Ψωριασική αρθρίτιδα και καρδιομεταβολικές συννοσηρότητες: δύο στόχοι, ένα πλάνο

Σιμοπούλου Θεοδώρα
Επίκουρη καθηγήτρια Ρευματολογίας
Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας
Κλινική Ρευματολογίας και κλινικής Ανοσολογίας, ΠΓΝΛ

Σύγκρουση συμφερόντων

Χορηγία για την παρούσα παρουσίαση από την εταιρεία Amgen

Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία διετία: Abbvie, Amgen, Boehrigher-Ingelheim, Elpen, Janssen, Lilly, Pfizer

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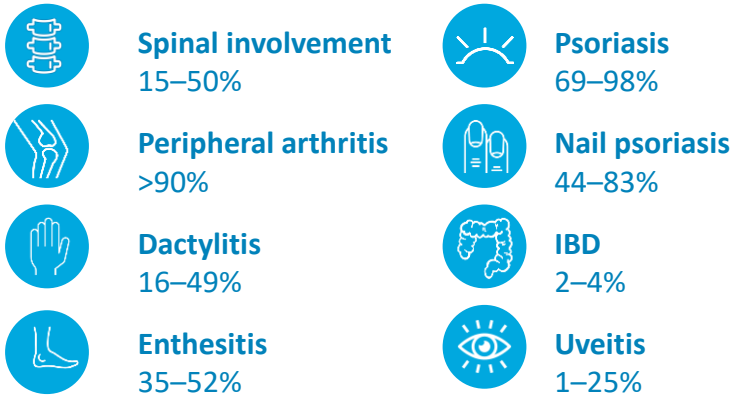
Ψωριασική νόσος

Χρόνια, συστηματική, φλεγμονώδης νόσος με αρθρικές και εξωαρθρικές εκδηλώσεις



Baraliakos X et al. Clin Exp Rheumatol 2015;33(Suppl. 93):S31–5;
Gladman DD et al. Q J Med 1987;62:127–141;
Kaeley GS et al. Semin Arthritis Rheum 2018;48:263–273;
Polachek A et al. Arthritis Care Res 2017;69:1685–1691;
Boehncke WH et al. J Eur Acad Dermatol Venereol 2020;34:2035– 2043;
Ogdie A et al. Ann Rheum Dis 2019;78:922–923;
Williamson L et al. Rheumatology 2004;43:790–794;
Mease PJ et al. RMD Open 2019 24;5:e000867;
Mease PJ et al. Arthritis Care Res 2017;69:1692–9;

Πολλαπλές συννοσηρότητες

- Υπέρταση
- Υπερλιπιδαιμία
- Παχυσαρκία
- CVD

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY | 34 4 2023

ORIGINAL PAPER

Disease Profile and Achievement of Therapeutic Goals in a Modern, Nationwide Cohort of 923 Patients with Psoriatic Arthritis

George E. Fragoulis[1*], Charalampos Papagoras[2*], Sousana Gazi[3], Evangelia Mole[3], Michael Krikelis[3], Paraskevi V. Voulgari[4], Evripidis Kaltsonoudis[4], Nikolaos Koletsos[4], Pelagia Katsimpri[5], Dimitrios Boumpas[5], Dimitrios Katsifis[5], Nikolaos Kougkas[6], Theodoros Dimitroulas[6], Petros P. Sfikakis[1], Maria G. Tektonidou[1], Chrysoula Gialouri[1], Dimitrios P. Bogdanos[7], Theodora Simopoulou[7], Christos Koutsianas[8], Eugenia Mavrea[8], Gkikas Katsifis[9], Konstantinos Kottas[9], Maria Konsta[10], Matthoula Tziafalia[10], Evangelia Kataxaki[11], Eleni Kalavri[12], Kalliopi Klavdianou[12], Eleftheria P. Grika[13], Charalampos Sfontouris[13], Dimitrios Daoussis[14], George Iliopoulos[14], Ilias Bournazos[15], Dimitrios Karokis[15], Konstantinos Georganas[15], Dimos Patrikos[15], Dimitrios Vassilopoulos[8]

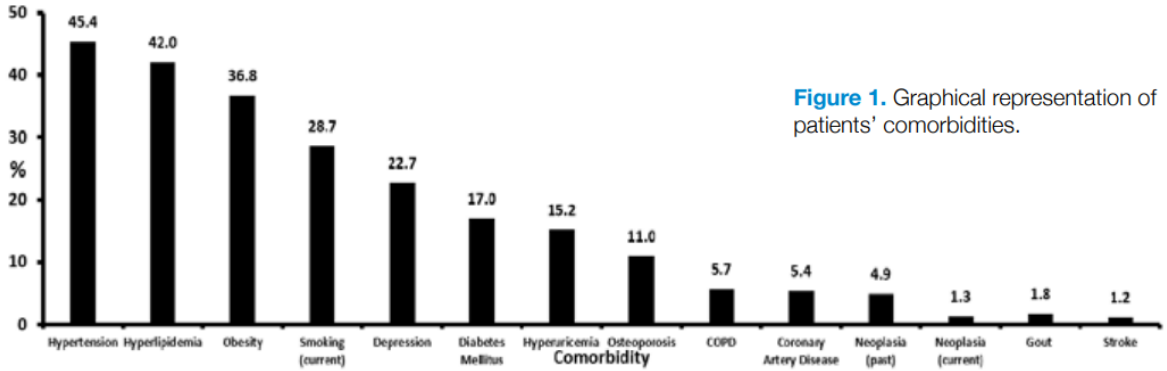


Figure 1. Graphical representation of patients' comorbidities.

Most comorbidities belonged to the spectrum of cardiometabolic diseases, with 6.6% having CAD or stroke, 17% type 2 diabetes while about half of them had hypertension and/or dyslipidaemia

Ψωριασική Αρθρίτιδα vs Ψωρίαση

Prevalence of psoriatic arthritis and its correlates among patients with psoriasis in Greece: results from a large retrospective study

E. Papadavid,[1,*] P. Katsimbri,[2] I. Kapniari,[1] D. Koumaki,[1] A. Karamparpa,[1] M. Dalamaga,[3] K. Tzannis,[4] D. Boumpas,[2] D. Rigopoulos[1]

Table 1 Clinical characteristics of psoriatic patients with PsA group A (*N* = 85) and psoriatic patients without PSA group B (*N* = 193)

Variables	All patients *N* = 278	Group A *N* = 85	Group B *N* = 193	*P*-value
Age (years), mean (SD)	51.41 (15.43)	53.63 (14.49)	50.54 (15.75)	0.137
Gender (*N*, %)				0.568
Male	144 (52%)	42 (49%)	102 (53%)	
Female	134 (48%)	43 (51%)	91 (47%)	
Nail involvement (*N*, %)	121 (43.5%)	43 (51%)	78 (41%)	0.123
Scalp involvement	175 (63%)	53 (62%)	122 (64%)	0.850
Comorbidities				
Hypertension (*N*, %)	68 (24.4%)	35 (41%)	33 (17%)	**0.001**
Dyslipidaemia (*N*, %)	72 (25.9%)	35 (41%)	37 (19%)	**0.004**
Diabetes (*N*, %)	32 (11.5%)	17 (20%)	15 (8%)	**0.021**
Cardiovascular disease (*N*, %)	26 (9.35%)	13 (17%)	13 (9%)	0.074
Age of psoriasis beginning, mean (SD)	34.52 (17.97)	32.62 (17.11)	35.41 (18.38)	0.333
Presence of arthritis (*N*, %)	85 (30%)		–	–

Data are expressed as number (percentage) or mean ± standard deviation; SD, standard deviation; in boldface statistically significant results when $P < 0.05$.

η αυξημένη συχνότητα εμφάνισης παραγόντων κινδύνου καρδιαγγειακών παθήσεων (CVD) στην ΨΑ σε σύγκριση με την ψωρίαση, υποδεικνύει μια πιθανή συμβολή της φλεγμονής των αρθρώσεων στην καρδιαγγειακή νοσηρότητα

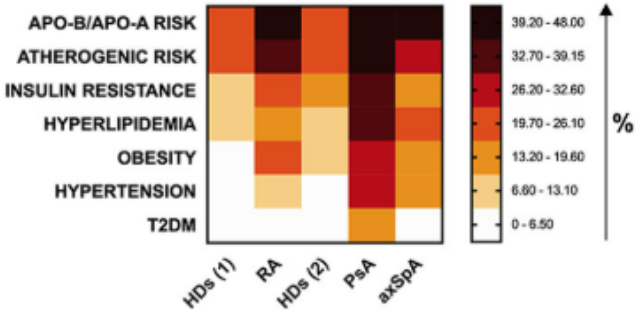
Η υποομάδα ασθενών με ΨΑ είχε σημαντικά υψηλότερα ποσοστά συννοσηροτήτων (vs Ps)

- αρτηριακή υπέρταση 41% vs. 17% (P = 0.001)
- σακχαρώδη διαβήτη 20% vs. 8% (P = 0.021)
- υπερχοληστερολαιμία 41% vs. 19% (P = 0.004)

J Eur Acad Dermatol Venereol. 2016 Oct;30(10):1749-1752.

PsA have a higher prevalence of CVD comorbidities compared to other types of inflammatory arthritis

- Cross-sectional study including 200 RA, 80 PsA, 150 axSpA patients and 100 healthy donors.
- Patients with PsA have a higher prevalence of CVD comorbidities compared to those with other types of inflammatory arthritis.
  - These comorbidities include an elevated ApoB/ApoA ratio, increased atherogenic risks, obesity, insulin resistance (IR), hyperlipidemia, arterial hypertension, and type 2 diabetes mellitus



Ther Adv Chronic Dis. 2020 Oct 21:11:2040622320965067.

Ψωριασική αρθρίτιδα και μη-αλκοολική νόσος του ήπατος

- PsA is strongly linked to non-alcoholic fatty liver disease
- 65% of patients with PsA have NAFLD
- NAFLD is not exclusively associated with the BMI, since its prevalence in patients with MetS and without obesity is alarmingly increased
  - it is estimated that 5-8% of lean subjects (BMI<30) display NAFLD
  - hypertriglyceridemia extensively contributes to the development of NAFLD
- NAFLD not only contributes to dyslipidemia but also serves as a source of systemic inflammation, which can exacerbate CVD risk
- NAFLD-associated MetS is a highly atherogenic condition. Patients with both conditions show an increase in the CIMT, as well as in the number of atherosclerotic plaques and plasma markers of endothelial dysfunction, thus increasing the prevalence of atherosclerosis

Nat Rev Rheumatol. 2019 Aug;15(8):461-474.
Front Immunol. 2022 Sep 23:13:997270.

Σακχαρώδης διαβήτης – Αντίσταση στην ινσουλίνη - Διαταραχή λιπιδαιμικού προφίλ

- Higher prevalence of T2DM
- Individuals with PsA have elevated fasting glucose levels

- Cohort of 283pts with PsA
  - IR was defined as an elevated homeostasis model assessment (HOMA-IR) value of > 2.5.
  - Severe PsA was defined as the presence of 1 or more of the PsA-related radiographic damage features (peripheral joint erosions, osteolysis, sacroiliitis), and PsA requiring tumor necrosis factor inhibitor therapy.
- A significant association of Insulin Resistance was noted with more severe PsA (OR 3.49, p = 0.03), later psoriasis age of onset (OR 1.07, p = 0.001), and higher body mass index (OR 1.22, p < 0.001).

J Rheumatol. 2014 Jul;41(7):1357-65.

- Reduced levels of high-density lipoproteins
- Elevated triglyceride levels
- Heightened levels of proteins associated with LDL, such as apolipoprotein B (Apo-B), when compared to healthy individuals

Αγγειοπάθεια

- Ενδοθηλιακή βλάβη
  - Endothelial dysfunction (ED) is defined as an impairment in the vasodilatory, anti-thrombotic, and anti-inflammatory properties of the cells that make up the lining of blood vessels. ED is considered a key step in the development of atherosclerotic cardiovascular disease
  - Compared with controls, PsA patients had significantly increased concentrations of ESR, CRP, TNF-α, IL-6, ICAM-1, and VCAM-1. In PsA, carotid intima-media thickness (CIMT) positively correlated with IL-6 and ICAM-1 and inversely correlated with Flow-mediated dilatation(FMD), HDL, and endothelial progenitor cells (EPCs) ($p < 0.05$).
  - In PsA, FMD and CIMT were impaired, indicating endothelial dysfunction and accelerated atherosclerosis, respectively.

Int J Angiol. 2016 Dec;25(4):222-228.

  - Coronary flow reserve was found to be significantly reduced in individuals with PsA

Rheumatol Int. 2024 Sep;44(9):1587-1606.

- Υποκλινική αθηροσκλήρωση
  - Patients with PsA exhibited greater carotid artery IMT than did matched controls (mean +/- SD 0.699 +/- 0.165 mm versus 0.643 +/- 0.111 mm; P = 0.031; difference of means 0.056; 95% CI 0.005-0.108).
    - Adjusted for age, the carotid IMT was correlated with age at the time of PsA diagnosis (partial correlation coefficient [r] = -0.264, P = 0.04), disease duration (r = 0.264, P = 0.04), total cholesterol (r = 0.233, P = 0.01), and low-density lipoprotein cholesterol (r = 0.243, P = 0.01).
  - High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors.

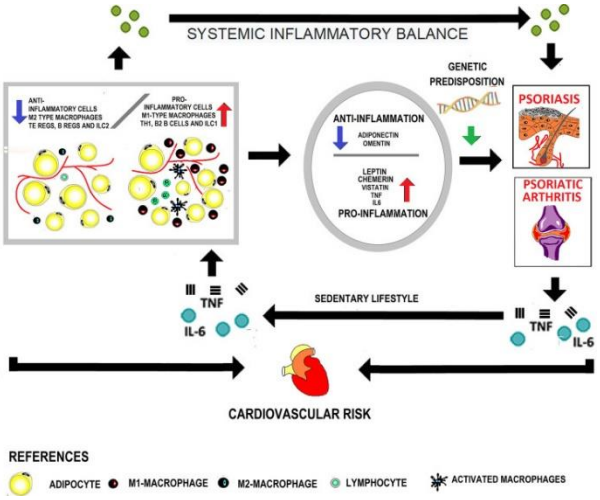
Arthritis Rheum. 2007 Aug 15;57(6):1074-80.

Αυξημένος καρδιαγγειακός κίνδυνος

- 32,973 patients with PsA (meta-analysis of 11 observational studies)
- 43% increased risk of developing CV disease (pooled OR 1.43)
- 55% increased risk of incident CV events (pooled OR 1.22-1.96)
- Morbidity risk for myocardial infarction was increased by 68%
- Morbidity risk for cerebrovascular diseases was increased by 22%
- Morbidity risk for heart failure was increased by 31%

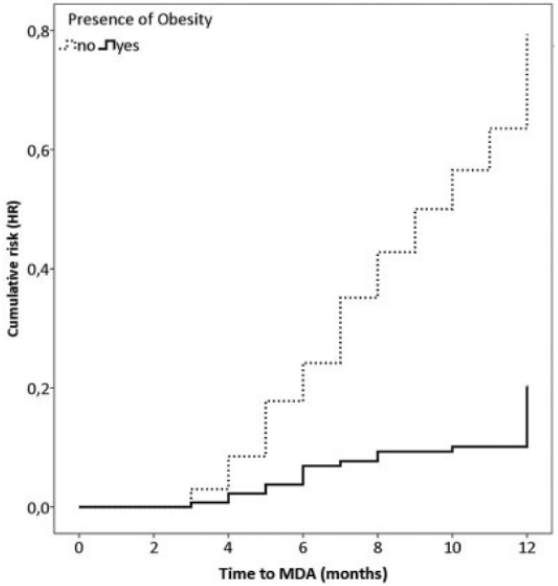
Arthritis Care Res (Hoboken). 2017 Jan;69(1):67-74.

Παχυσαρκία



PsA obesity: difficult to reach and maintain good outcome

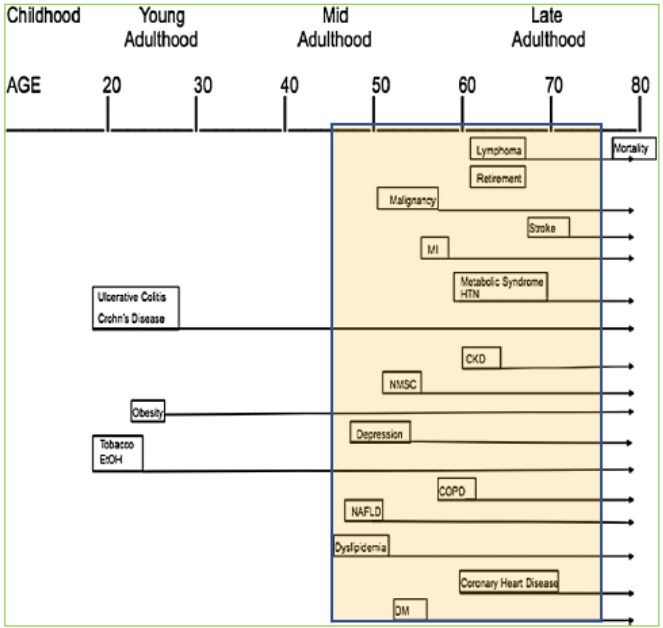
- Obese PsA patients less likely to achieve MDA at month 12
- Those who achieve MDA, increased BMI was an adverse prognostic factor for maintain MDA at month 24



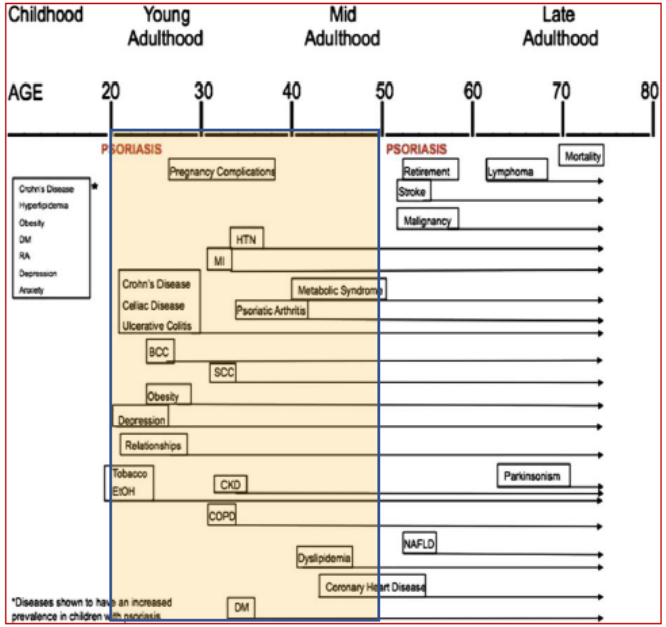
Arthritis Care Res (Hoboken). 2013 Jan;65(1):141-7.

Πρώιμη εμφάνιση συννοσηροτήτων σε ασθενείς με ψωριασική νόσο

Γενικός Πληθυσμός

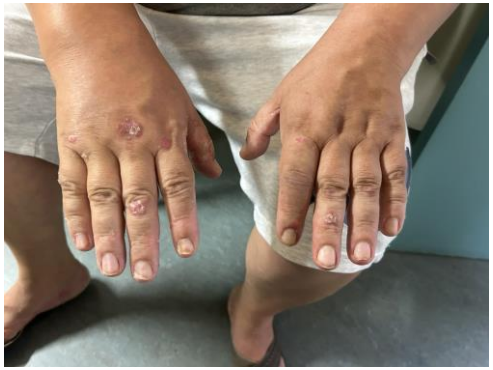


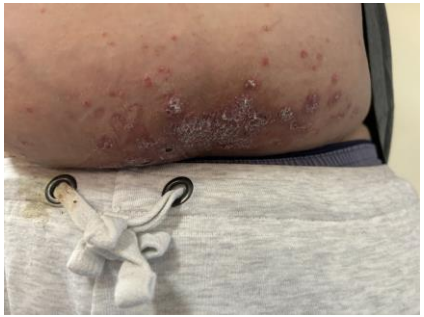
Ασθενείς με ψωριασική νόσο

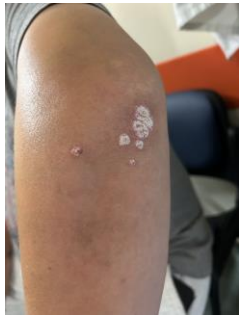


M. K. Garshick et al, Dermatol Clin 33 (2015) 25–39

Ο κ. Νίκος, ένας τυπικός ασθενής







- Άνδρας, 48ετών
- Παχυσαρκία (172cm, 102kg, BMI 34.5)
- Υπέρταση
- Υπερχοληστερολαιμία
- πρώην καπνιστής
- αλκοόλ: κοινωνική χρήση

- Ψωρίαση από 20ετίας (τοπική αγωγή)

- Ασύμμετρη ολιγοαρθρίτιδα (SJC:2, TJC:4)

- Ραγοειδίτιδα (-)
- ΙΦΝΕ (-)

- ΤΚΕ 34mm/hr, CRP 1.0 mg/dl

- Προηγηθείσα θεραπεία: ανεπαρκής ανταπόκριση σε MTX 17.5mg/w

Επιλέγοντας θεραπεία για τον ασθενή με ΨΑ και ↑καρδιαγγειακό κίνδυνο

Cardiovascular risk: screen, treat!

Guidelines address the **link between PsO/PsA and cardiometabolic comorbidities**.[1-4] **Screening**[1,2] **and managing**[1-3] PsO/PsA patients **for cardiometabolic comorbidities** (eg, cardiovascular disease, metabolic syndrome) **is recommended**

AAD-NPF Guidelines in PsO[1]

GRAPPA Treatment Recommendations in PsA[2]

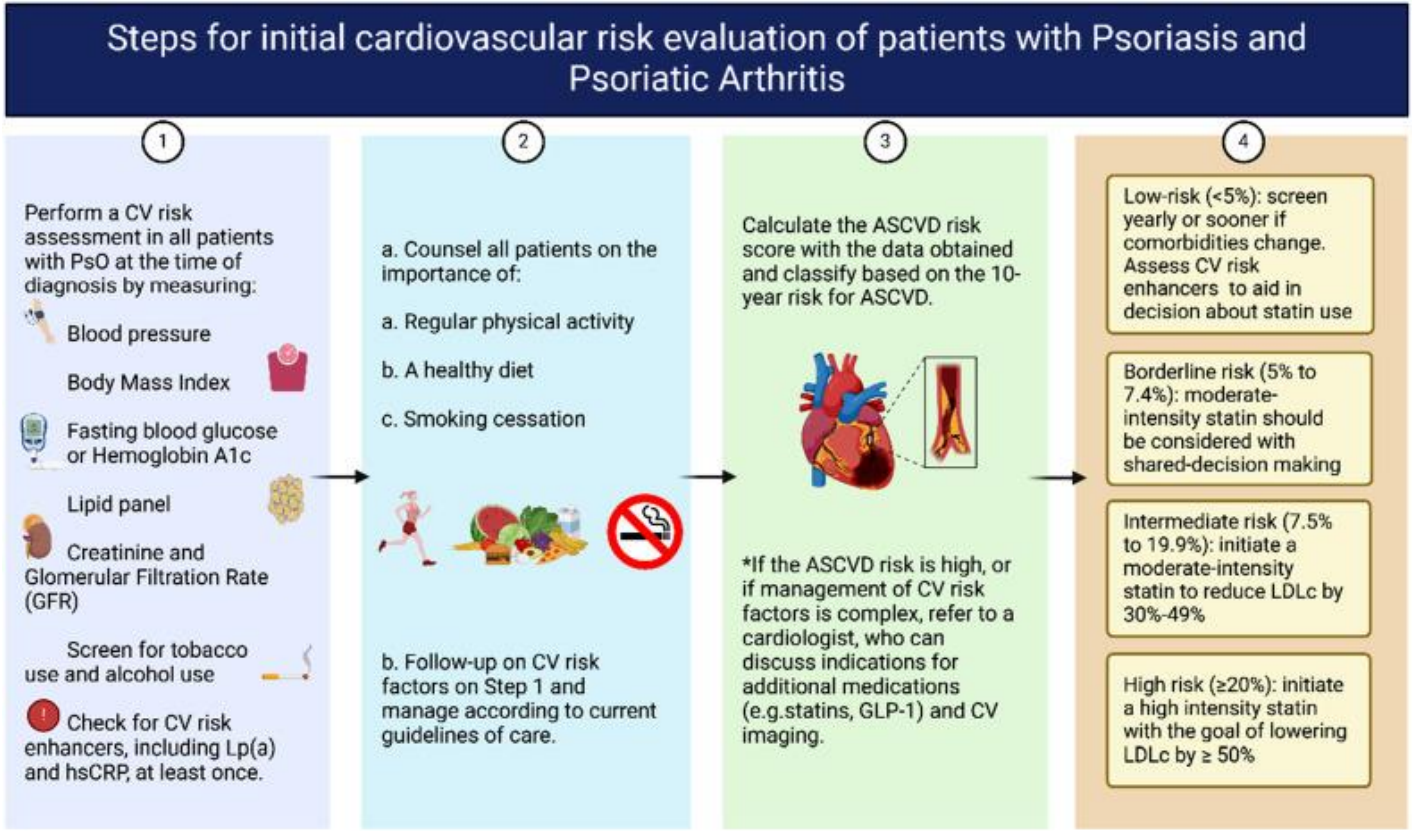
EULAR Recommendations for the Management of PsA with Pharmacological Therapies[3]

ACC/AHA Guidelines on the Primary Prevention of Cardiovascular Disease[4]

AAD = American Association of Dermatology; ACC = American College of Cardiology; AHA = American Heart Association; EULAR = European Alliance of Associations for Rheumatology; NPF = National Psoriasis Foundation; GRAPPA = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; PsA = psoriatic arthritis; PsO = psoriasis.

1. Elmets CA, et al. *J Am Acad Dermatol*. 2019;80:1073-1113. 2. Coates LC, et al. *Nat Rev Rheumatol*. 2022;18:465-479. 3. Gossec L, et al. *Ann Rheum Dis*. 2020;79:700-712.
4. Arnett DK, et al. *Circulation*. 2019;140:e596-e646.

Practical Recommendations on Cardiovascular Risk Evaluation in Patients With Psoriasis and Psoriatic Arthritis for Dermatologists, Rheumatologists, and Primary Care Physicians by the Psoriasis and Psoriatic Arthritis Clinics Multicenter Advancement Network

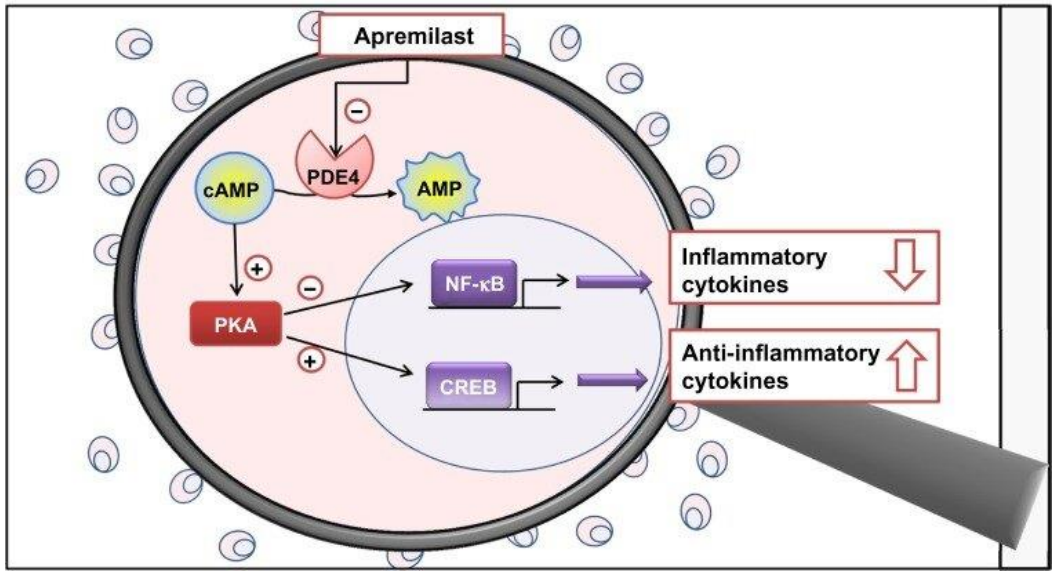


J Psoriasis Psoriatic Arthritis. 2025 May 28:24755303251337020

- Evidence for the Role of Apremilast in Improving Cardiometabolic Parameters

Apremilast: mechanism of action

- PDE4 acts as an intracellular non-receptor enzyme that regulates inflammation and epithelial integrity
- **Inhibiting PDE4 increases cellular cAMP levels**

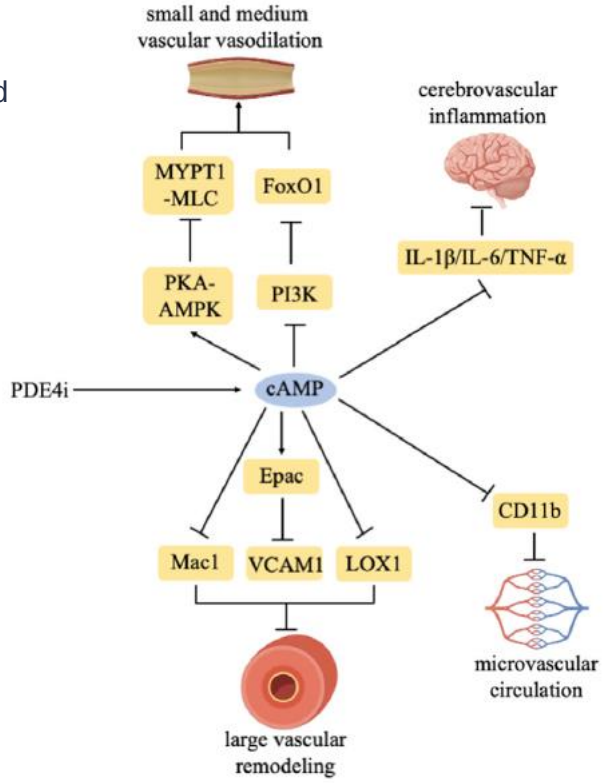


PDE4 inhibitors: potential protective effects in inflammation and vascular diseases

- Inhibits the expression and secretion of pro-inflammatory cytokines, chemokines and adhesion molecules (VCAM, ICAM, MMP9, e-selectin)
- Protective effects in atherosclerosis by reducing scavenger receptors LOX-1 and CD36
- PDE4 inhibitors inhibit cerebrovascular inflammation
- Improve microvascular circulation by inhibiting CD11b
- Promote vasodilation through the PKA-AMPK/MYPT1-MLC/Fox01 pathway

- η σηματοδότηση cAMP/PKA είναι κεντρική στη ρύθμιση της συσταλτικότητας της καρδιάς, του καρδιακού ρυθμού, της σύζευξης διέγερσης-συστολής, καθώς και στον αγγειακό τόνο.

- There is also some evidence that higher basal or dysregulated intracellular cAMP in certain cell types correlates with cardiovascular risk — e.g., studies in hypertension showing that intra-lymphocyte cAMP level (and beta-adrenergic receptor density, catecholamine levels) are predictors of future cardiovascular events



Effects of PDE4 inhibitors on vascular dysfunction

Front Pharmacol. 2024 Jun 10:15:1407871.

The molecular dimensions of apremilast's effect on CVD

Study type	Conditions	Sample/Cell type	Effect of apremilast
Observational: real world evidence- molecular study	PsA patients	Blood-based biomarkers: circulating CVD-plasma levels	A decrease is noted in CD-163, FABP-4, RARRES-2, CCL-15, MMP-3, vWF, GDF-15, TPA, TIMP-4, TR-AP, IL-2RA, CTSD, CNTN-1, GAL-3, LTBR, OPG and NT-proBNP at 6 months, previously identified as being altered in the plasma of PsA patients when compared to healthy donors.
Interventional: VIP-A Phase 4 clinical trial	Pso patients	Blood-based biomarkers: circulating plasma and serum levels	Changes in cardiometabolic biomarkers related to lipoprotein characterization, inflammation and glucose metabolism.
			At week 16, there was a reduction in IL-1β, valine, leucine, and feutin A, along with a decrease in branched-chain amino acids. By week 52, a decline was observed in ferritin, β-hydroxybutyrate, acetone, and ketone bodies, accompanied by an increase in apolipoprotein A-1.
Molecular study	*In vitro*: gene and protein expression	Human aortic endothelial cells (HAECs) and U937 monocytic cells	Apremilast exhibited the capacity to decrease the expression of crucial receptors involved in oxidized ox-LDL scavenging, along with a reduction in inflammatory cytokines such as IL-6, TNF-α, and IL-8 upon stimulation with ox-LDL.
			Apremilast successfully hindered the attachment of monocytes to HAECs, primarily due to the diminished levels of MCP-1 and VCAM-1.
Molecular study	*In vitro: gene and protein expression*	Human umbilical vein endothelial cells (HUVEC) and THP1 monocytic cells	Apremilast effectively inhibited the TNF-α-induced expression and secretion of crucial pro-inflammatory factors in both endothelial and monocytic cells. These factors encompass GM-CSF, CXCL-10, CCL-2, VCAM-1, E-selectin, and MMP-9.
			Apremilast diminished the adhesion of THP-1 cells to activated HUVECs and the Transwell Endothelial Migration in response to TNF-α.
			Apremilast inhibited the activation of NFκB and MAPK signaling in activated HUVECs.
			Apremilast decreased IL-17A-induced secretion of IL-6 and CCL2.
Observational: real world evidence- molecular study	Pso patients	Blood-based biomarkers	Decreased levels of IL-1β, IL-6, IL-17A, IL-17F, IL-17C, IL-21, IL-22, IL-23, IL-36γ, TGF-β1, and TNF-α, alongside an elevation in inhibitory cytokines such as IL-10 and IL-35.

Key Evidence Supporting the Role of Apremilast in Improving Cardiometabolic Parameters

Obesity, diabetes mellitus, cardiovascular disease

Pooled analysis of 5 Phase 3 PsA clinical studies (PALACE 1-4 and ACTIVE)
Mease PJ, et al. EULAR 2023, Poster POS1527

Pooled analysis of 2 Phase 3 PsO clinical studies (ESTEEM 1 and 2)
Strober B, et al. AAD 2024.

Obesity and diabetes mellitus

Real-world analysis in PsO/PsA (US-OM1)
Cavanaugh C, et al. *JAAD International*. 2024.

Real-world analysis in PsO/PsA (US-OM1)
Cavanaugh C, et al. EADV 2023.

Obesity and cardiovascular disease

Retrospective pooled analysis in PsO/PsA
Hu X, et al. EADV 2023, Poster 2346.

US non-randomized clinical study in PsO (VIP-A)
Gelfand JM, et al. *JAMA Dermatol*. 2022;158:1394-403.

Obesity

Prospective open-label study in PsO/PsA (IMAPA)
Ferguson LD, et al. *Rheumatology (Oxford)*. 2022;61:1026-1034.

Diabetes mellitus

Pooled analysis of 6 Phase 3 clinical studies in PsO/PsA
Puig L, et al. AAD 2019, DC. Poster 9706

Cardiovascular disease

Analysis of 99 cardiovascular biomarkers in PsA
Arias de la Rosa I, et al. *J Intern Med* . 2022;291:676-693.

Long-term safety and tolerability

Pooled analysis of 15 randomized, controlled clinical trials in PsO/PsA/BS
Mease PJ, et al. *Am J Clin Dermatol*. 2023;24:809-820.

BS = Behçet's Syndrome; PsA = psoriatic arthritis; PsO = psoriasis.

Apremilast has been associated with weight loss in clinical studies

Cellular cAMP levels are increased due to PDE4 inhibition and may lead to weight loss through the following mechanisms

Organ-specific mechanisms[1]

Immune cells
Activation of alternative macrophages and regulatory T-cells → reduced inflammation

Fat tissue
Stimulation of thermogenesis and lipolysis in white and brown adipocytes

Liver
Reduction of hepatic lipid deposition and improvement of liver steatosis

Brain
PDE4 expression is concentrated in the hypothalamus, which controls food consumption and central sympathetic discharge

Pancreas
Promotion of insulin secretion into the bloodstream by the pancreas

Organ-overarching mechanisms[2-6]

Decreased food intake
Potentially altered food intake since PDE4 expression is concentrated in the hypothalamus, a central regulator of appetite

Altered hormone levels
Increased levels of adiponectin, an anti-inflammatory marker, and reduced levels of serum leptin, a pro-inflammatory regulator of energy homeostasis

Increased thermogenesis and lipolysis
Reduction of inflammation stimulates lipolysis and brown adipose tissue-mediated thermogenesis

Increased energy expenditure
Increased locomotor activity of PDE4-deficient mice. Stimulation of mitochondrial biogenesis and enhanced respiratory capacity upon roflumilast therapy

Improved glucose metabolism
Reduced glucose levels in type II diabetes patients after roflumilast therapy, potentially due to release of glucagon-like peptide (GLP1)

Bodyweight loss and improved insulin sensitivity

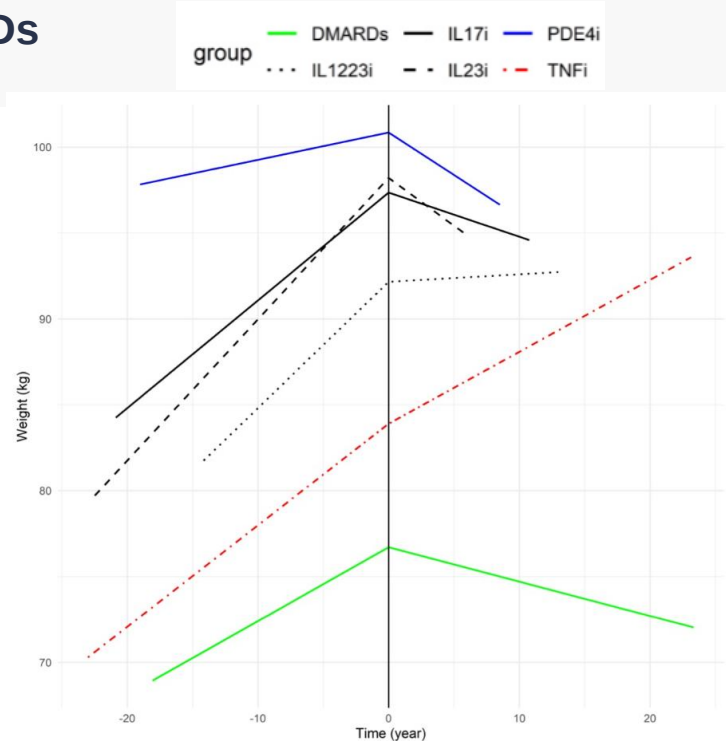
1. Wu C, et al. *Obes Rev*. 2016;17:429-41. 2. Elllulu MS, et al. *Arch Med Sci*. 2017;13:851-863. 3. Kraynik SM, et al. *Mol Pharmacol*. 2013;83:1155-65. 4. Möllmann J, et al. *Diabetes Obes Metab*. 2017;19:496-508.
5. Wouters EFM, et al. *J Clin Endocrinol Metab*. 2012;97:E1720-5. 6. Zhang R, et al. *Endocrinology*. 2009;150:3076-82. 7. Otezla [package insert]. Thousand Oaks, CA; Amgen, Inc.; 2023.

Μεταβολή του σωματικού βάρους με τη χρήση DMARDs

- 1754 patients with PsA with at least two weight measurements over follow-up
  - 473 λάμβαναν ΜΣΑΦ ή καμία φαρμακευτική αγωγή, 571 λάμβαναν csDMARDs, 702 bDMARDs, 42 JAKi και 70 apremilast

- Με βάση τη μοντελοποίηση σημείου αλλαγής (change-point modelling), παρατηρήθηκε σημαντική μείωση στον ρυθμό μεταβολής του σωματικού βάρους μετά την έναρξη θεραπείας με αναστολείς IL-17 (κλίση 0,63 ± 0,20 έναντι −0,26 ± 0,25, P<0.01) IL-23 (0,82 ± 0,34 έναντι −0,56 ± 0,56, P<0.01), και csDMARDs (0,43 ± 0,24 έναντι −0,20 ± 0,26, P<0.01) σε σύγκριση με την περίοδο πριν από την έναρξη της θεραπείας.

- Παράγοντες που συσχετίστηκαν με αύξηση βάρους κατά την παρακολούθηση ήταν η χρήση TNFi, IL-12/23i, το ανδρικό φύλο, η διάρκεια παρακολούθησης και το υψηλότερο αρχικό σωματικό βάρος, ενώ παράγοντες που σχετίστηκαν με απώλεια βάρους ήταν η χρήση apremilast, η μεγαλύτερη ηλικία και ο σακχαρώδης διαβήτης.
- Σε σύγκριση με το σωματικό βάρος κατά την έναρξη της θεραπείας, η χρήση TNFi συσχετίστηκε με αύξηση βάρους στον έναν χρόνο (1,54 κιλά, P<0.01)



	Slope before drug initiation, mean (SD)	Slope after drug initiation, mean (SD)	p-value
TNFi, n=274	0.59 (0.14)	0.42 (0.14)	0.202
IL-17i	0.63(0.20)	-0.26(0.25)	<0.001
IL-12/23i	0.73 (0.43)	0.04 (0.50)	0.102
IL-23i	0.82 (0.34)	-0.56 (0.56)	0.005
Apremilast	0.16 (0.46)	-0.49 (1.14)	0.586
csDMARDs	0.43 (0.24)	-0.20 (0.26)	<0.001

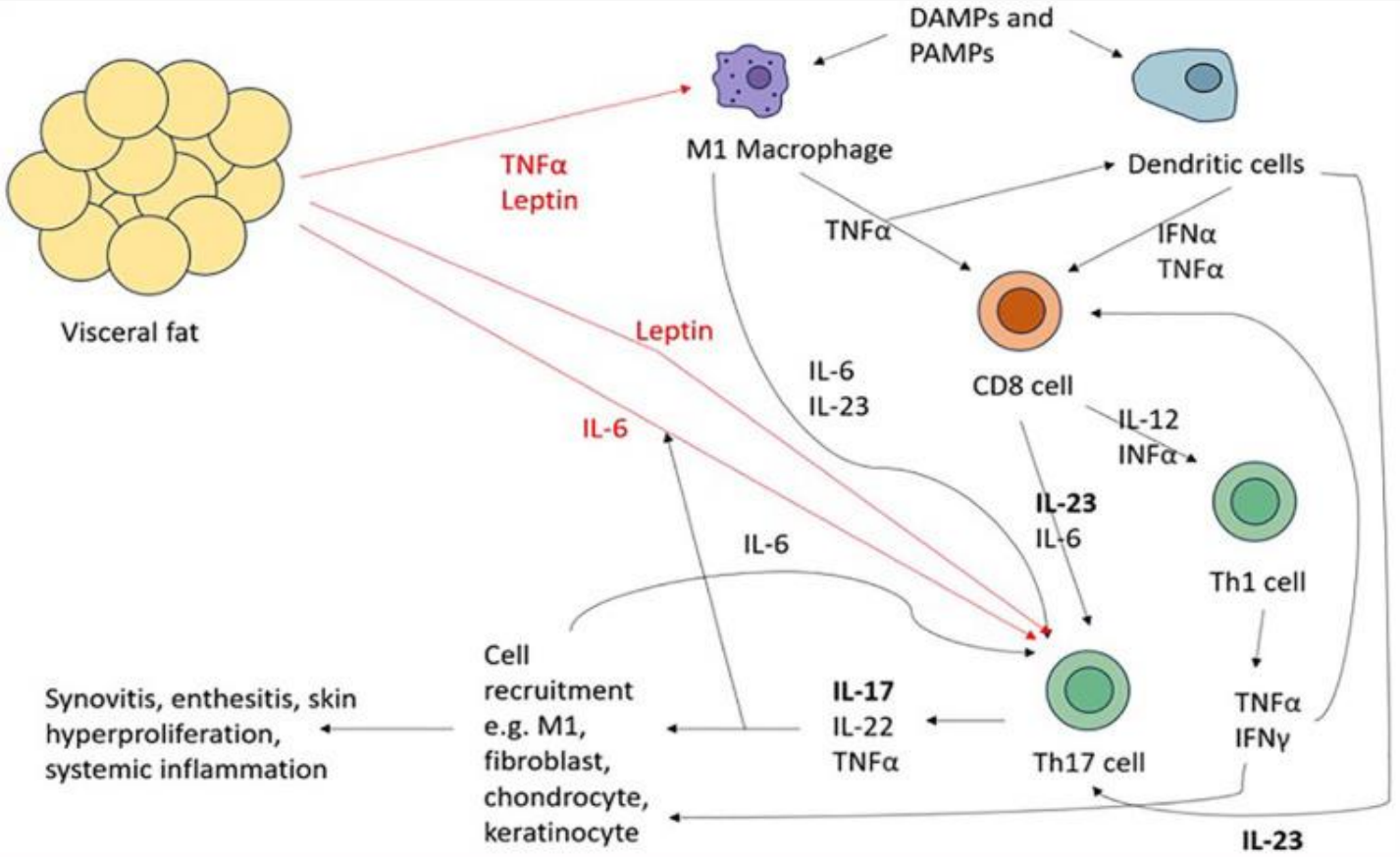
Mehta P, Kharouf F, Gao S, Gladman D, Chandran V. Exploring Weight Trends in Psoriatic Arthritis: Unraveling Effects of Drugs [abstract]. *Arthritis Rheumatol.* 2024; 76 (suppl 9).

Adiposity reduction

- In the *VIP-A trial* (patients with moderate-severe psoriasis), apremilast treatment was associated with **reductions** in visceral and subcutaneous adiposity (~5-6%) at 16 weeks that persisted to 52 weeks.
- Also favorable changes in several biomarkers: IL-1β, fetuin A, branched chain amino acids, apolipoprotein A-1, etc.
- However, aortic vascular inflammation (measured by FDG-PET/CT) had a neutral outcome (no significant change).

JAMA Dermatol. 2022 Sep 21:158(12):1394–1403.

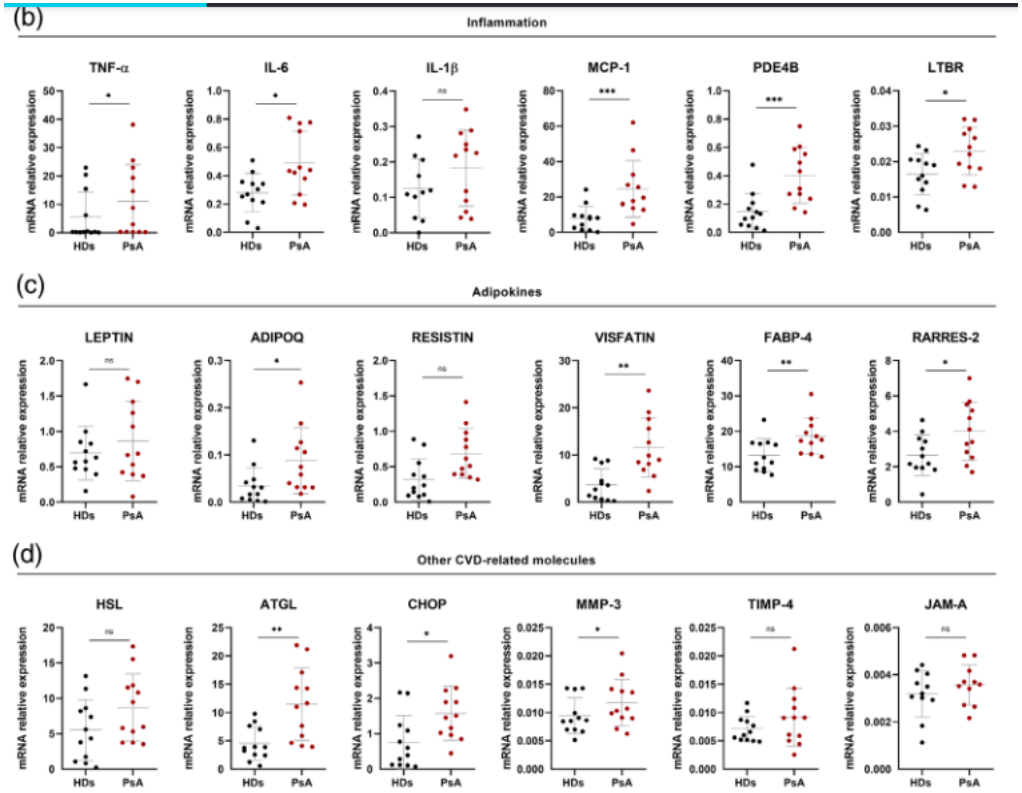
The adipose tissue is not a mere energy store



The potential pro-inflammatory mechanisms of obesity in PsO/PsA

The “clinical and molecular cardiometabolic fingerprint” study

- cross-sectional study
- in PsA patients, many CVD-related proteins were elevated in those with metabolic comorbidities
- cardiometabolic comorbidities were associated with disease activity and long-term inflammatory status.
- after 24 weeks of apremilast (monotherapy or with MTX):
  - **Apremilast significantly reduced the levels of the insulin resistance index** (HOMA-IR) in patients with high prevalence of metabolic comorbidities
  - **Apremilast**, whether used alone or in combination with MTX, **significantly reduced CVD-related markers**, while MTX did not have a positive impact on these markers



HOMA-IR = Homeostatic Model Assessment for Insulin Resistance

**Cardiometabolic comorbidities included increased Apo-B/Apo-A ratio and atherogenic risks, obesity, insulin resistance, hypertension and metabolic syndrome. These patients showed significantly higher DAPSA scores, and higher fasting glucose, insulin, and ESR levels*

J Intern Med. 2022 May;291(5):676-693.

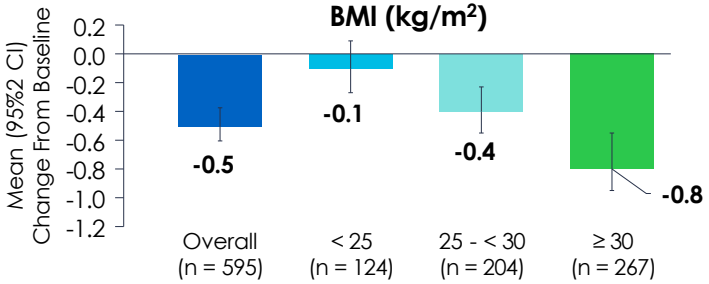
Apremilast Lowered LDL Cholesterol, HbA1c, BMI, and Improved HDL Cholesterol

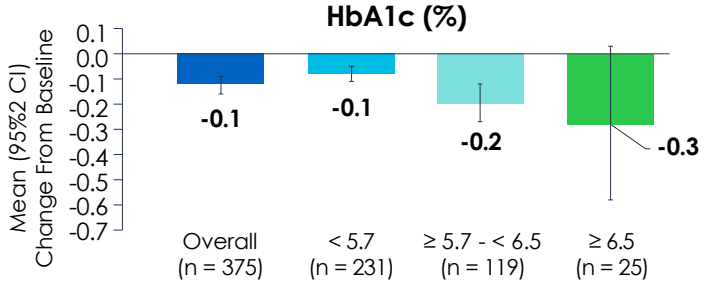
Data from pooled analysis of 5 randomized, placebo-controlled, phase 3 PsA studies (PALACE 1–4 and ACTIVE)

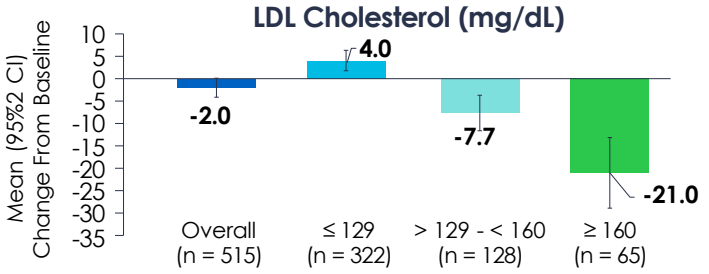
Changes from baseline to week 52 in BMI, HbA1c, and LDL and HDL cholesterol

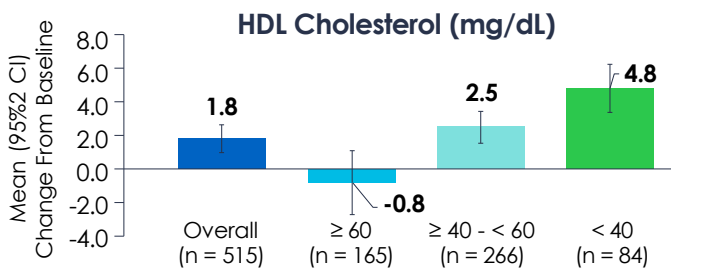
N = 781 patients with PsA

Improvements in BMI, HbA1c, LDL, and HDL cholesterol after 52 weeks of apremilast treatment were greater in patients in higher risk categories at baseline









Mease PJ, et al. Poster presented at: EULAR: May 31 – June 3, 2023; Milan, Italy. Poster POS1527.

In the Real-world Setting, Apremilast Reduced BMI, Bodyweight, and HbA1c Levels, Independent of Diabetes Status at 6 and 12 Months

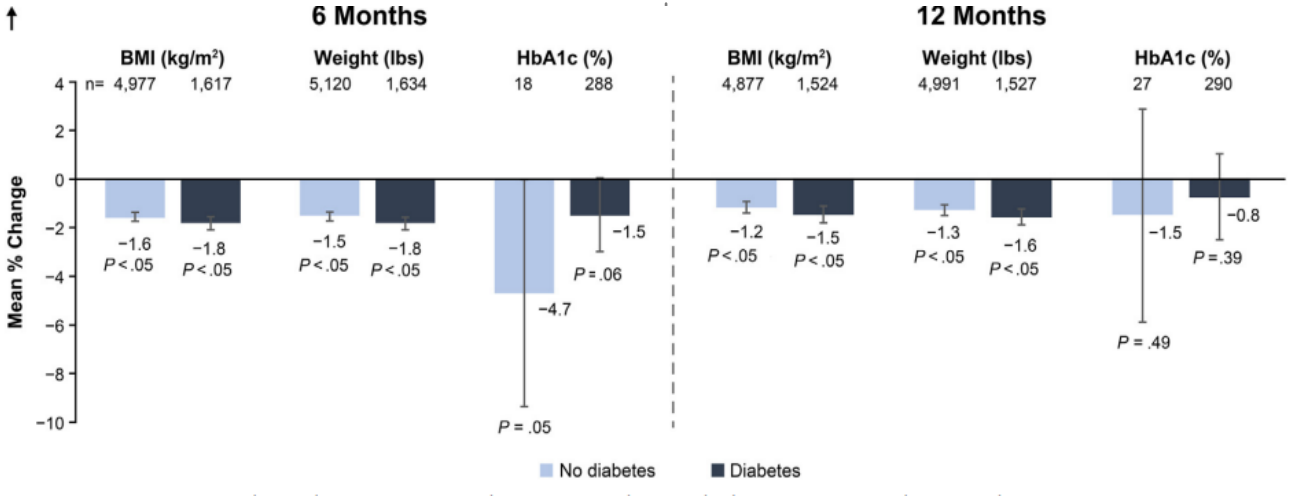
Real-world, retrospective, longitudinal cohort study of patients with PsO and/or PsA who newly initiated apremilast*

Changes (mean, %) from baseline in BMI, weight, HbA1c, and lipids at 6 and 12 months by prediabetes/ diabetes or obesity status

N = 8,487 patients
- 2,004 (24%) patients had diabetes†
- Of those with diabetes, 25% had prediabetes and 87% had T2DM

Patients experienced decreases in BMI and weight at 6 and 12 months regardless of diabetes status

The greatest reductions in BMI and weight were seen in patients with diabetes



*Patients were ≥ 18 years old at index date (first apremilast prescription or fill [March 2014 to November 2021]) and new initiators of apremilast with a PsO or PsA diagnosis within 12 months on or before index date. Included were patients with BMI, weight, or laboratory measures in the 3 months before and including index date and 6 or 12 months after index date, persistent on apremilast for at least 6 months (6-month analysis) or 12 months (12-month analysis).

†Of those with diabetes, 25% had prediabetes and 87% had T2DM (patients could be classified as both prediabetic and T2DM). Pre-diabetes: either two diagnosis codes at least 30 days apart, HbA1c levels between 5.7% to 6.4%, or fasting glucose levels between 100–125 mg/dL. T2DM: two diagnosis codes at least 30 days apart or evidence of antidiabetic medication during the baseline period.

Cavanaugh C, et al. *JAAD International*. 2024. https://doi.org/10.1016/j.jdin.2024.02.016.

JAAD Int. 2024 Mar 9:16:244-251.

In the Real-world Setting, Apremilast Reduced Total and LDL Cholesterol, Independent of Diabetes Status at 6 and 12 Months

Real-world, retrospective, longitudinal cohort study of patients with PsO and/or PsA who newly initiated apremilast*

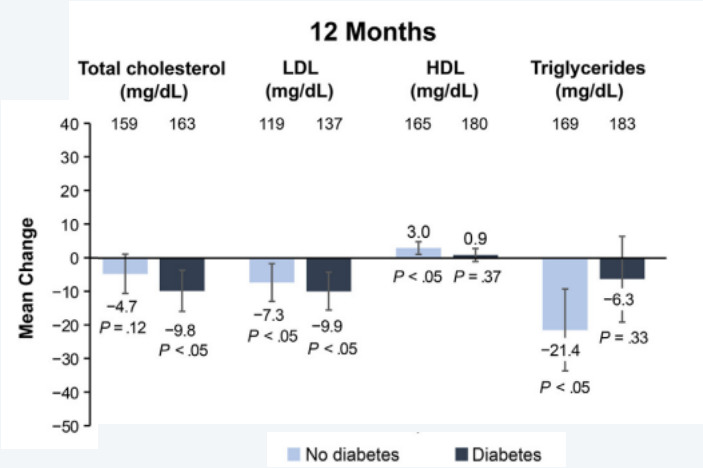
Changes (mean) from baseline in BMI, weight, HbA1c, and lipids at 6 and 12 months by prediabetes/ diabetes or obesity status

N = 8,487 patients
- 2,004 (24%) patients had diabetes†

Patients with diabetes experienced significant decreases in total cholesterol at 12 months

Regardless of diabetes status, LDL cholesterol decreased significantly at 12 months

HDL cholesterol increased significantly in the no diabetes group at 12 months



BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PsA = psoriatic arthritis; PsO = psoriasis. T2DM = type 2 diabetes mellitus.

*Patients were ≥ 18 years old at index date (first apremilast prescription or fill [March 2014 to November 2021]) and new initiators of apremilast with a PsO or PsA diagnosis within 12 months on or before index date. Included were patients with BMI, weight, or laboratory measures in the 3 months before and including index date and 6 or 12 months after index date, persistent on apremilast for at least 6 months (6-month analysis) or 12 months (12-month analysis).

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Real-world, retrospective, longitudinal cohort study of patients with PsO and/or PsA who newly initiated apremilast*

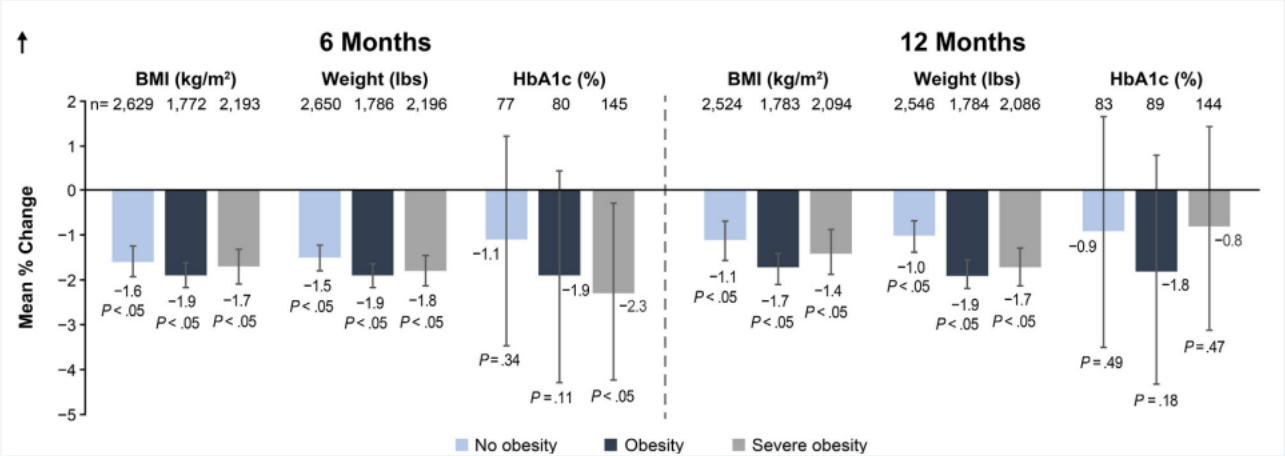
Changes (mean, %) from baseline in BMI, weight, HbA1c, and lipids at 6 and 12 months by prediabetes/ diabetes or obesity status

N = 8,487 patients

- 8,250 patients with BMI data, 40% were not obese, 27% were obese, and 33% were severely obese†

Regardless of obesity status, significant decreases in BMI and weight were seen at 6 and 12 months

A significant reduction in HbA1c was only seen in the severe obesity group at month 6



BMI = body mass index; HbA1c = hemoglobin A1c; PsA = psoriatic arthritis; PsO = psoriasis.

*Patients were ≥ 18 years old at index date (first apremilast prescription or fill [March 2014 to November 2021]) and new initiators of apremilast with a PsO or PsA diagnosis within 12 months on or before index date. Included were patients with BMI, weight, or laboratory measures in the 3 months before and including index date and 6 or 12 months after index date, persistent on apremilast for at least 6 months (6-month analysis) or 12 months (12-month analysis).

†Obesity status was defined as no obesity (BMI < 30 kg/m²), obesity (BMI ≥ 30–34.9 kg/m²), or severe obesity (BMI ≥ 35 kg/m²).

Cavanaugh C, et al. *JAAD International*. 2024. https://doi.org/10.1016/j.jdin.2024.02.016.

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N = 8,487 patients

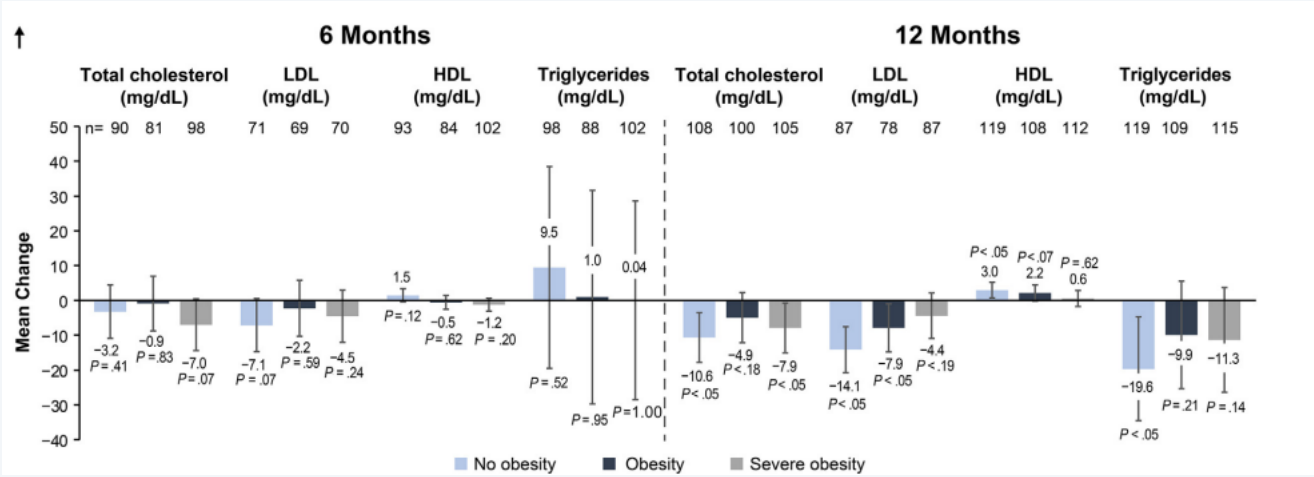
- 8,250 patients with BMI data, 40% were not obese, 27% were obese, and 33% were severely obese†

Regardless of obesity status, total and LDL cholesterol decreased at 6 and 12 months

Significant decreases in total cholesterol were seen in the no obesity and severe obesity groups at 12 months

Significant decreases in LDL cholesterol were seen in the no obesity and severe obesity groups at 12 months

Significant increases in HDL cholesterol were seen in the no obesity group at 12 months



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Cavanaugh C, et al. *JAAD International*. 2024. https://doi.org/10.1016/j.jdin.2024.02.016.

The Benefits of Apremilast (Beyond Skin and Joint Disease)

Obesity

PDE4 inhibition with apremilast impacts visceral adiposity

- Clinically meaningful reduction in weight (≥ 5% weight loss) in up to 27% of patients[1-5]
- Improvements in BMI[2,4-8]
- Reduction of 5-6% of visceral and subcutaneous fat[5]

Diabetes Mellitus

PDE4 inhibition with apremilast improves glucose control and diabetes status

- Reduction of HbA1c in patients with normal or pre-diabetic/ diabetic HbA1c status[4,7,8]

Cardiovascular Disease

PDE4 inhibition with apremilast impacts lipid metabolism

- Reduction of CV risk markers, increase of HDL cholesterol,[1,5,7,8] and reduction of LDL cholesterol[4,7,8]
- Improvement of vascular endothelial injuries[9]

1. Hu X, et al. Poster presented at: the 32nd European Academy of Dermatology and Venereology (EADV) Congress; October 11–14, 2023, Berlin, Germany. Poster: 2346.
2. Ferguson LD, et al. *Rheumatology (Oxford)*. 2022;61:1026-34. 3. Cavanaugh C, et al. Poster presented at: the 32nd European Academy of Dermatology and Venereology (EADV) Congress; October 11–14, 2023, Berlin, Germany. 4. Cavanaugh C, et al. *JAAD International*. 2024. https://doi.org/10.1016/j.jdin.2024.02.016. 5. Gelfand JM, et al. *JAMA Dermatol*. 2022;158:1394-403. 6. Arias de la Rosa I, et al. *J Intern Med*. 2022;291:676-93. 7. Mease PJ, et al. Presented at: EULAR 2023, Milan, Italy POS 1527. 8. Strober B, et al. Poster presented at: the American Academy of Dermatology (AAD) Annual Meeting; March 8-12, 2024; San Diego, CA. 9. Ikonomidis I, et al. *Pharmaceuticals (Basel)*. 2022;15:172.

The Benefits of Apremilast (in Skin and Joint Disease)

- The FOREMOST study, a phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group study aimed to evaluate the efficacy and safety of apremilast in subjects with early (disease duration ≤ 5 years) oligoarticular PsA
- This patient population, which comprises up to 50% of all PsA patients suffer from a significant burden of disease[4,5]
- In majority of PsA registration trials in PsA, mean joint counts are high and result in very limited enrollment of patients with oligoarticular PsA, if any. This has resulted in paucity of clinical data and absence of relevant treatment options in guidelines (GRAPPA, EULAR, ACR/NPF)

- Primary endpoint: MDA-Joints response at Week 16

Gladman DD, et al. *J Rheumatol*. 2021;48:1824-1829.
Gossec L, et al. *Ann Rheum Dis*. 2024.83:1480-1488..

FOREMOST: MDA-Joints as the Primary Endpoint

In the FOREMOST study, the primary endpoint was MDA-Joints score at Week 16, a novel endpoint chosen for its specificity in assessing PsA rather than ACR20 which does not provide the necessary sensitivity in this limited joint population[1,2]

MDA-Joints[2,3]	ACR20[2]
Validated multidomain comprehensive endpoint	Validated composite endpoint
Does not require high disease activity at baseline	Requires high disease activity at baseline
PsA-specific endpoint; more sensitive for oligoarticular PsA	Non-PsA–specific arthritis endpoint; not sensitive for oligoarticular PsA
Takes important domains into account (enthesitis, skin involvement)	Does not take important domains into account (enthesitis, skin involvement)

In the FOREMOST study, MDA-Joints was defined as the proportion of patients who achieved a clinical state of minimal disease activity:[1,*]

And **3 out of 5** of the remaining cutoff values

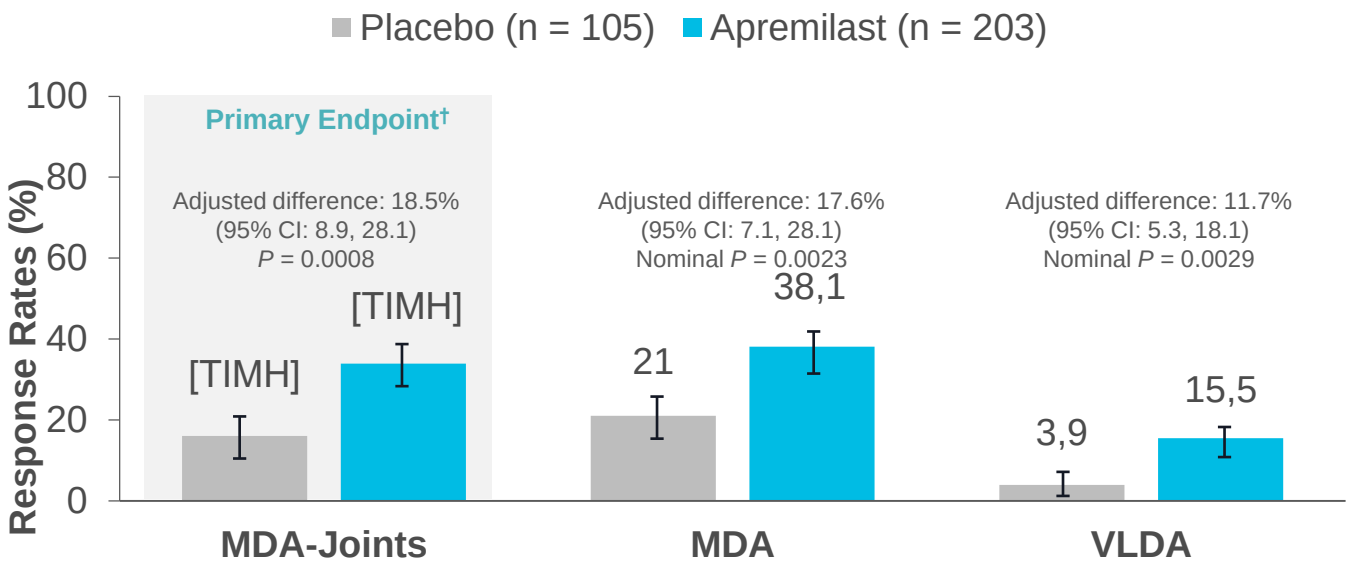
- BSA **≤ 3%**
- Patient pain (VAS) **≤ 15**
- Patient's Global Assessment of Disease (VAS) **≤ 20**
- HAQ-DI **≤ 0.5**
- Enthesitis count **≤ 1**†

*Based on sentinel joints (those affected at baseline). †Based on LEI.
ACR = American College of Rheumatology; BSA = body surface area; FOREMOST = Efficacy, Safety, and Tolerability Study of Apremilast to Treat Early Oligoarticular Psoriatic Arthritis; HAQ-DI = Health Assessment Questionnaire Disability Index; LEI = Leeds Enthesitis Index; MDA-Joints = minimal disease activity in joints; PsA = psoriatic arthritis; SJC = swollen joint count; TJC = tender joint count;
VAS = visual analog scale.
1. Gossec L, et al. *Ann Rheum Dis*. 2024;83:1480-1488. 2. Ogdie A, et al. Arthritis Care Res (Hoboken). 2020;72(Suppl 10):82-109. 3. Coates LC, et al. *J Rheumatol*. 2016;43:371-375.

Achievement of MDA-Joints, MDA, and VLDA Was Greater With Apremilast vs Placebo at Week 16

- The MDA-Joints response rate was two times greater with apremilast vs placebo at Week 16

Overall Achievement of MDA-Joints, MDA, and VLDA at Week 16

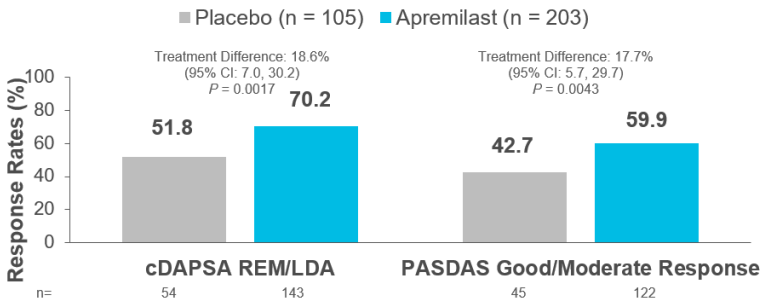


1. Gossec L, et al. *Ann Rheum Dis*. 2024;83:1480-1488. 2. Mease P, et al. Presented at: American College of Rheumatology Convergence 2023; November 10-16, 2023; San Diego, CA. OP #1691. 3. Gossec L, et al. *Ann Rheum Dis*. 2024;83:1480-1488 (online supplement).

Achievement of cDAPSA REM/LDA and PASDAS Good/Moderate Response Was Greater With Apremilast vs Placebo at Week 16

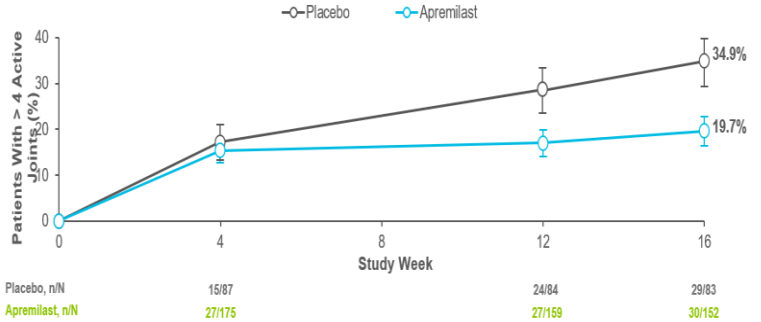
Joint Count Increased From ≤ 4 to > 4 for a Higher Proportion of Patients Treated With Placebo vs Apremilast Over 16 Weeks

Proportion of Patients Achieving cDAPSA REM/LDA and PASDAS Good/Moderate Response



In the overall population, cDAPSA REM/LDA was achieved in 70.2% of APR patients vs 51.8% in PBO patients at weeek16

Proportion of Patients Progressing From Oligoarticular PsA to Polyarticular PsA*



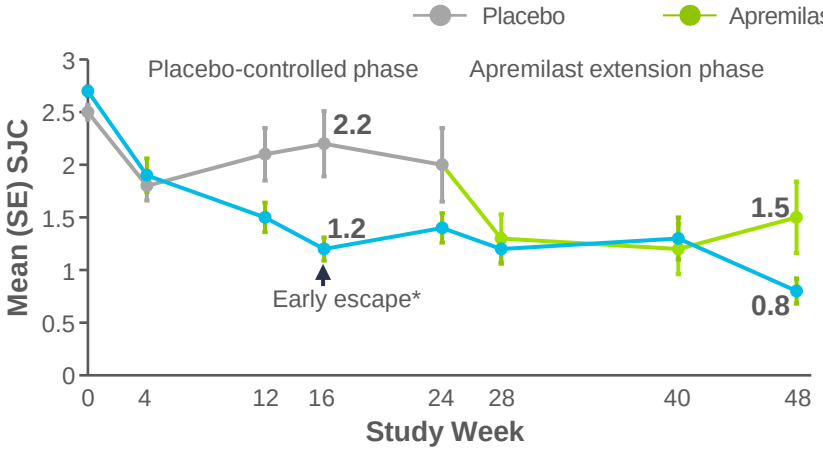
There was an increase in the proportion of patients who switched to a joint count >4 through week 16 among those receiving PBO but not among those receiving APR

Gossec L, et al. *Ann Rheum Dis*. 2024;83:1480-1488.

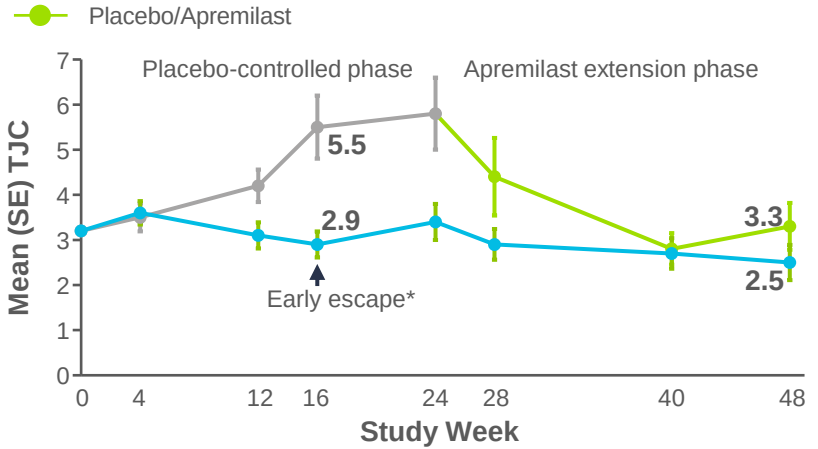
Patients Treated With Apremilast Achieved Greater Improvements in SJC and TJC vs Placebo Through Week 48

- During the placebo-controlled phase, mean SJC and TJC improved in the apremilast group and worsened in the placebo group; further improvements were sustained through Week 48 in patients who continued or transitioned to apremilast

SJC



TJC



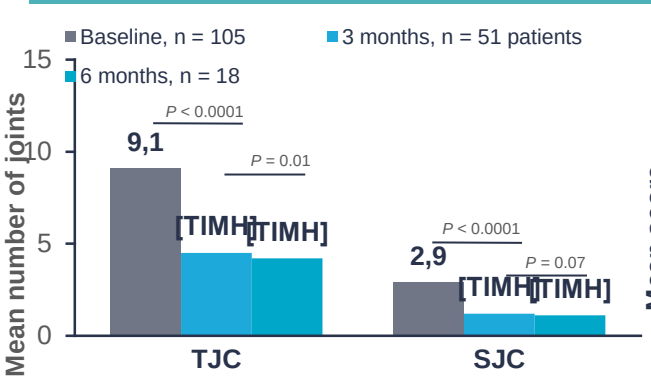
*Patients undergoing early escape at Week 16 (placebo, n = 24; apremilast, n = 21) were analyzed at Week 24 per randomization. Apremilast patients as randomized or transitioned. Data as observed and based on all joints.
FOREMOST = Efficacy, Safety, and Tolerability Study of Apremilast to Treat Early Oligoarticular Psoriatic Arthritis; PsA = psoriatic arthritis; SE = standard error; SJC = swollen joint count; TJC = tender joint count .
Gossec L, et al. Poster presented at: European Alliance of Associations for Rheumatology (EULAR) 2024; June 12-15, 2024; Vienna, Austria. Poster POS0976.

RWE Show That Apremilast May Be Effective in Patients With Oligoarticular PsA Who Are Not Typically Seen in RCTs

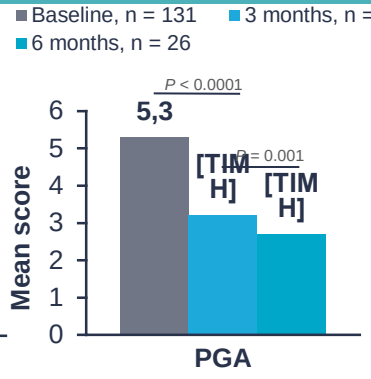
- In a retrospective study (n = 131) of an Italian multicentric cohort of patients (58%) with oligoarticular PsA:*,†
  - More than 70% of patients received apremilast after first failing at least two csDMARDs‡
  - 58% of the patients showed an oligoarticular pattern (< 5 affected joints)

Baseline Characteristics	
Patients, n	131
Female, %	63.3
Age, mean year (SD)	57.5 (12)
TJC, mean (SD)	9.1 (8.4)
SJC, mean (SD)	2.9 (2.6)

Change in SJC and TJC From Baseline§



Change in PGA From Baseline§



*Patients had at least one comorbidity (64.1%, in particular, history of malignancies [25.9%] and latent TB [16.3%]) and were treated with apremilast as first-line targeted therapy (47.7%) or in biologics failures (52.3%); †This percentage was calculated out of 62 patients who received apremilast as first-line targeted therapy; ‡According to Italian reimbursement conditions, treatment with apremilast should be limited to adult patients who have responded inadequately or have been intolerant to at least two DMARDs and in whom the use of biologic drugs is contraindicated or not tolerated; §n at 3 and 6 months represents patients who have reached these points at the time of data collection.
csDMARD = conventional synthetic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; PGA = physician's global assessment; PsA = psoriatic arthritis; RCTs = randomized controlled trials; RWE = real-world evidence; SD = standard deviation; SJC = swollen joint count; TB = tuberculosis; TJC = tender joint count.
Favalli EG, et al. *Clin Exp Rheumatol*. 2020;38:19-26.

Low discontinuation rates in patients with metabolic conditions

- 7773 Pso patients with and without metabolic conditions newly initiating a biological or apremilast treatment
- 47.5-56.7% had a metabolic condition

- nearly half of the patients discontinued their index medication over 24 months

- Except for the apremilast group, patients with metabolic conditions had higher discontinuation (secukinumab: 50.6% vs. 43.7%; adalimumab*: 53.9% vs. 48.7%; ustekinumab*: 41.9% vs. 35.1%; etanercept: 42.8% vs. 41.2%; apremilast: 43.1% vs. 46.1%) and switching (secukinumab: 48.1% vs. 41.2%; adalimumab*: 47.8% vs. 41.9%; ustekinumab*: 34.5% vs. 25.3%; etanercept*: 53.6% vs. 51.5%; apremilast: 45.8% vs. 44.6%) than patients without (*$p < .05$).

- patients with metabolic conditions had higher discontinuation rates than those without in all treatment cohorts except apremilast

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ORIGINAL RESEARCH ARTICLE

Apremilast Long-Term Safety Up to 5 Years from 15 Pooled Randomized, Placebo-Controlled Studies of Psoriasis, Psoriatic Arthritis, and Behçet's Syndrome

Philip J. Mease[1] · Gülen Hatemi[2] · Maria Paris[3] · Sue Cheng[3] · Peter Maes[3] · Wendy Zhang[3] · Rebecca Shi[3] · Andrea Flower[3] · Hernan Picard[3] · Linda Stein Gold[4]

Ανάλυση Τυχαιοποιημένων μελετών –Χαμηλά ποσοστά MACEs

Objective

APR is **approved for the treatment** of PsO, PsA, and Behçet's syndrome in **56** countries

To **analyze long-term** (up to 5 years) **safety of APR** with specific focus on adverse events of special interest

Methods

Pooled analysis of **15 RCTs** of APR 30 mg BID in patients with PsO, PsA, or Behçet's syndrome

4,183 patients with **6,788 patient-years** of total APR exposure

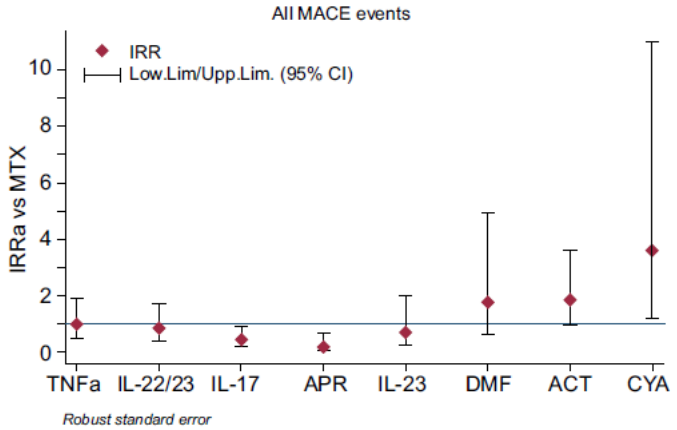
Results

TEAEs of special interest	Placebo-controlled period				All apremilast exposure	
	Placebo [n = 2084] 622.2 patient-years		Apremilast 30 mg bid [n = 2673] 848.8 patient-years		Apremilast 30 mg bid [n = 4183] 6788.0 patient-years	
	n (%)	EAIR/100 patient-years	n (%)	EAIR/100 patient-years	n (%)	EAIR/100 patient-years
Depression	12 (0.6)	1.94	38 (1.4)	4.51	118 (2.8)	1.78
Suicidal ideation/behavior	0 (0)	0.0	1 (<0.1)	0.12	3 (0.1)	0.04
MACE[a]	2 (0.1)	0.32	3 (0.1)	0.35	20 (0.5)	0.30
Malignancies	9 (0.4)	1.45	8 (0.3)	0.94	70 (1.7)	1.0
Nonmelanoma skin cancer	7 (0.3)	1.13	6 (0.2)	0.71	32 (0.8)	0.48
Lymphomas	0 (0)	0.0	0 (0)	0.0	2 (<0.1)	0.03
Serious infections[b]	9 (0.4)	1.45	7 (0.3)	0.83	74 (1.8)	1.10
Serious opportunistic infections	3 (0.1)	0.48	2 (0.1)	0.24	14 (0.3)	0.21
Thrombotic events[c]	0 (0)	0.0	1 (<0.1)	0.12	7 (0.2)	0.10

EAIR=exposure-adjusted incidence rate

Cardiovascular safety of systemic psoriasis treatments: A prospective cohort study in the BIOBADADERM registry

analyzed data from 5622 patients, 11,368 treatment cycles and 21,762 patient-years



Adjusted incidence rate ratio of all Major Adverse Cardiovascular Events with systemic psoriasis treatment compared to MTX

Systemic therapy for psoriasis	Number of person years of exposure	All MACE events: Number of events	All MACE events: Incidence (95% CI)
TNFa	7029	39	5.5 (4.1; 7.6)
IL-12/23	4134	30	7.3 (5.1; 10.4)
IL-23	1943	9	4.6 (2.4; 8.9)
IL-17	3176	11	3.5 (1.9; 6.3)
ACI	1335	27	20.2 (13.9; 29.5)
CYC	440	7	15.9 (7.6; 33.3)
APR	888	3	3.4 (1.1; 10.5)
DMF	114	1	8.8 (1.2; 62.5)
MTX	2704	19	7 (4.5; 11)

Note: Incidences rates (per 1000 person-years).

Adverse events incidence rates

Systemic therapy for psoriasis	Number of person years of exposure	All MACE events: IRR adjusted (95% CI)	All MACE events: *p*-Value
TNFa	7029	0.98 (0.51; 1.91)	0.956
IL-12/23	4134	0.85 (0.43; 1.68)	0.636
IL-23	1943	0.68 (0.23; 2.03)	0.494
IL-17	3176	0.43 (0.20; 0.91)	0.028*
ACI	1335	1.85 (0.94; 3.64)	0.075
CYC	440	3.59 (1.17; 10.99)	0.025*
APR	888	0.17 (0.04; 0.70)	0.014*
DMF	114	1.76 (0.63; 4.93)	0.284
MTX	2704	Reference:1	

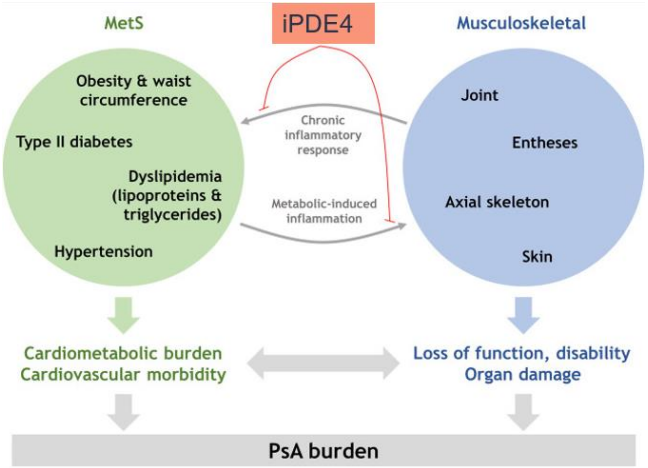
Adjusted incidence rate ratios compared to MTX.

J Eur Acad Dermatol Venereol. 2025 Sep;39(9):1631-1642.

Συμπερασματικά

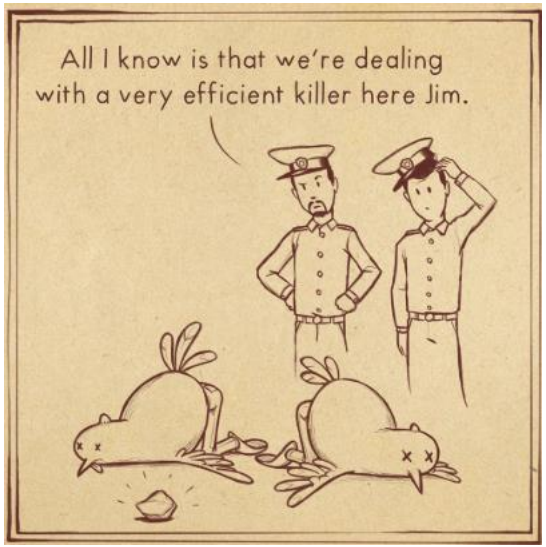
- Η ψωριασική αρθρίτιδα συχνά σχετίζεται με καρδιομεταβολικές συννοσηρότητες

- Η PDE4 έχει αναγνωρισμένο ρόλο στη φλεγμονή και έναν αναδυόμενο ρόλο στον μεταβολισμό του λίπους και της γλυκόζης
- Η αναστολή της PDE4 από την απρεμιλάστη σχετίζεται με μειωμένο βάρος και σπλαχνική παχυσαρκία και αυξημένα επίπεδα HDL χοληστερόλης, επηρεάζοντας ενδεχομένως τον μεταβολισμό των λιπιδίων και βελτιώνοντας το καρδιομεταβολικό προφίλ των ασθενών
- Ο μακροπρόθεσμος κίνδυνος καρδιαγγειακών επεισοδίων έχει αναφερθεί ότι είναι χαμηλός σε μελέτες για την απρεμιλάστη



Η απρεμιλάστη προσφέρει την ευκαιρία στους ασθενείς με ψωρίαση να ελέγξουν τη συστηματική φλεγμονή και να βελτιώσουν την ποιότητα ζωής, βελτιώνοντας παράλληλα το μεταβολικό τους προφίλ.

- Ευχαριστώ!


All I know is that we're dealing with a very efficient killer here Jim.

Βοηθήστε να γίνουν τα φάρμακα πιο ασφαλή και Αναφέρετε ΟΛΕΣ τις ανεπιθύμητες ενέργειες για ΟΛΑ τα φάρμακα συμπληρώνοντας την "ΚΙΤΡΙΝΗ ΚΑΡΤΑ"

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