HSP60	+	+	
HSP65	+	+	
HSP70	+	+	
MMP-2	+	+	
MMP-9	+	+	
Oxidized LDL	+	+	
S100A7	+	-	No
TLR4	+	+	
TLR9	+	+	
S100A8 .A9 TLR2	+ +	+ +	

Adhesion & costimulatory molecules

	Pso	ATH	Both
CD80, CD28	+	+	
VCAM-1 .VLA-4	+	+	
CD40 .CD40L	+	+	
ICAM .LFA-1	+	+	
OX40 .OX40L	+	+	

Cytokines

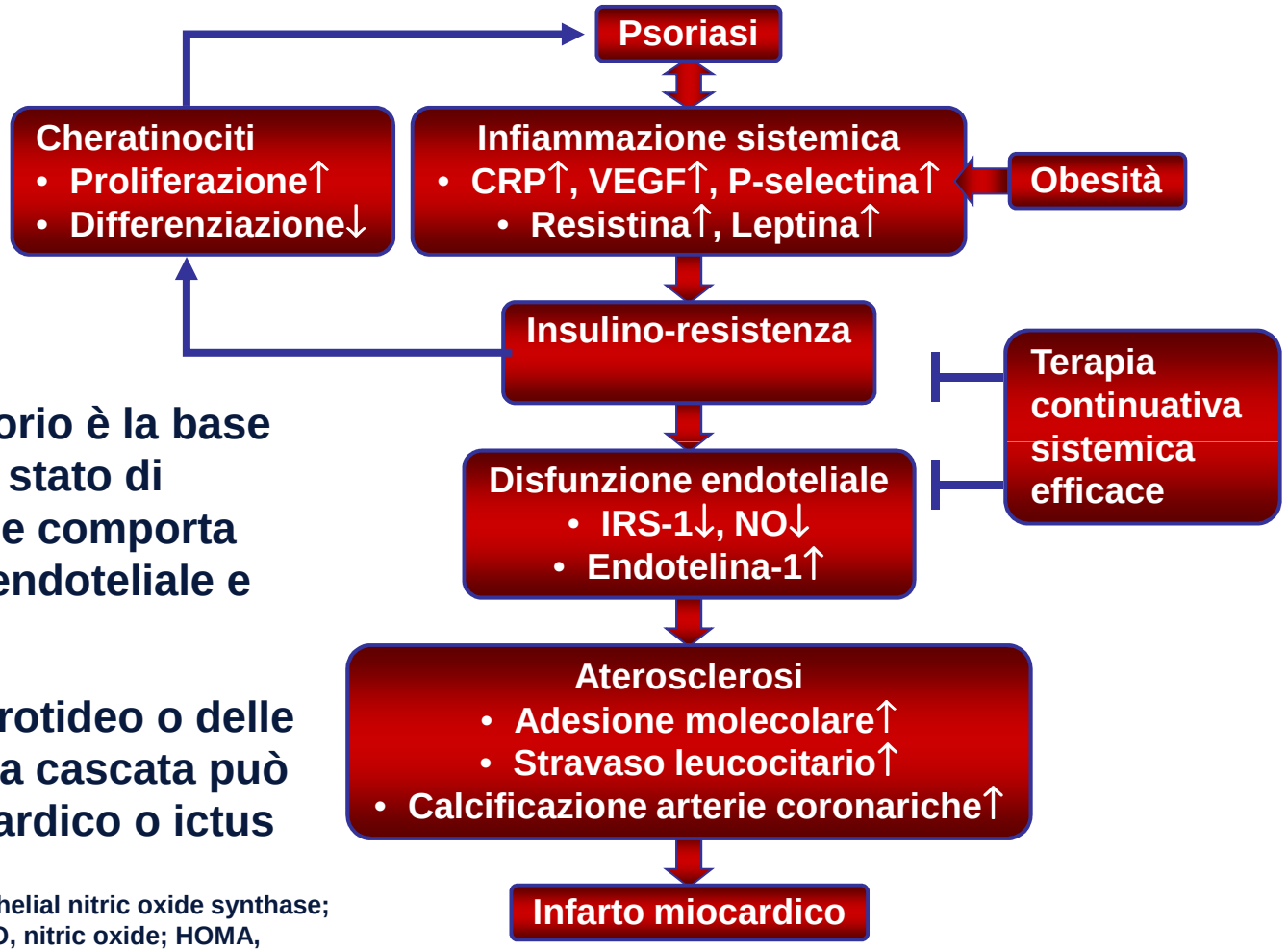
	Pso	ATH	Both
TNF-a	+	+	
IL-2	+	+	
IL-6	+	+	
IL-15	+	+	
IL-17	+	+	
IL-18	+	+	
IL-20	+	+	
IL-23	+	+	
IFN-a	+	+	
IFN-c	+	+	
Oncostatin M	+	+	
VEGF	+	+	

Chemokines

	Pso	ATH	Both
Fractalkine	+	+	
GRO-a	+	+	
IP-10	+	+	
IL-8	+	+	
MCP-1	+	+	
MIG	+	+	

50/53 (~94%) were observed in both disease states

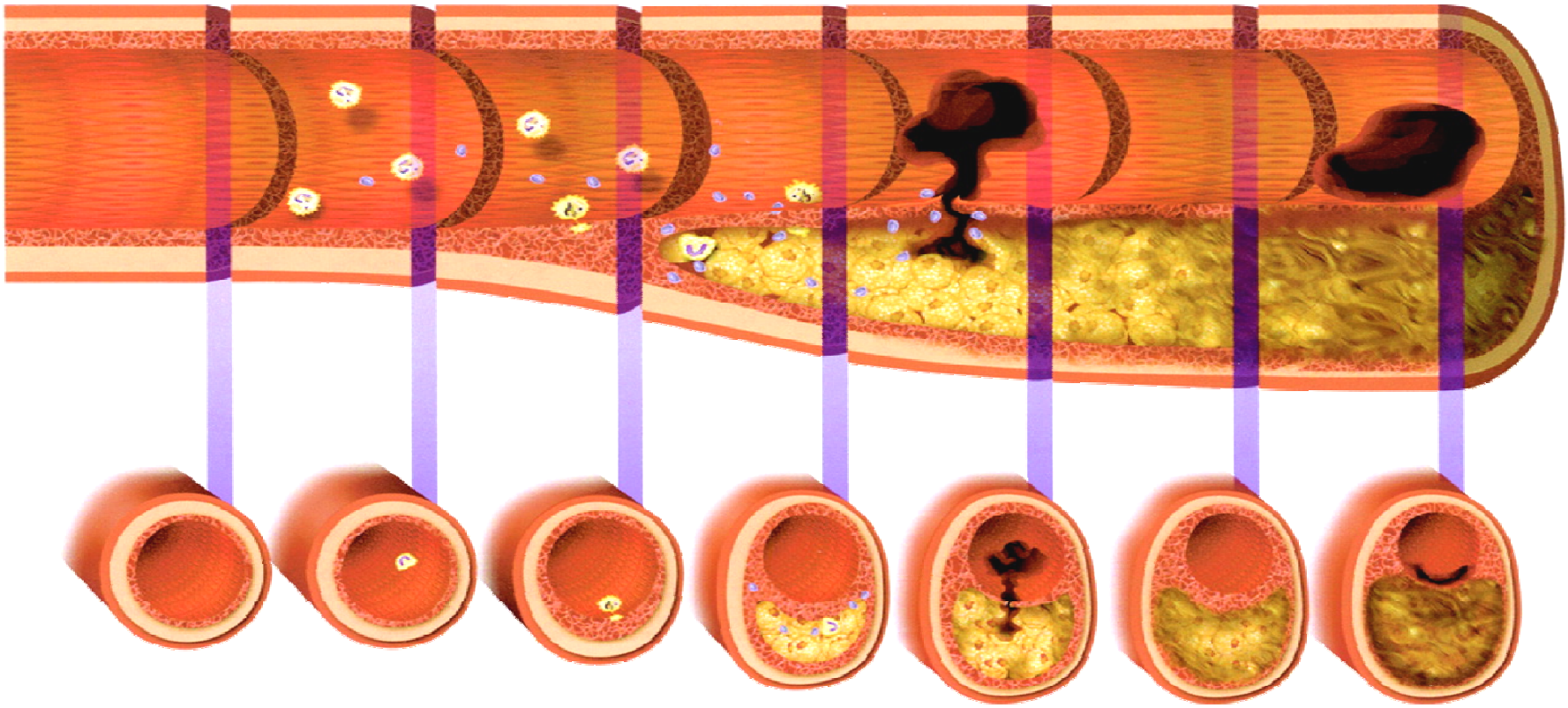
La marcia psoriasica



- **Il processo infiammatorio è la base per lo sviluppo di uno stato di insulino-resistenza che comporta disfunzione cellulare endoteliale e aterosclerosi**
- **A livello coronario, carotideo o delle arterie cerebrali questa cascata può portare a infarto miocardico o ictus**

CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; IRS-1, insulin receptor substrate 1; NO, nitric oxide; HOMA, Homeostasis Model Assessment, VEGF, vascular endothelial growth factor.

Boehncke WH, *et al. Exp Dermatol* 2011;20(4):303–7.



arteria normale | attivazione endoteliale

progressione | complicanze

strie lipidiche	ateroma intramurale maturo	rottura cappa fibrosa	placca fibrosa/ calcifica	erosione endoteliale
RIMODELLAMENTO		TROMBOSI	STENOSI	TROMBOSI

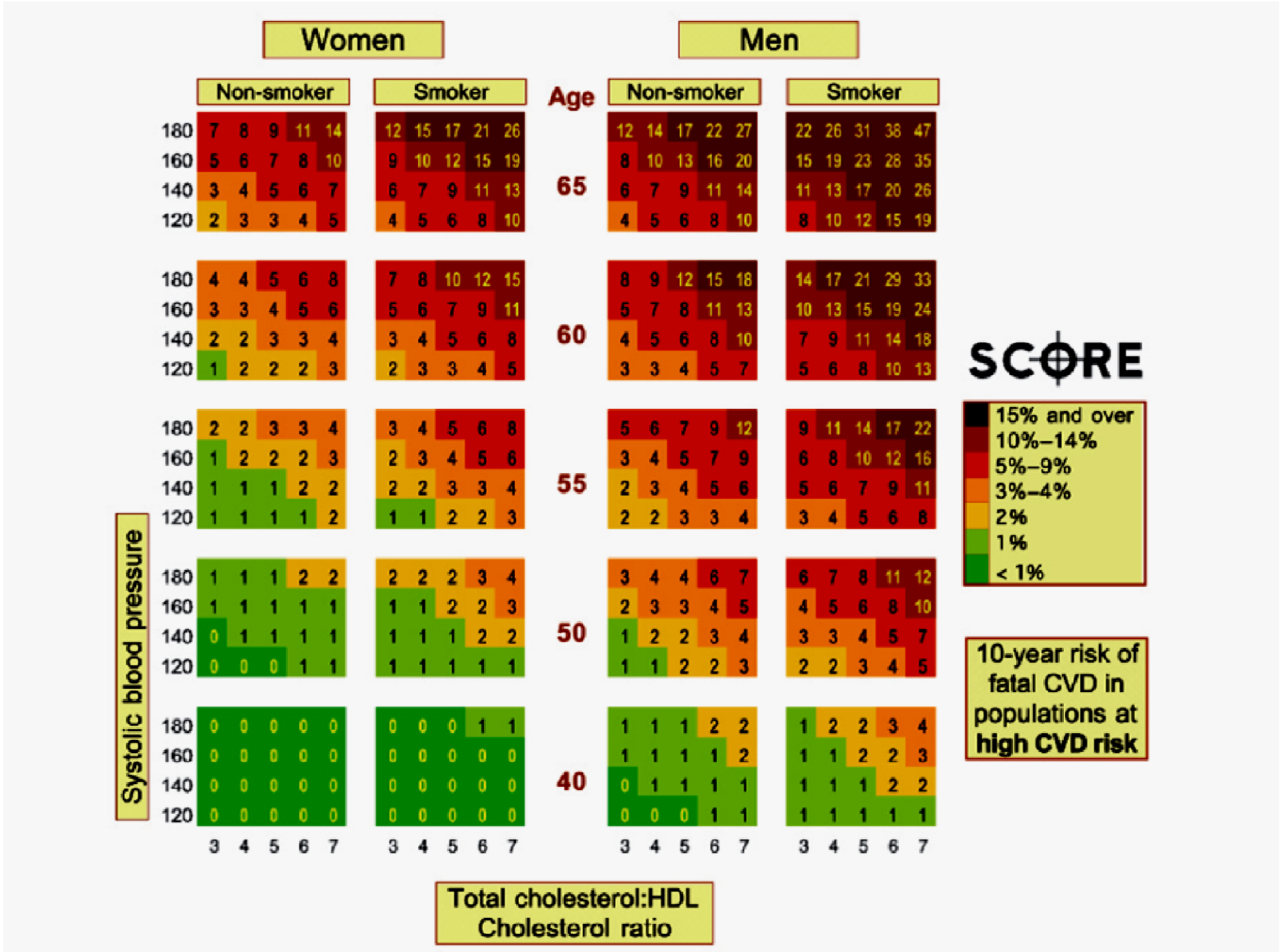
Assessment of CVD risk in PsA

No increased CVD risk

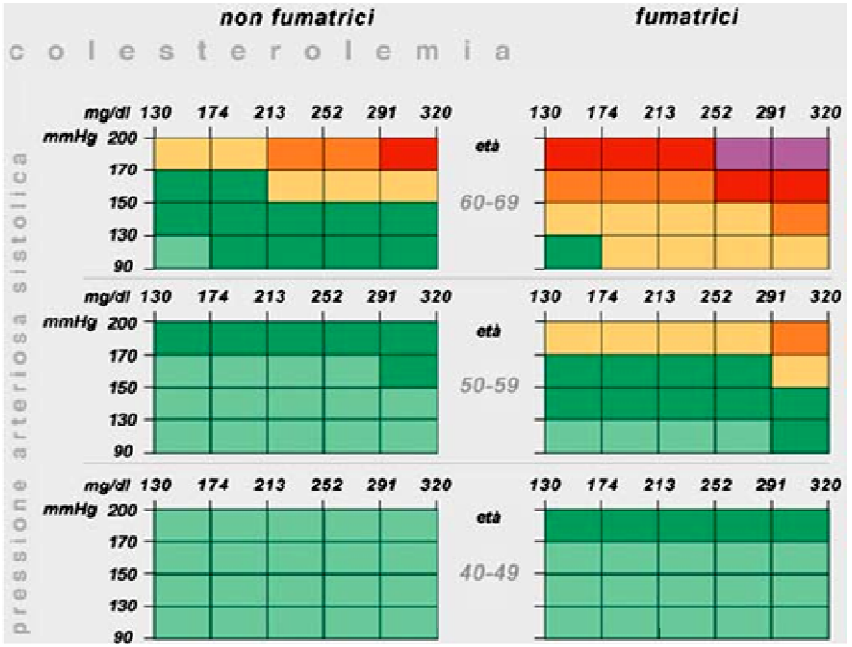
- BMI = 23
- PASI = 1
- Blood pressure: 120/80 mmHg
- Fasting glucose: 90 mg/dl
- Lipid profile: normal
- hsCRP <0.5
- No smoke
- Arthritis:
  - Achilles enthesitis

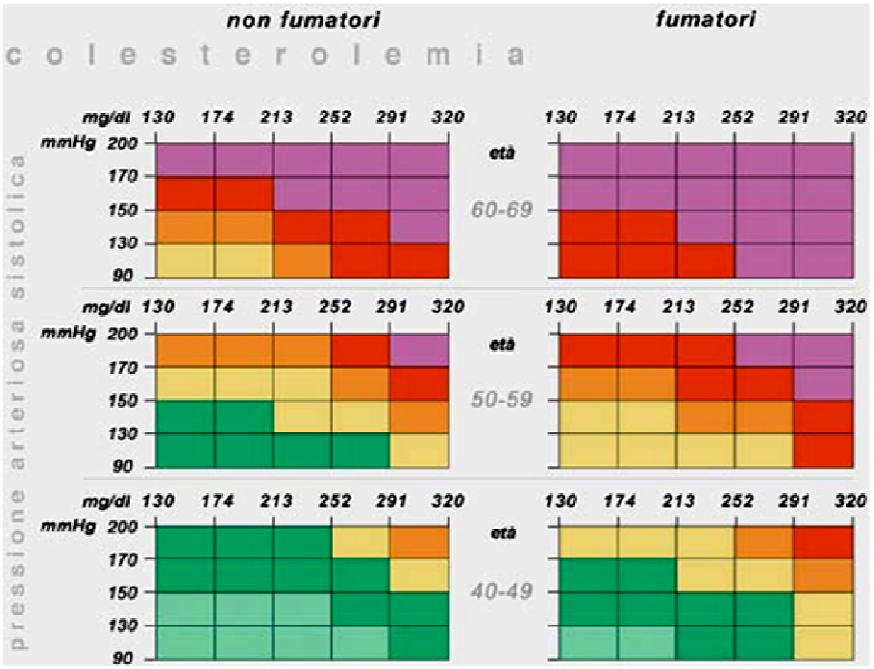
Increased CVD risk

- BMI = 31
- PASI = 15
- On anti-hypertensive therapy
- Fasting glucose: 120
- Lipid profile:
  - HDL cholesterol: 35
  - triglycerides: 350
- hsCRP = 1,5
- Smoke (10 cigarettes/day)
- Arthritis:
  - polyarthritis (DAS28 = 5.6)

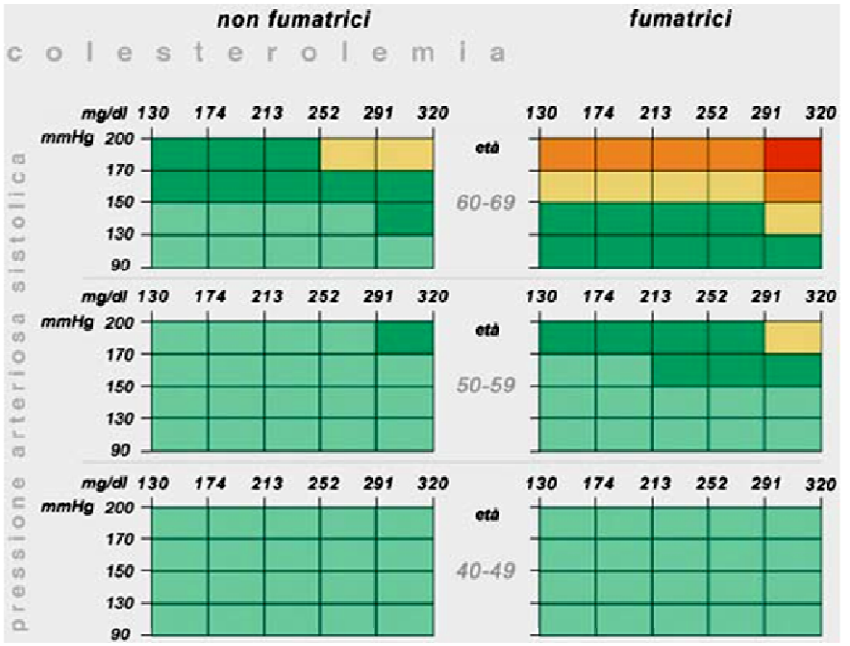

Women
Men
Non-smoker
Smoker
Non-smoker
Smoker
Age
65
60
55
50
40
180 7 8 9 11 14
160 5 6 7 8 10
140 3 4 5 6 7
120 2 3 3 4 5
12 15 17 21 26
9 10 12 15 19
6 7 9 11 13
4 5 6 8 10
12 14 17 22 27
8 10 13 16 20
6 7 9 11 14
4 5 6 8 10
22 26 31 38 47
15 19 23 28 35
11 13 17 20 26
8 10 12 15 19
180 4 4 5 6 8
160 3 3 4 5 6
140 2 2 3 3 4
120 1 2 2 2 3
7 8 10 12 15
5 6 7 9 11
3 4 5 6 8
2 3 3 4 5
8 9 12 15 18
5 7 8 11 13
4 5 6 8 10
3 3 4 5 7
14 17 21 29 33
10 13 15 19 24
7 9 11 14 18
5 6 8 10 13
180 2 2 3 3 4
160 1 2 2 2 3
140 1 1 1 2 2
120 1 1 1 1 2
3 4 5 6 8
2 3 4 5 6
2 2 3 3 4
1 1 2 2 3
5 6 7 9 12
3 4 5 7 9
2 3 4 5 6
2 2 3 3 4
9 11 14 17 22
6 8 10 12 16
5 6 7 9 11
3 4 5 6 8
180 1 1 1 2 2
160 1 1 1 1 1
140 0 1 1 1 1
120 0 0 0 1 1
2 2 2 3 4
1 1 2 2 3
1 1 1 2 2
1 1 1 1 1
3 4 4 6 7
2 3 3 4 5
1 2 2 3 4
1 1 2 2 3
6 7 8 11 12
4 5 6 8 10
3 3 4 5 7
2 2 3 4 5
180 0 0 0 0 0
160 0 0 0 0 0
140 0 0 0 0 0
120 0 0 0 0 0
0 0 0 1 1
0 0 0 0 0
0 0 0 0 0
0 0 0 0 0
1 1 1 2 2
1 1 1 1 2
0 1 1 1 1
0 0 0 1 1
1 2 2 3 4
1 1 2 2 3
1 1 1 2 2
1 1 1 1 1
3 4 5 6 7
3 4 5 6 7
3 4 5 6 7
3 4 5 6 7
Systolic blood pressure
Total cholesterol:HDL Cholesterol ratio
SCORE
15% and over
10%–14%
5%–9%
3%–4%
2%
1%
< 1%
10-year risk of fatal CVD in populations at high CVD risk

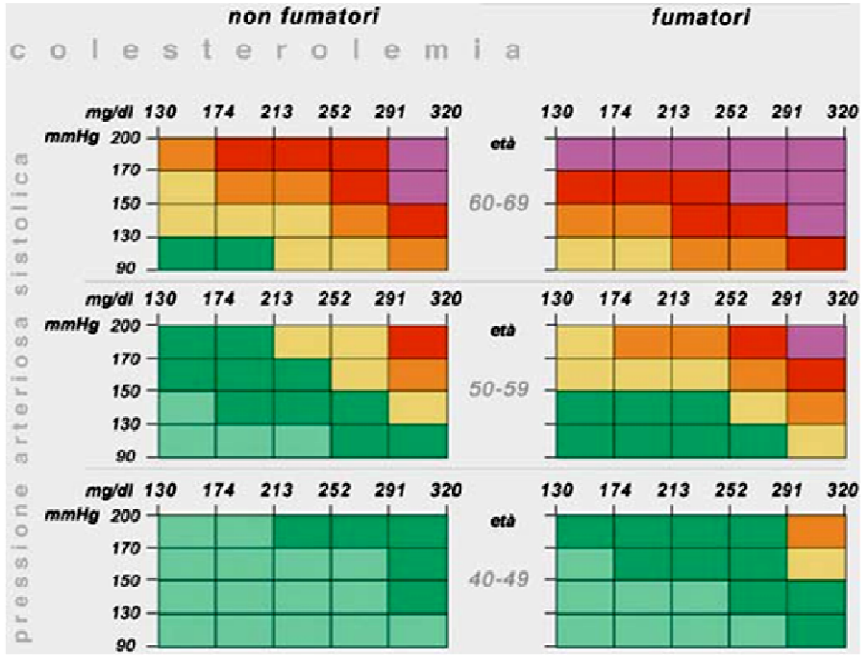
Diabetici





Non diabetici





Eular recommendations for CV risk in RA

Recommendations	Level of evidence	Strength of recommendation
1. RA should be regarded as a condition associated with higher risk for CV disease. This may also apply to AS and PsA, although the evidence base is less. The increased risk appears to be due to both an increased prevalence of traditional risk factors and the inflammatory burden	2b–3	B
2. Adequate control of disease activity is necessary to lower the CV risk	2b–3	B
3. CV risk assessment using national guidelines is recommended for all patients with RA and should be considered annually for all patients with AS and PsA. Risk assessments should be repeated when antirheumatic treatment has been changed	3–4	C
4. Risk score models should be adapted for patients with RA by introducing a 1.5 multiplication factor. This multiplication factor should be used when the patient with RA meets two of the following three criteria: – Disease duration of more than 10 years – RF or anti-CCP positivity – Presence of certain extra-articular manifestations	3–4	C
5. TC/HDL cholesterol ratio should be used when the SCORE model is used	3	C
6. Intervention should be carried out according to national guidelines	3	C
7. Statins, ACE inhibitors and/or AT-II blockers are preferred treatment options	2a–3	C-D
8. The role of coxibs and most NSAIDs in CV risk is not well established and needs further investigation. Hence, we should be very cautious about prescribing them, especially for patients with a documented CV disease or in the presence of CV risk factors	2a–3	C
9. Corticosteroids: use the lowest dose possible	3	C
10. Recommend smoking cessation	3	C

Peters MJL et al. Ann Rheum Dis 2010;69:325

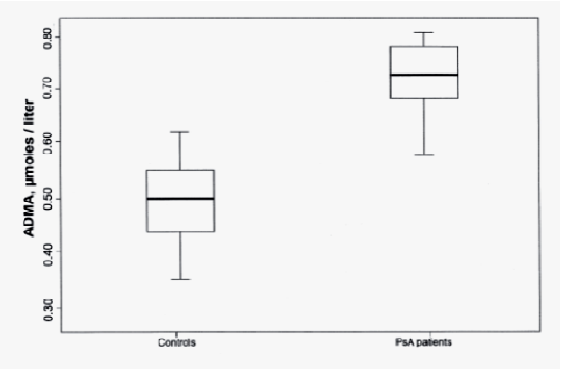
Assessment and monitoring of CVD

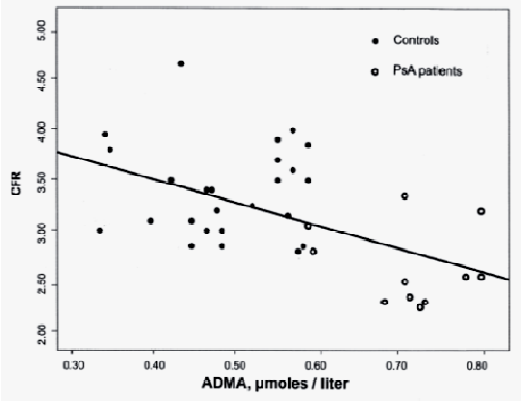
- **Carotid duplex ultrasonography (plaques, CIMT)**
- **Coronary flow reserve (CRF)**
- **Arterial stiffness (pulse-wave velocity [PWV]) and augmentation index [Aix])**
- **Flow-mediated endothelial-dependent vasodilatation (FMD)**
- **Soluble biomarkers?**

Coronary Flow Reserve and Asymmetric Dimethylarginine Levels: New Measurements for Identifying Subclinical Atherosclerosis in Patients with Psoriatic Arthritis

FABIOLA ATZENI, PIERCARLO SARZI-PUTTINI, SIMONA SITIA, LIVIO TOMASONI, LUIGI GIANTURCO, MICHELE BATTELLINO, LAURA BOCCASSINI, VITO DE GENNARO COLONNA, ANTONIO MARCHESONI, and MAURIZIO TURIEL

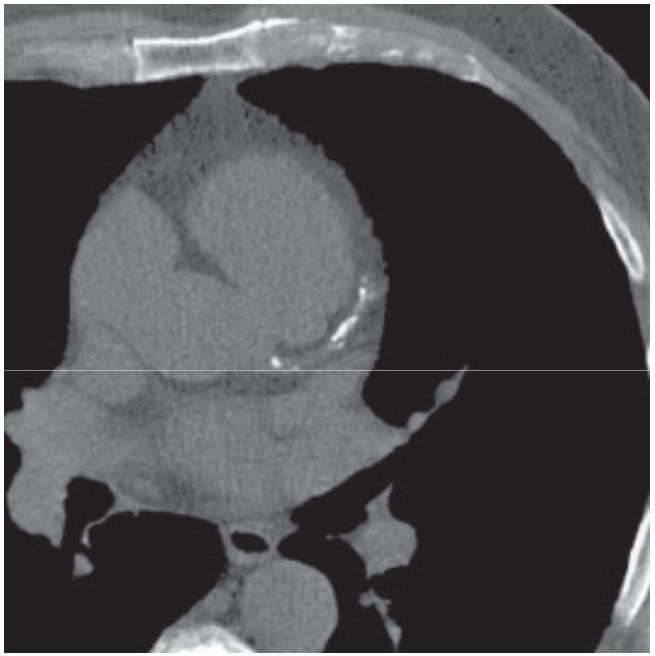
J Rheumatol 2011;38;1661-1664





Livelli elevati di calcificazione delle arterie coronarie sono indice di patologia coronarica nella psoriasi

- Calcificazione dell'arteria coronaria (CAC):
  – Pazienti psoriasici vs. controlli
  (59.4% vs. 28.1%, p=0.015)
- La psoriasi è stata identificata come fattore di rischio indipendente per CAC
- CAC è un fattore predittivo indipendente di patologia cardiovascolare aterosclerotica



Sezione trasversa di una scansione tomografica computed. Il punteggio di calcificazione dell'arteria coronaria è 145 e le placche sono limitate ai segmenti mediali dell'arteria coronaria sinistra.

Ludwig RJ, *et al. Br J Dermatol* 2007;156(2):271–6.

Risk Factor	Preventive strategy
Hypertension	Antihypertensive therapy, minimize NSAID and steroid use, diet, exercise
Obesity	Counseling, diet, exercise
Smoking	Counseling, others
Hyperlipidemia	Diet/exercise, statins, anti-TNF, minimze steroids, antimalarials
Inflammation	DMARDs, biologicals, low-dose aspirin, statins
Insulin resistance	DMARDs, biologicals
Hyperhomocysteinemia	Folic acid supplemantation with MTX or SSZ use
Family history of CVD	Counseling, monitoring risk factors
Additional thrombotic risks	Low-dose aspirin, consider anticoagulation
Abormal vasculogenesis	Statins, anti-TNF agents

Monitoring CVD risk in psoriatic patients

J Am Acad Dermatol 2008;58:1031

Measure	Recommendation by the American Heart Association[34]
Blood pressure	• Evaluate at least every 2 years • Target < 120/80 mm Hg
Body mass index	• Evaluate at least every 2 years • Target < 25 kg/m^2

Waist circumference	• Evaluate at least every 2 years
	• Target:
	  • < 102 cm males
	  • < 88 cm females

Pulse	• Evaluate at least every 2 years

Fasting blood lipids	• Evaluate at least every 5 years or every 2 years if risk factors* are present
	• Total cholesterol ≤ 200 mg/dl
	• LDL:
	  • Optimal: < 100 mg/dl
	  • Near optimal: 100–129 mg/dl
	  • Borderline: 130–159 mg/dl
	  • High: 160–189 mg/dl
	  • Very high: ≥ 190 mg/dl

Fasting blood glucose	• Evaluate at least every 5 years or every 2 years if risk factors* are present • Target: < 100 mg/dl

Experimental Dermatology ADF

DOI:10.1111/j.1600-0625.2011.01308.x
www.blackwellpublishing.com/EXD

Viewpoint

A tale of two plaques: convergent mechanisms of T-cell-mediated inflammation in psoriasis and atherosclerosis

April W. Armstrong[1], Stephanie V. Voyles[1], Ehrin J. Armstrong[2], Erin N. Fuller[3] and John C. Rutledge[2]

Can we kill two birds with one stone?

Shared immunological mechanisms in the development of psoriasis and atherosclerosis present potential common therapeutic targets. Targeting Th1 and Th17 responses and/or restoring a healthy ratio between Treg and effector T-cell activity may prove effective treatments for both psoriasis and atherosclerosis. Current systemic therapies, such as biologics for psoriasis, target these inflammatory pathways, but further translational and clinical research is necessary to examine their effect on cardiovascular outcomes in patients with psoriasis

ONLINE FIRST

Association Between Tumor Necrosis Factor Inhibitor Therapy and Myocardial Infarction Risk in Patients With Psoriasis

Jashin J. Wu, MD; Kwun-Yee T. Poon, MS; Jennifer C. Channual, MD; Albert Yuh-Jer Shen, MS, MD

ARCH DERMATOL/ VOL 148 (NO. 11), NOV 2012

Table 5. Multivariable Proportional Hazards Model Assessing Factors Associated With Incident Myocardial Infarction Comparing TNF Inhibitors vs Methotrexate vs Topical Agents

Factor	Hazard Ratio (95% CI)	*P* Value
TNF inhibitors	0.50 (0.32-0.81)	.004
Methotrexate	0.52 (0.31-0.85)	.01
Topical agents	1 [Reference]	
Female sex	0.51 (0.38-0.68)	<.001
Age ≤65 y	0.45 (0.34-0.61)	<.001
Psoriatic arthritis	1.63 (1.12-2.38)	.01
Diabetes mellitus	2.22 (1.64-3.00)	<.001
Dyslipidemia	5.30 (3.08-9.12)	<.001
Hypertension	8.38 (4.02-17.47)	<.001
β-Blockers	1.06 (0.80-1.42)	.68
Statins	0.31 (0.22-0.42)	<.001

- ✓ **This is the first large scale retrospective cohort study to show that the use of TNF inhibitors for psoriasis is associated with a clinically and statistically significant reduction in MI risk and incident rate compared with the use of topical agents for psoriasis.**

- ✓ **There is a trend that the use of TNF inhibitors for psoriasis is associated with a non statistically significant lower MI incident rate compared with the use of oral agents/phototherapy**

Arch Dermatol Res (2013) 305:467–472
DOI 10.1007/s00403-013-1374-1

REVIEW ARTICLE

Rational for statin use in psoriatic patients

Jerzy Mosiewicz · Aldona Pietrzak · Grażyna Chodorowska · Marcin Trojnar · Jacek Szepietowski · Kristian Reich · Manfredi Rizzo

Peroxisome proliferator-activated receptor agonists (PPARs): a promising prospect in the treatment of psoriasis and psoriatic arthritis*

Emerson de Andrade Lima[1]
Cláudia Diniz Lopes Marques[3]
Ivan da Rocha Pita[5]
Mariana Modesto Dantas de Andrade Lima[2]
Angela Luzia Branco Pinto Duarte[4]
Maira Galdino da Rocha Pita[6]

An Bras Dermatol. 2013;88(6):1029-35.

Association of 25-hydroxyvitamin D serum levels and metabolic parameters in psoriatic patients with and without arthritis

Jacinto Orgaz-Molina, MD,[a] Cesar Magro-Checa, MD,[b] José Luis Rosales-Alexander, MD,[b] Miguel A. Arrabal-Polo, PhD,[c] Agustín Buendía-Eisman, PhD,[c] Enrique Raya-Alvarez, PhD,[b] and Salvador Arias-Santiago, MD, PhD[a,c]
Granada, Spain

J Am Acad Dermatol
Volume 69, Number 6

Major cardiovascular events associated with anti-IL 12/23 agents: A tale of two meta-analyses

Erica D. Dommasch, MD,[a] Andrea B. Troxel, ScD,[b,c] and Joel M. Gelfand, MD, MSCE[b,c,d]
Boston, Massachusetts, and Philadelphia, Pennsylvania

J Am Acad Dermatol
May 2013

Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish Nationwide Cohort Study

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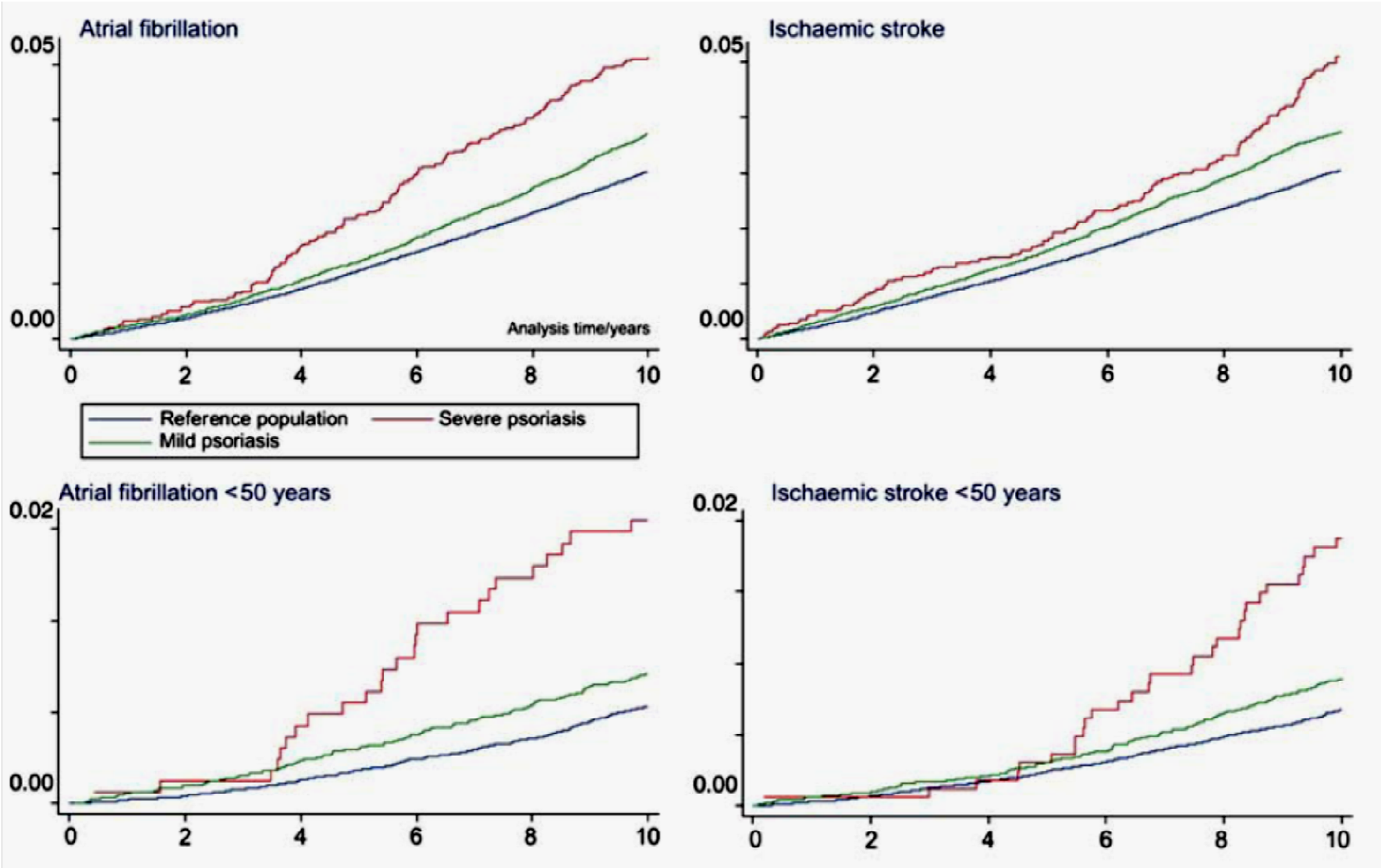

Inflammation as a Risk Factor for Atrial Fibrillation

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Background—The presence of systemic inflammation determined by elevations in C-reactive protein (CRP) has been associated with persistence of atrial fibrillation (AF). The relationship between CRP and prediction of AF has not been studied in a large population-based cohort.

Methods and Results—CRP measurement and cardiovascular assessment were performed at baseline in 5806 subjects enrolled in the Cardiovascular Health Study. Patients were followed up for a mean of 6.9±1.6 (median 7.8) years. AF was identified by self-reported history and ECGs at baseline and by ECGs and hospital discharge diagnoses at follow-up. Univariate and multivariate analyses were used to assess CRP as a predictor of baseline and future development of AF. At baseline, 315 subjects (5%) had AF. Compared with subjects in the first CRP quartile (<0.97 mg/L), subjects in the fourth quartile (>3.41 mg/L) had more AF (7.4% versus 3.7%, adjusted OR 1.8, 95% CI 1.2 to 2.5; $P=0.002$). Of 5491 subjects without AF at baseline, 897 (16%) developed AF during follow-up. Baseline CRP predicted higher risk for developing future AF (fourth versus first quartile adjusted hazard ratio 1.31, 95% CI 1.08 to 1.58; $P=0.005$). When treated as a continuous variable, elevated CRP predicted increased risk for developing future AF (adjusted hazard ratio for 1-SD increase, 1.24; 95% CI 1.11 to 1.40; $P<0.001$).

Conclusions—CRP is not only associated with the presence of AF but may also predict patients at increased risk for future development of AF. **(*Circulation*. 2003;108:3006-3010.)**

Thank you for your attention