

# Artriti microcristalline

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CARLO ALBERTO SCIRÈ

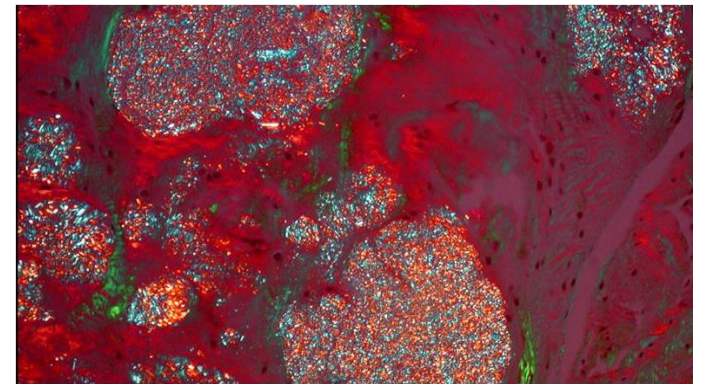
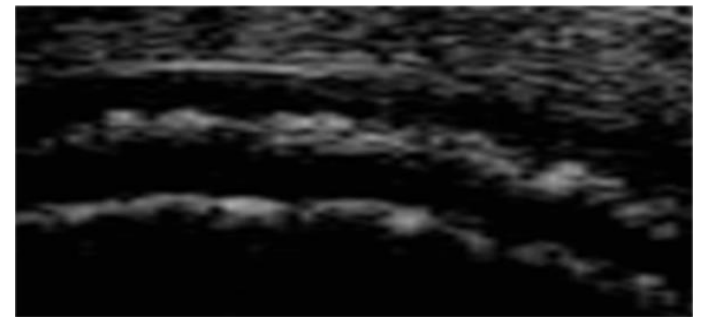
*SEZIONE DI REUMATOLOGIA – DIPARTIMENTO DI SCIENZE MEDICHE*

*SCUOLA DI SPECIALIZZAZIONE DI REUMATOLOGIA – UNIVERSITÀ DI FERRARA*

[CARLOALBERTO.SCIRE@UNIFE.IT](mailto:CARLOALBERTO.SCIRE@UNIFE.IT)

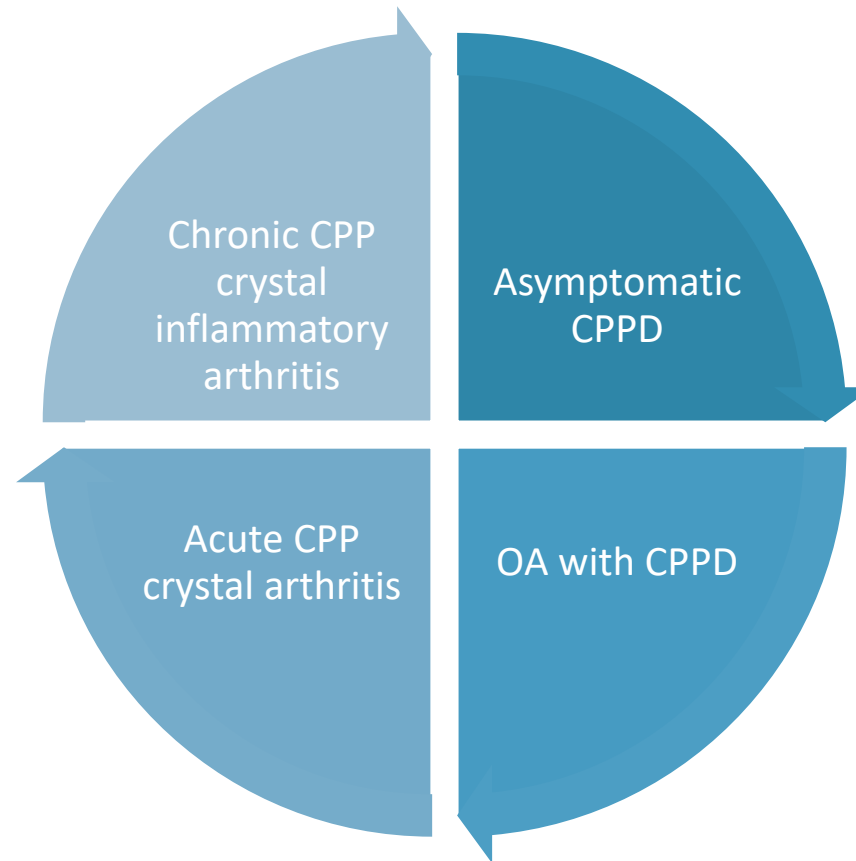
# CPPD

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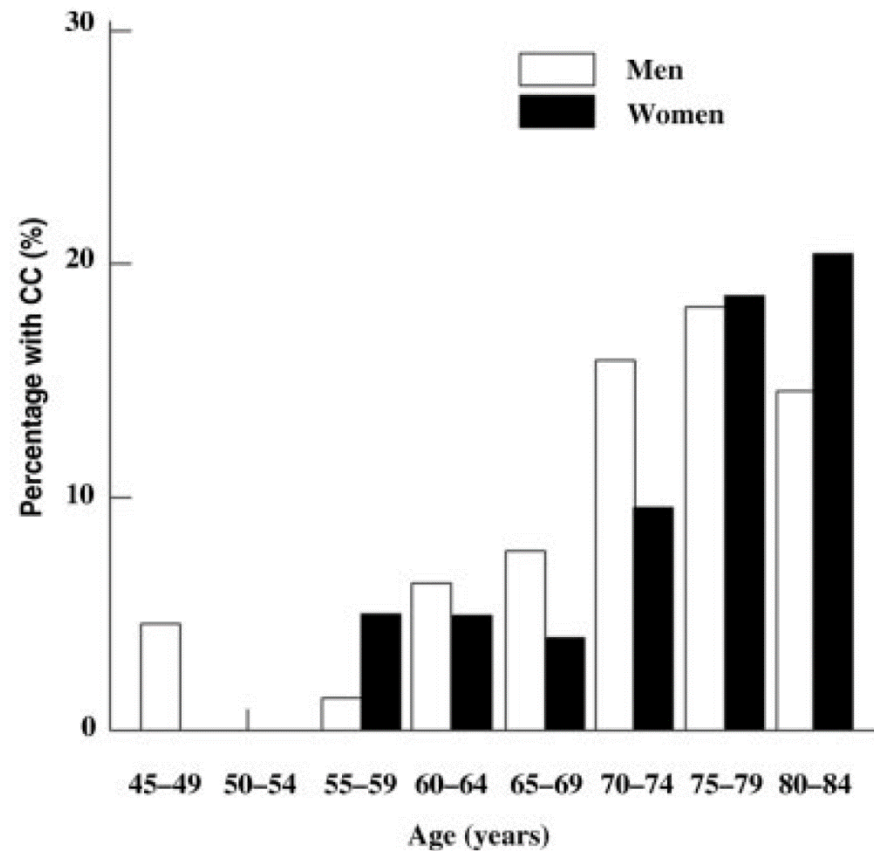
# CPPD - clinical

o



Zhang W, Doherty M, Bardin T, *et al.* European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. *Annals of the Rheumatic Diseases* 2011;**70**:563-570.

# Epidemiologia -*CPPD*



Disorder	Probability of association
Hemochromatosis	Definite
Hyperparathyroidism	Definite
Hypophosphatasia	Definite
Hypomagnesemia	Definite
Gitelman's syndrome	Definite
Gout	Possible
X-linked hypophosphatemic rickets	Possible
Familial hypocalciuric hypercalcemia	Possible
Hemosiderosis	Possible

# CPPD - Terapia

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## **Acute CPP crystal arthritis**

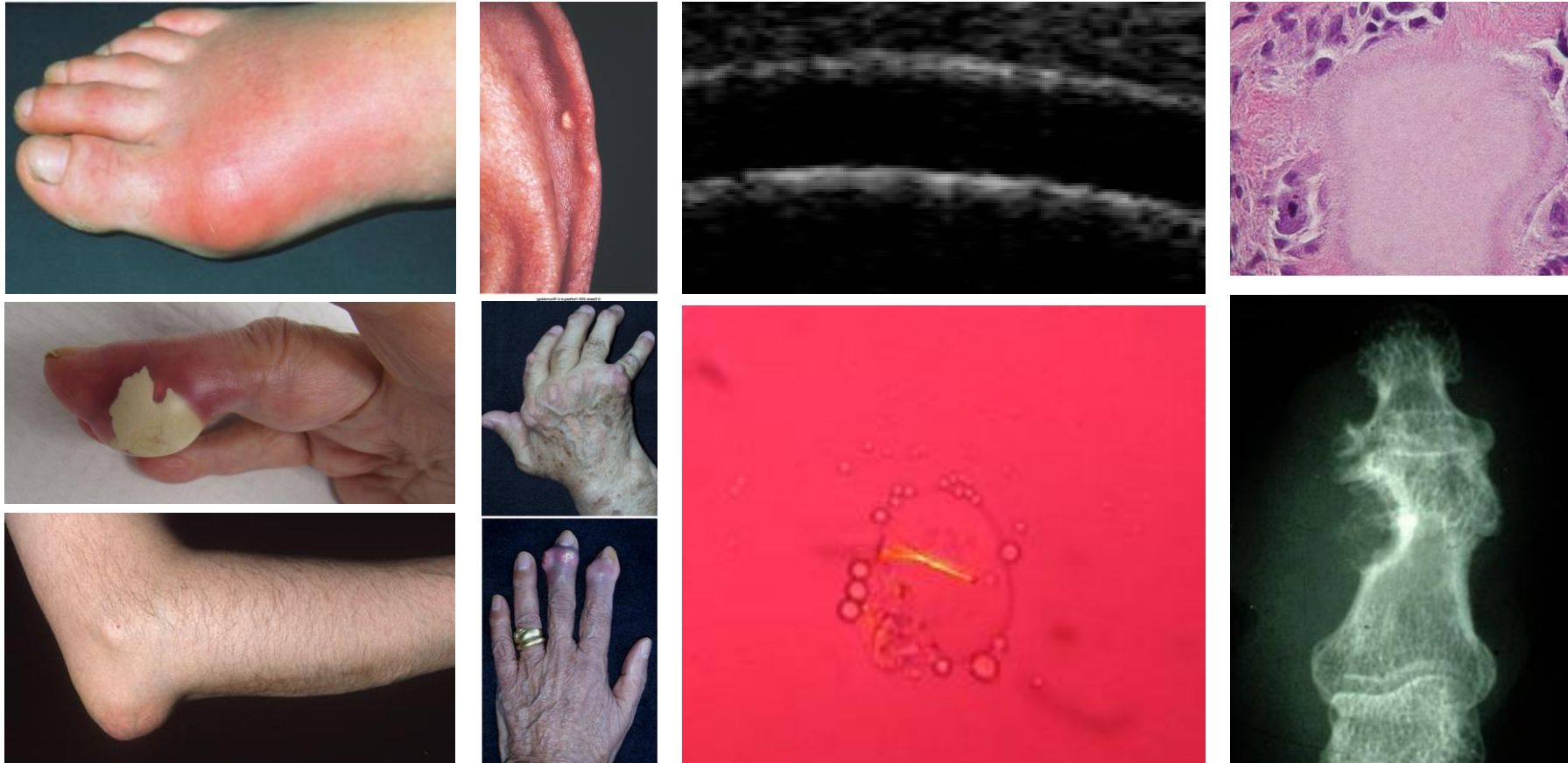
- Intra-articular corticosteroid
- Oral colchicine
- NSAIDs
- Systemic corticosteroid
- IL-1 $\beta$  inhibitors
- Analgesics
- Joint lavage

## **Chronic CPP crystal arthritis**

- Intra-articular corticosteroid
- Oral colchicine
- NSAIDs
- Low-dose systemic corticosteroid
- Hydroxychloroquine
- Methotrexate
- IL-1 $\beta$  inhibitors

Status	Study Title	Conditions	Interventions	Study Type	Phase	Outcome Measures
Recruiting	<a href="#">Effect of Probenecid on Synovial Fluid ATP Levels in CPPD</a>	• <b>Calcium Pyrophosphate Deposition Disease</b>	•Drug: Probenecid	RCT	Early Phase 1	•ATP levels in synovial fluid
Not yet recruiting	<a href="#">Trial of Colchicine Versus Prednisone for the Treatment of Acute CPPD Arthritis</a>	• <b>Chondrocalcinosis</b>	•Drug: Colchicine opocalcium 1mg •Drug: Prednisone : Cortancyl 20mg	RCT	Phase 3	<ul style="list-style-type: none"> <li>•Change from baseline in the pain VAS at 24 hours</li> <li>•Proportion of patients with at least one adverse event within 48 hours</li> <li>•Change from baseline of biological inflammatory syndrome at 48 hours</li> <li>•(and 8 more...)</li> </ul>

# Gotta

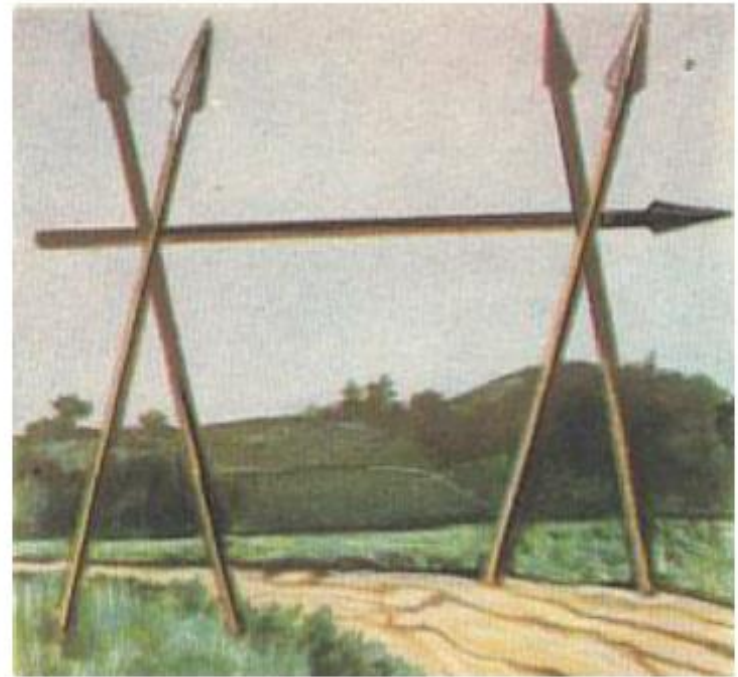




# Myths and Realities



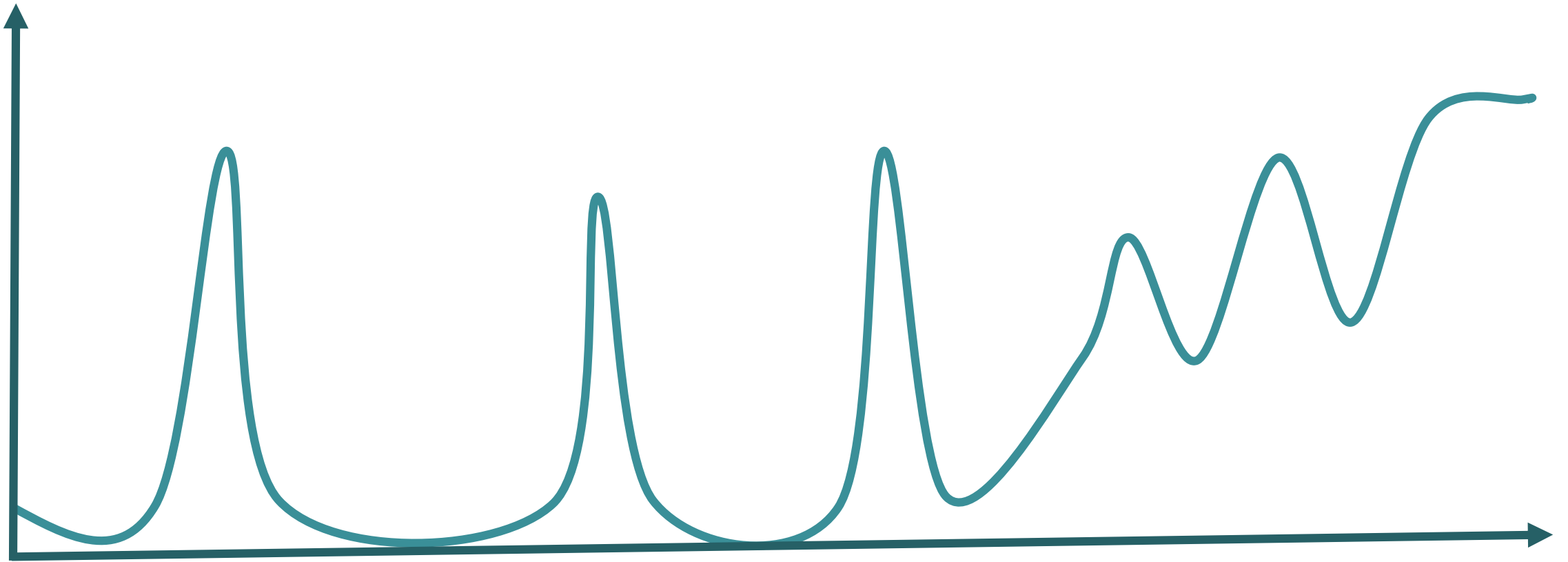




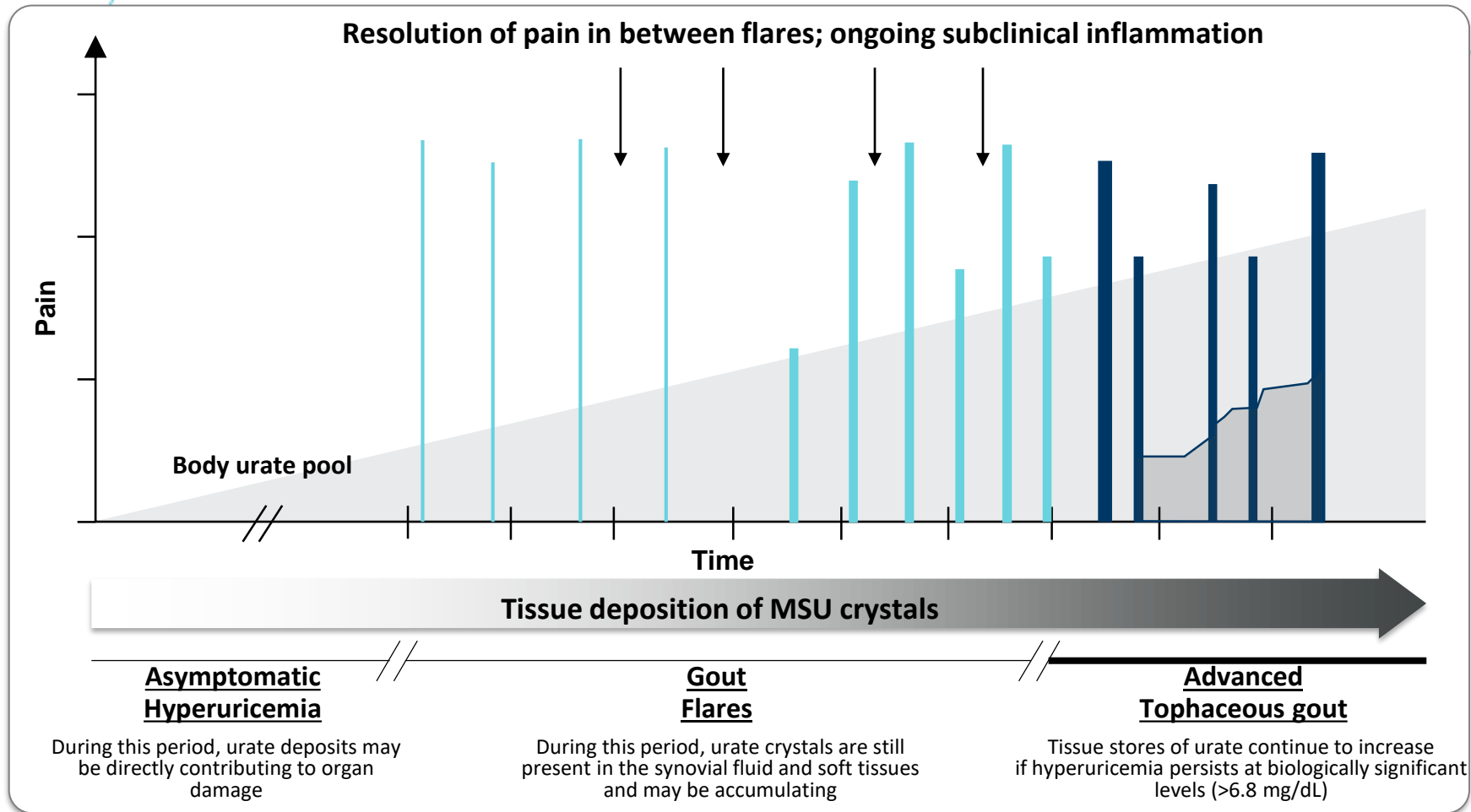
La gotta è una malattia acuta

# Gotta storia naturale

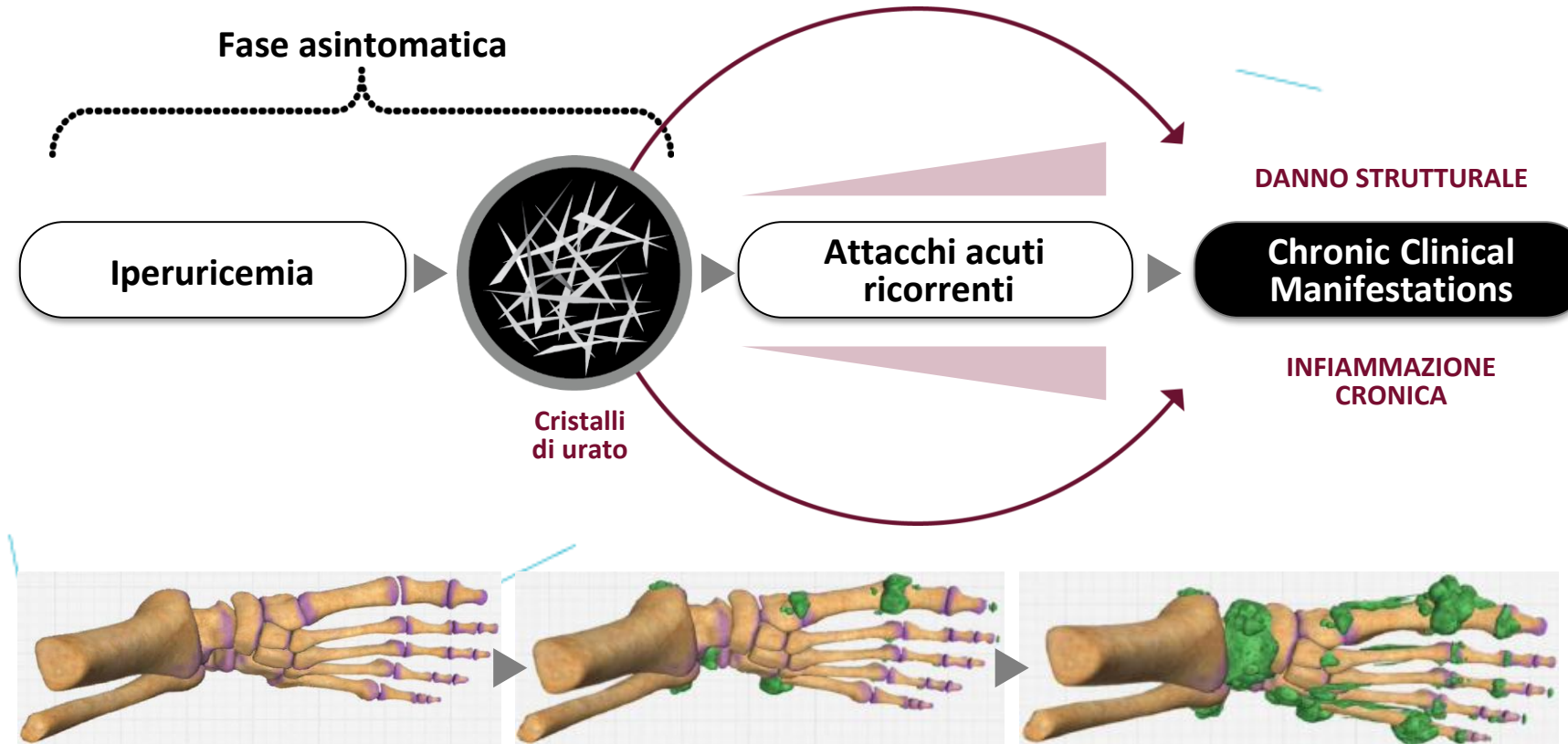
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# La gotta è una malattia da deposito



# La gotta è una malattia cronica



DECT scan showing  
MSU crystal deposition (green)

DECT=Dual-energy computerized tomography.

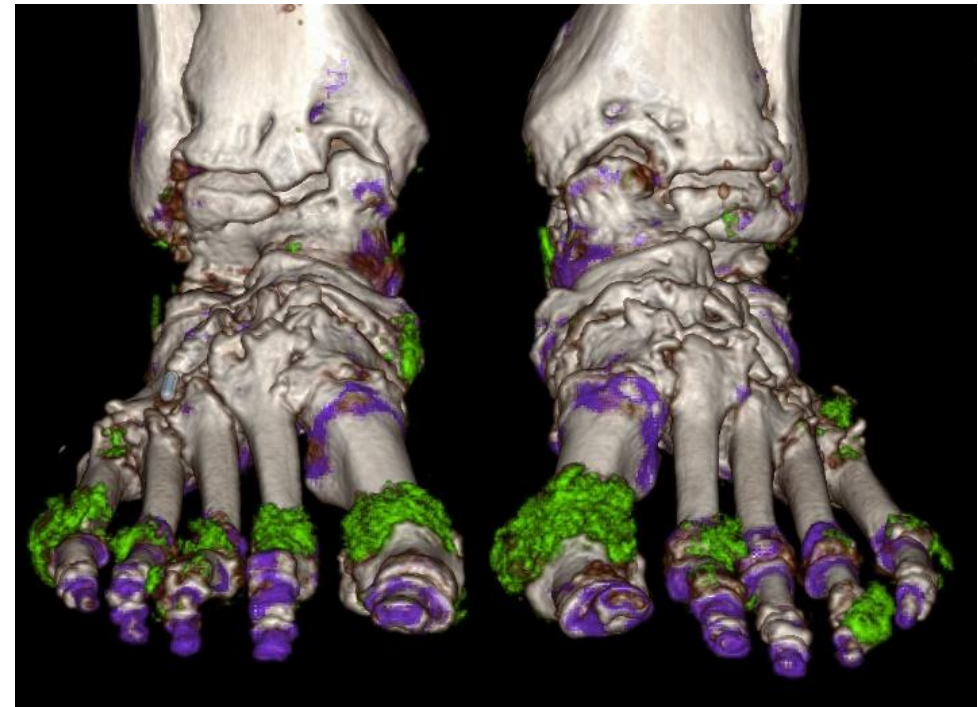
1. Wollaston WH. *Philos Trans Royal Soc Lond.* 1797;87:386-400. 2. Seegmiller JE, et al. *JAMA.* 1962;180:469-475. 3. McCarty DJ, et al. *Ann Intern Med.* 1961;54:452-460. 4. Martinon F, et al. *Nature.* 2006;440:237-241. 5. Howell RR, et al. *Arthritis Rheum.* 1963;6:97-103. 6. Gutman AB. *Arthritis Rheum.* 1973;16:431-445. 7. Bloch C, et al. *AJR Am J Roentgenol.* 1980;134:781-787. 8. Dalbeth N, et al. *Ann Rheum Dis.* 2014;74:1030-1036. 9. Pineda C, et al. *Arthritis Res Ther.* 2011;13:R4.

# Deposition necessarily predates gout

DECT – ASYMPTOMATIC GOUT

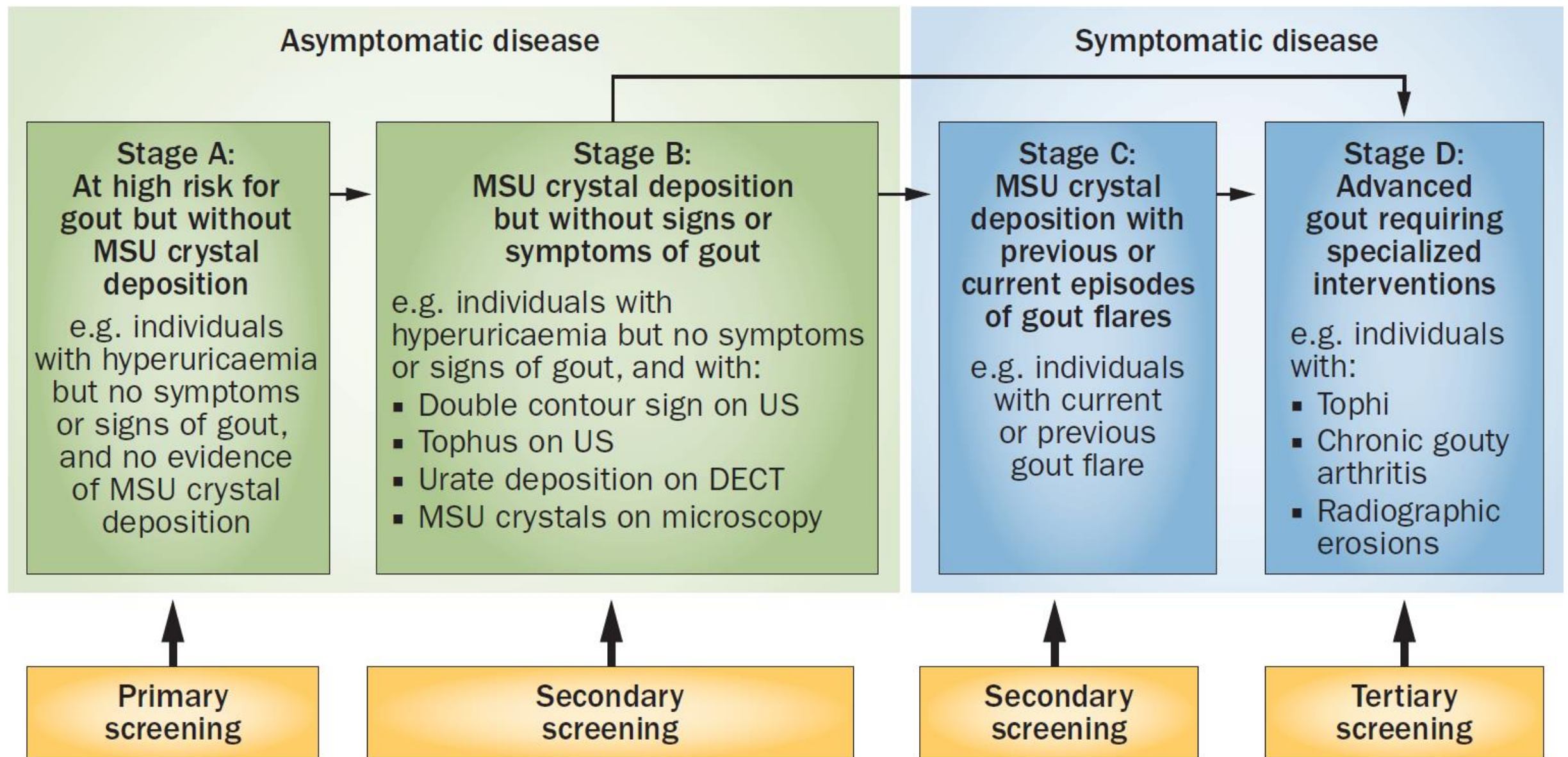


DECT – CLINICAL GOUT



Terkeltaub R, Edwards NL. Chapter 3. In: Terkeltaub R, Edwards NL (eds). Gout: Diagnosis and Management of Gouty Arthritis and Hyperuricemia (Third edition). Oklahoma: Professional Communications, Inc, 2013. Nicola Dalbeth courtesy





Stamp, L. & Dalbeth, N. *Nat. Rev. Rheumatol.* advance online publication 19 August 2014; doi:10.1038/nrrheum.2014.139





La gotta è una malattia del passato

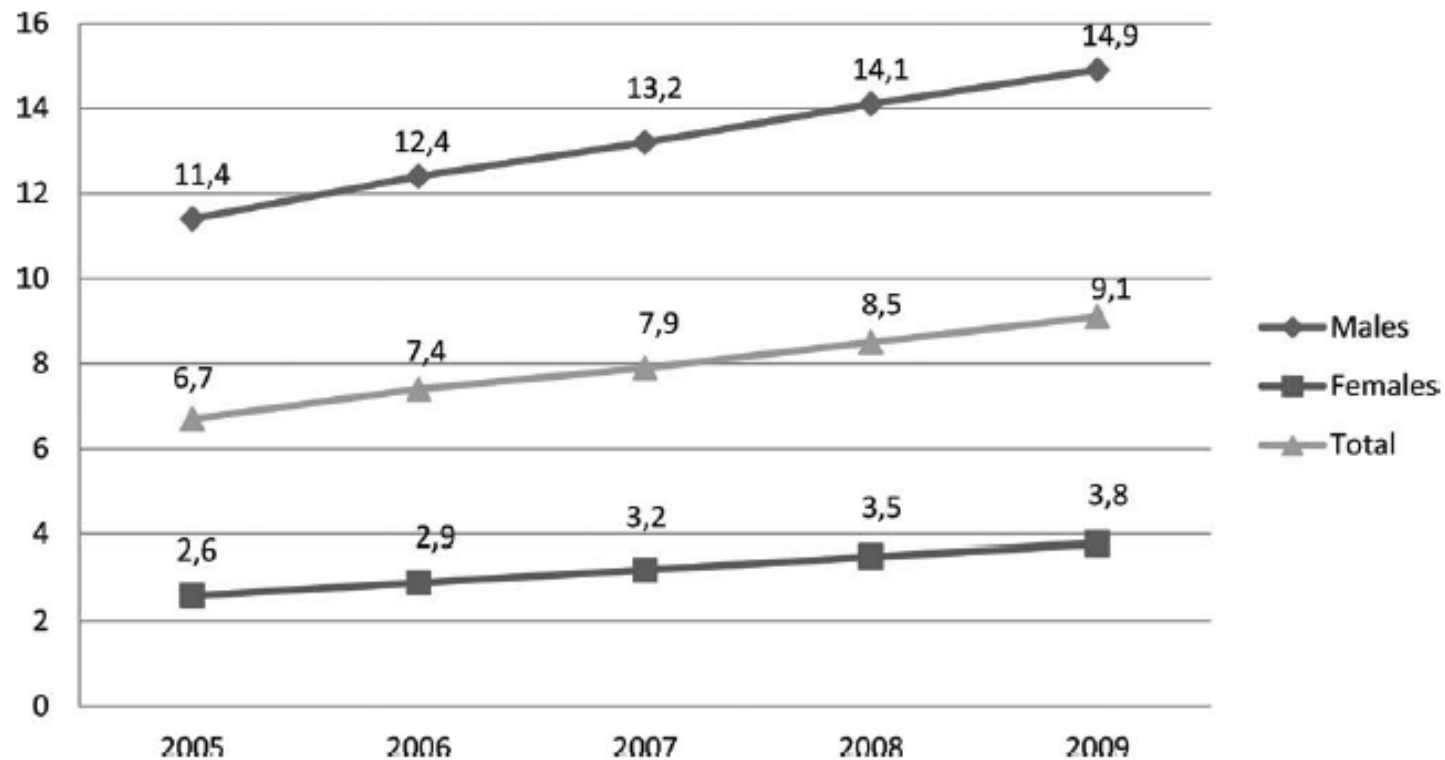




*Kuo, C.-F. et al. Nat. Rev. Rheumatol. advance online publication 7 July 2015; doi:10.1038/nrrheum.2015.91*

# Gotta

PREVALENZA PER 1000 PERSONE

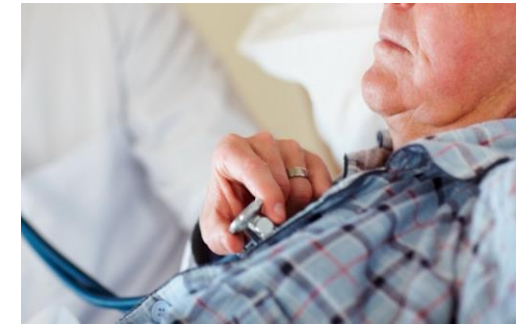
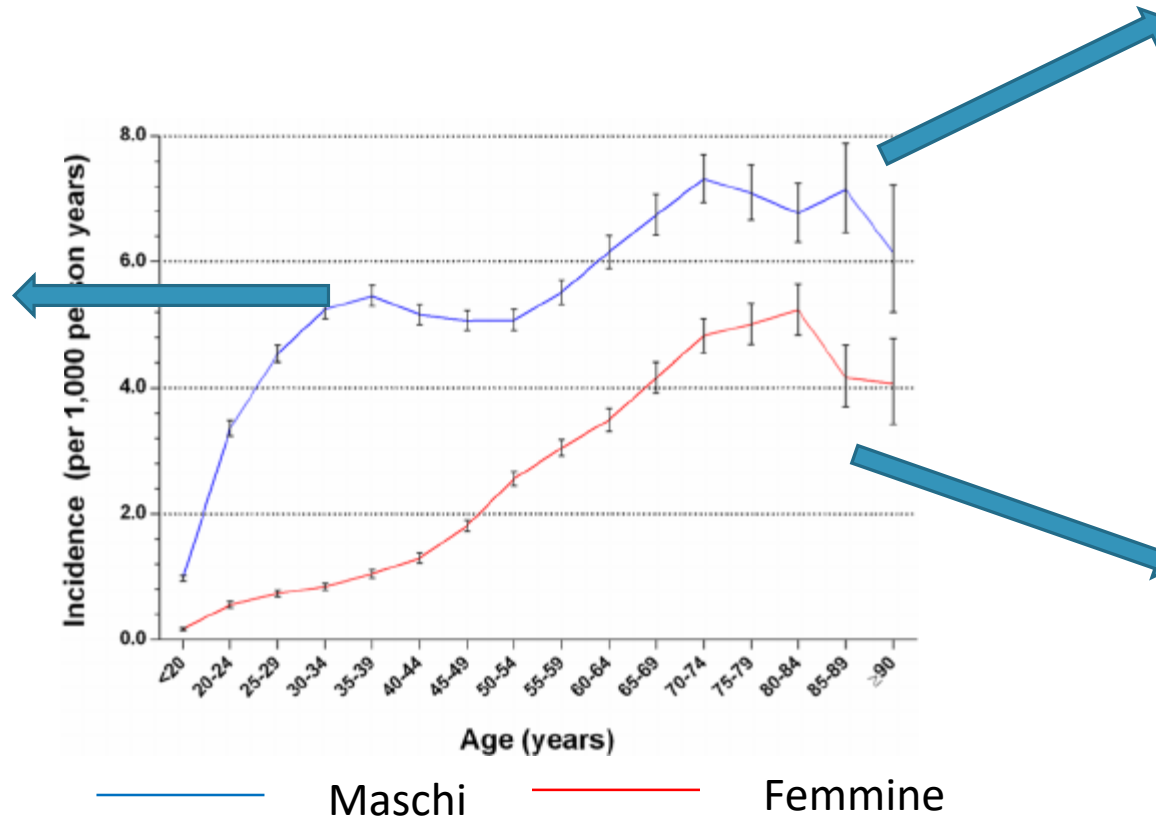


*Ann Rheum Dis 2013;72:694–700. doi:10.1136/annrheumdis-2011-201254*

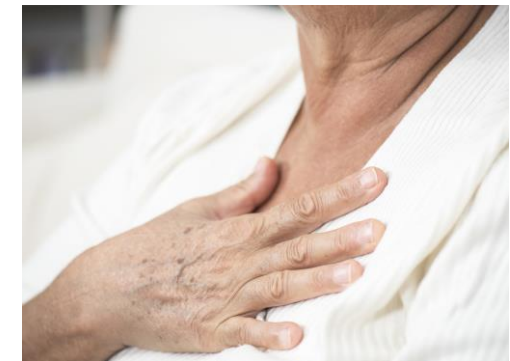
# Il paziente tipo con gotta è ...



Maschio adulto



Paziente anziano (M – F)  
con multi-morbilità e poli-  
trattamento

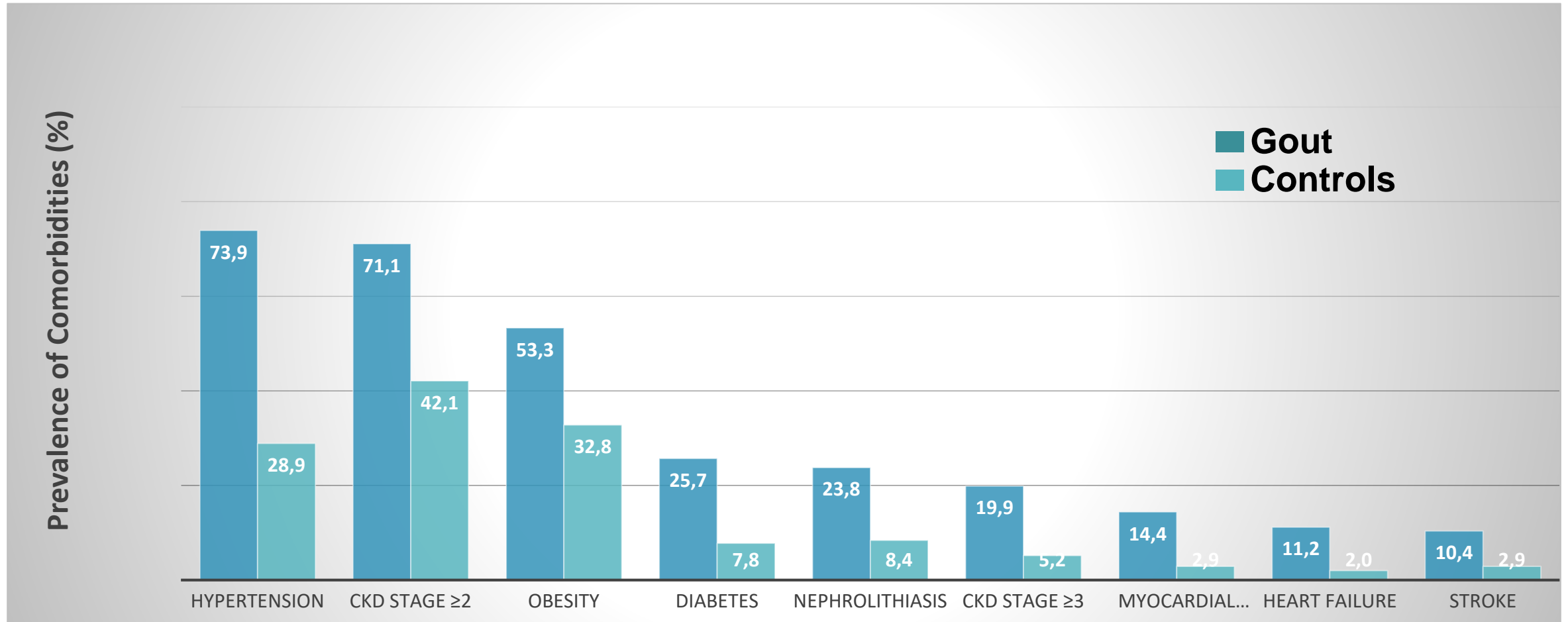






La gotta è dolorosa ma non ha un impatto a lungo termine

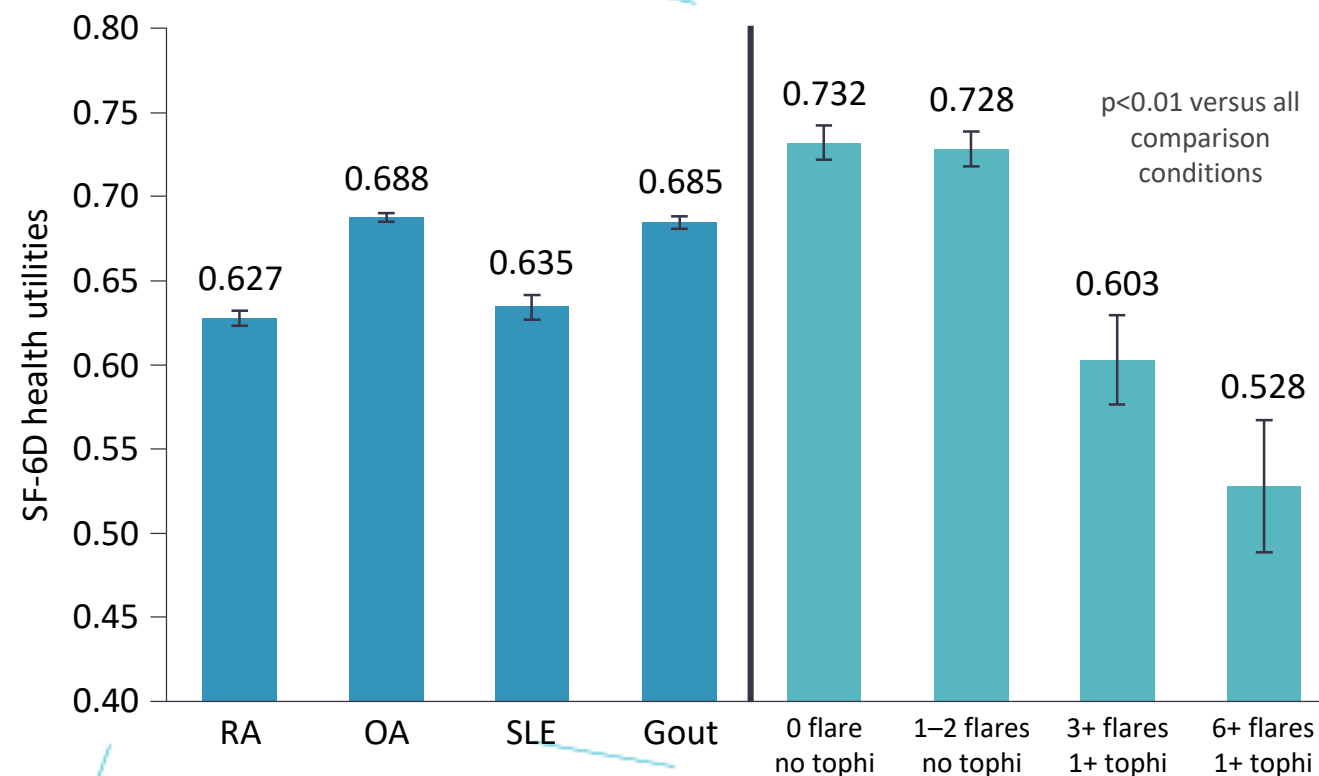
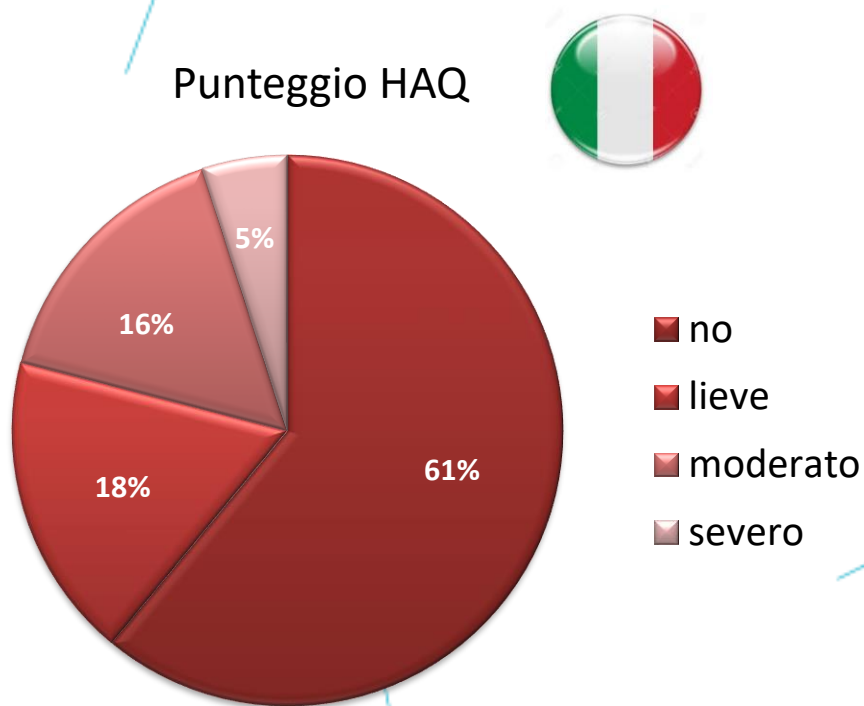
# Comorbidities associated with gout



Zhu Y, et al. *Am J Med.* 2012;125:679-687.

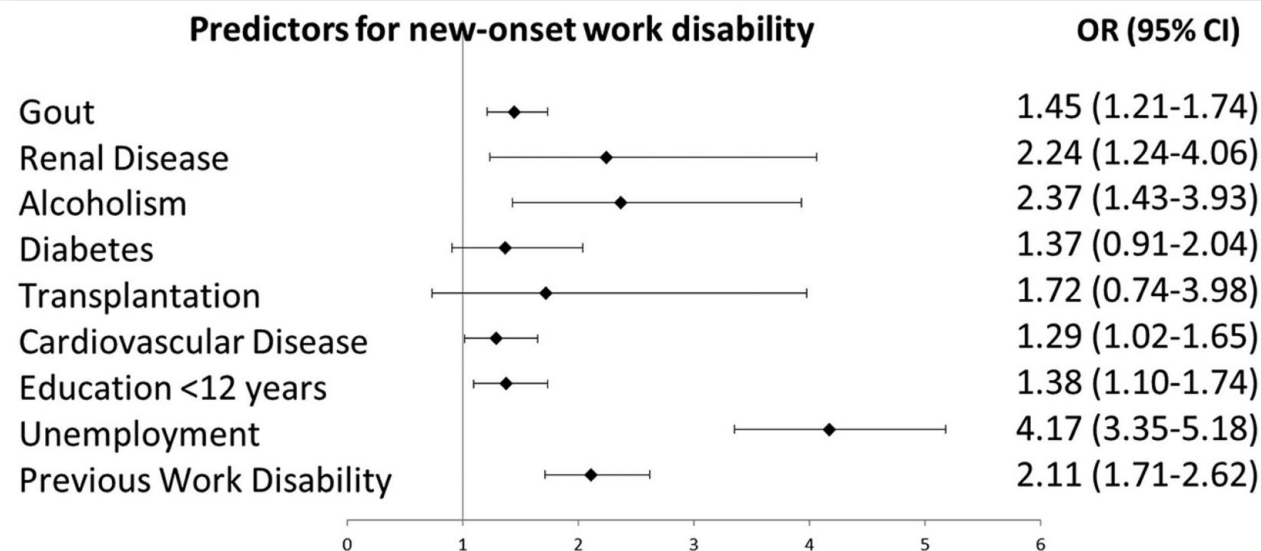
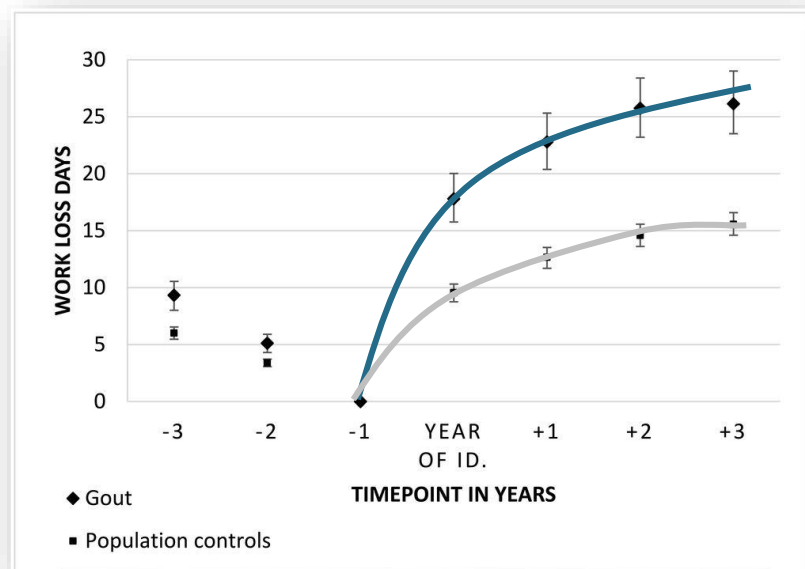
# La gotta si associa a disabilità e bassa QoL

Punteggio HAQ



OA=osteoarthritis; RA=rheumatoid arthritis; SF=Short Form; SLE=systemic lupus erythematosus.  
Scirè et al. Arthritis Research & Therapy 2013, 15:R101  
Khanna et al. Health and Quality of Life Outcomes 2012, 10:117

# La gotta induce disabilità lavorativa



# La gotta aumenta la spesa sanitaria

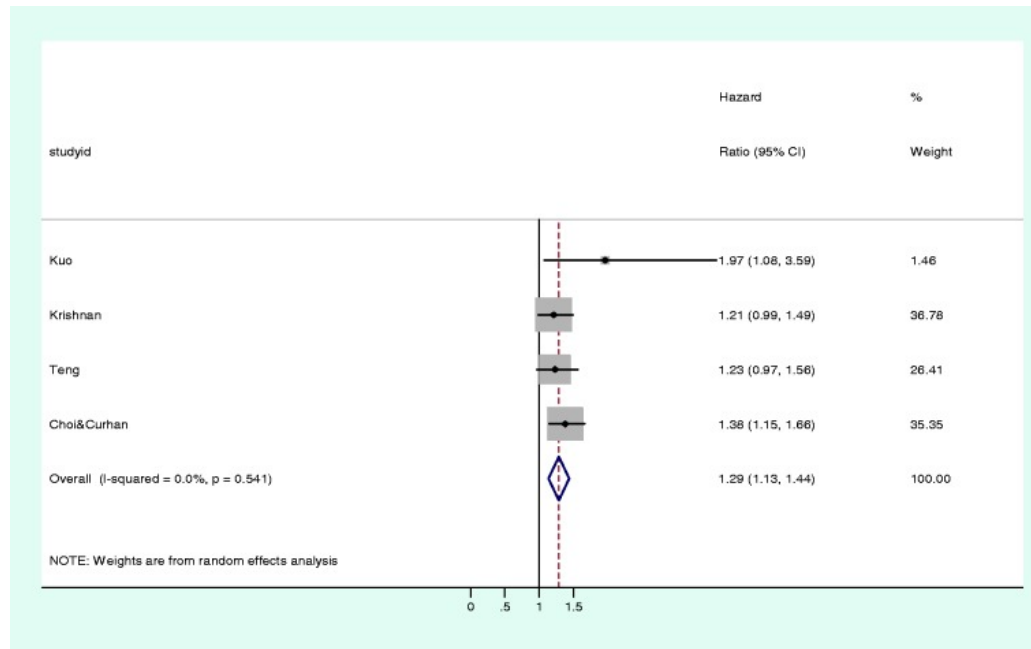
1st author	Mean age (yr)	%Male	Population	Gout patients	Gout-free individuals	Total gout-related direct cost
Brook et al.	46	85%	Employed population	\$4733	\$2562	\$172
Wu et al.	71	74%	Elderly population	\$16,925	\$10,590	\$1006
Wu et al.	50	92%	Treatment-refractory gout	\$18,362	\$7188	\$6179

Incremento di 1.5-2 volte dalla spesa sanitaria



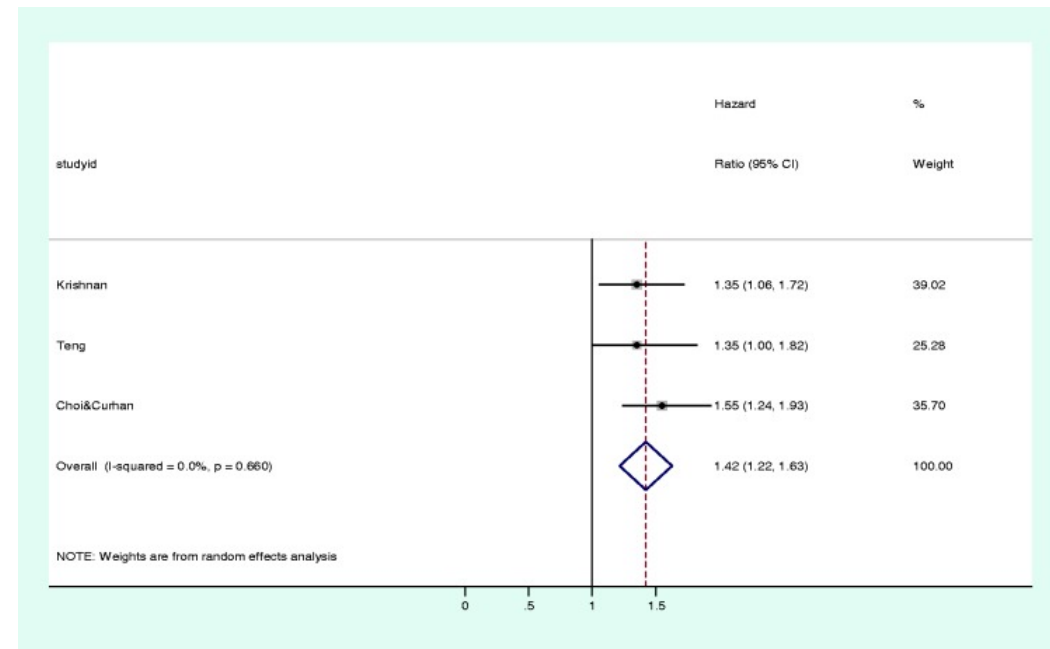
# La gotta riduce la sopravvivenza

## MORTALITA' CARDIOVASCOLARE



$$\frac{\text{Mortalità gotta}}{\text{Mortalità non gotta}} = 1.29$$

## MORTALITÀ PER MALATTIA CORONARICA



$$\frac{\text{Mortalità gotta}}{\text{Mortalità non gotta}} = 1.42$$

Clarson LE, et al. Eur J Prev Cardiol. 2015 Mar;22(3):335-43.



La gotta è facile da diagnosticare

## EXTENDED REPORT

# Performance of classification criteria for gout in early and established disease

William J Taylor,<sup>1</sup> Jaap Fransen,<sup>2</sup> Nicola Dalbeth,<sup>3</sup> Tuhina Neogi,<sup>4</sup>  
H Ralph Schumacher,<sup>5</sup> Melanie Brown,<sup>1</sup> Worawit Louthrenoo,<sup>6</sup>  
Janitzia Vazquez-Mellado,<sup>7</sup> Maxim Eliseev,<sup>8</sup> Geraldine McCarthy,<sup>9,10</sup> Lisa K Stamp,<sup>11</sup>  
Fernando Perez-Ruiz,<sup>12</sup> Francisca Sivera,<sup>13</sup> Hang-Korng Ea,<sup>14,15,16</sup> Martijn Gerritsen,<sup>17</sup>  
Carlo Scire,<sup>18</sup> Lorenzo Cavagna,<sup>19</sup> Chingtsai Lin,<sup>20</sup> Yin-Yi Chou,<sup>21</sup>  
Anne-Kathrin Tausche,<sup>22</sup> Geraldo da Rocha Castelar-Pinheiro,<sup>23</sup> Matthijs Janssen,<sup>24</sup>  
Jiunn-Horng Chen,<sup>25,26</sup> Ole Slot,<sup>27</sup> Marco Cimmino,<sup>28</sup> Till Uhlig,<sup>29</sup> Tim L Jansen<sup>2</sup>

**ARD Online First, published on October 28, 2014 as 10.1136/annrheumdis-2014-206364**



### ARA 1977 Criteria

**MSU crystals** in synovial fluid / tophus **OR**

**Six or more of the following criteria:**

1. More than one attack of acute arthritis
2. Maximum inflammation developed within 1 day
3. Monoarthritis attack
4. Redness observed over joints
5. First MTP joint painful or swollen
6. Unilateral first MTP joint attack

7. Unilateral tarsal joint attack

**8. Tophus** (suspected or proven)

9. Hyperuricemia

10. Asymmetric swelling within a joint on X-ray

11. Subcortical cysts without erosions on X-ray

12. Joint fluid culture negative for organisms during attack

### Rome 1963 Criteria

**2 or more of the following criteria:**

1. sUA >7 mg/dL in men  
sUA >6 mg/dL in women
2. Presence of tophi
3. **MSU crystals** in synovial fluid or tissue
4. History of attacks of painful joint swelling with abrupt onset and resolution within 2 wks

### New York 1966 Criteria

**MSU crystals** in synovial fluid / tissue (tophi) **OR**

**2 or more of the following criteria:**

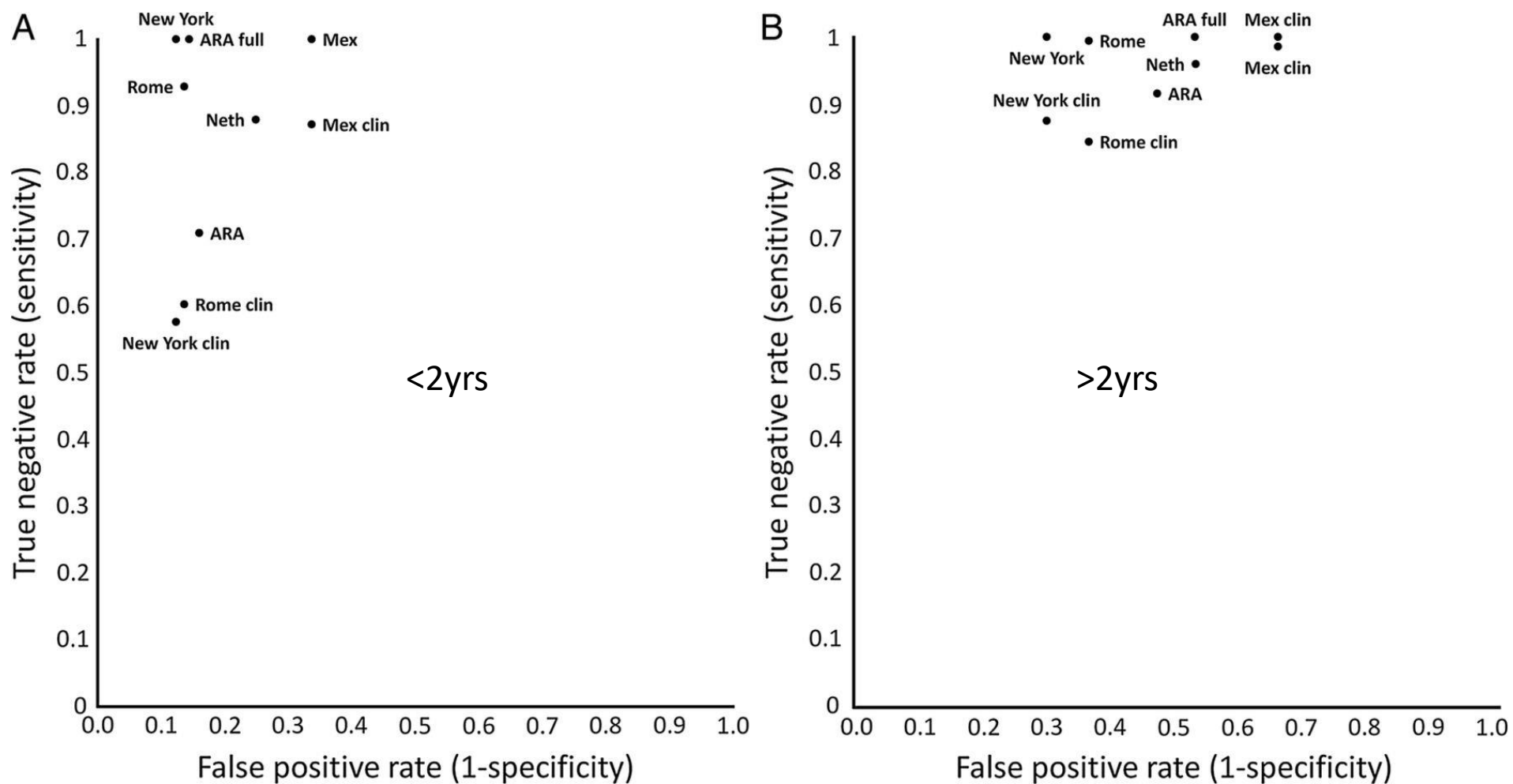
1. At least 2 attacks of painful arthritis + complete resolution within 2 wks
2. A history or observation of podagra
3. Presence of tophi
4. Rapid response to colchicine treatment, defined as a major reduction in the objective signs of inflammation within 48 hours

<http://www.umcn.nl/goutcalc>

Criteria	Sensitivity	Specificity	Problem
Rome 1963	0.64 – 0.82	0.99	not highly sensitive
New York 1966	0.64 - 0.80	0.99	requires SF microscopy
ARA 1977	0.70 – 0.85	0.64 – 0.97	requires SF microscopy; not sensitive/ variable specificity
Mexico 2010	0.88-0.97	0.96	no SF microscopy in controls most cases had tophi
Netherlands 2010	0.91	0.68	originally designed as diagnostic aid for PCP



Performance of each criteria-set is shown on a receiver operating characteristic plot.

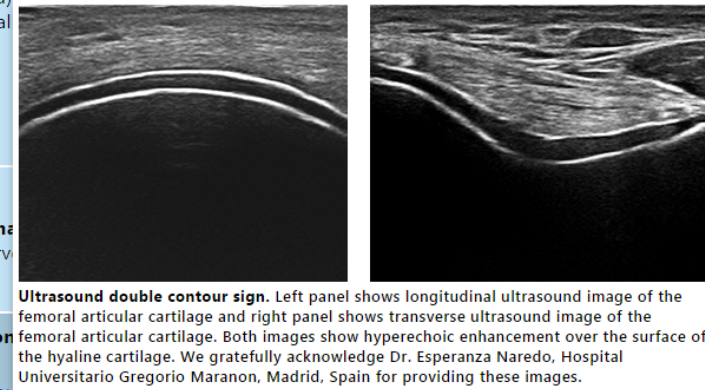


Taylor W J et al. Ann Rheum Dis doi:10.1136/annrheumdis-2014-206364

# ACR/EULAR 2015 Classification Criteria

Criteria	Categories	Score
C L I N I C	Pattern of involvement	Ankle/midfoot 1 MTP1 2
	Characteristics of episode(s) ever	One 1 Two 2 Three 3
A L	Time-course of episode(s) ever	One typical 1 Recurrent 2
	Clinical tophus	Present 4
L A B	Serum Urate	6-<8mg/dL 2
		8-<10mg/dL 3
		≥10mg/dL 4

LAB	treatment and patient was beyond 4 weeks of the start of an episode (i.e., during intercritical period) if practicable, retest under those conditions. The highest value should be scored.	6-<8mg/dL [0.36-<0.48mM]	<input checked="" type="radio"/>
	Synovial fluid analysis of a symptomatic joint. Should be assessed by a trained observer.		<input type="radio"/>
IMAGING	Imaging evidence of urate deposition in joint or bursa:		<input checked="" type="radio"/>
	Ultrasound evidence of double-contour sign or DECT demonstrating urate deposition.	Present (either modality)	<input type="radio"/>
	Imaging evidence of gout-related joint damage: Conventional radiography of the hands and/or feet demonstrate at least one erosion.	Absent OR Not done	<input checked="" type="radio"/>
		Present	<input type="radio"/>
TOTAL SCORE			6
Subject does not meet the clinical criteria for gout classification (score <8)			



**Sensitivity and specificity of the criteria: 92% and 89%.**

<http://goutclassificationcalculator.auckland.ac.nz/>



Dieta iperproteica e alcolici causano la gotta



# Serum urate mean differences

	Mean difference*	95% IC
Total alcohol (1 serving/day vs. none)	0.33	0.21, 0.45
Beer (1 serving/day vs. none)	0.42	0.25, 0.59
Liquor (1 serving/day vs. none)	0.26	0.07, 0.45
Wine (1 serving/day vs. none)	0.00	-0.16, 0.16
Sugar-sweetened soft drinks (1 serving/day vs. none)	0.33	0.21, 0.46
Coffee ( $\geq 4$ serving/day vs. none)	-0.22	-0.35, -0.09
Dairy foods (higher quintile vs. lowest)	-0.21	-0.37, -0.04
Meats (higher quintile vs. lowest)	0.48	0.34, 0.61
Seafood (higher quintile vs. lowest)	0.16	0.06, 0.27
Vitamin C (any supplementation vs. none)	-0.35	-0.66, -0.03
Xantine Oxidase inhibitor use	-3.64	-5.00, -2.29

Choi HK, Curhan G. Arthritis Rheum. 2004 Dec 15;51(6):1023-9.



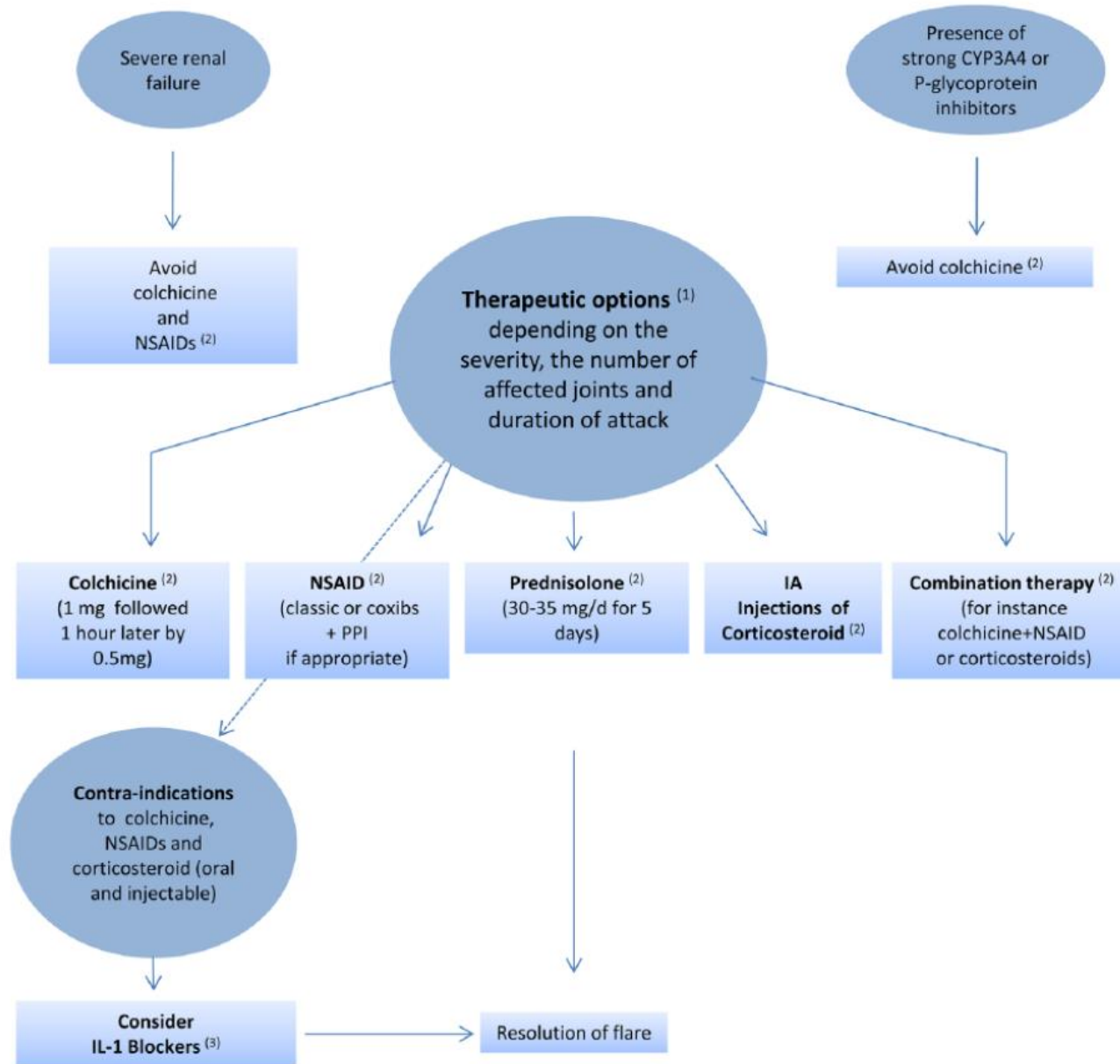
La gotta è facile da curare

# 2016 updated EULAR evidence-based recommendations for the management of gout

P Richette,<sup>1</sup> M Doherty,<sup>2</sup> E Pascual,<sup>3</sup> V Barskova,<sup>4</sup> F Becce,<sup>5</sup> J Castañeda-Sanabria,<sup>6</sup> M Coyfish,<sup>7</sup> S Guillo,<sup>6</sup> T L Jansen,<sup>8</sup> H Janssens,<sup>9</sup> F Lioté,<sup>1</sup> C Mallen,<sup>10</sup> G Nuki,<sup>11</sup> F Perez-Ruiz,<sup>12</sup> J Pimentao,<sup>13</sup> L Punzi,<sup>14</sup> T Pywell,<sup>7</sup> A So,<sup>15</sup> A K Tausche,<sup>16</sup> T Uhlig,<sup>17</sup> J Zavada,<sup>18</sup> W Zhang,<sup>2</sup> F Tubach,<sup>6</sup> T Bardin<sup>1</sup>

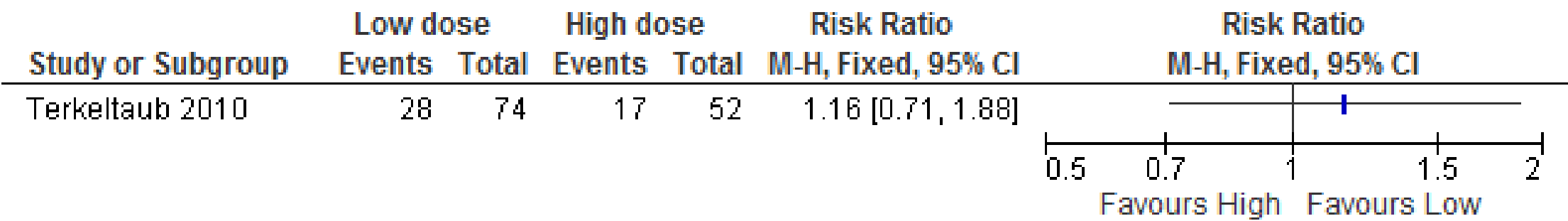
Panel: 15 rheumatologists, 1 musculoskeletal radiologist, 2 general practitioners (GPs), 1 research fellow, 2 patients and 3 experts in epidemiology/methodology from 12 European countries.





# Acute gout: low dose vs high dose colchicine

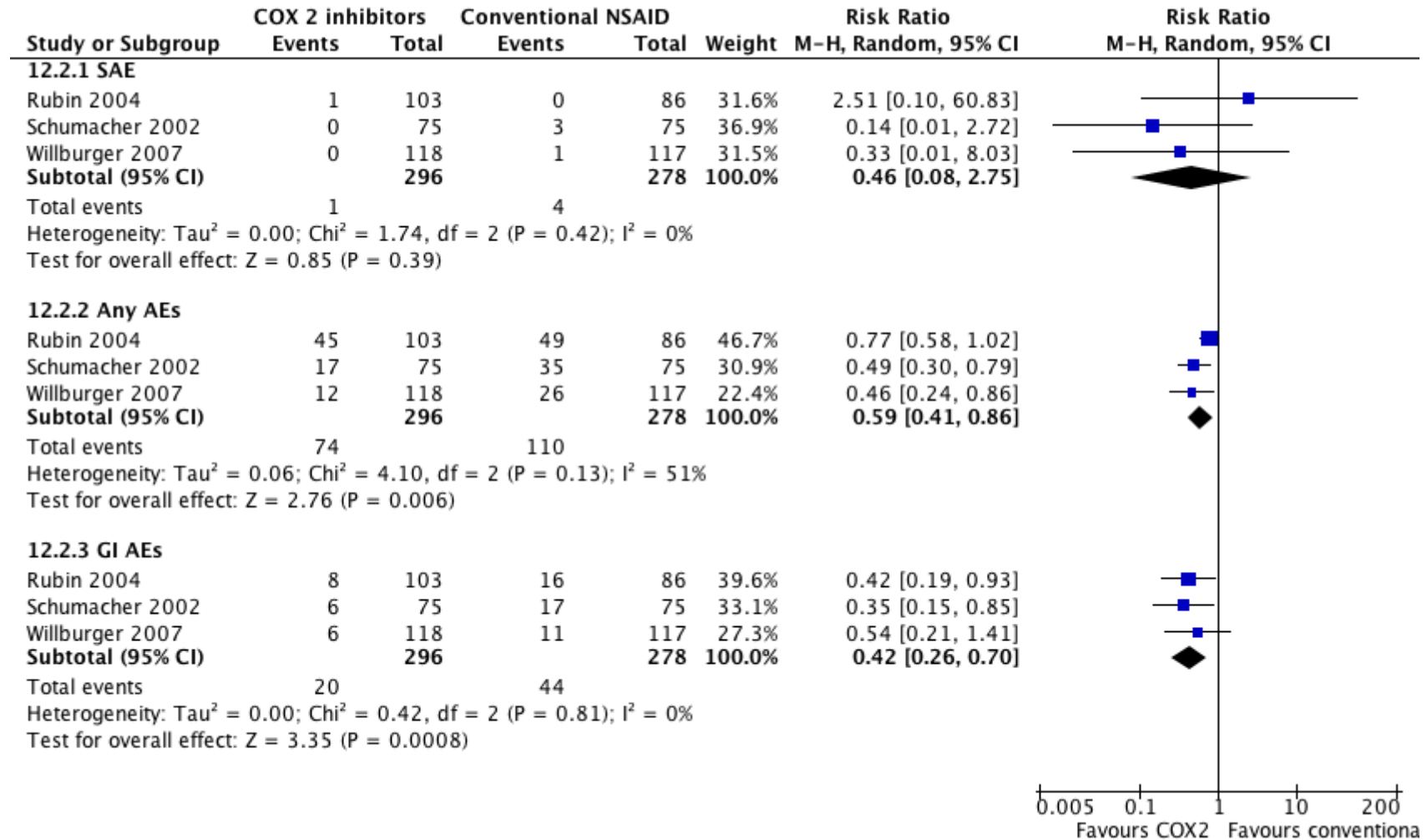
## 50% Pain Improvement



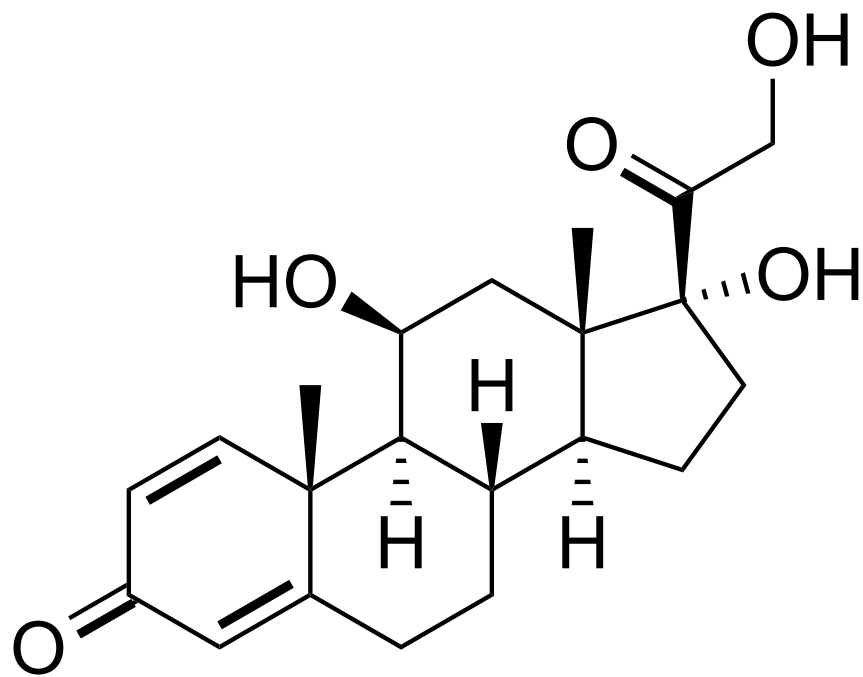
A. Bortoluzzi, I. Prevete, M. Favero 2013

# Acute gout: COX 2 inhibitors vs NSAIDs

## Adverse events

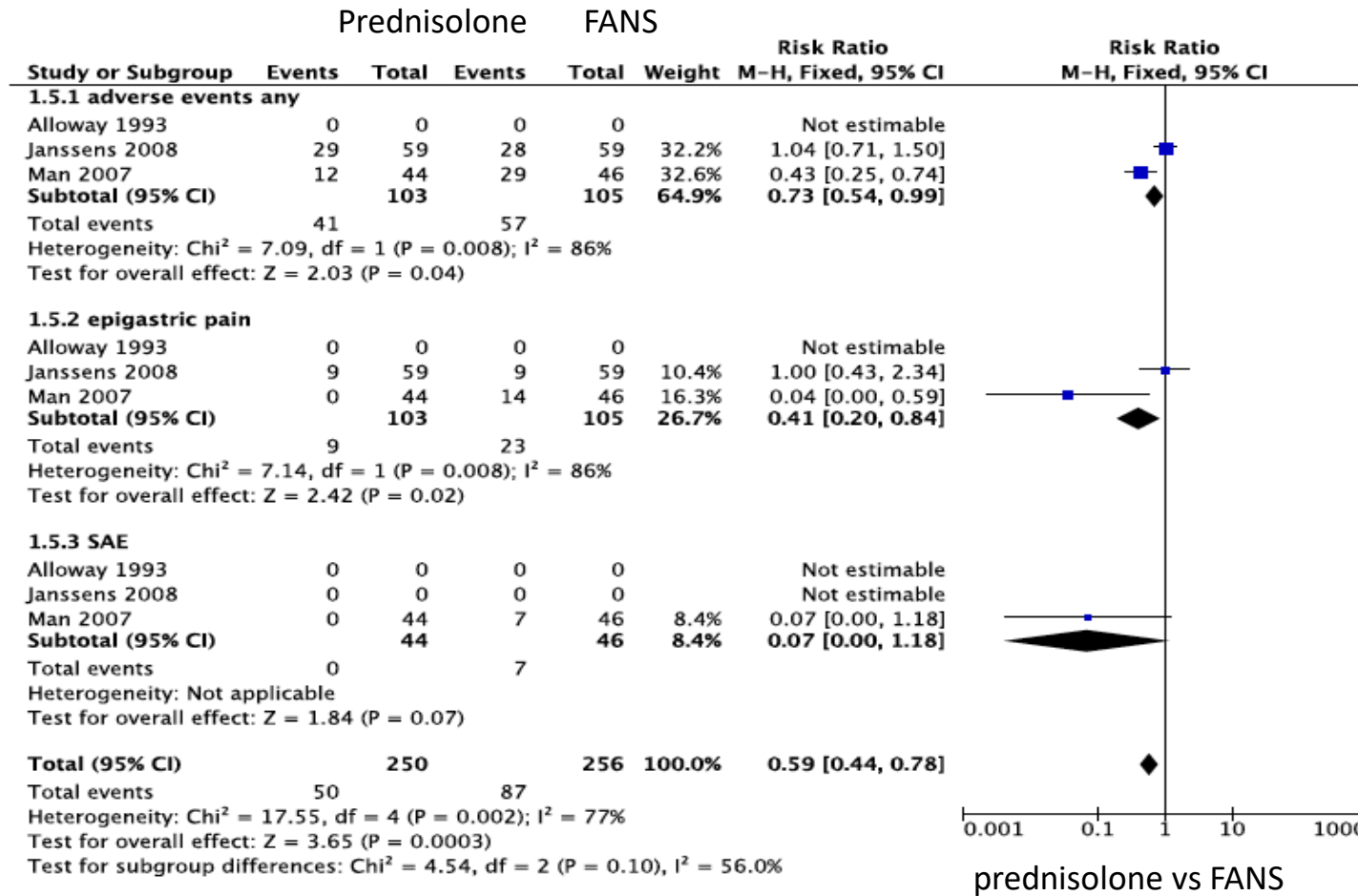


A. Bortoluzzi, I. Prevete, M. Favero 2013



# Acute gout: GC vs NSAIDs

## Adverse events



A. Bortoluzzi, I. Prevete, M. Favero 2013

# Colchicine – statins - CKD

## AHA SCIENTIFIC STATEMENT

### Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease

A Scientific Statement From the American Heart Association

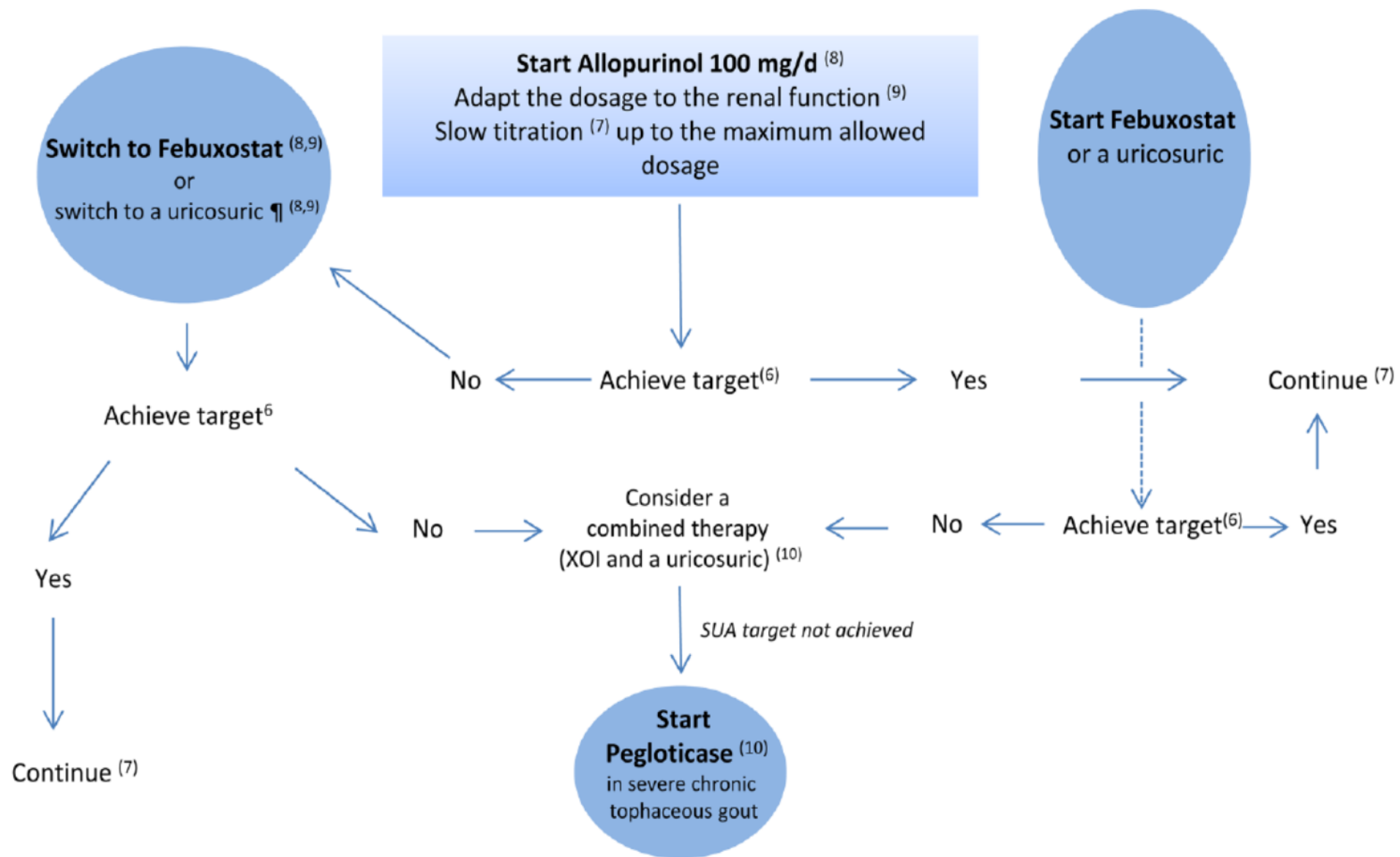
Coadministration of colchicine and rosuvastatin, fluvastatin, lovastatin, pitavastatin, and pravastatin is reasonable when clinically indicated.

Dose reductions may be considered for atorvastatin, simvastatin, and lovastatin, given the potential for interactions mediated by both CYP3A4 and permeability glycoprotein (P-gp) pathways.

Creatinine clearance (mL/min)	Colchicine dose
≥ 50	0.6 mg twice daily
35–49	0.6 mg once daily
10–34	0.6 mg every two 2 or three 3 days
<10, or on hemodialysis, or combined moderate-to-severe renal and hepatobiliary disease	Do not use colchicine

*Circulation.* 2016;134:00-00. DOI: 10.1161/CIR.0000000000000456





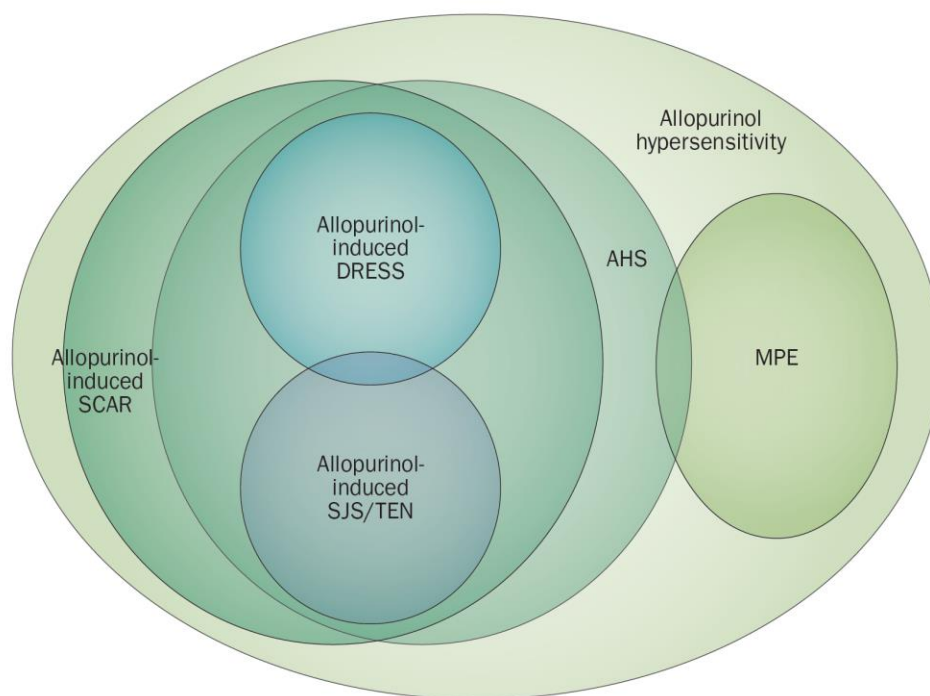
# Allopurinol as 'anchor drug'

Reference		n	Time (m)	Prophylaxis (m)	Medications	Risk of Bias
Schumacher 2008	RCT	1072	7	2 (C or N)	Allopurinol (300mg/100mg) vs Placebo, vs Febuxostat (80mg, 120mg, 240mg)	Unclear

Relative Risk [95%CI]*		
	sUA<6mg/dl	Attack
Allopurinol vs Placebo	49.25 [6.95,349.02]	1.13[0.76,1.69]

# L'ipersensibilità severa ad allopurinolo è rara

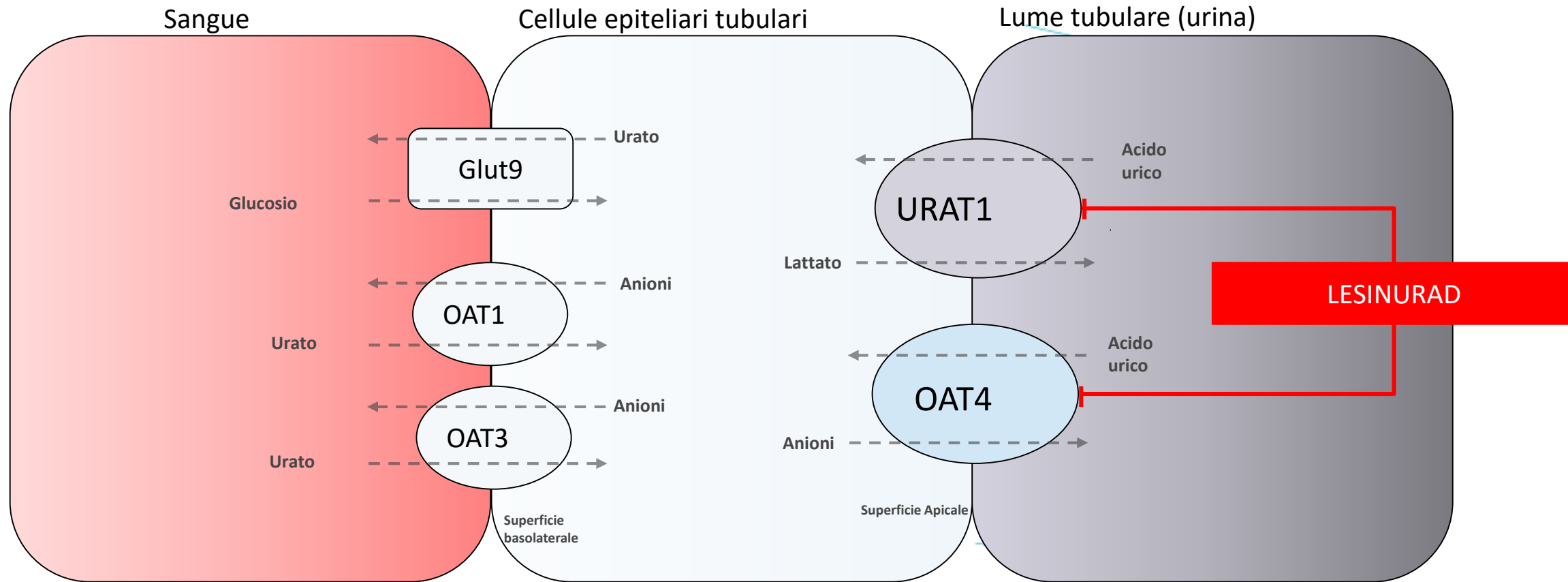


I fattori di rischio per eventi avversi seri da allopurinolo sono

- Recente introduzione di allopurinolo
- Presenza dell'allele HLA-B\*58:01
- Elevato dosaggio iniziale
- Uso concomitante di diuretici
- Insufficienza renale (aggiustamento dosaggio):
  - CrCl 0 ml/min: allopurinolo dose 100 mg ogni 2° giorno
  - CrCl 10 ml/min: allopurinolo dose 100 mg a gg alerni
  - CrCl 20 ml/min: allopurinolo dose 100 mg die
  - CrCl 40 ml/min: allopurinolo dose 150 mg die
  - CrCl 60 ml/min: allopurinolo dose 200 mg die
  - CrCl 80 ml/min: allopurinolo dose 250 mg die
  - CrCl 100 ml/min: allopurinolo dose 300 mg die
  - CrCl 120 ml/min: allopurinolo dose 350 mg die
  - CrCl 140 ml/min: allopurinolo dose 400 mg die

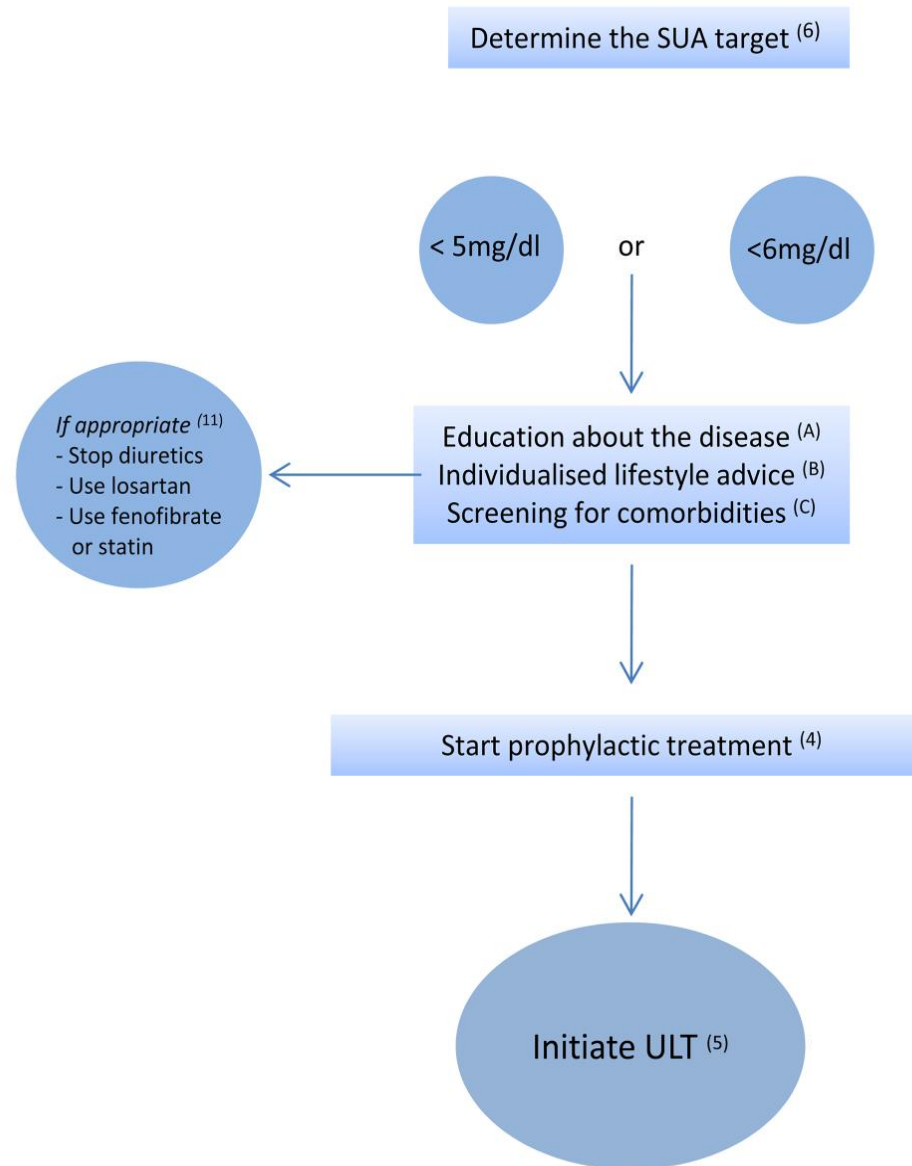
Stamp, L. K. et al. Nat. Rev. Rheumatol. advance online publication 29 September 2015; doi:10.1038/nrrheum.2015.132

# Lesinurad

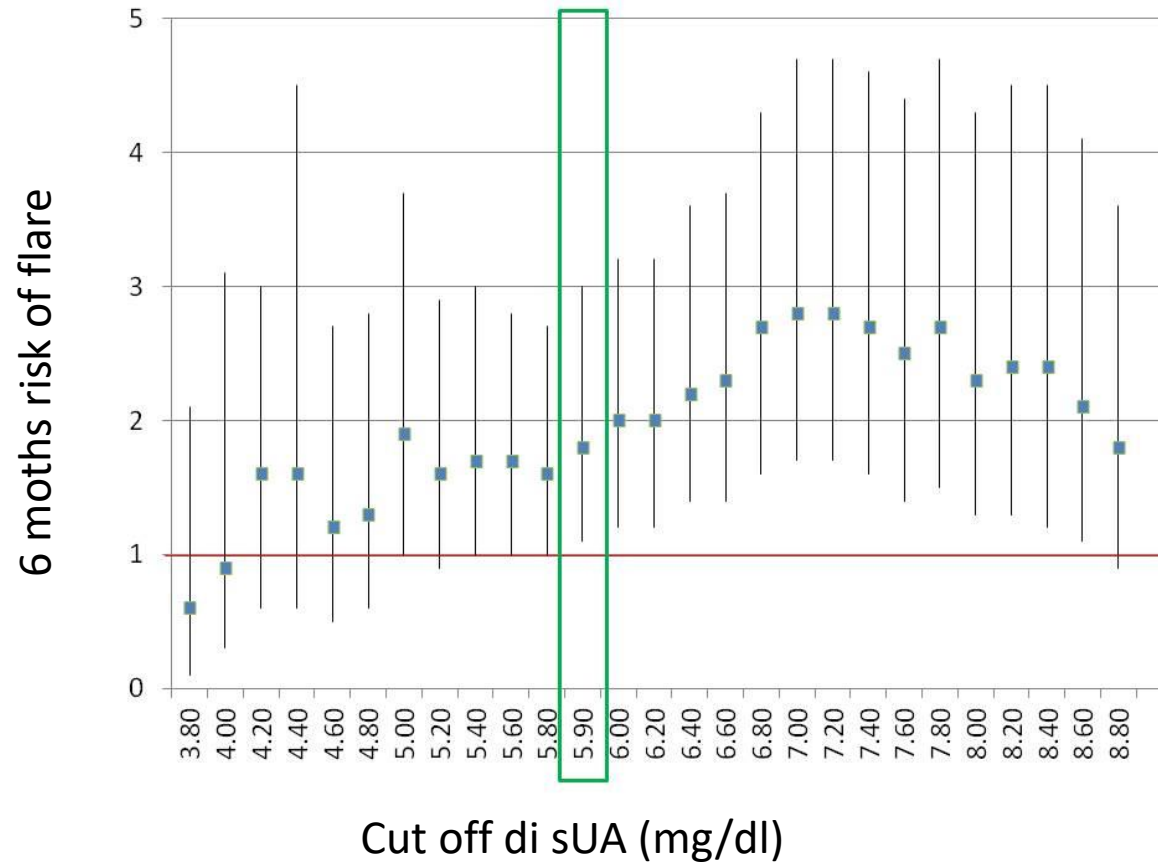


Inibitore selettivo del riassorbimento dell'acido urico che inibisce i trasportatori di acido urico URAT1 e OAT4 a livello dei tubuli prossimali dei reni.



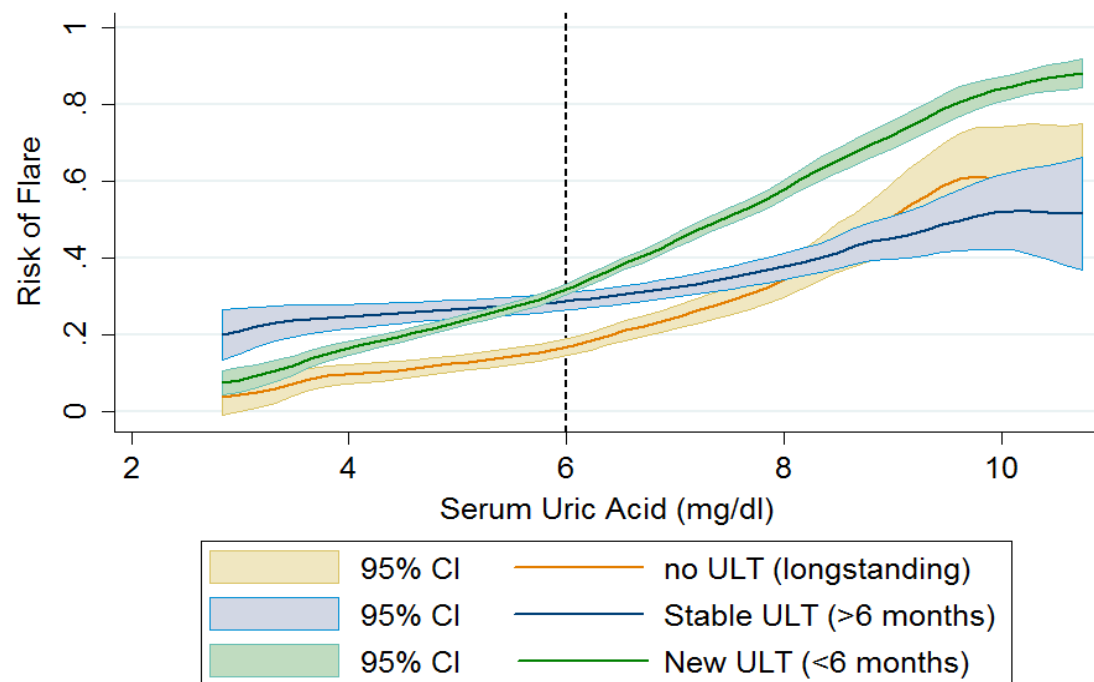


# Optimal target 6 mg/dl



*Risk of flare starts to be significantly lower below 6mg/dl cut-off*

# Empty dish hypothesis



*Adjusted for use of age, disease duration, NSAIDs, colchicine*

## ***Empty dish hypothesis:***

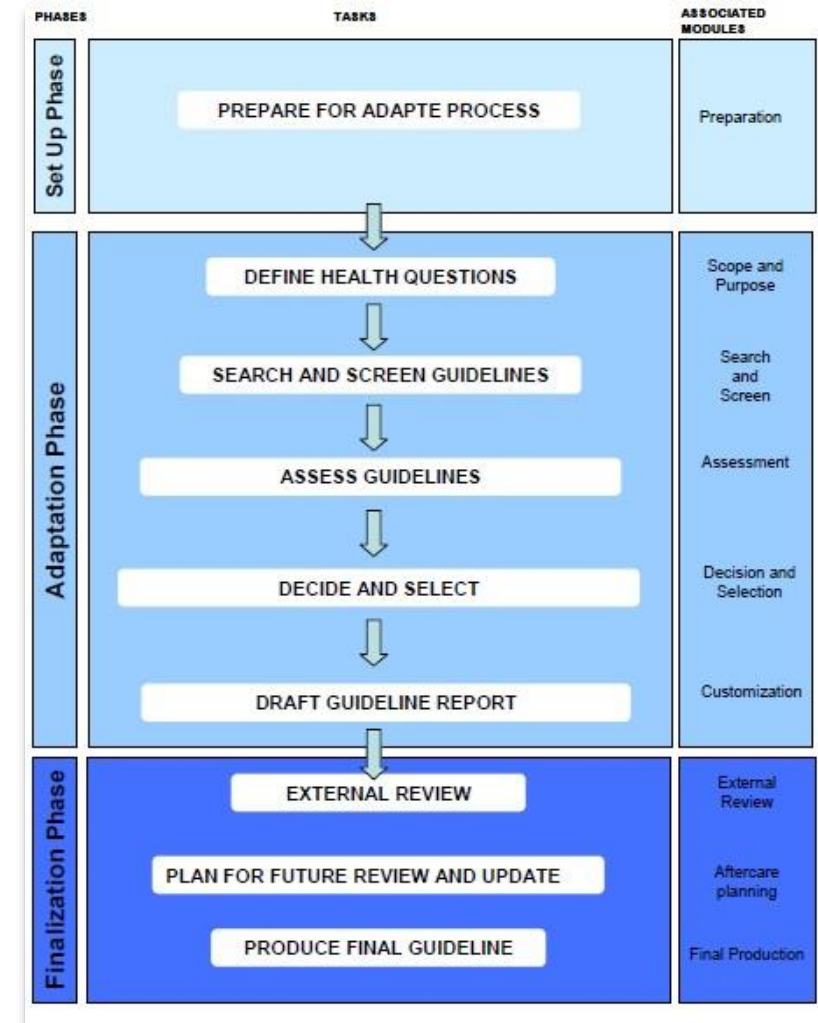
*I pazienti all'inizio del trattamento hanno un rischio di flare più elevato dei pazienti in trattamento a lungo termine.*

*Il target può essere meno stringente in pazienti che hanno eliminato i depositi tissutali (pazienti in remissione)*

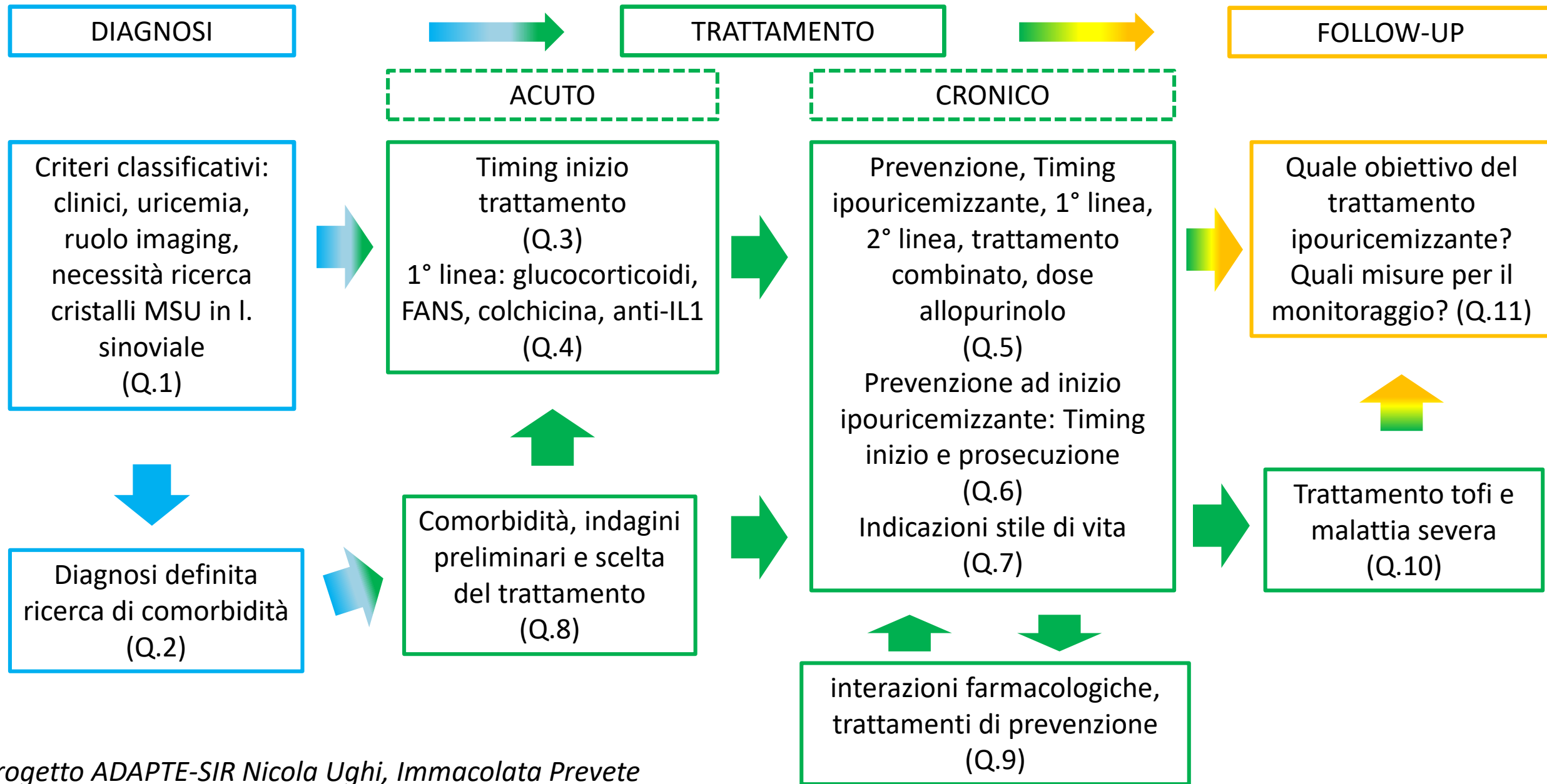
Manara et al EULAR 2013

# Summary of the ADAPTE

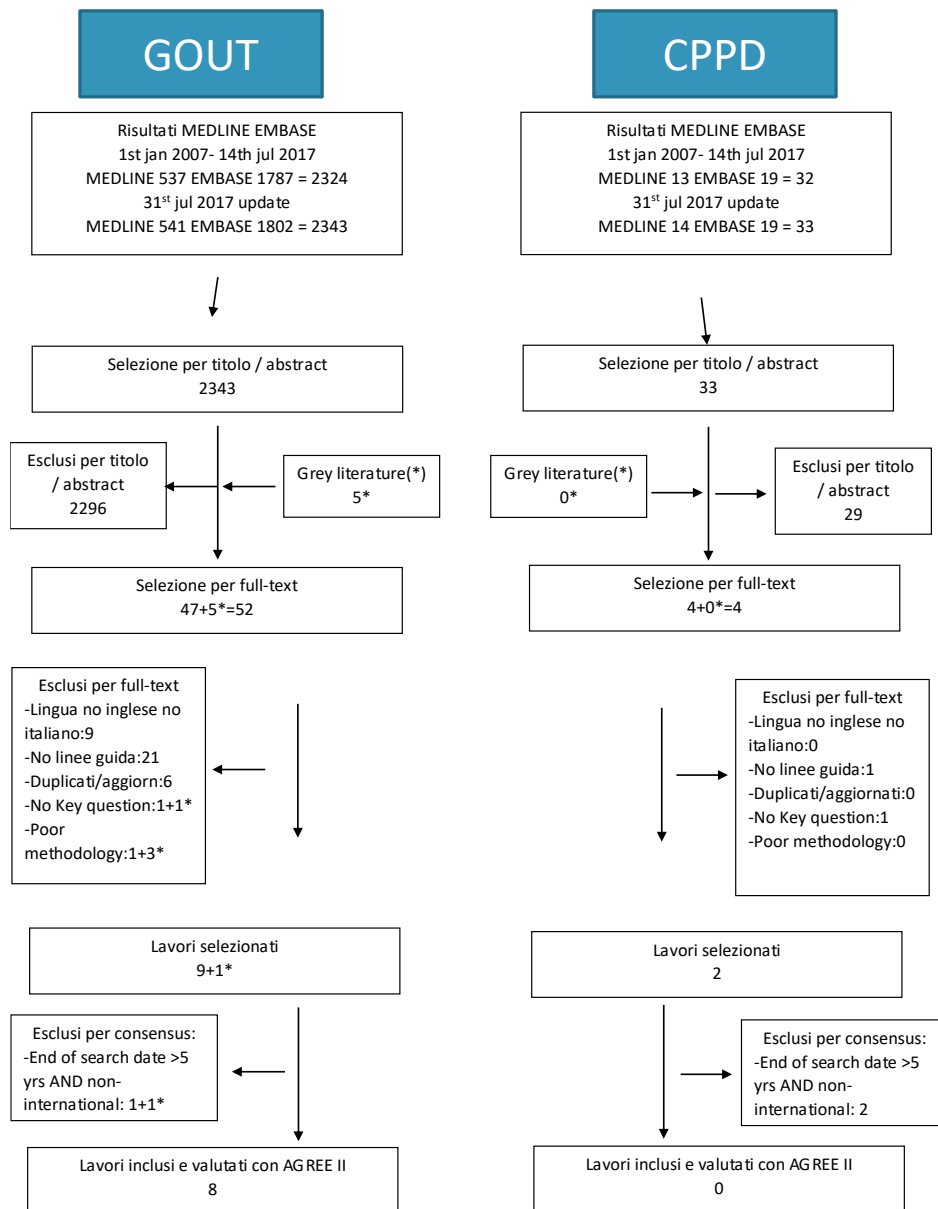
*‘existing high quality CPGs as a resource may be an alternative to de novo development to reduce duplication of effort, enhance efficiency, and promote local uptake of quality CPG recommendations’*







Progetto ADAPTE-SIR Nicola Ughi, Immacolata Prevete



Title	Publisher	Country, language	Publication date	End of search date	Comments (i.e.:
CPG #1	Updated BSR	UK, English	2017	June 2015	AGREE II yes
CPG #2	ACP Diagnosis	USA, English	2016	Feb 2016	AGREE II yes
CPG #3	ACP Management	USA, English	2016	March 2016	AGREE II yes
CPG #4	T2T EULAR	Europe, English	2016	April 2015	AGREE II yes
CPG #5	Updated EULAR	Europe, English	2016	May 2016	AGREE II yes
CPG #6*	Hamburgher M et al	USA, English	2015	Feb 2011	AGREE II no
CPG #7	Multinational 3e	Multinational, English	2013	October 2011	AGREE II yes
CPG #8	ACR Part 1	USA, English	2012	March 2011	AGREE II yes
CPG #9	ACR Part 2	USA, English	2012	March 2011	AGREE II yes
CPG #10*	Sociedad Española de Reumatología	Spain, English	2012	Nov 2011	AGREE II no

# Aknowlegments



**Alarico Ariani**

**Alessandra Bortoluzzi**

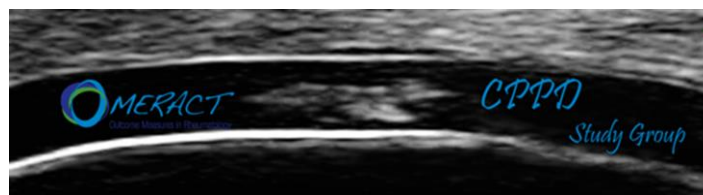
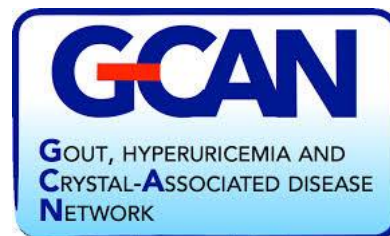
**Maria Manara**

**Simone Parisi**

**Immacolata Prevete**

**Nicola Ughi**

**Greta Carrara**



**Georgios Filippou**

