70 ANNI DI REUMATOLOGIA ALLE MOLINETTE

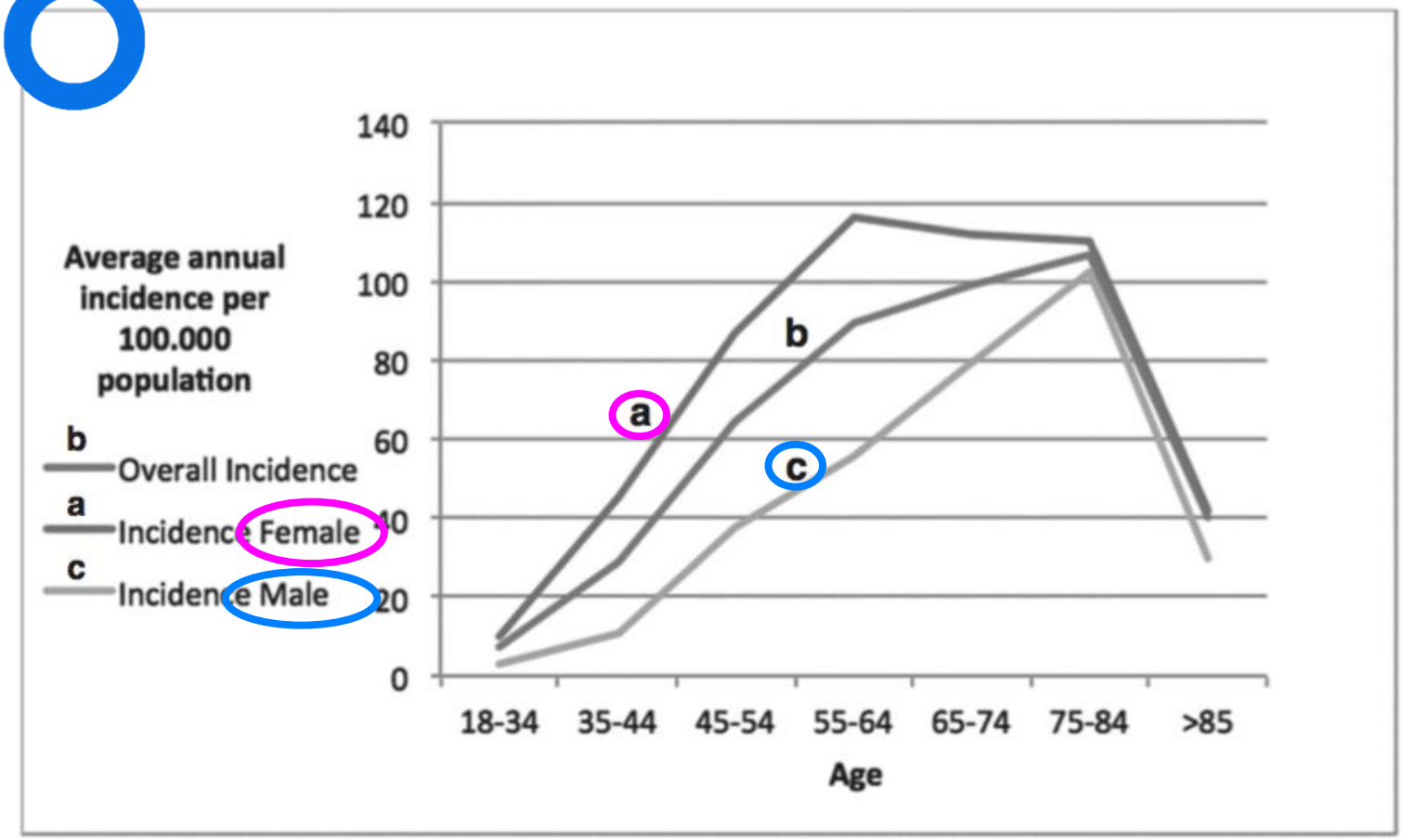
TORINO
11-12 OTTOBRE 2019

Artrite Reumatoide: quando età e genere possono fare la differenza

Maria Chiara Gerardi
UO Reumatologia e Immunologia Clinica, Spedali Civili, Brescia
Dipartimento di Medicina clinica e sperimentale
Università di Brescia

Epidemiologia

Rochester, Minnesota, USA: **609** pz **AR 1955-1995**



Doran MF, et al. Arthritis Rheum. 2002;46:625-31.

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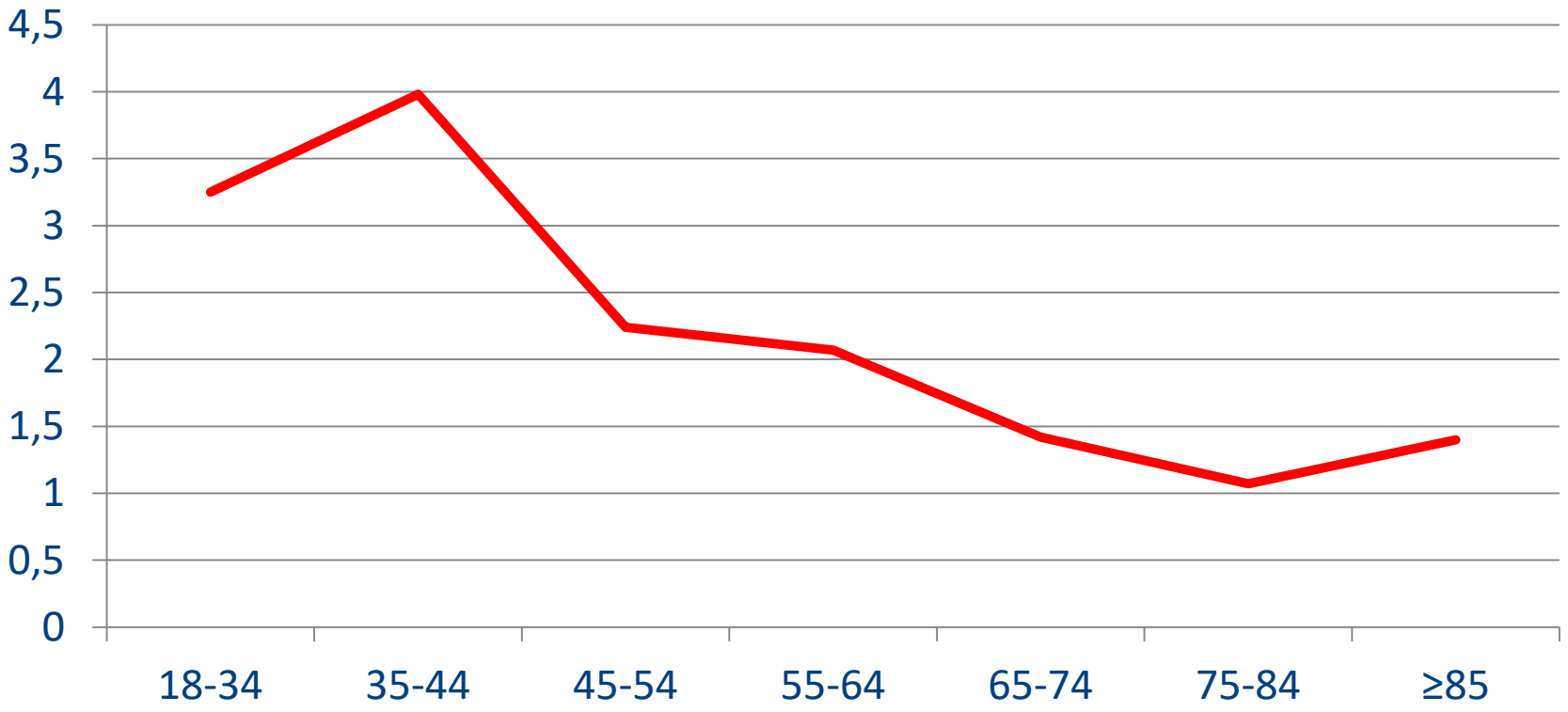
Rapporto incidenza Donne : Uomini nei differenti gruppi di età



3:1 18-34 aa

4:1 35-44 aa

2:1 45-64 aa

1.5:1 >65 aa

1:1 >75 aa

Doran MF, et al. Arthritis Rheum. 2002;46:625-31.

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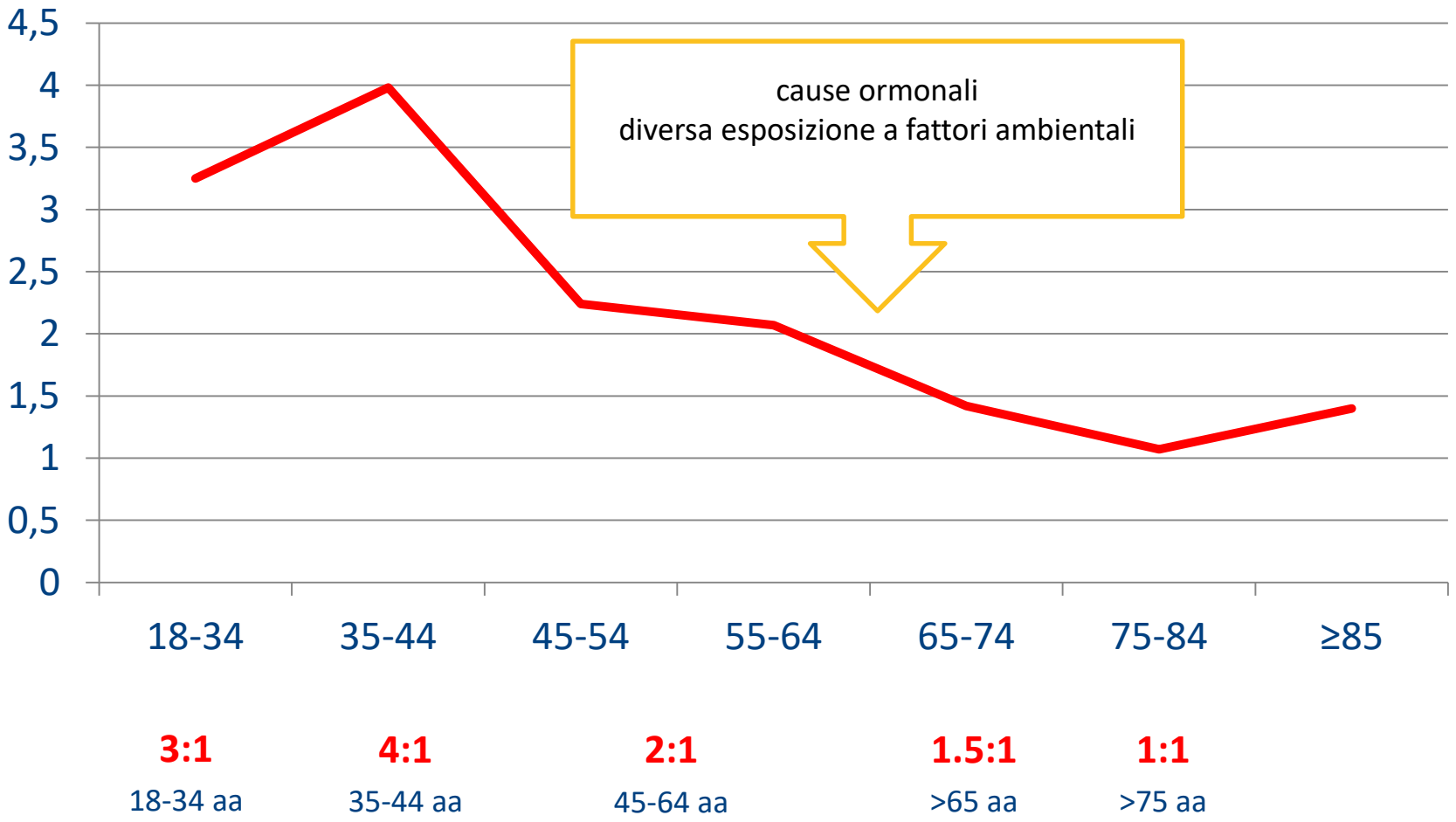


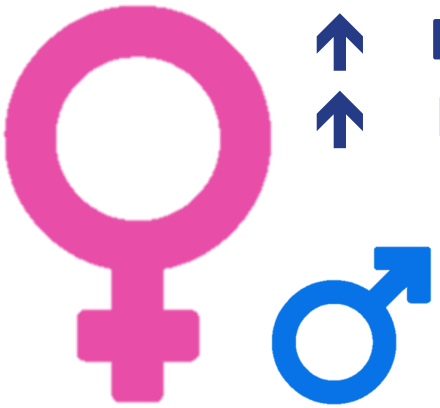
Doran MF, et al. Arthritis Rheum. 2002;46:625-31.

Presentazione clinica: attività di malattia e disabilità

STUDIO BARFOT
844 pz con early AR, Svezia
donne: >> DAS28 e HAQ-DI

STUDIO QUEST-RA
6004 pz con AR in 25 nazioni
donne: >> DAS28 , SJC, HAQ-DI

STUDIO CORONNA
10 299 pz con early AR e AR, USA
donne: >> CDAI, HAQ-DI



↑ **DAS28/CDAI**
↑ **HAQ-DI**

Tengstrand B, et al. J Rheumatol.2004;31:214-22.
Sokka T, et al. Arthritis Res Ther. 2009;11:R7.
Jawaheer D, et al. Arthritis Care Res (Hoboken). 2012;64:1811-8.

Risposta alla terapia-**csDMARD/TNFi**

Uomini:
maggiore percentuale di remissione a 6 mesi -5 anni

	Study	Study design	No. of patients (F)	Mean disease duration	Response outcome measures and gender influence	
csDMARDs	BARFOT	Multicenter observational prospective study	689 (446)	6.2 months	DAS28 remission at 18 and 24 months—more frequent in male (OR 1.557 [CI 1.062–2.283] and 1.713 [CI 1.208–2.431], respectively)	♂
	CORRONA (early RA)	Multicenter observational prospective study	3017 (2263)	0.9 years	CDAI remission at 6 months—more frequent in male (OR 1.38 [CI 1.07–1.78])	♂
	ERAS	Multicenter observational cohort study	704 (462)	< 6 months	DAS28 remission at 3, 4, and 5 years—more frequent in male (OR 2.6 [CI 1.6–4.56])	♂
	CORRONA (established RA)	Multicenter observational prospective study	7282 (5630)	13 years	CDAI remission at 6 months—no sex differences (OR 0.93 [CI 0.75–1.22])	=
	QUEST-RA	Multicenter cross-sectional cohort study	6004 (4755)	11.2 years	DAS28 remission—more frequent in male versus female (30 versus 16.9%, respectively)	♂
bDMARDs - TNFi	BRSBR	Multicenter observational prospective study	2711 (2114)	15 years	DAS28 remission at 6 months—less frequent in female (ETN, OR 0.61 [CI 0.38–0.94]; IFX, OR 0.60 [CI 0.40–0.89])	♂
	GISEA	Multicenter observational cohort study	591 (404)	11.6 years	DAS28 remission at 6 months—more frequent in male (OR 0.659 [CI 0.450–0.965], $p = 0.032$)	♂
	DANBIO (early RA)	Multicenter observational prospective cohort study	476 (328)	1.22 years	EULAR good/moderate response at 48 months—more frequent in male (OR 0.93 [CI 0.31–1.55], $p = 0.003$)	♂
	Hellenic registry	Multicenter observational prospective cohort study	2216 (1297)	Established RA	DAS28 low disease activity and EULAR good response at 12 months—more frequent in male (HR 1.33 [CI 1.02–1.73] and 1.45 [CI 1.10–1.90], respectively)	♂

Favalli EG, et al. Clinical Reviews in Allergy & Immunology 2019; 56:333–45

Retention rate - **bDMARD**

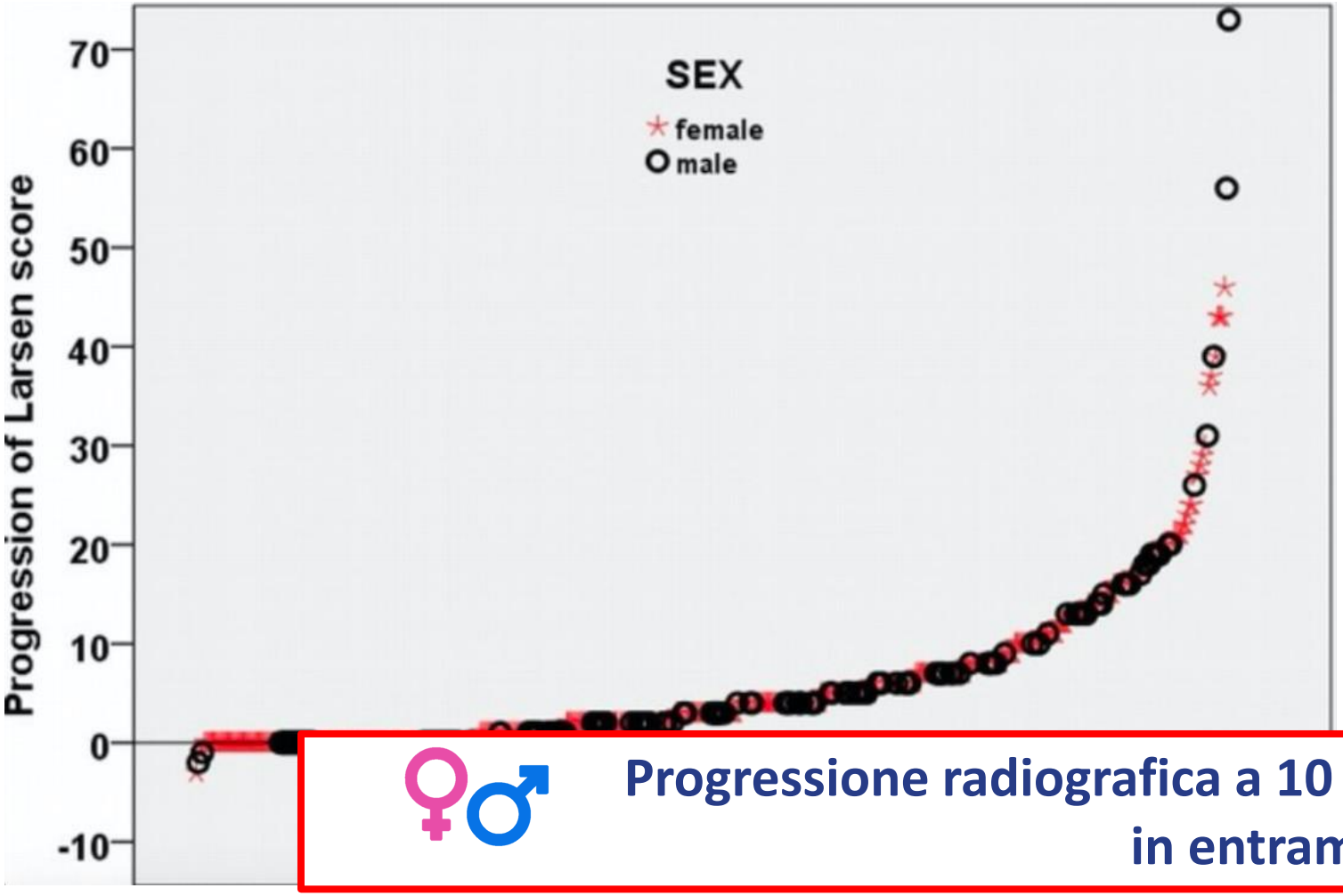
Study	Study design	No. of patients (F)	Mean disease duration	Response outcome measures and gender influence	
LORHEN	Multicenter observational cohort study	1064 (885)	9.44 years	TNFi retention rate at 12, 24, and 36 months—no sex differences (p = n.s.)	=
RADIUS	Multicenter observational cohort study	2418 (1881)	Established RA	TNFi discontinuation—higher in female for IFX (HR 1.24 [CI 1.01–1.51], p = 0.040), ETN (HR 1.3 [CI 0.95–1.78], p = n.s.) and ADA (HR 1.08 [CI 0.70–1.64], p = n.s.)	
GOAREL	Longitudinal prospective observational study	88 (71)	8.1 years	Golimumab 2-year discontinuation risk—higher in female (HR 1.9 [CI 1.182–3.236]; p = 0.009)	
DREAM	Multicenter observational cohort study	1560 (1085)	Established RA	TNFi retention rate at 5 years—no sex differences (p = n.s.)	=
SSATG	Multicenter observational cohort study	1565 (1212)	Established RA	TNFi retention rate at 6 months—no sex differences (p = n.s.)	=
Meta-analysis	Up to February 2014	> 200,000	n.a.	TNFi retention rate at 4 years—no sex differences (HR 1.18 [CI 1.03–1.36], p = n.s.)	=
DANBIO	Multicenter observational cohort study	150 (116)	8.5 years	ABT retention rate at 48 weeks—no sex differences (p = n.s.)	=
ORA	Multicenter observational cohort study	773 (608)	14 years	ABT retention rate at 6 months—no sex differences (p = n.s.)	=
ROC	Multicenter pragmatic open-label randomized clinical study	300 (243)	10 years	ABT retention rate at 52 weeks—no sex differences (HR1.01 [CI 0.85–1.20], p = n.s. including ACPA status; or HR 0.98 [CI 0.84–1.14], p = n.s. including RF status)	=
ACTION	Non-interventional international multicenter cohort study	865 (719)	n.a.	ABT retention rate at 2 years—no sex differences (p = n.s.)	=
BSRBR	National prospective cohort study	646 (497)	14.3 years	RTX retention rate at 6 months—no sex differences (p = n.s.)	=
AIR	Multicenter prospective cohort study	1709 (1321)	16 years	RTX retention rate at 18 months—no sex differences (p = n.s.)	=
Pers et al.	Retrospective cohort study	222 (183)	14 years	TCZ retention rate at 6 months—no sex differences (p = n.s.)	=

minore % *retention rate*

Favalli EG, et al. Clinical Reviews in Allergy & Immunology 2019; 56:333–45

Danno radiografico

Studio longitudinale finlandese, 10 aa di follow-up: **1046** pz **early AR**



Progressione radiografica a 10 aa simile in entrambi i sessi

Aisikainen J et al. Poster EULAR 2016

Ridotta percentuale di remissione: influenza della FM?

Fibromialgia

Italia 2017: **117 pz AR** (77.2% donne)

età media 59 aa (25–83)
durata media di malattia 11.2 aa

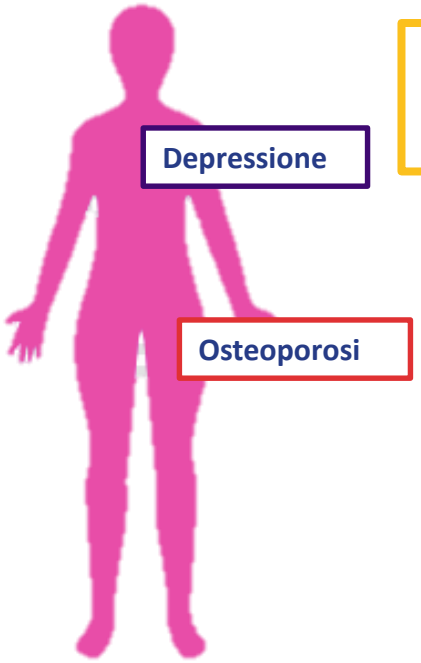
Dopo 6 mesi dall'inizio di csDMARD e/o bDMARD: **remissione SDAI: 24 (20.4%)**

Table 2 Logistic regression analysis with the Simplified Disease Activity Index remission as the dependent variable

Independent variables	Odds ratios	95% CI	*P*
Overall statistics	29.85		
Age (years)	0.22	0.08–0.78	0.423
Gender	0.68	0.29–1.09	0.559
BMI	0.26	0.07–0.80	0.304
Disease duration (years)	0.19	0.01–0.68	0.534
Education (years)	1.98	0.65–3.09	0.513
ACPA (titre)	0.13	0.06–0.42	0.355
RF (titre)	0.40	0.20–0.59	0.323
PDQ	0.59	0.27–0.89	0.978
COMORBILITA' mRDCI	9.59	4.06–14.88	0.000
SDAI	0.64	0.43–0.92	0.357
FIBROMIALGIA WPI + SS	9.14	4.95–13.66	0.000
SF-36- SALUTE MENTALE SF36-MCS	2.35	1.02–3.97	0.008
SF36-PCS	1.29	0.64–2.07	0.887

Salaffi F, et al. Rheumatol Int.2017;37:2035-42.

HAQ- Influenza delle comorbilità



Gender-associated comorbidities in rheumatoid arthritis and their impact on outcome: data from **GENIRA**

studio *cross-sectional* Spagna 2017: **140 pz AR** (70 donne e 70 uomini)

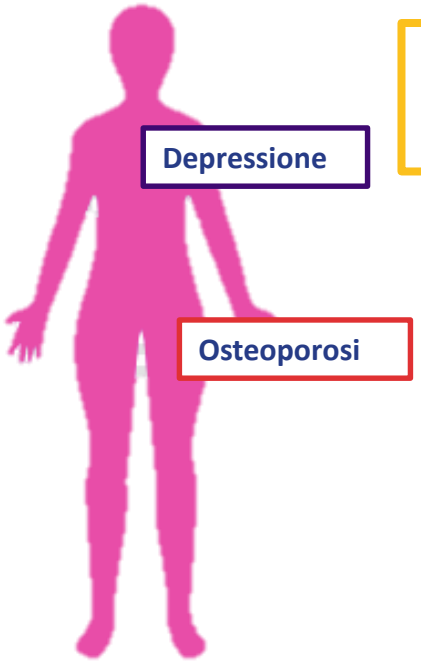
comparabili per età e durata di malattia

Table 3 SF-36 summary measures and sub-scales and M-HAQ scores as a function of gender

	Women, $n = 70$	Men, $n = 70$	p value
SF-36			
Physical functioning	57.7 (±22.1)	67.3 (±22.7)	0.01
Role physical	66.0 (±25.7)	68.4 (±25.5)	0.50
Bodily pain	52.0 (±27.1)	60.0 (±27.3)	0.08
General health	41.3 (±21.7)	50.0 (±24.3)	0.02
Vitality	55.2 (±20.6)	61.2 (±19.3)	0.07
Social functioning	73.7 (±26.7)	74.6 (±23.9)	0.80
Role emotional	77.7 (±26.3)	79.1 (±24.7)	0.70
Mental health	63.7 (±22.0)	71.8 (±21.1)	0.02
Physical component summary score	39.3 (±8.9)	42.4 (±9.3)	0.04
Mental component summary score	47.6 (±12.2)	49.5 (±10.0)	0.31
M-HAQ	0.89 (±2.6)	0.22 (±0.9)	0.04

Aurrecoechea E, et al. Rheumatol Int. 2017;37:479-485.

HAQ- Influenza delle comorbilità



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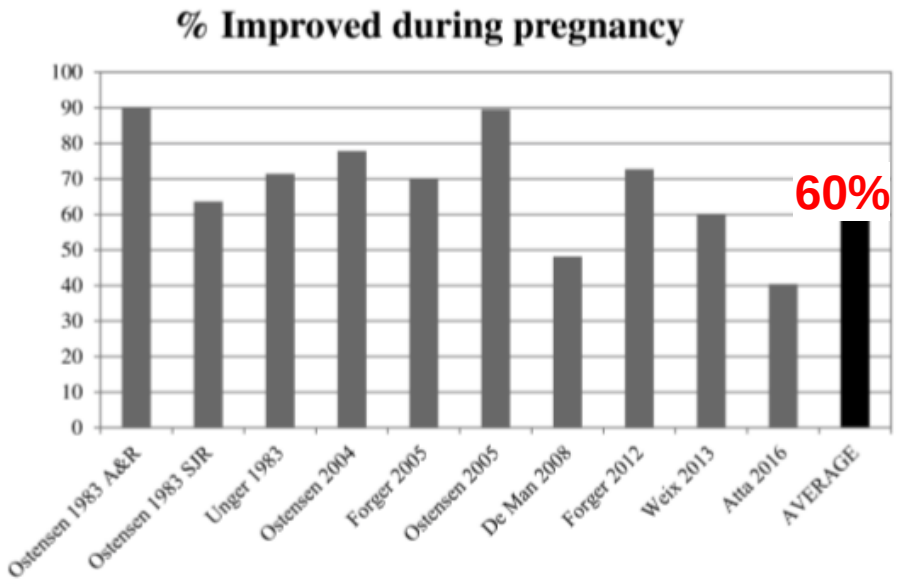
Role physical	66.0 (±25.7)	68.4 (±25.5)	0.50	
Bodily pain	52.0 (±27.1)	60.0 (±27.3)	0.08	
General health	41.3 (±21.7)	50.0 (±24.3)	0.02	**depressione**
Vitality	55.2 (±20.6)	61.2 (±19.3)	0.07	
Social functioning	73.7 (±26.7)	74.6 (±23.9)	0.80	
Role emotional	77.7 (±26.3)	79.1 (±24.7)	0.70	
Mental health	63.7 (±22.0)	71.8 (±21.1)	0.02	**depressione**
Physical component summary score	39.3 (±8.9)	42.4 (±9.3)	0.04	**OP**
Mental component summary score	47.6 (±12.2)	49.5 (±10.0)	0.31	
M-HAQ	0.89 (±2.6)	0.22 (±0.9)	0.04	**depressione, OP**

Fattori associati a peggiori punteggi all'HAQ e SF-36:

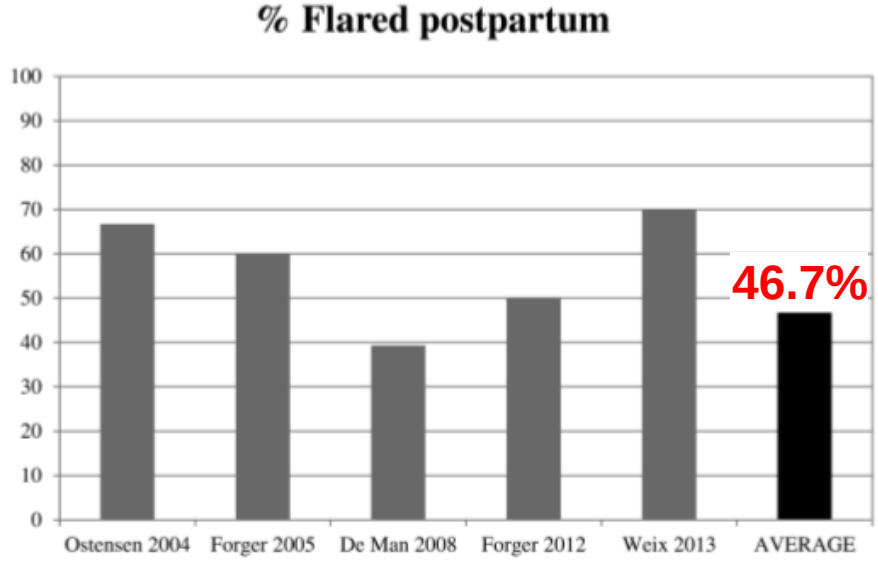
Aurrecoechea E, et al. Rheumatol Int. 2017;37:479-485.

AR: **in gravidanza e post-partum?**

AR: in gravidanza e post-partum?



METANALISI:
10 studi: 237 pz in gravidanza,
135 pz post-partum



60%: malattia migliora in gravidanza
46.7%: riacutizzazioni nel post-partum

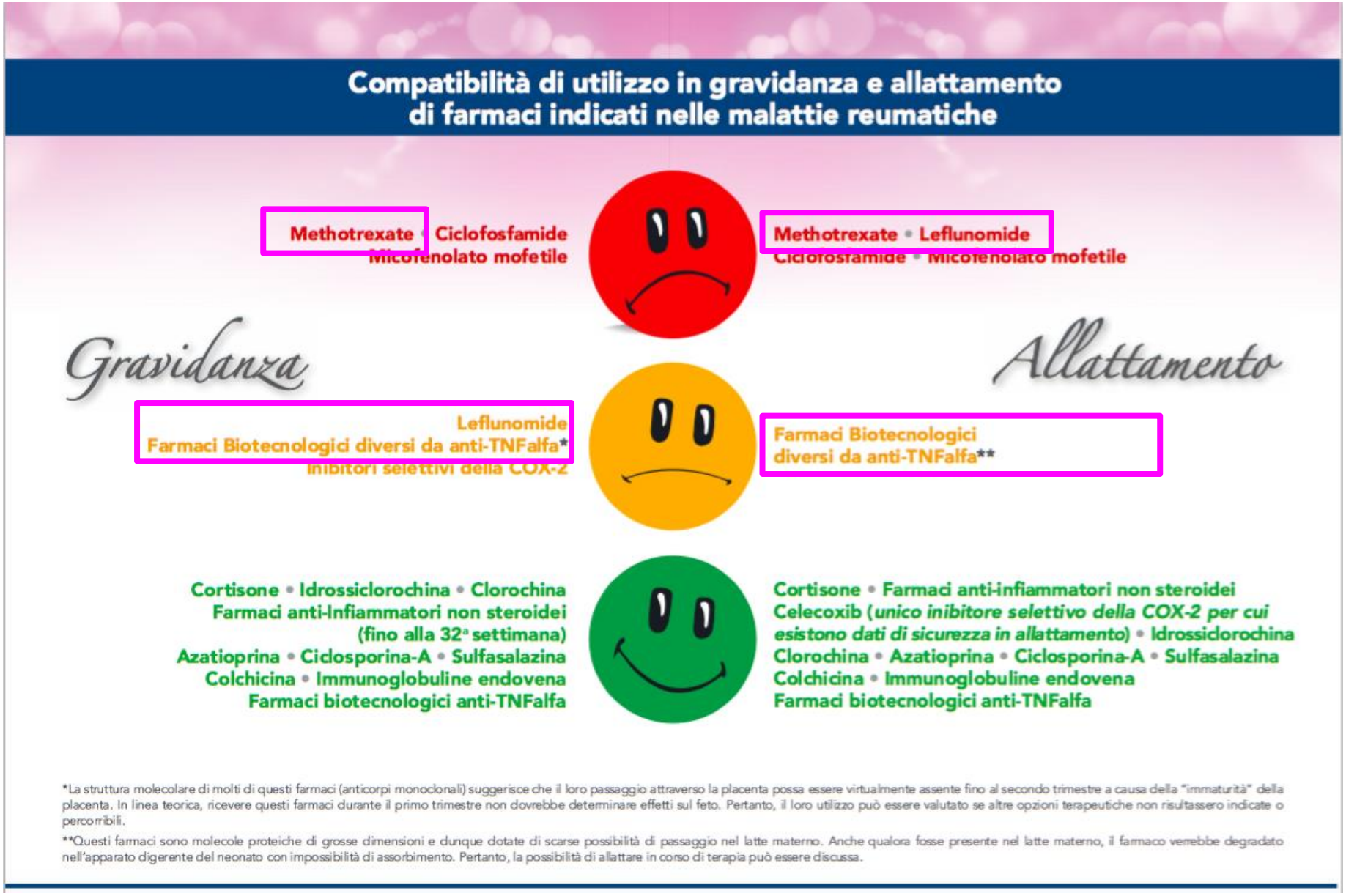
Pz ACPA e/FR +:
minore percentuale di miglioramento
de Man YA et al. 2010

POSSIBILI SPIEGAZIONI:

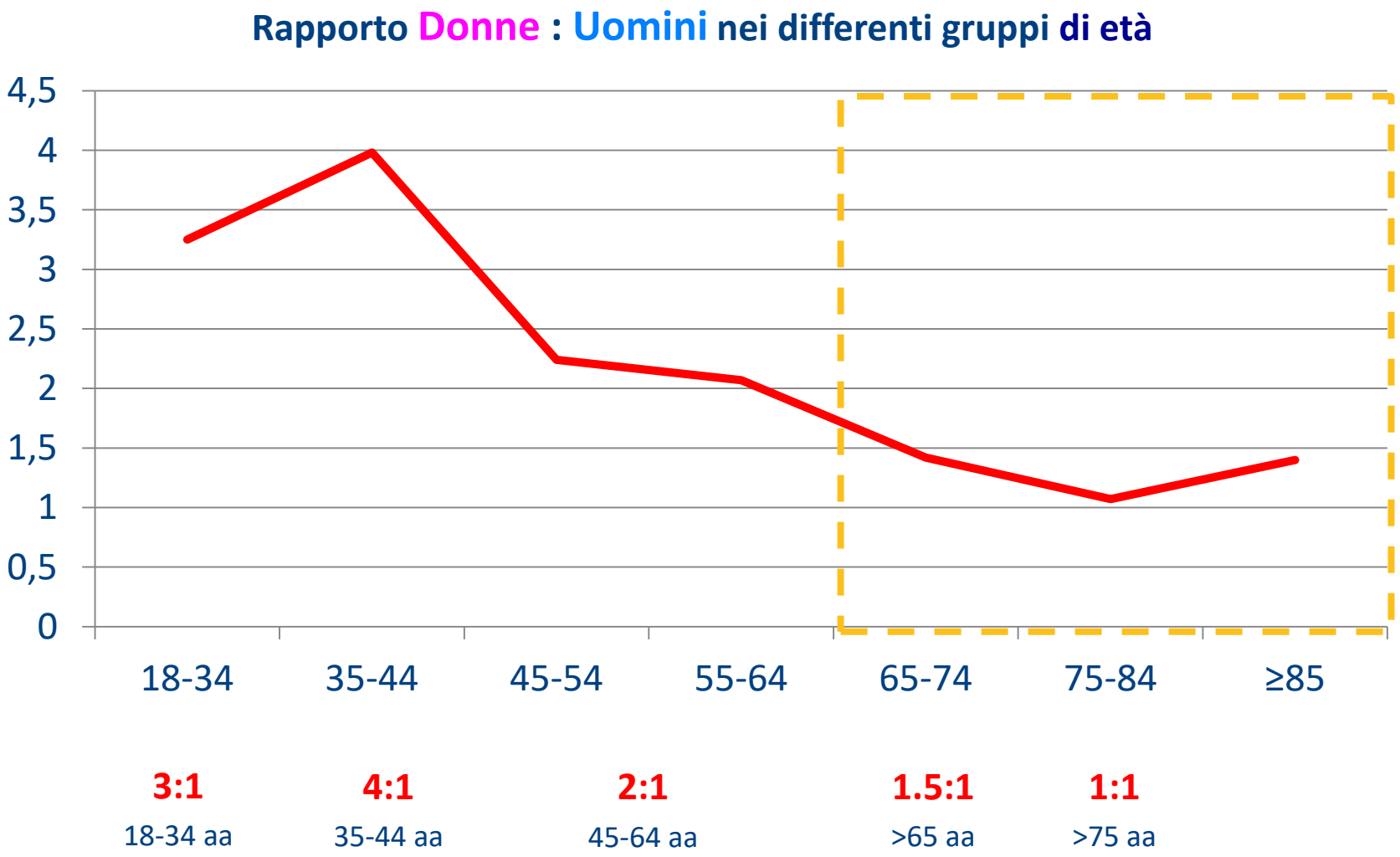
1. Misurazioni soggettive *vs* strumenti oggettivi
2. Diverse popolazioni
3. Inclusione di pz con malattia più aggressiva?

Jethwa H et al, J Rheumatol 2019; 46:245-50

Terapia – età fertile

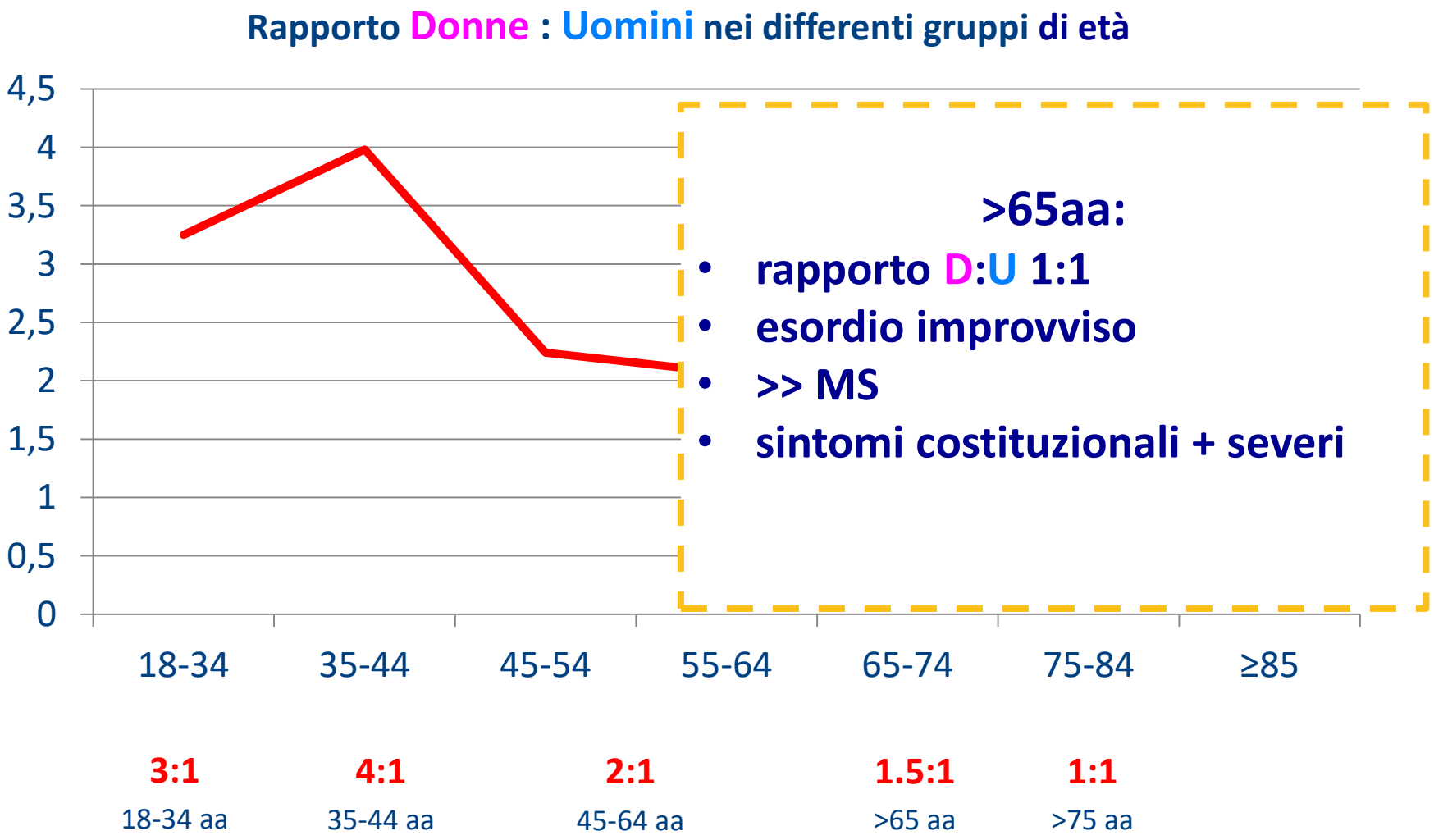


Terapia dopo i 65 anni



Lahaye C, et al. Rheumatology (Oxford). 2019;58:748-64..

Terapia dopo i 65 anni



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Terapia dopo i 65 anni

Registro americano CORRONA: **9381** pz con **EORA** *vs* **2101** pz con **YORA**

Table 2 Characteristics of patients by comorbidities

	Age at onset of RA						
	≥60 years			40–60 years			
	%	Freq	n	%	Freq	n	p Value
Sex (female)	69.3	1440	2077	71.9	1506	2094	0.072
Use of methotrexate	63.9	1342	2101	59.6	1253	2101	0.005
Use of biological agent	25.0	525	2101	33.1	696	2101	0.000
Use of >1 DMARD	30.9	649	2101	40.5	851	2101	0.000
Use of prednisone	41.0	837	2039	37.64	778	2067	0.025
Hx of peptic ulcer disease	6.4	135	2101	5.6	118	2101	0.299
Hx of CAD	8.9	187	2101	3.7	77	2101	0.000
Hx of GERD	16.8	353	2101	16.7	352	2101	1.000
Hx of MI	5.9	125	2101	3.0	63	2101	0.000
Hx of hypertension	41.4	870	2101	27.4	575	2101	0.000
Hx of stroke	3.8	79	2101	1.4	30	2101	0.000
Hx of CVD*	14.4	303	2101	6.6	138	2101	0.000

CAD, coronary artery disease; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatic drug; Freq, frequency; GERD, gastroesophageal reflux disease; Hx, history; MI, myocardial infarction; RA, rheumatoid arthritis.
*CAD, MI, stroke combined.

<<MTX
<<bDMARD
<< DMARD>1
>> GCs
COMORBILITA' CV

Tutuncu Z, et al. Ann Rheum Dis 2006;65:1226–9.

Terapia dopo i 65 anni:

INFEZIONI

NEOPLASIE

CV

OSTEOPOROSI

POP GENERALE >65 aa

⇧ ⇧ ⇧ ⇧

Lahaye C, et al.Rheumatology (Oxford). 2019;58:748-64.

Terapia dopo i 65 anni:

INFEZIONI

NEOPLASIE

CV

OSTEOPOROSI

POP GENERALE >65 aa	⇧	⇧	⇧	⇧
AR		⇧	⇧	⇧

Lahaye C, et al.Rheumatology (Oxford). 2019;58:748-64.

Terapia dopo i 65 anni:

INFEZIONI

NEOPLASIE

CV

OSTEOPOROSI

POP GENERALE >65 aa

- **multi-comorbilità**
  - IRC (MTX)
  - Ipertensione arteriosa (LEF)
  - DM (> rischio di infezioni)
- **terapia polifarmacologica** (rischio interazioni farmacologiche)

AR

Lahaye C, et al.Rheumatology (Oxford). 2019;58:748-64.

bDMARD >65aa e rischio di infezioni

183 pz con AR >65 aa
3 anni di follow-up:

bDMARD 64 *vs* non-bDMARD 119

tasso di incidenza di infezioni severe
8.0 (95% IC 4.7–13.5) e 6.3 (95% IC 4.1–9.5) eventi per 100 persone-anni di follow-up, *P* = 0.78

Risk factors for serious infections in biologics group of elderly RA patients

	Serious infection (+) (*n* = 10)	(−) (*n* = 54)	*P*
Age (years, mean ± SD)	74.5 ± 4.4	73.6 ± 5.3	0.63
Female, *n* (%)	7 (70.0%)	43 (79.6%)	0.49
Disease duration (years, mean ± SD)	15.4 ± 9.4	12.2 ± 9.7	0.34
Observation period (months), median (IQR)	35 (21–36)	36 (27–36)	0.60
RF positive, *n* (%)	9 (90.0%)	48 (88.9%)	0.92
ESR 60 (mm, mean ± SD)	69.2 ± 43.7	59.2 ± 31.2	0.40
CRP (mg/L, mean ± SD)	29.3 ± 24.7	27.7 ± 36.0	0.89
Steinbrocker stage (I + II/III + IV)	3/7	28/26	0.20
Comorbidities, *n* (%)			
Coexisting lung disease	3 (30.0%)	18 (33.3%)	0.83
Diabetes mellitus	0 (0%)	3 (5.5%)	0.44
Medications, *n* (%)			
Methotrexate	8 (80.0%)	43 (79.6%)	0.98
Other DMARDs	2 (20.0%)	19 (35.2%)	0.34
PSL (mg/day)	4.7 ± 3.2	1.3 ± 2.0	<0.001
PSL, any dose (%)	9 (90.0%)	19 (35.2%)	0.001
PSL ≧5 mg/day	6 (60.0%)	6 (11.1%)	<0.001
Biologics, *n* (%)			
TNF inhibitors	4 (40.0%)	32 (59.2%)	0.10
Tocilizumab	3 (30.0%)	3 (5.6%)	

Kawashima H, et al. Rheumatol Int. 2017;37:369-76.

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GCs: aumentato rischio di **OSTEOPOROSI, DM**

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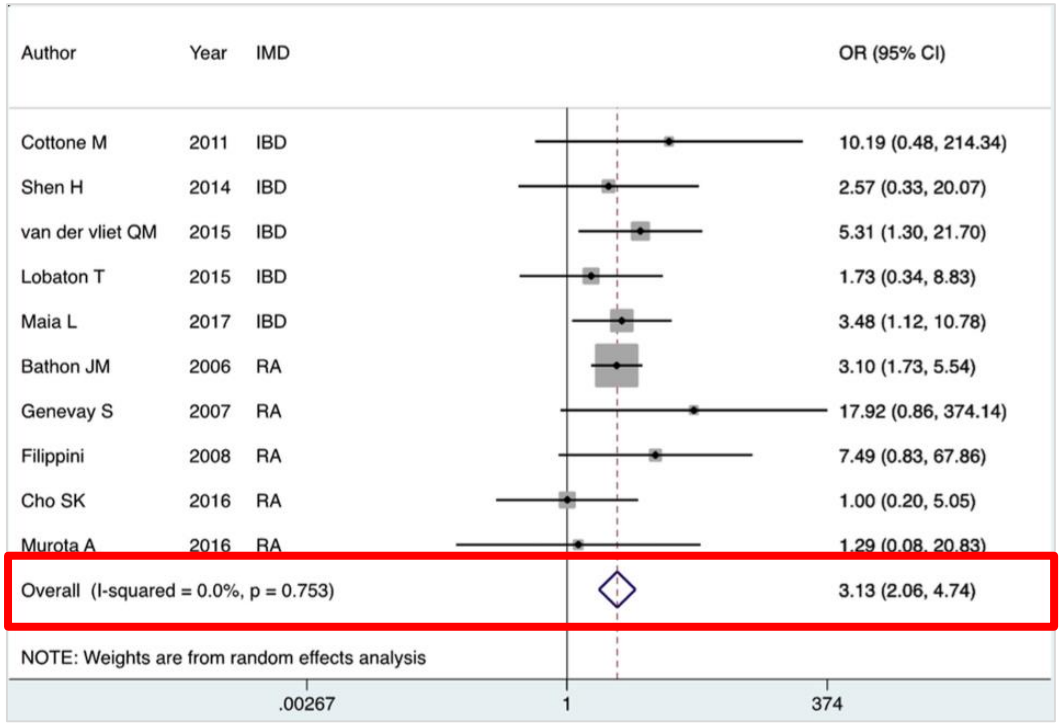
Medications, *n* (%)			
Methotrexate	8 (80.0%)	43 (79.6%)	0.98
Other DMARDs	2 (20.0%)	19 (35.2%)	0.34
PSL (mg/day)	4.7 ± 3.2	1.3 ± 2.0	<0.001
PSL, any dose (%)	9 (90.0%)	19 (35.2%)	0.001
PSL ≧5 mg/day	6 (60.0%)	6 (11.1%)	<0.001
Biologics, *n* (%)			
TNF inhibitors	4 (40.0%)	32 (59.2%)	0.10
Tocilizumab	3 (30.0%)	3 (5.6%)	

Kawashima H, et al. Rheumatol Int. 2017;37:369-76.

bDMARD >65aa e rischio neoplasie

Older biologic users *vs* younger biologic users



Borden NZ & Ananthakrishnan AN. Clin Gastroenterol Hepatol. 2019;17:1736-43.

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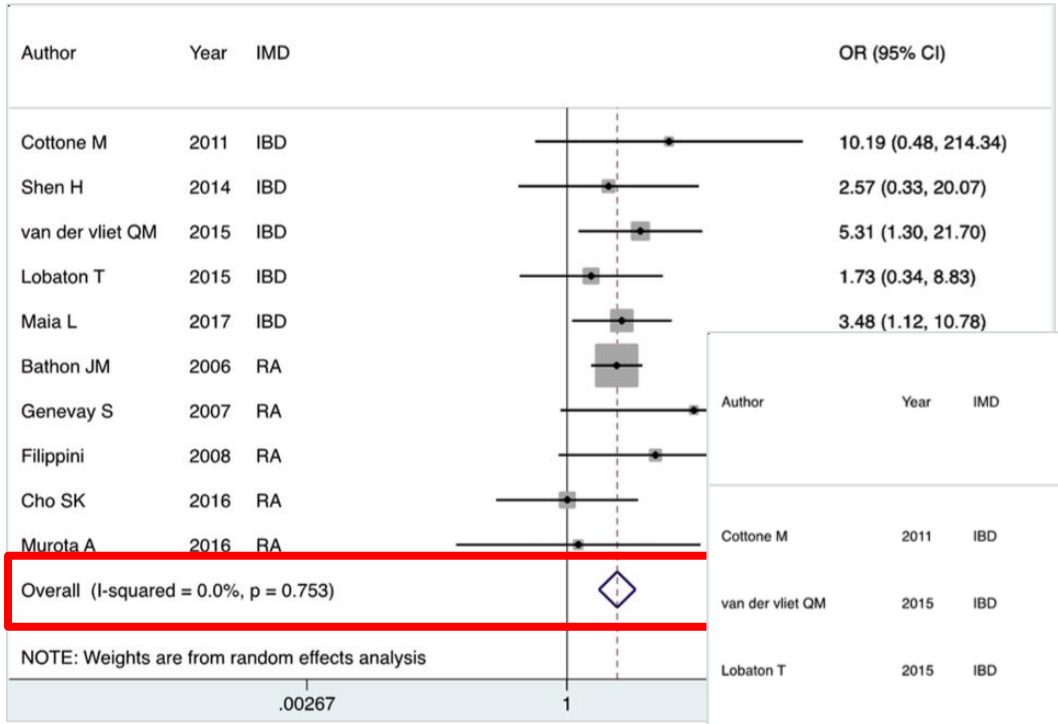
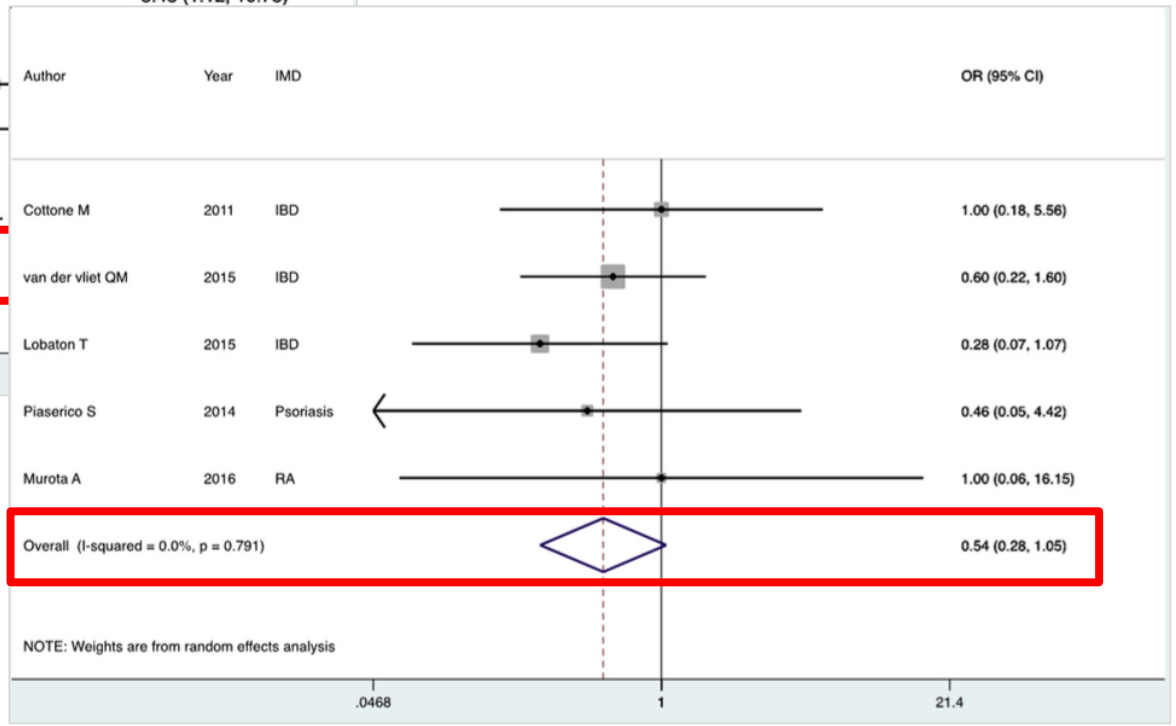


Older biologic users *vs* older nonusers



Borden NZ & Ananthakrishnan AN. Clin Gastroenterol Hepatol. 2019;17:1736-43.

Conclusioni

- Il **genere** influisce su diversi aspetti dell'AR, come l'epidemiologia, la presentazione della malattia e il trattamento in momenti particolari come la gravidanza e l'allattamento.

- La gestione dei pazienti con **età** superiore a 65 anni richiede un'attenta valutazione dei maggiori rischi legati a questa età (infezioni, neoplasie, osteoporosi) e delle altre comorbilità associate.

Tutti questi aspetti

dovrebbero essere sempre in considerazione

nella gestione individualizzata dei pazienti

11th International Conference on Reproduction, Pregnancy and Rheumatic diseases

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AIM GROUP INTERNATIONAL

AIM Group International - Milan Office
Via G. Ripamonti, 129- 20141 Milan, Italy
Ph. +39 02 566011 - Fax +39 02 70048578
info@rheumapreg2020.com
www.rheumapreg2020.com