

# Reazioni Avverse a Farmaci: come prevederle e prevenirle?

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# Reazioni Avverse a Farmaci (ADR)

Le reazioni avverse a farmaci (ADR) rappresentano un importante problema medico ed economico, in quanto determinano:

- 3-5% di tutti i ricoveri ospedalieri;
- 5-10% dei costi ospedalieri;
- sostanziale incremento di mortalità.

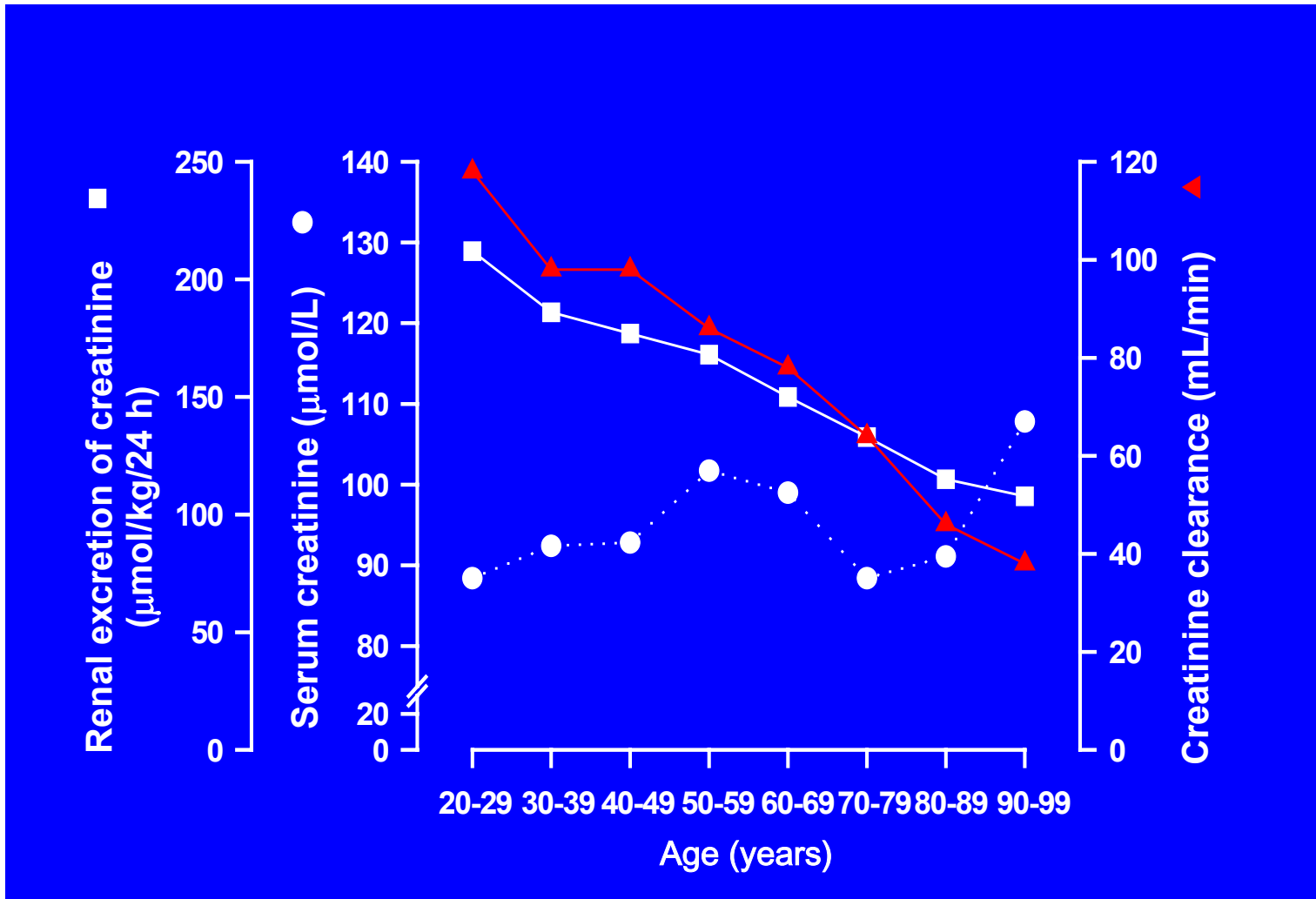
# ADR e anziani

Gli anziani sono particolarmente a rischio di ADR perché:

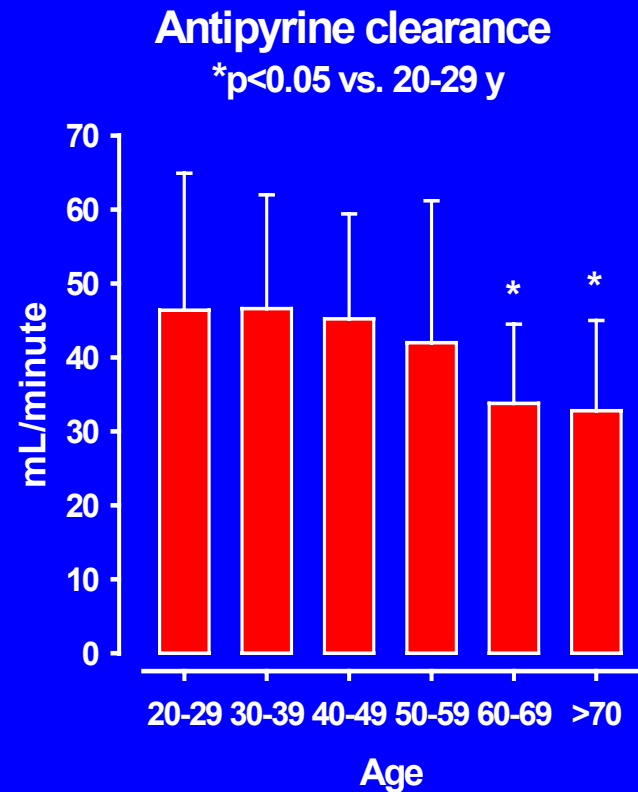
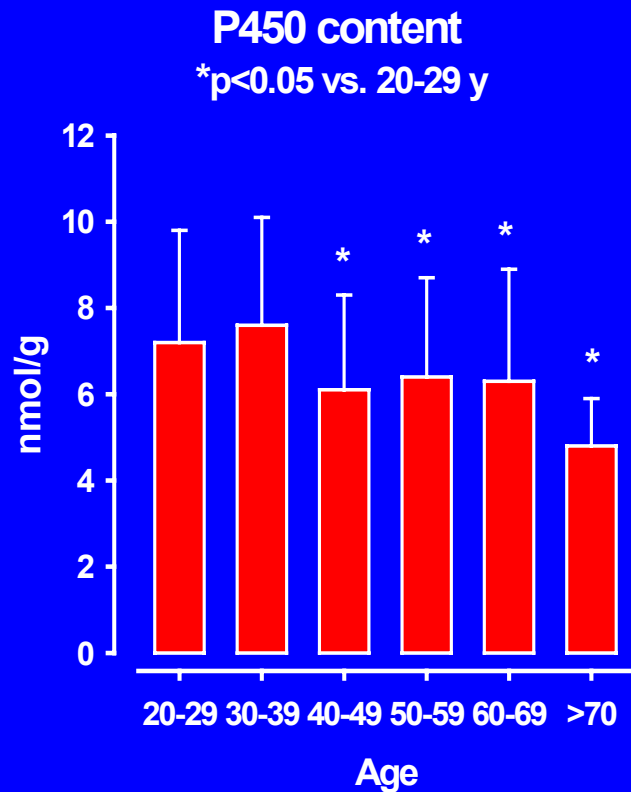
1. cambiamenti farmacocinetica e farmacodinamica;



# Funzione renale ed età



# Effect of age on CYP450 content and activity



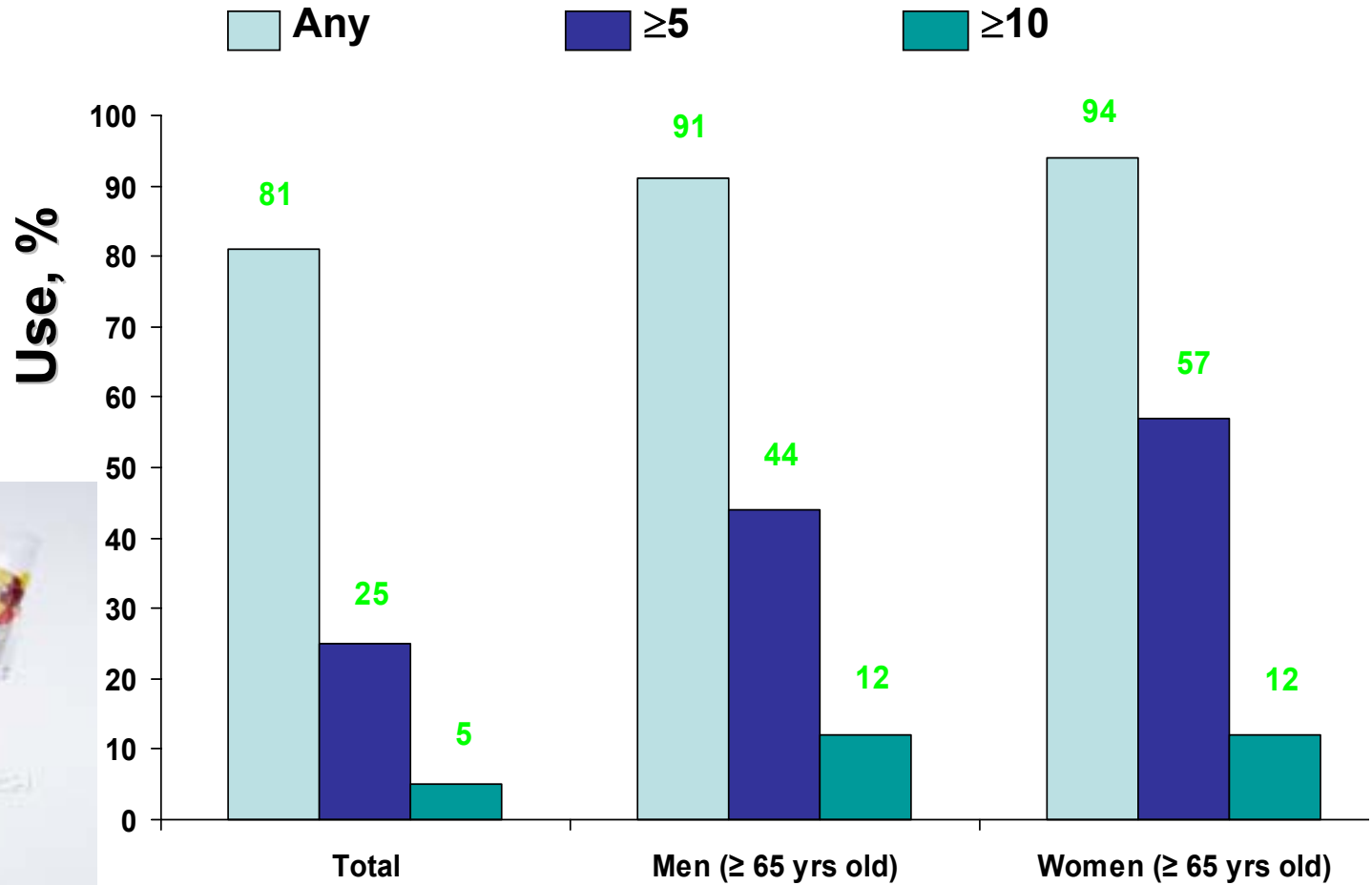
# ADR e anziani

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1. cambiamenti farmacocinetica e farmacodinamica;
2. complessi regimi farmacologici;



# Use of Medications



Kaufman, JAMA 2002

# ADR e anziani

Gli anziani sono particolarmente a rischio di ADR perché:

1. cambiamenti farmacocinetica e farmacodinamica;
2. complessi regimi farmacologici;
3. ridotta capacità di gestire i farmaci.



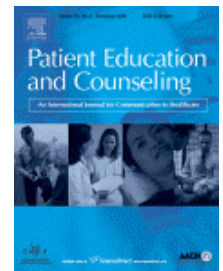


# Medication management by age

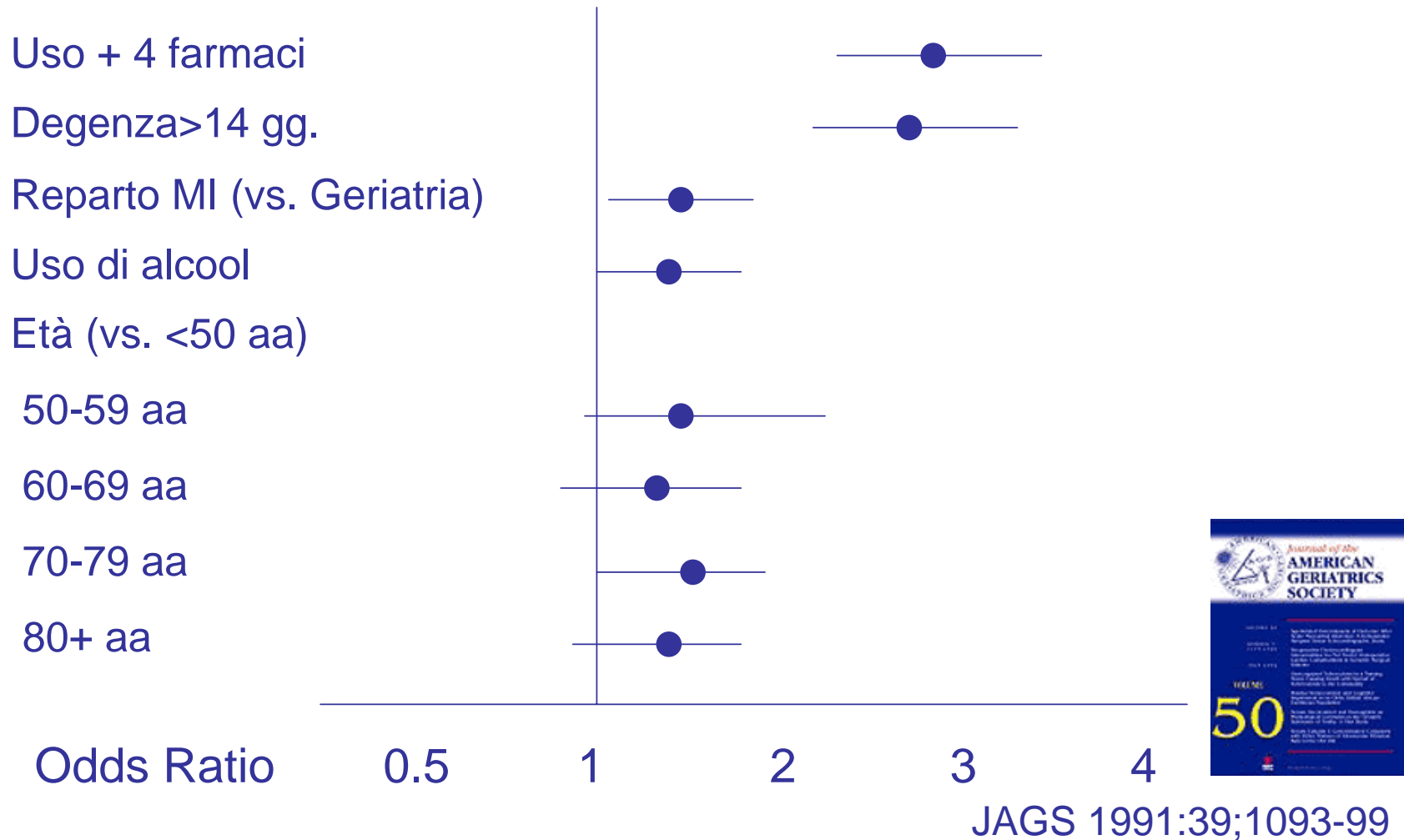
	Age groups		
	77-79	80-84	85+
<b>Tests</b>			
<u>Open bottle</u> ( <i>n</i> = 487)	<u>8.3</u>	<u>10.9</u>	<u>24.8</u>
<u>Read instructions</u> ( <i>n</i> = 489)	<u>0.8</u>	<u>6.9</u>	<u>20.1</u>
<u>Understand instructions</u> ( <i>n</i> = 423)	<u>23.6</u>	<u>31.5</u>	<u>38.4</u>
Calculate number of days ( <i>n</i> = 441)	43.0	44.5	56.6
Calculate change ( <i>n</i> = 491)	13.6	26.2	39.4
Did not pass all tests	57.6	61.4	79.9



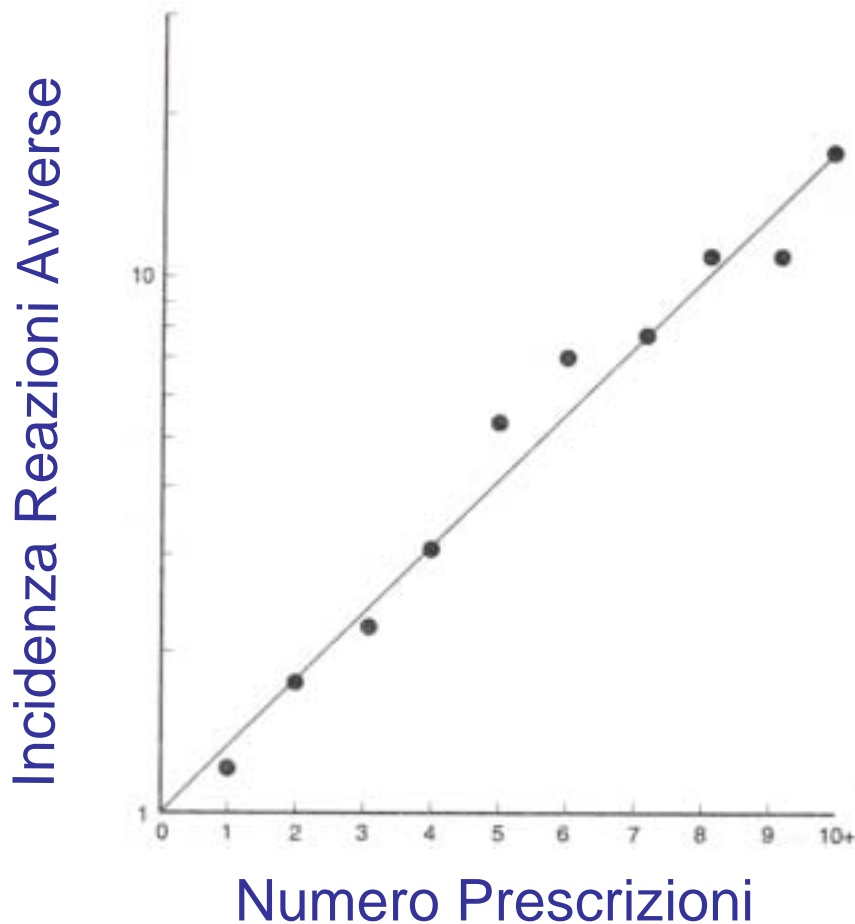
Beckmen A Patient Educ Couns. 2005



# Fattori di rischio per Reazioni Avverse da Farmaci in pazienti ospedalizzati



# Numero prescrizioni e ADR



Considerando globalmente tutte le ADR, non è tanto l'età quanto il numero di prescrizioni ad essere correlato con il rischio di ADR.

Carbonin PU et al. JAGS 1991  
Ripreso da 'Merck Manual of Geriatrics'

# Predittori di ammissione per ADR

	Tutte ADRs (n=964)	ADRs severe (n=187)
	OR (95% CI)	OR (95% CI)
Età (anni)		
< 65	1	1
65-79	1.05 (0.90-1.23)	1.50 (1.00-2.23)
≥ 80	0.91 (0.76-1.09)	1.53 (1.01-2.33)
Sesso femminile	1.30 (1.10-1.54)	1.35 (0.91-2.00)
Uso di alcolici	1.39 (1.20-1.60)	0.92 (0.67-1.25)
Fumo	0.96 (0.81-1.14)	1.32 (0.90-1.95)
Indice di Charlson (1 punto)	0.99 (0.95-1.03)	1.12 (1.05-1.20)
N di farmaci (1 farmaco)	1.24 (1.20-1.27)	1.18 (1.11-1.25)



# Development and Validation of a Score to Identify older Adults at Risk of ADR

‘... study aimed to develop and validate among in-hospital older adults a practical, efficient and simple method to identify pts. at increased risk of an ADR.’

‘This approach ... may be useful to identify a population that can benefit from interventions aimed to reduce drug related illness.’



# Development and Validation of a Score to Identify older Adults at Risk of ADR

Phase I: an ADR risk score will be developed, based on data available in the medical literature and on secondary analysis of the GIFA database;

# GIFA database

- Dati sul oltre 32.000 pazienti ammessi in centri ospedalieri e universitari in Italia tra il 1988 ed il 1998
- Oltre 300.000 prescrizioni intraospedaliere
- Oltre 4000 reazioni avverse valutate con l'algoritmo di Naranjo
- Valutazione stato funzionale, cognitivo, parametri laboratoristici.



# Variables in the score

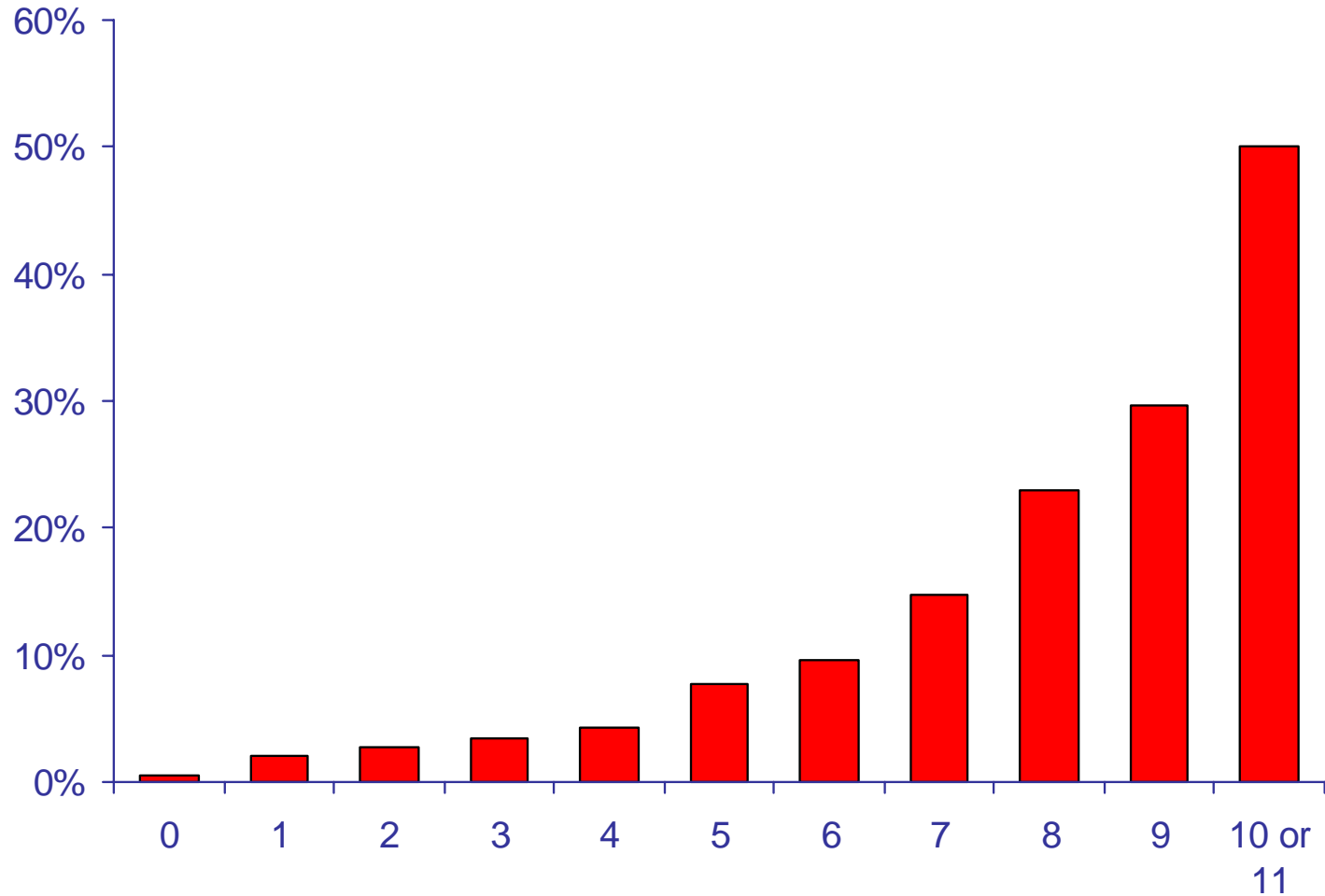
	OR	Score (points)
Female gender	1.33	1
4 or more comorbid conditions	1.23	1
Congestive heart failure	1.54	1
Liver disease	1.64	1
Use of 6 or more drugs	1.78	1
Previous ADR	2.44	1
Use of anticoagulants	1.44	1
Use of NSAIDS	1.71	1
Use of drugs with NTI	1.30	1
Use of vasodilator	1.62	1
Use of beta blockers	1.99	1
Use of ACE-I or ARB	1.44	1
Use of benzodiazepines	1.23	1



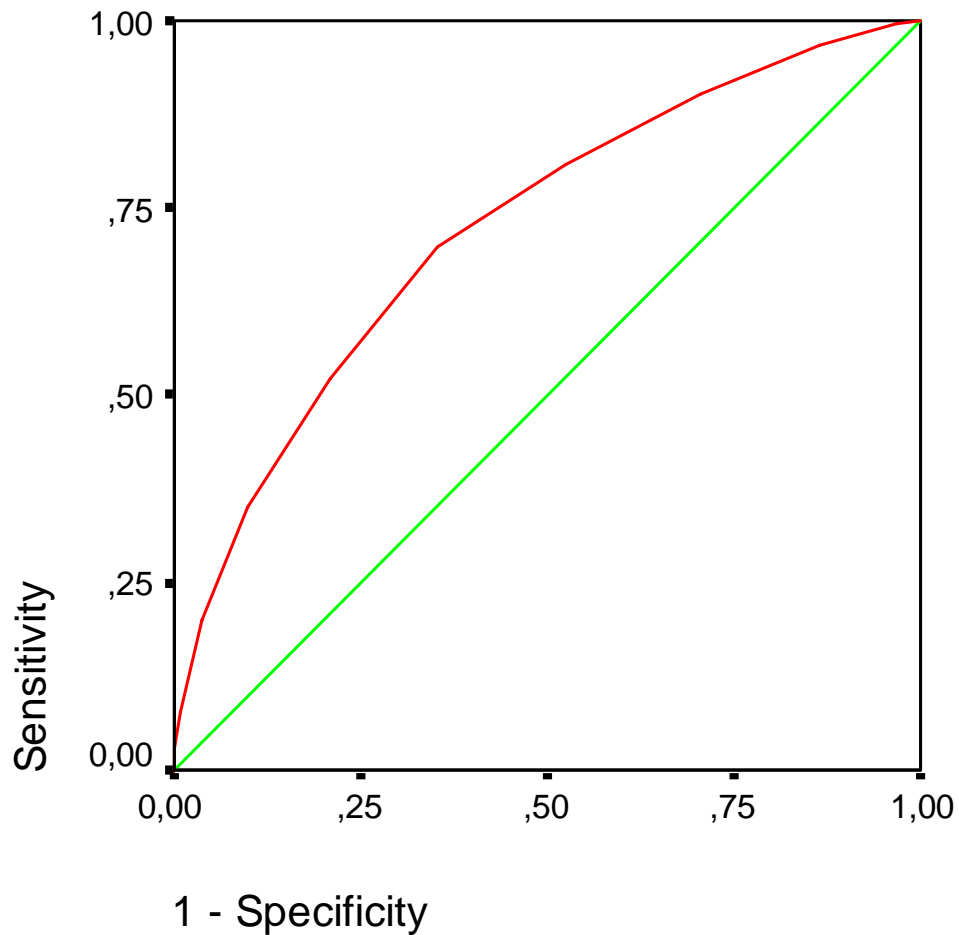




# ADR and risk score



# Predictive ability of risk score



AUC=0.73 (0.70-0.75)





# Development and Validation of a Score to Identify older Adults at Risk of ADR

Phase I: an ADR risk score will be developed, based on data available in the medical literature and on secondary analysis of the GIFA database;

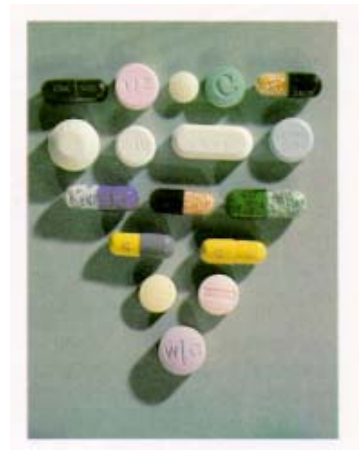
Phase II: the score will be validated among in-hospital older adults in Europe  
→ **ongoing.**

# Prevenzione?

## Medication review

Rivalutazione dei regimi terapeutici (spesso svolta da farmacisti), volta a:

1. valutare appropriatezza della terapia farmacologica;
2. ottimizzare i regimi farmacologici;
3. incrementare compliance.



# Does home based medication review keep older people out of hospital? The HOMER RCT

No meds  
review

Meds  
review

## Risk Ratios:

Ospedalizzazione	1	1.30 (1.07-1.58)
Morte	1	0.75 (0.52-1.10)
Ricovero in RSA	1	1.00 (0.74-1.35)

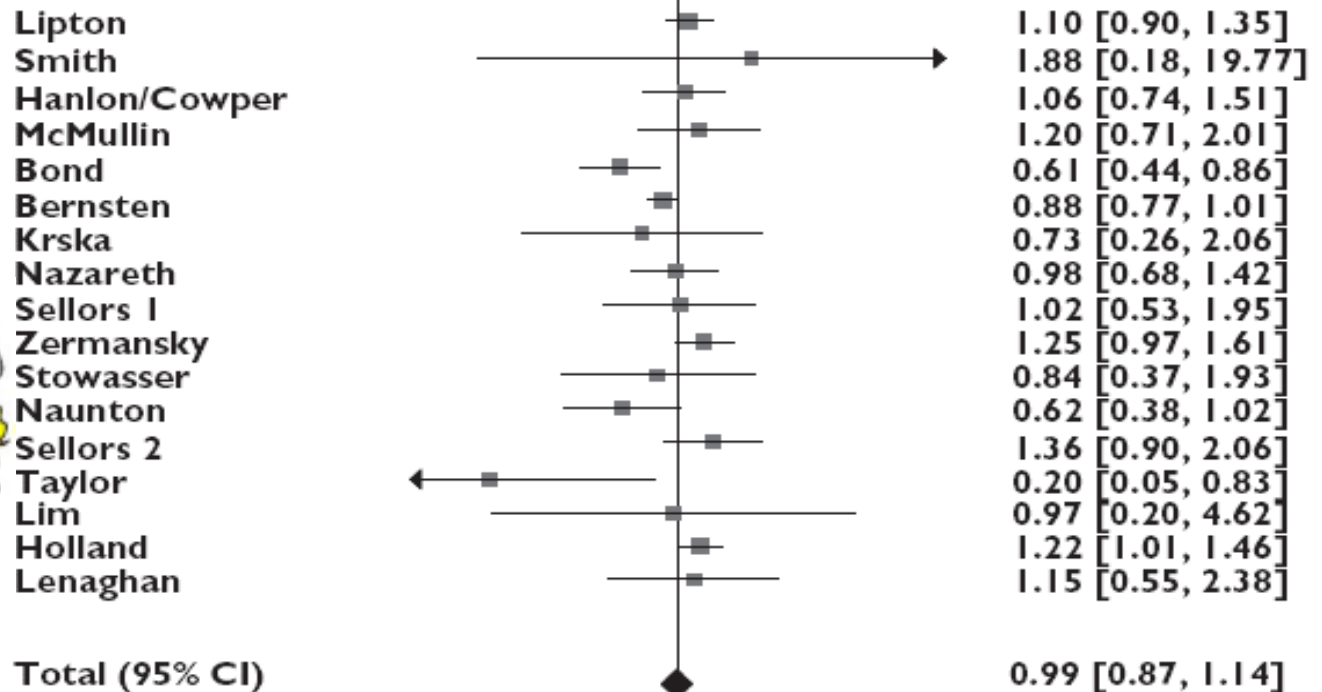
# Medication review ospedalizzazione



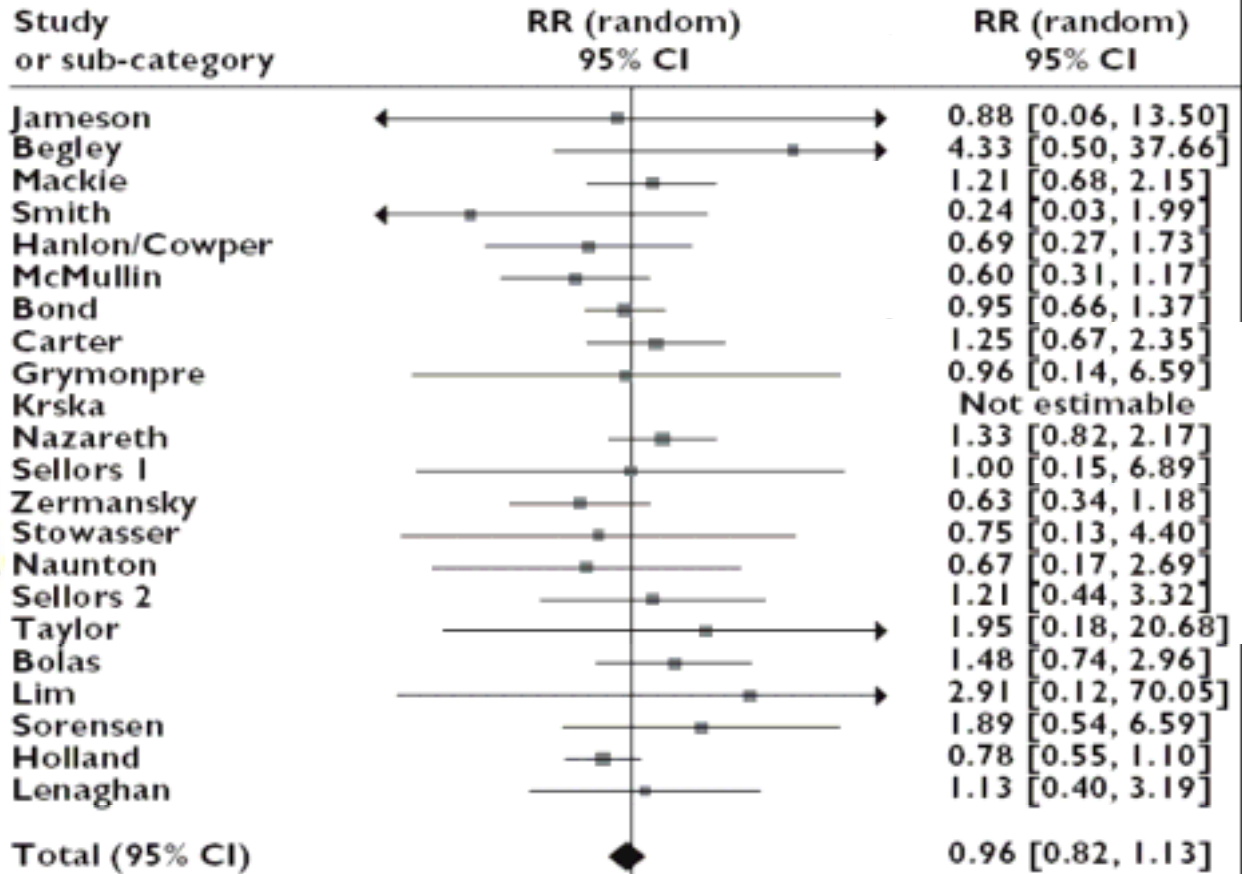
Study  
or sub-category

RR (random)  
95% CI

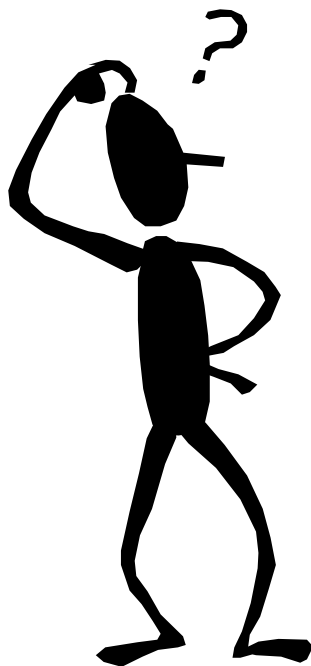
RR (random)  
95% CI



# Medication review mortalità



# Trattamento in base alle linee guida di una paziente di 79 anni con ipertensione, diabete mellito, osteoporosi, osteoartrosi e BPCO



Time	Medications†	Other
7:00 AM	Ipratropium metered dose inhaler 70 mg/wk of alendronate	Check feet Sit upright for 30 min on day when alendronate is taken Check blood sugar
8:00 AM	500 mg of calcium and 200 IU of vitamin D 12.5 mg of hydrochlorothiazide 40 mg of lisinopril 10 mg of glyburide 81 mg of aspirin 850 mg of metformin 250 mg of naproxen 20 mg of omeprazole	Eat breakfast 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
12:00 PM		Eat lunch 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
1:00 PM	Ipratropium metered dose inhaler 500 mg of calcium and 200 IU of vitamin D	
7:00 PM	Ipratropium metered dose inhaler 850 mg of metformin 500 mg of calcium and 200 IU of vitamin D 40 mg of lovastatin 250 mg of naproxen	Eat dinner 2.4 g/d of sodium 90 mmol/d of potassium Low intake of dietary saturated fat and cholesterol Adequate intake of magnesium and calcium Medical nutrition therapy for diabetes‡ DASH‡
11:00 PM	Ipratropium metered dose inhaler	
As needed	Albuterol metered dose inhaler	

Boyd, C. M. et al. JAMA 2005;294:716-724.

JAMA



# Potenziabili interazioni farmacologiche

Type of Disease	Medications With Potential Interactions	Type of Interaction		
		Medication and Other Disease	Medications for Different Diseases	Medication and Food
Hypertension	Hydrochlorothiazide, lisinopril	Diabetes: diuretics increase serum glucose and lipids*	Diabetes medications: hydrochlorothiazide may decrease effectiveness of glyburide	NA
Diabetes	Glyburide, metformin, aspirin, and atorvastatin	NA	Osteoarthritis medications: NSAIDs plus aspirin increase risk of bleeding Diabetes medications: glyburide plus aspirin may increase the risk of hypoglycemia; aspirin may decrease effectiveness of lisinopril	Aspirin plus alcohol: increased risk of gastrointestinal tract bleeding Atorvastatin plus grapefruit juice: muscle pain, weakness Glyburide plus alcohol: low blood sugar, flushing, rapid breathing, tachycardia Metformin plus alcohol: extreme weakness and heavy breathing Metformin plus any type of food: medication absorption decreased
Osteoarthritis	NSAIDs	Hypertension: NSAIDs: raise blood pressure†; NSAIDs plus hypertension increase risk of renal failure	Diabetes medications: NSAIDs in combination with aspirin increase risk of bleeding Hypertension medications: NSAIDs decrease efficacy of diuretics	NA
Osteoporosis	Calcium, alendronate	NA	Diabetes medications: calcium may decrease efficacy of aspirin; aspirin plus alendronate can cause upset stomach Osteoporosis medications: calcium may lower serum alendronate level	Alendronate plus calcium: take on empty stomach (>2 h from last meal) Alendronate: avoid orange juice Calcium plus oxalic acid (spinach and rhubarb) or phytic (bran and whole cereals): eating these foods may decrease amount of calcium absorbed (>2 h from last meal)
Chronic obstructive pulmonary disease	Short-acting $\beta$ -agonists	NA	NA	NA

Abbreviations: NA, no interaction is known; NSAIDs, nonsteroidal anti-inflammatory drugs.

\*Thiazide-type diuretics may worsen hyperglycemia, but effect thought to be small and not associated with increased incidence of cardiovascular events.

†This interaction is noted to be particularly relevant for individuals with diabetes; no recommendation for treatment is given.

# Prevenzione ADR

1. Dare una priorità patologie e relativo trattamento malgrado la mancanza di regole precise.
2. Considerare le caratteristiche del paziente, come la sua aspettativa di vita.
3. Nella scelta tra decisioni terapeutiche, primo obiettivo deve essere la qualità della vita



# Guidelines for Improving the Care of the Older Persons With Diabetes

1. Estimate the patient's approximate **life expectancy**
2. Help the patient to **prioritize** treatment options
3. For older adults with DM and an absence of significant **medical illness or disability**, intensive management have the greatest chance of benefit within 2 to 3 years
4. Consider intensive glycemic targets for older adults with a life expectancy of longer than 8 years and a low risk of hypoglycemia
5. Frail older adults are more likely to benefit from **symptom management** and strategies to improve quality of life

# Effects of Geriatric Evaluation and Management on ADR

**Aim:** To determine if geriatric evaluation and management, as compared with usual care, reduces ADR and suboptimal prescribing in frail elderly patients.

**Intervention:** geriatric teams evaluated and managed patients.

**FU:** 12 months.

Schmader et al AmJ Med. 2004



# Effects of Geriatric Evaluation and Management on ADR

**Results:** geriatric evaluation and management resulted in a 35% reduction in the risk of a serious ADR compared with usual care (RR 0.65; 95% CI: 0.45 to 0.93) and with a reduction in unnecessary and inappropriate drug use ( $p=0.05$ ).

**Conclusion:** geriatric evaluation and management reduces serious ADR and suboptimal prescribing in the elderly.

Schmader et al AmJ Med. 2004



# Medication reviews in the community: results of a RCT

**Aim:** To examine the effectiveness of a multidisciplinary service model in the prevention of ADR.

**Intervention:** The multidisciplinary service model consisted of GP education, patient home visits, pharmacist medication reviews, team conferences, GP implementation of action plans in consultation with patients, and follow-up visits.



# Medication reviews in the community: results of a RCT

**Results:** positive trends in clinical outcomes (ADEs and severity of illness) and costs (an ongoing trend towards reduction in healthcare service costs) were evident, although the trial was limited to a 6-month intervention time.

**Conclusion:** a service based on this model can achieve relevant benefits in practice.



# Farmacogenomica



E' lo studio dei geni che determinano la risposta ai farmaci e studia i geni di:

- recettori dei farmaci;
- enzimi responsabili del trasporto dei farmaci;
- enzimi responsabili del metabolismo dei farmaci.





# ADR: role of pharmacogenomics

- Understanding of the genes that modulate response to medications may change the way medications are prescribed.
- The goal is to check the genetic background in order to ensure that the prescribed medications are effective and free from *side effects*.



# Evidence for a genetic modulation of the response to opiates



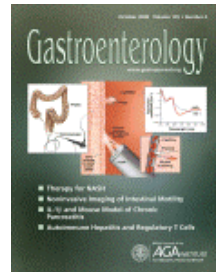
Gene	Variant <sup>a</sup>	Frequency of affected subjects [%] <sup>f</sup>	Factor by which standard dose may be multiplied for similar effects <sup>b</sup> (if only this particular SNP is present)
<i>OPRM1</i> ( $\mu$ -opioid receptor)	118A > G	17.2	2
	880G > C	3 (Mogil et al., 2005)	
<i>CYP2D6</i> (cytochrome P450 2D6)	2549A > del	2 (Sachse et al., 1997)	$\gg 1$ (almost ineffective; use other analgesic)
	1846G > A	20.7 (Sachse et al., 1997)	1.3
	Gene deleted	2 (Sachse et al., 1997)	
	1707T > del	0.9 (Sachse et al., 1997)	
	2935A > C	0.1 (Sachse et al., 1997)	
	1758G > T	0 (Sachse et al., 1997)	
	Gene duplication/ amplification	2 (Sachse et al., 1997)	$\ll 1$ (unknown dose adaptation)
<i>ABCB1</i> (P-glycoprotein)	3435C > T	47.6	Not specified

# Genetic Susceptibility to Nonsteroidal Anti-Inflammatory Drug–Related Gastroduodenal Bleeding



Genotype	Bleeding <sup>a</sup> (n = 26)		Controls <sup>b</sup> (n = 52)		Adjusted analysis		
	N	(%)	n	(%)	P value	OR	95% CI
<i>CYP2C9</i> *1/*1	9	(34.6)	39	(75.0)		Reference	
<i>CYP2C9</i> *1/*2	7	(26.9)	8	(15.4)	0.034	4.2	1.112–16.205
<i>CYP2C9</i> *1/*3	9	(34.6)	3	(5.8)	0.000	15.8	3.355–74.813
<i>CYP2C9</i> *2/*3	1	(3.8)	2	(3.8)	0.356	3.6	0.240–52.379

Pilotto A et al. *Gastroenterology* 2007



# Conclusioni

- Le ADR rappresentano negli anziani un importante problema medico ed economico;
- L'identificazione dei pazienti a rischio di ADR è possibile in base a specifiche scale;
- L'assistenza geriatrica e la VMD rappresentano ad oggi l'unico intervento in grado di ridurre il rischio di ADR;
- La farmacogenomica rappresenta il futuro della prevenzione delle ADR.



Grazie