Iperuricemia

Massimo Procopio
SCDU Endocrinologia, Diabetologia e Metabolismo
Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino

IPERURICEMIA

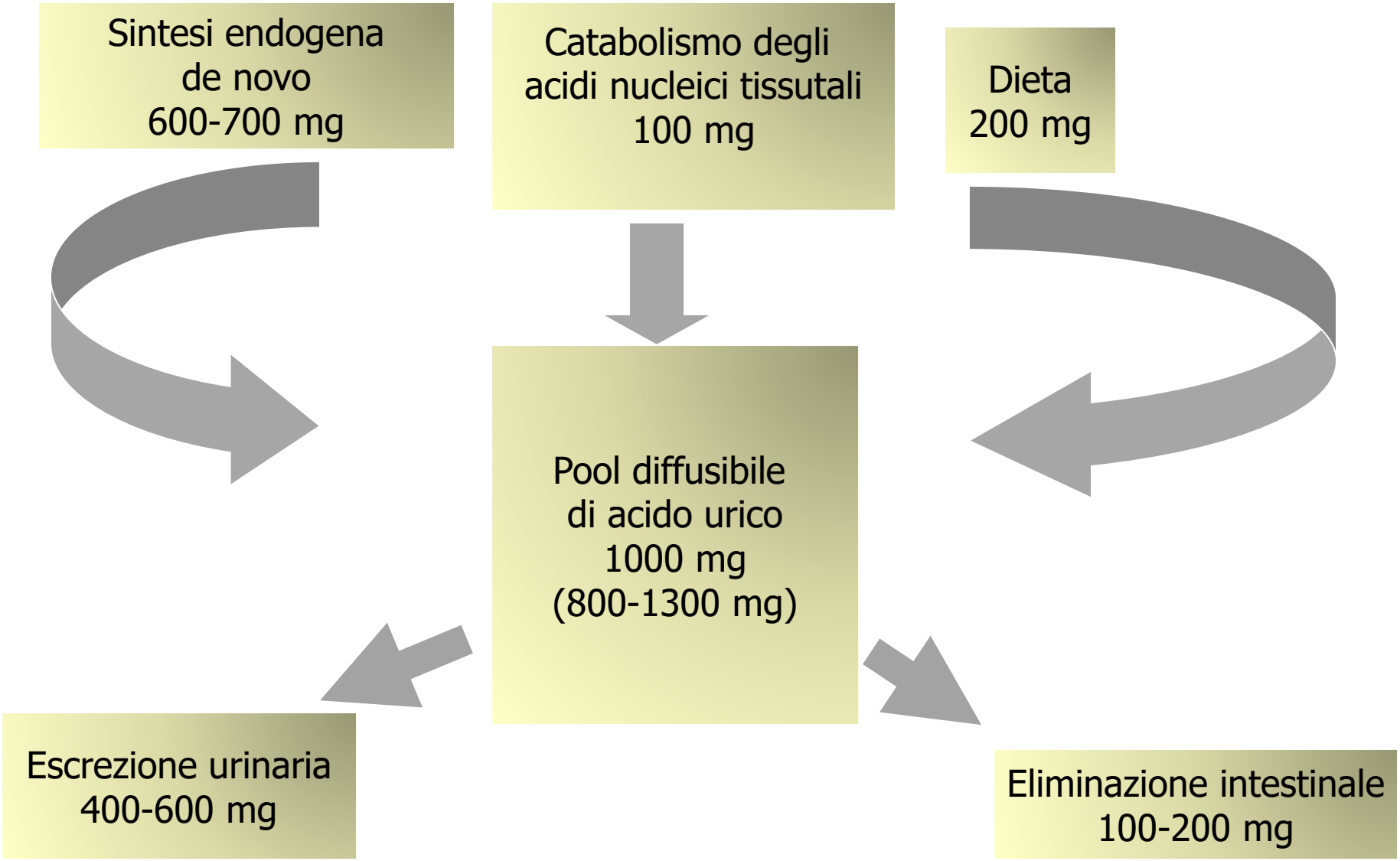
- L'iperuricemia può essere definita da un livello sierico (o plasmatico) di acido urico maggiore di **6.8 mg/dL** (>380 µmol/L)

Harrison's™ Principles of Internal Medicine, Nineteenth Edition, 2015

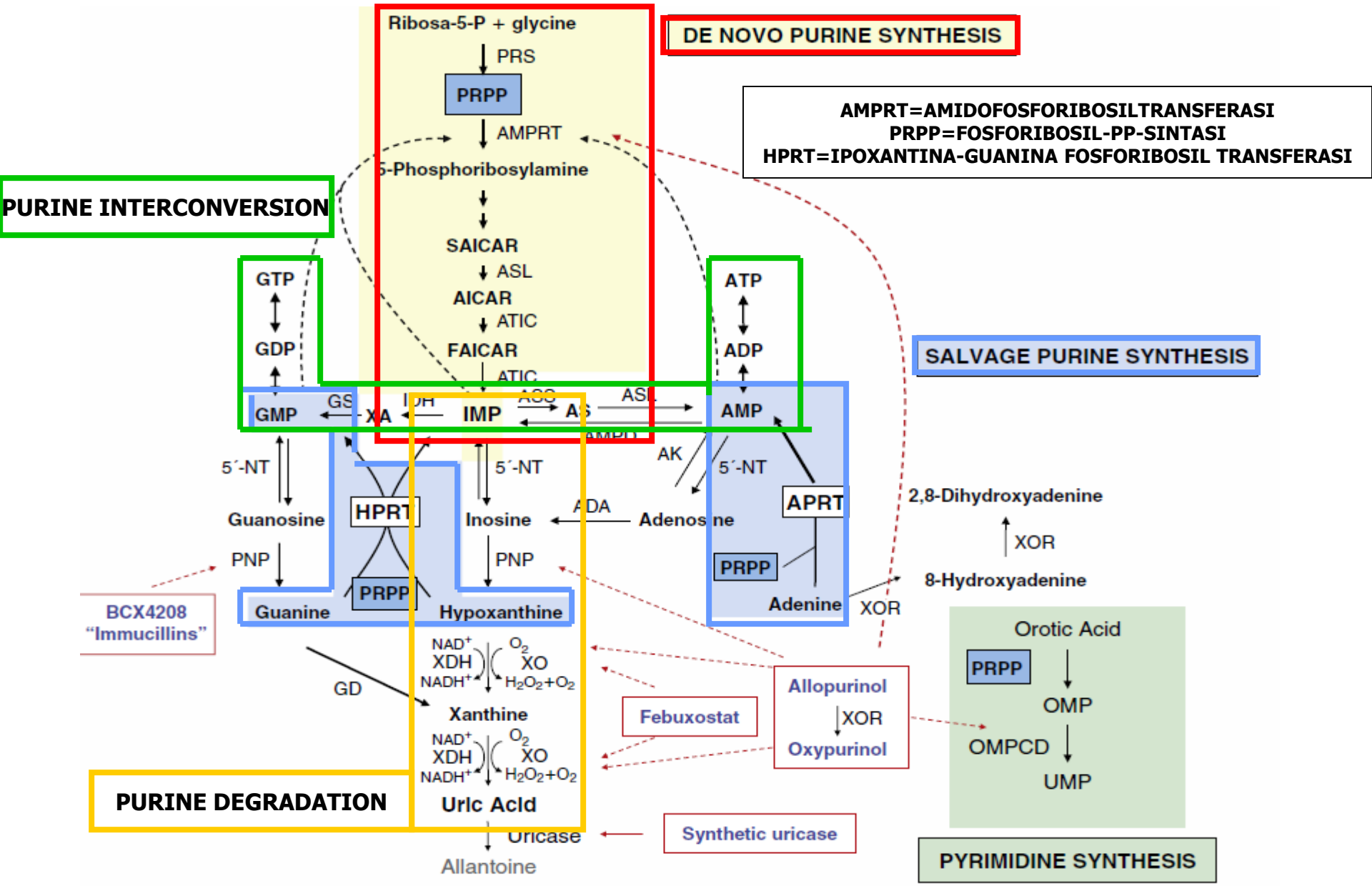
Il limite superiore di solubilità dell'urato monosodico nel plasma è 6.8 mg/dL (380 µmol/L).

Nell' urina, che è acidificata lungo il tubulo renale, l'urato è trasformato in acido urico che è meno solubile.

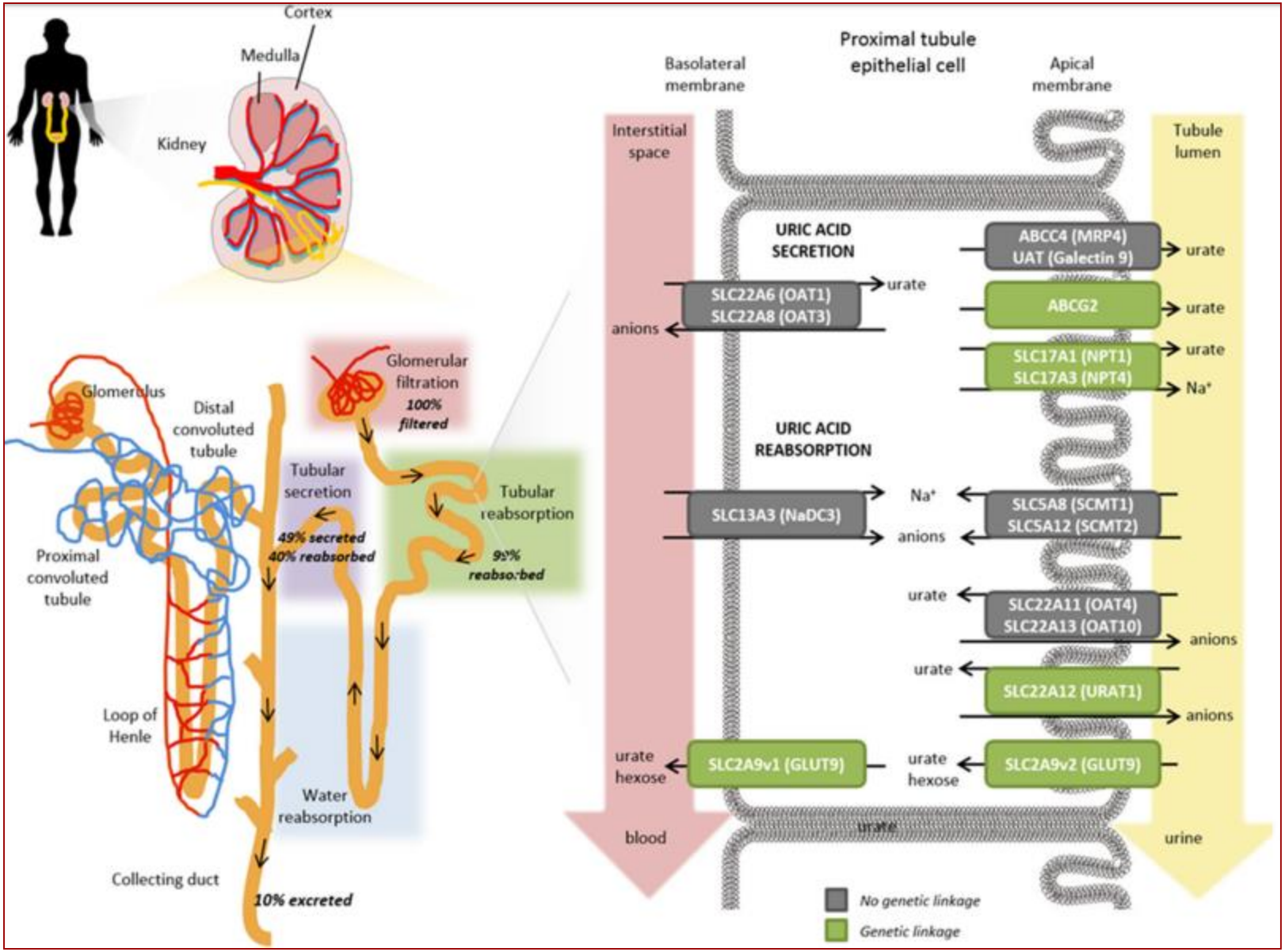
Omeostasi del pool miscibile o diffusibile di acido urico



METABOLISMO PURINICO



Metabolismo renale dell'acido urico



Benn CL et al. Front Med 5:160, 2018

Classification of Hyperuricemia by Pathophysiology

Urate Overproduction		
Primary idiopathic	Myeloproliferative diseases	Rhabdomyolysis
HPRT deficiency	Polycythemia vera	Exercise
PRPP synthetase overactivity	Psoriasis	Alcohol
Hemolytic processes	Paget's disease	Obesity
Lymphoproliferative diseases	Glycogenosis III, V, and VII	Purine-rich diet
Decreased Uric Acid Excretion		
Primary idiopathic	Starvation ketosis	Drug ingestion
Renal insufficiency	Berylliosis	Salicylates (<2 g/d)
Polycystic kidney disease	Sarcoidosis	Diuretics
Diabetes insipidus	Lead intoxication	Alcohol
Hypertension	Hyperparathyroidism	Levodopa
Acidosis	Hypothyroidism	Ethambutol
Lactic acidosis	Toxemia of pregnancy	Pyrazinamide
Diabetic ketoacidosis	Bartter's syndrome	Nicotinic acid
	Down syndrome	Cyclosporine
Combined Mechanism		
Glucose-6-phosphatase deficiency	Fructose-1-phosphate aldolase deficiency	Alcohol Shock

Harrison's™ Principles of Internal Medicine, Nineteenth Edition, 2015

Farmaci che aumentano o riducono i livelli sierici di acido urico

Aumentano

- Diuretici tiazidici e dell'ansa ¶
- Etambutolo ¶
- Pirazinamide ¶
- Salicilato ¶ (dose< 75 mg die)
- Acido nicotinico ¶
- Teriparatide ¶
- Ormone paratiroideo ¶
- Tacrolimus ¶
- Ciclosporina ¶
- Ribavirina e interferone ¶
- Levodopa ¶
- Chemioterapia citotossica ¶ ¶
- Etanolo ¶ ¶

Riducono

- Benzbromarone*
- Probenecid*
- Sulfinpirazone*
- Lesinurad*
- Acido Ascorbico*
- Citrato*
- Estrogeni*
- Salicilato* (dose>3 g die)
- Fenofibrato*
- Losartan*
- Calcitonina*
- Allopurinolo**
- Febuxostat**
- Rasburicase***
- Pegloticase***

¶ Riducono l'escrezione renale di acido urico

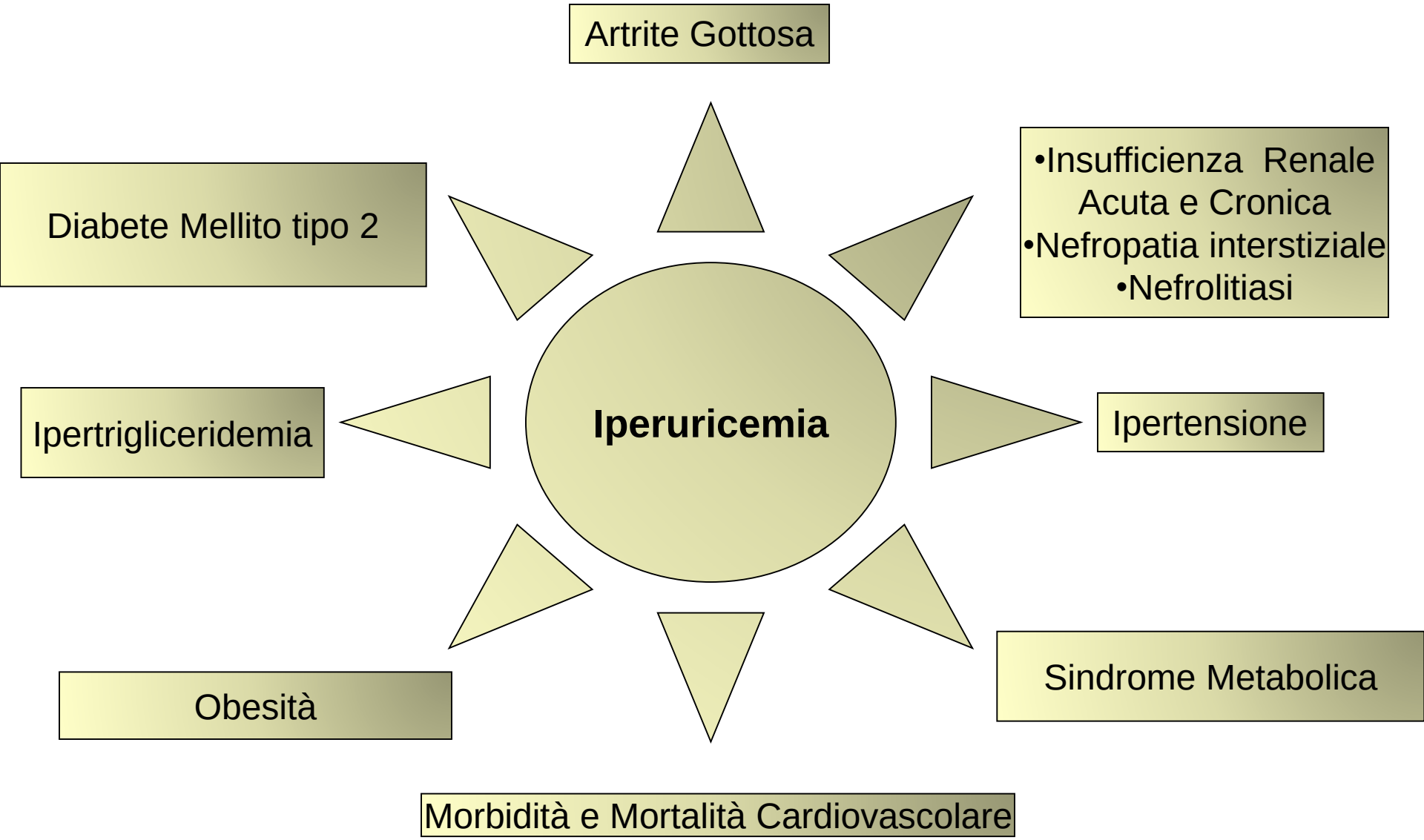
¶ ¶ Aumentano la produzione di purine

* Uricosurici

** Uricostatici

*** Uricolitici

Malattie associate all'Iperuricemia



Prevalence of hyperuricemia in Italy

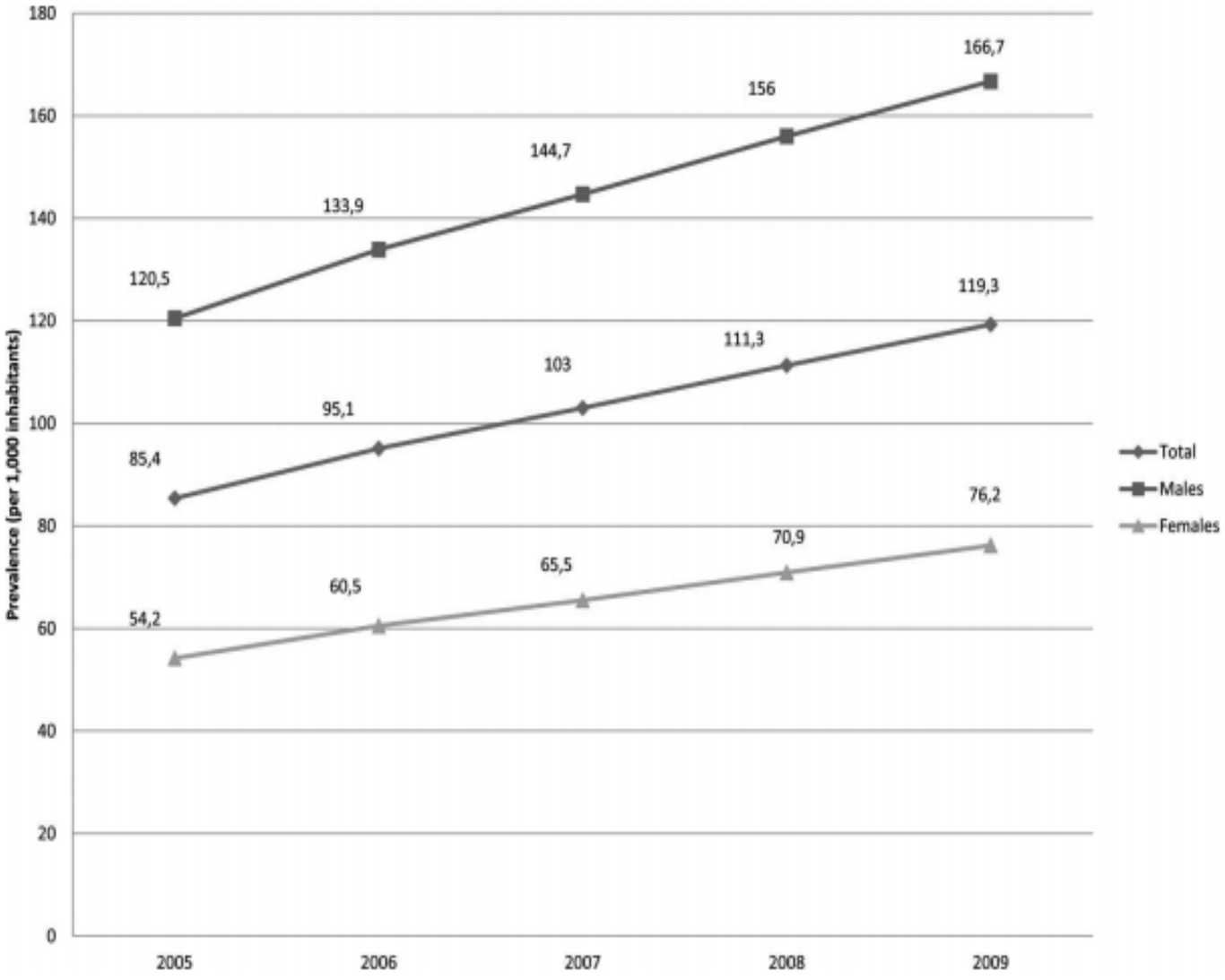


Figure 2 Prevalence of hyperuricaemia (serum uric acid >6 mg/dl) per 1000 inhabitants by gender and calendar year.

Trifirò G et al. Ann Rheum Dis. 72:694-700, 2013

Prevalence of gout and hyperuricemia in Italy

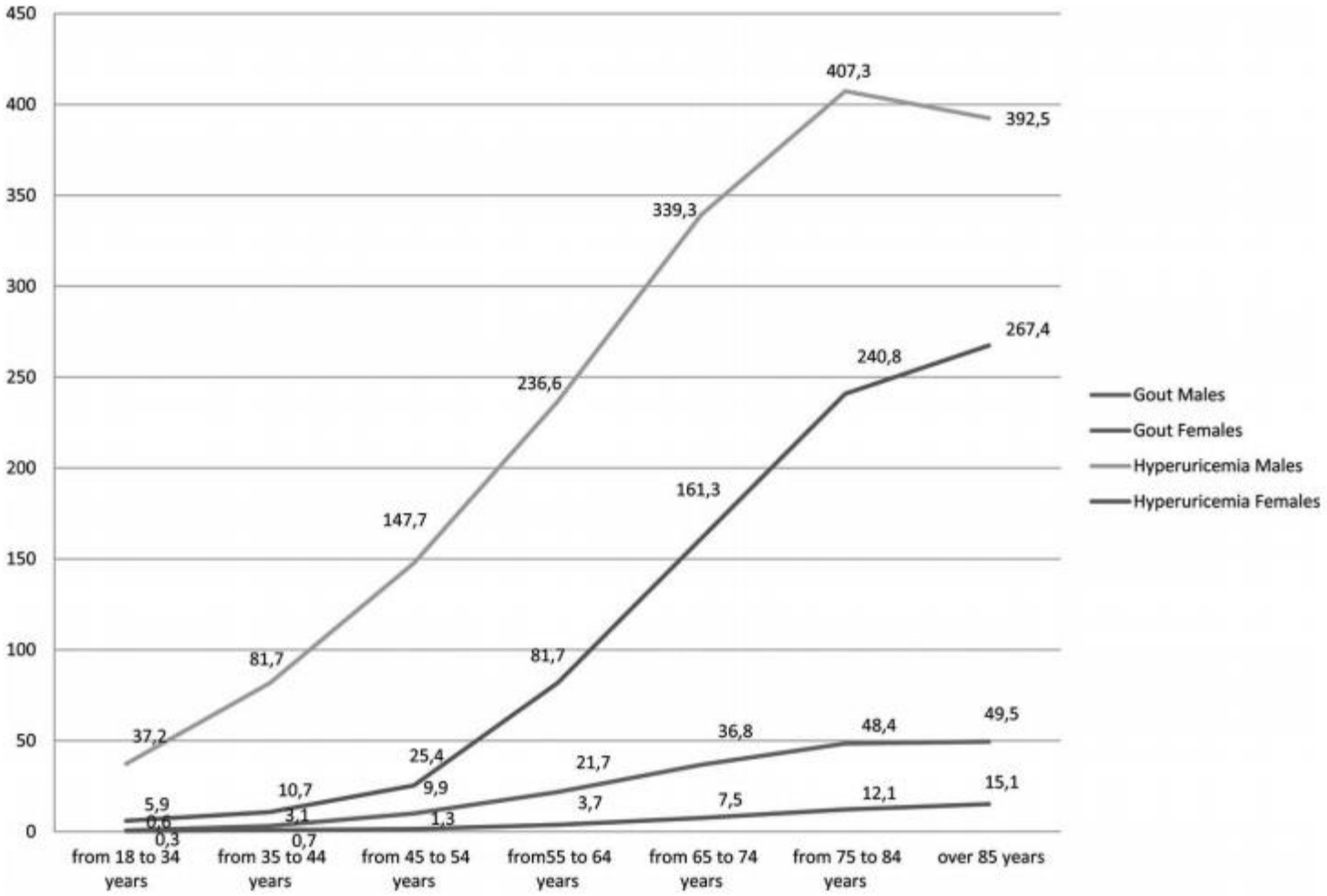


Figure 3 Prevalence of gout and hyperuricaemia (serum uric acid >6 mg/dl) per 1000 inhabitants by gender and age groups in 2009.

Trifirò G et al. Ann Rheum Dis. 72:694-700, 2013

Risk factors for onset and development of hyperuricemia and gout in elderly people

Constitutional factors	Diseases	Lifestyle	Drugs
Age	Hypertension	Weight gain	Loop diuretics and thiazides
Male sex	Tumor lysis syndrome	Overweight and obesity	Immunosuppressive therapy
Post-menopausal	Metabolic syndrome	Poor physical activity	
	Chronic renal failure	Northern Europe diet	

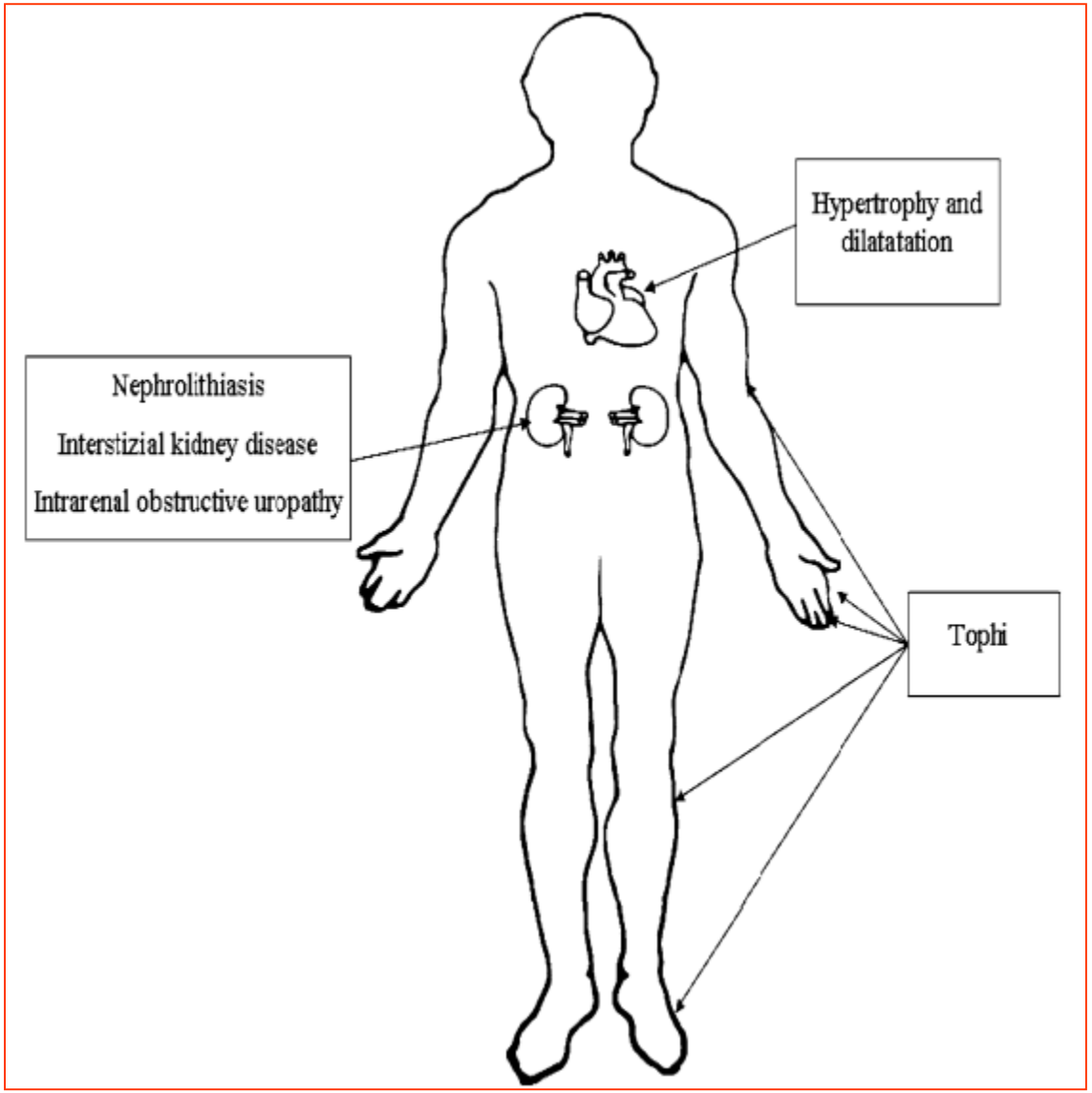
Bolzetta F et al. Aging Clin Exp Res 25:129–137, 2013

Table I. Atypical characteristics of gout presentation in the older adult.[7]

Traditional Presentation of Gout	Presentation of Gout in the Older Adult
Monoarticular	May be polyarticular
Sudden onset	Onset may be gradual
<10% of cases in women	Incidence in women approaches that seen in men
Etiology variable	Declining renal function with age and polypharmacy are common etiologies
Monosodium urate crystal formation; primarily affects great toe	Possible calcium pyrophosphate dihydrate crystal formation (pseudogout); primarily affects knee, wrist, shoulder, and ankle

Fravel MA et al. Am J Geriatr Pharmacother. 9:271-85, 2011

Clinical aspects and complications of the chronic gout in elderly



Bolzetta F et al. Aging Clin Exp Res 25:129–137, 2013

Terapia della gotta nel paziente anziano

Attacco acuto

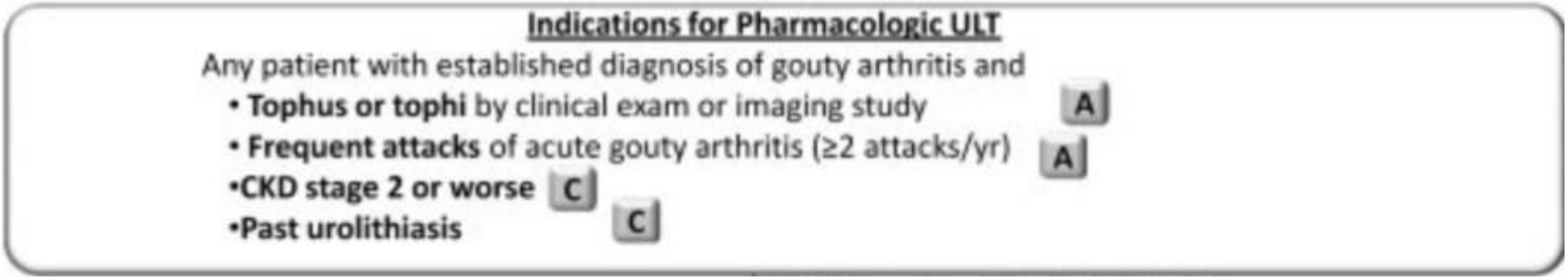
- Cortisonici per via sistemica o intra-articolare
- Attenzione all'uso di FANS, inibitori della ciclo-ossigenasi 2 e colchicina (interazione con altri farmaci, comorbidità)

Iperuricemia cronica

- Allopurinolo: iniziare da dosaggi bassi
- Febuxostat
- Lesinurad

Indications for pharmacologic ULT

American College of Rheumatology 2012



Indications for Pharmacologic ULT

Any patient with established diagnosis of gouty arthritis and

- **Tophus or tophi** by clinical exam or imaging study **A**
- **Frequent attacks** of acute gouty arthritis (≥2 attacks/yr) **A**
- **CKD stage 2 or worse** **C**
- **Past urolithiasis** **C**

Eular 2016

ULT should be considered and discussed with every **patient with a definite diagnosis of gout** from the first presentation.

ULT is indicated in all patients with **recurrent flares**, **tophi, urate arthropathy and/or renal stones**.

Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at **a young age (<40 yr) or** with a **very high SUA levels** (8.0 mg/dL; 480 mmol/L) **and/or comorbidities** (renal impairment, hypertension, ischaemic heart disease, heart failure). Patients with gout should receive full information and be fully involved in decision-making concerning the use of ULT.

SUMMARY OF THREE PHASE 3 RANDOMISED CONTROLLED TRIALS OF FEBUXOSTAT

	FACT (n=762), 52 weeks	APEX (n=1072), 28 weeks	CONFIRMS (n=2269), 26 weeks
Treatment (n)	Febuxostat 80 mg (256) Febuxostat 120 mg (251) Allopurinol 300 mg (253)	Febuxostat 80 mg (267) Febuxostat 120 mg (269) Febuxostat 240 mg (134) Allopurinol 100–300 mg (268) Placebo (134)	Febuxostat 40 mg (757) Febuxostat 80 mg (756) Allopurinol 200/300 mg (755) 300 mg (611); 200 mg (145 with creatinine clearance of 30–59 mL/min)
Primary Endpoint	Serum urate <357 µmol/L last three monthly visits	Serum urate <357 µmol/L last three monthly visits	Serum urate <357 µmol/L at last visit
Primary endpoint achieved	Febuxostat 80 mg: 53% (p<0·001 vs allopurinol) Febuxostat 120 mg: 62% (p<0·001 vs allopurinol) Allopurinol 300 mg: 21%	Febuxostat 80 mg: 48% (p<0·001 vs allopurinol, placebo) Febuxostat 120 mg: 65% (p<0·001 vs allopurinol, placebo) Febuxostat 240 mg: 69% (p<0·001 vs allopurinol, placebo) Allopurinol 100/300 mg: 22% (p<0·001 vs placebo) Placebo: 0%	Febuxostat 40 mg: 45% Febuxostat 80 mg: 67% (p<0·001 vs febuxostat 40 mg, allopurinol) Allopurinol 200/300 mg: 42%
Primary endpoint achieved in renal insufficiency	NA	Subset: creatinine clearance >1·5, ≤2·0 (n=40) Febuxostat 80 mg: 4/9=44% (p<0·05 vs allopurinol) Febuxostat 120 mg: 5/11=45% (p<0·05 vs allopurinol) Febuxostat 240 mg: 3/5=60% (p<0·05 vs allopurinol) Allopurinol 100 mg: 0/10=0% Placebo: 0/5=0%	Subset: creatinine clearance 30–89 ml/min (n=1483) Febuxostat 40 mg: 50% (p=0·021 vs allopurinol) Febuxostat 80 mg: 72% (p<0·001 vs febuxostat 40 mg, allopurinol) Allopurinol 200/300 mg: 42%

CM Burns, RL Wortmann, Gout therapeutics: new drugs for an old disease, Lancet 2010

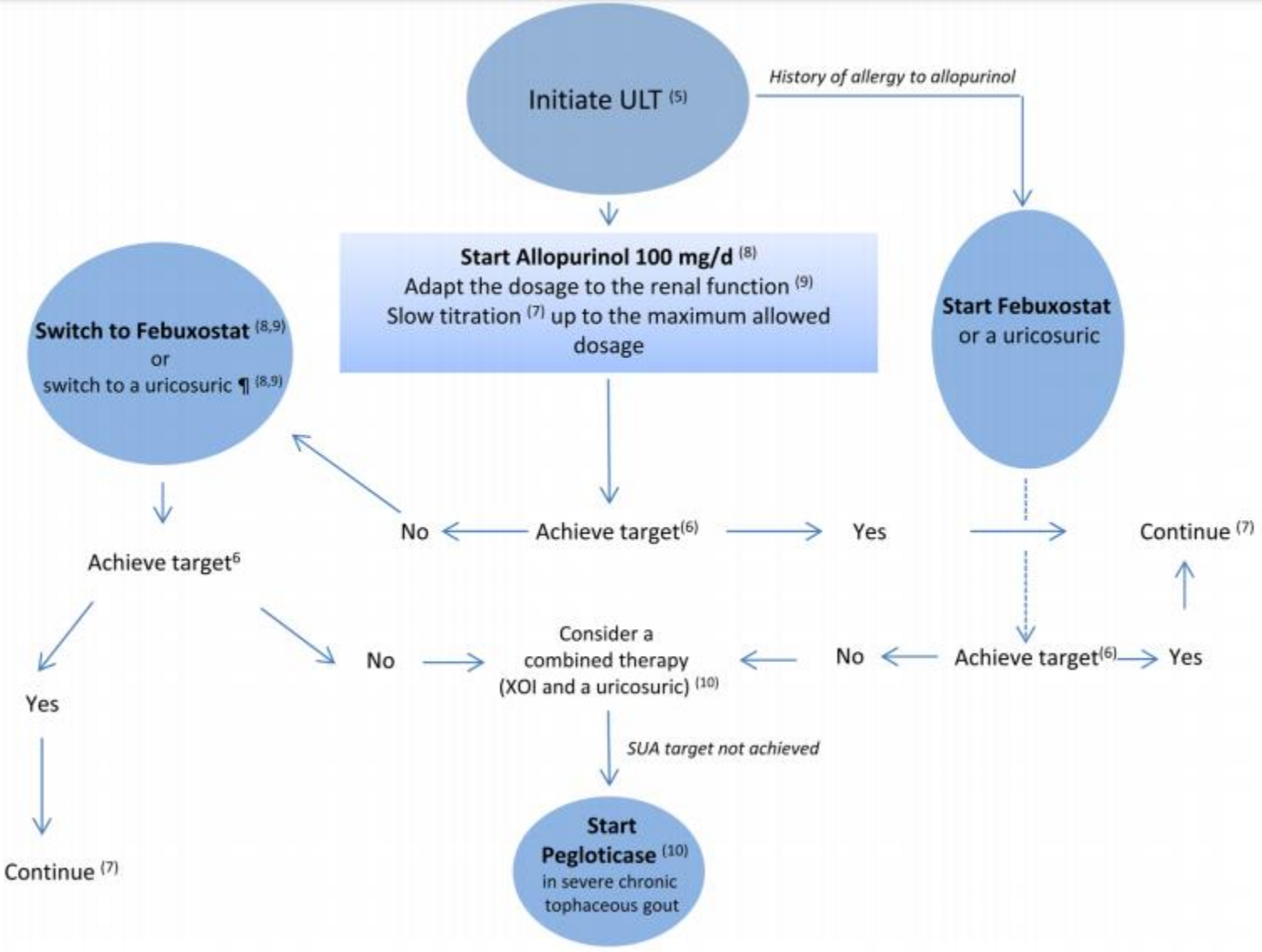
Lesinurad: clinical considerations in hyperuricaemia
Lowers serum UA concentrations via inhibition of URAT1 and OAT4 (UA transporters of the kidney)
Administered orally once daily in combination with an XOI
Added to an XOI regimen, enables many gout patients with hyperuricaemia to achieve target sUA levels
Improves clinical parameters (e.g. tophus number/size and rate of gout flares needing treatment) in the long term (over up to 24 months)
Generally well tolerated, with most adverse events being mild to moderate and transient

Table 1 Antihyperuracaemic efficacy of oral lesinurad in adults with gout [15, 16] or tophaceous gout [17] in phase 3 trials

Study	Regimen (mg) [no. of pts]	% of pts with an sUA of							Mean sUA level at 12 mo [BL]
		<6 mg/dL		<5 mg/dL		<4 mg/dL		<3 mg/dL	
		6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo/12 mo	
CLEAR 1 [15]	LES 200 + ALP [201]	54.2[a]**	53[b]**	28[b]**	27[b]**	8[b]*	8[b]**		5.7[b]** [7.0]
	PL + ALP [201]	27.9[a]	25[b]	11[b]	7[b]	2[b]	0[b]		6.7[b] [6.9]
CLEAR 2 [16]	LES 200 + ALP [204]	55.4[a]**	49[b]**	35[b]**	31[b]**	12[b]**	10[b]**		5.8[b]* [6.8]
	PL + ALP [206]	23.3[a]	26[b]	4[b]	5[b]	1[b]	0[b]		6.7[b] [7.0]
CRYSTAL [17]	LES 200 + FEB [106]	68	59	57[a]	57*	44*	46*	26*/31*	
	PL + FEB [109]	63	59	46[a]	41	19	17	1/6	

Deeks ED. Drugs Aging 34:401-410, 2017

Eular 2016


Initiate ULT [5]
History of allergy to allopurinol
Start Allopurinol 100 mg/d [8]
Adapt the dosage to the renal function [9]
Slow titration [7] up to the maximum allowed dosage
Switch to Febuxostat [8,9]
or
switch to a uricosuric ¶ [8,9]
Start Febuxostat
or a uricosuric
No
Achieve target[6]
Yes
Continue [7]
Achieve target[6]
Yes
No
Consider a combined therapy (XOI and a uricosuric) [10]
No
Achieve target[6]
Yes
Continue [7]
SUA target not achieved
Start Pegloticase [10]
in severe chronic tophaceous gout

AIFA
Agenzia Italiana del Farmaco

Farmaco in nota

- Febuxostat

Nota 91

Determinazione 2 novembre 2010 (GU 12 novembre 2010, n. 265): Modifiche, relative all'inserimento della Nota 91, alla determinazione 4 gennaio 2007 : "Note AIFA 2006-2007 per l'uso appropriato dei farmaci".

La prescrizione a carico del SSN è limitata alle seguenti condizioni:

- Trattamento dell'iperuricemia cronica con anamnesi o presenza di tofi e/o di artrite gottosa in soggetti che non siano adeguatamente controllati con allopurinolo o siano ad esso intolleranti.

SERIE GENERALE

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 158° - Numero 269

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

Art. 1.

Classificazione ai fini della rimborsabilità

Il medicinale ZURAMPIC nelle confezioni sotto indicate è classificato come segue:

Indicazioni terapeutiche oggetto della negoziazione: «Zurampic», in associazione con un inibitore della xantina ossidasi, è indicato in soggetti adulti per il trattamento aggiuntivo dell'iperuricemia in pazienti con gotta (con o senza tofi) che non abbiano raggiunto livelli sierici target di acido urico con una dose adeguata di un inibitore della xantina ossidasi in monoterapia.

Confezione:

200 mg - compressa rivestita con film - uso orale - blister (PCTFE/PVC/ALU) - 30 compresse A.I.C. n. 044727030/E in base 32: 1BNYRQ (in base 32);

Classe di rimborsabilità: A;

Prezzo ex factory (IVA esclusa): € 25,76;

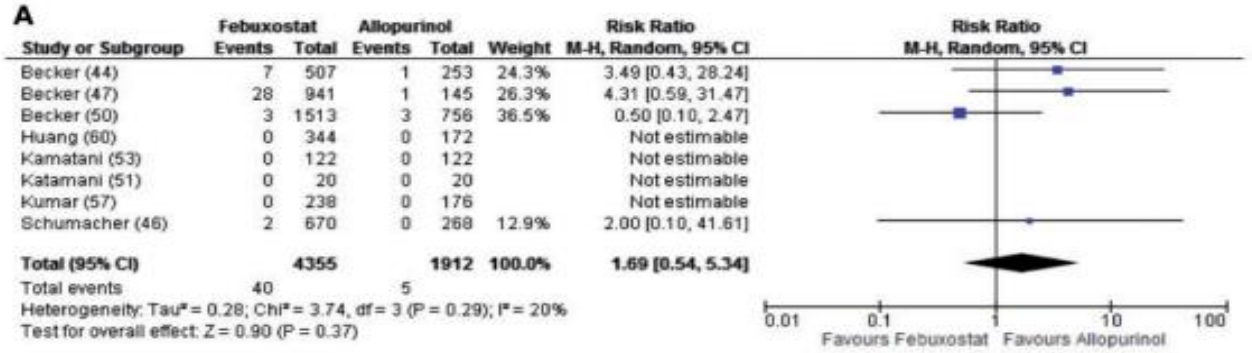
Prezzo al pubblico (IVA inclusa): € 42,51.

Terapia dell'Iperuricemia

Iperuricemia: colpevole, vittima o spettatore innocente?

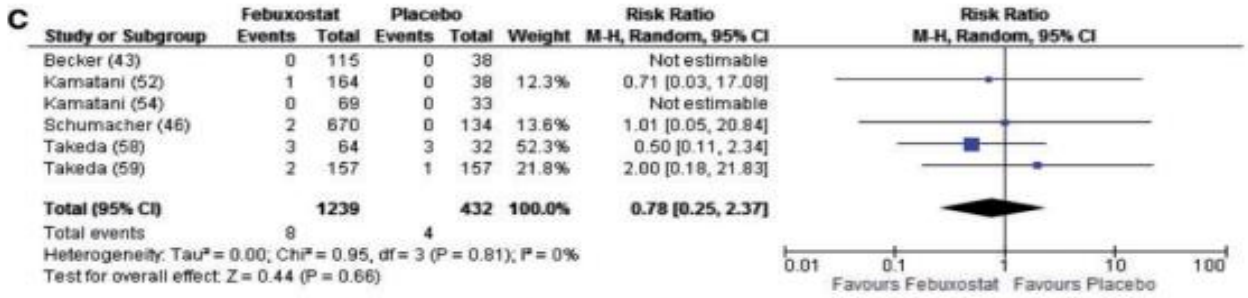
- Obesità
- Ipertrigliceridemia
- Diabete Mellito tipo 2
- Ipertensione
- Sindrome Metabolica
- Insufficienza Renale Cronica
- Nefropatia interstiziale

Cardiovascular effects of urate-lowering therapies in patients with chronic gout: a systematic review and meta-analysis



Rheumatology key messages

- Uricosuric medications initially increase gout flares and could elevate cardiovascular risk.
- Long-term uricosuric medications decrease gout flares and inflammation and may decrease subsequent cardiovascular events.
- No cardiovascular differences among uricosuric drugs in gout were found, but trials were underpowered.



(**A**) Febuxostat *vs* allopurinol. (**B**) ULT *vs* placebo. (**C**) Febuxostat *vs* placebo.

Zhang T & Pope JE Rheumatology 2017;56:11441153

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

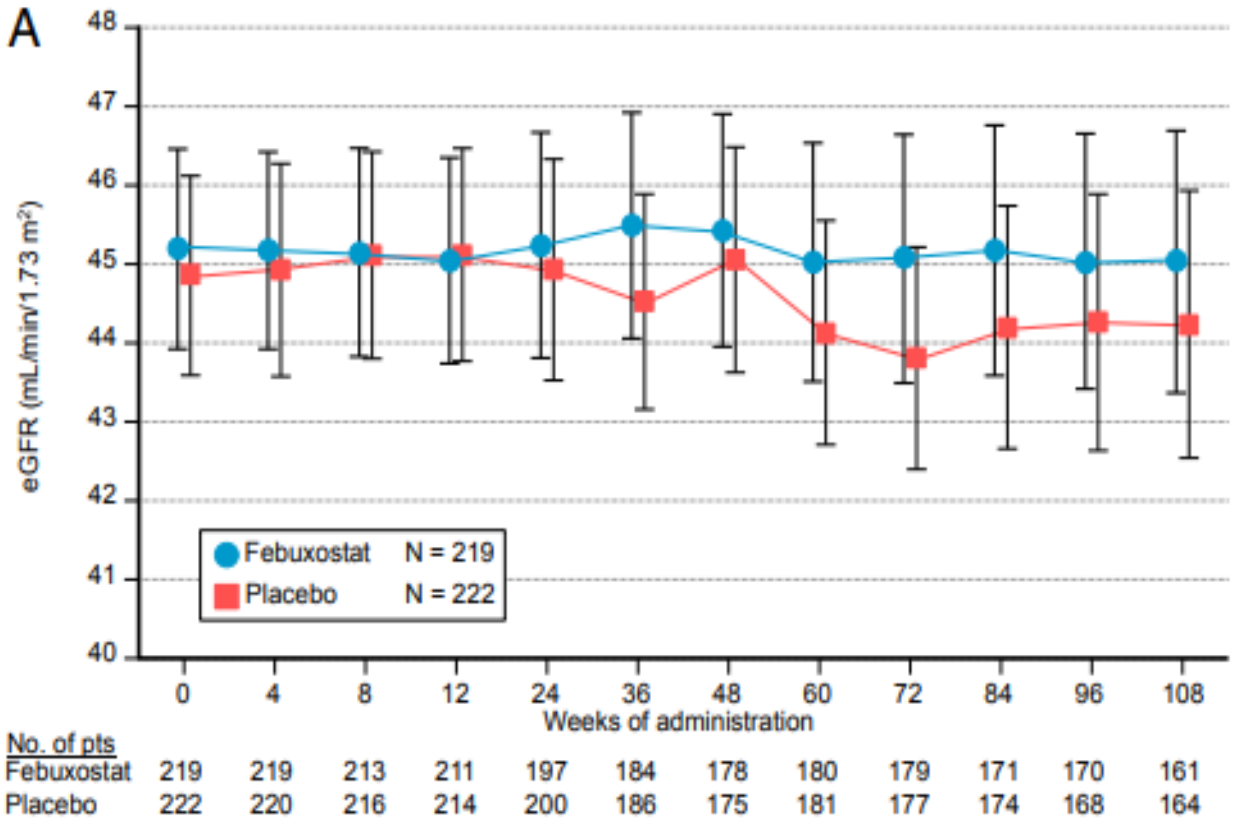
Table 2. Major Safety End Points (Modified Intention-to-Treat Analysis).*

End Point	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina	335 (10.8)	321 (10.4)	1.03 (0.87–1.23)‡	0.66 (0.002)
Secondary end points				
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03–1.73)	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72–1.21)	0.61
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73–1.41)	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59–1.26)	0.44
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92–1.28)	0.33
Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01–1.47)	0.04

White WB et al. N Engl J Med 378:1200-10, 2018

The Feather study

Pz with stage 3 CKD and asymptomatic hyperuricemia



Am J Kidney Dis. XX(XX): 1-13. Published online 2018. doi: 10.1053/ j.ajkd.2018.06.028

Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies

thebmj

What is already known on this topic

Observational studies suggest that high serum uric acid (SUA) levels are associated with multiple health outcomes, including cardiovascular and metabolic diseases (increased risk) or neurological diseases (decreased risk), yet it remains to be determined whether these observed associations are causal

Clinical trials of SUA lowering have shown that xanthine oxidase inhibition decreases blood pressure and improves renal function

There is still debate as to whether SUA level is simply a marker of xanthine oxidase activity or a causal factor involved in systemic inflammation

What this study adds

Of the 136 health outcomes related to SUA level that were examined in meta-analyses of observational studies, meta-analyses of randomised controlled trials, and Mendelian randomisation studies, convincing evidence of a clear association exists only for gout and nephrolithiasis

The available evidence does not support any change in the existing clinical recommendations in relation to hyperuricemia

Li X et al. BMJ 357:j2376 doi: 10.1136/bmj.j2376,2017

Conclusioni

- L'iperuricemia è frequente nell'anziano di entrambi sessi (dieta, inattività fisica, ipertensione arteriosa, sindrome metabolica, riduzione della funzionalità renale, farmaci)
- Presentazione atipica della gotta nell'anziano
- Complessità di trattamento per presenza di comorbidità, polifarmacoterapia, IRC
- Consente di trattare adeguatamente i fattori di rischio cardiometabolico e di ridurre il rischio cardiovascolare di tali pazienti
- *Terapia ipouricemizzante e rischio cardiometabolico e renale*

Grazie dell'attenzione