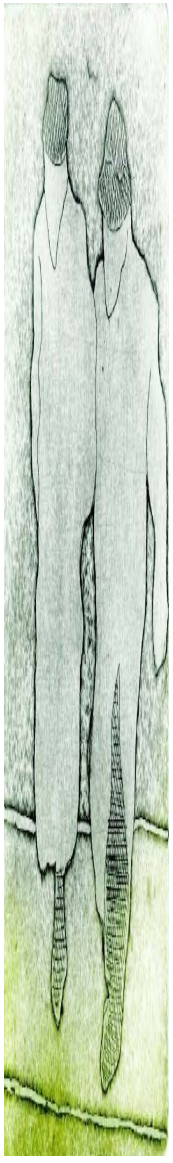


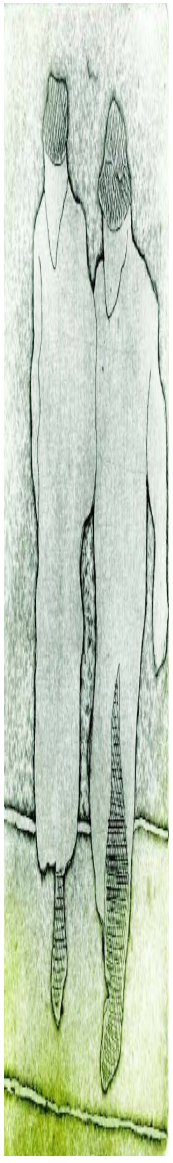
Società Italiana Gerontologia e Geriatria 53° Congresso Nazionale
Firenze 26-29 Novembre 2008

FARMACI E ANZIANI: AMICI O NEMICI?

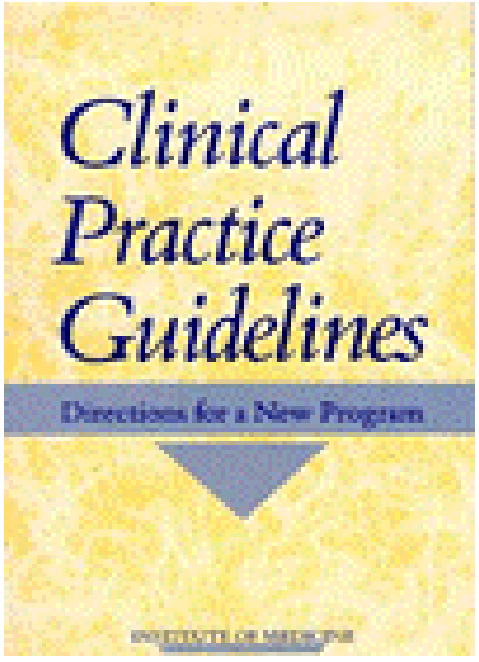
Linee guida nell'anziano con polipatologia: utili o dannose?

Stefano Volpato

**Sezione di Medicina Interna,
Gerontologia e Geriatria
Università di Ferrara**



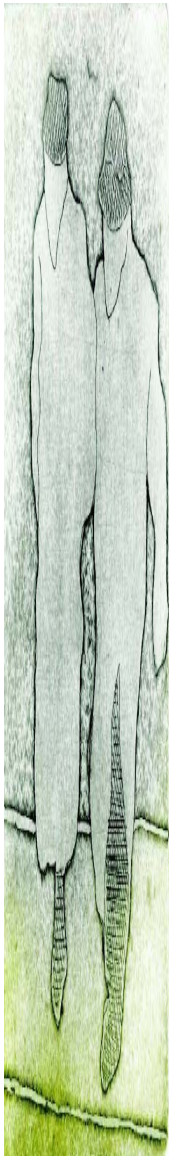
Linee guida di pratica clinica



- "… sistematically developed statements to *assist practitioner and patient* decisions about appropriate health care for *specific clinical circumstances*…"

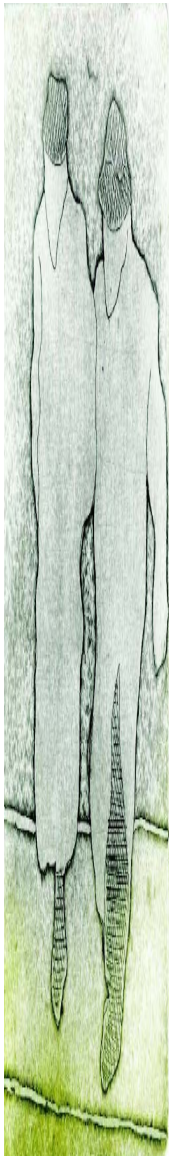
- "…affermazioni sviluppate in modo sistematico allo scopo di assistere le decisioni del medico e del paziente circa l'appropriatezza delle cure in specifiche condizioni cliniche…"

Field MJ, Lohr KN (eds). Guidelines for Clinical Practice: from development to use. 1992, Institute of Medicine, National Academy Press, Washington, DC.)



Linee guida e qualità delle cure

- Descrivono in modo articolato ma sintetico gli obbiettivi terapeutici per una determinata patologia
- Elencano i differenti approcci terapeutici potenzialmente benefici
- Sono sostenute dai risultati di trial clinici randomizzati di elevata qualità (quando disponibili)
- Cercano di favorire una gestione clinica razionale delle più comuni e importanti patologie
- Tendono a omogeneizzare e ottimizzare i processi di cura sul nei diversi setting assistenziali



Medicina basata sull'evidenza e linee guida di pratica clinica

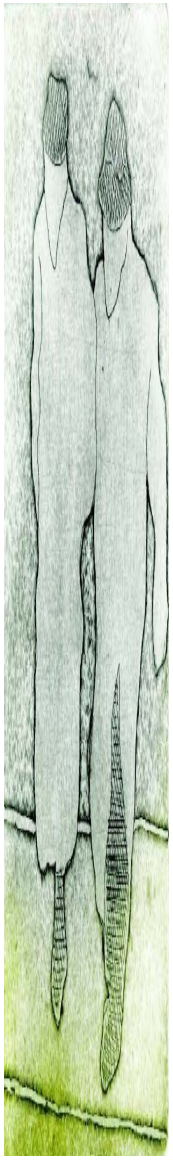
The Rational Clinical Examination

Evidence-Based Medicine

A New Approach to Teaching the Practice of Medicine

Evidence-Based Medicine Working Group

***JAMA* 1992;268(17):2420-2425**



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

SHATTUCK LECTURE

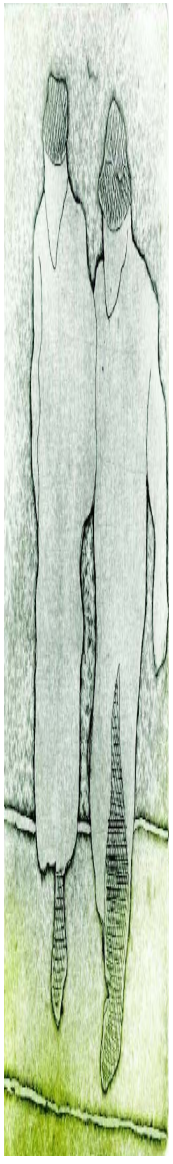
Clinical Research to Clinical Practice — Lost in Translation?

Claude Lenfant, M.D.

Practice is science touched with emotion.

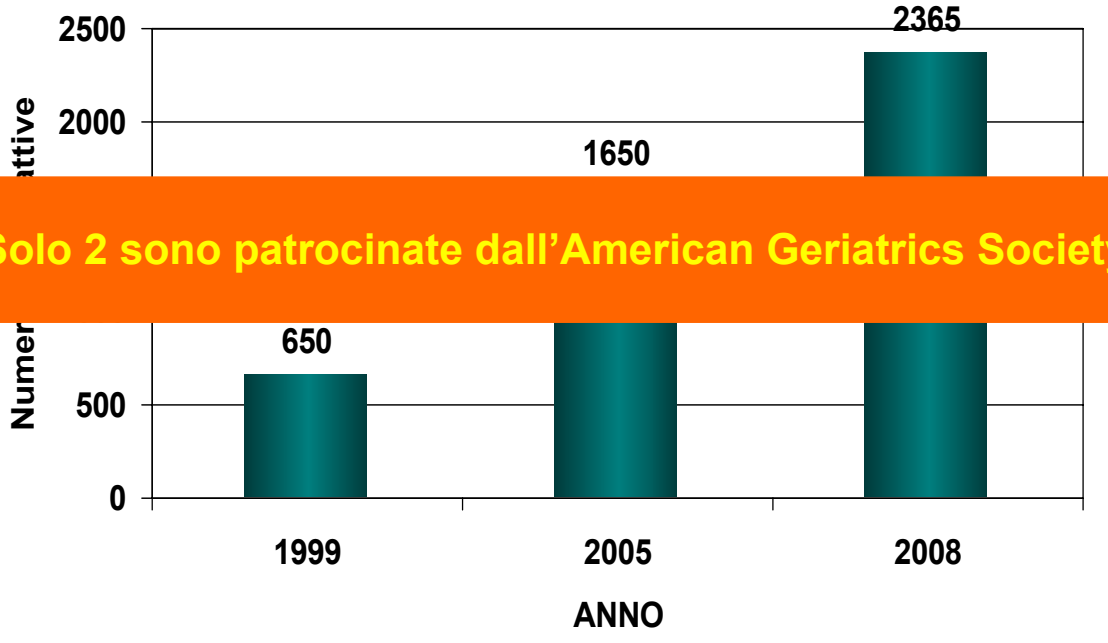
Confessio Medici
Stephen Paget, 1909

N Engl J Med, 2003; 349: 868-874

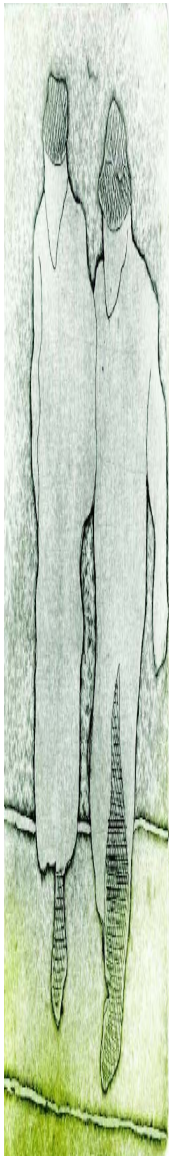


National Guideline Clearinghouse
www.guideline.gov

Crescente Diffusione delle linee guida



Solo 2 sono patrocinate dall'American Geriatrics Society!!!



Linee guida nell'anziano con polipatologia: utili o dannose?

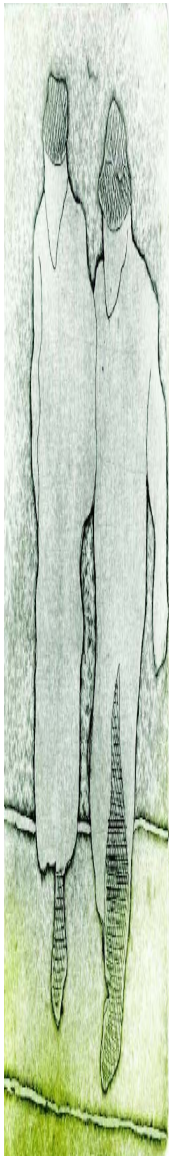
Paziente "Geriatrico"

- Comorbilità
- Politerapia
- Età > 75 aa
  - Incontinenza
  - Cadute
  - Problemi nutrizionali
  - Osteoporosi
  - Anemia
  - Sarcopenia
  - Instabilità clinica
  - Patologia a cascata

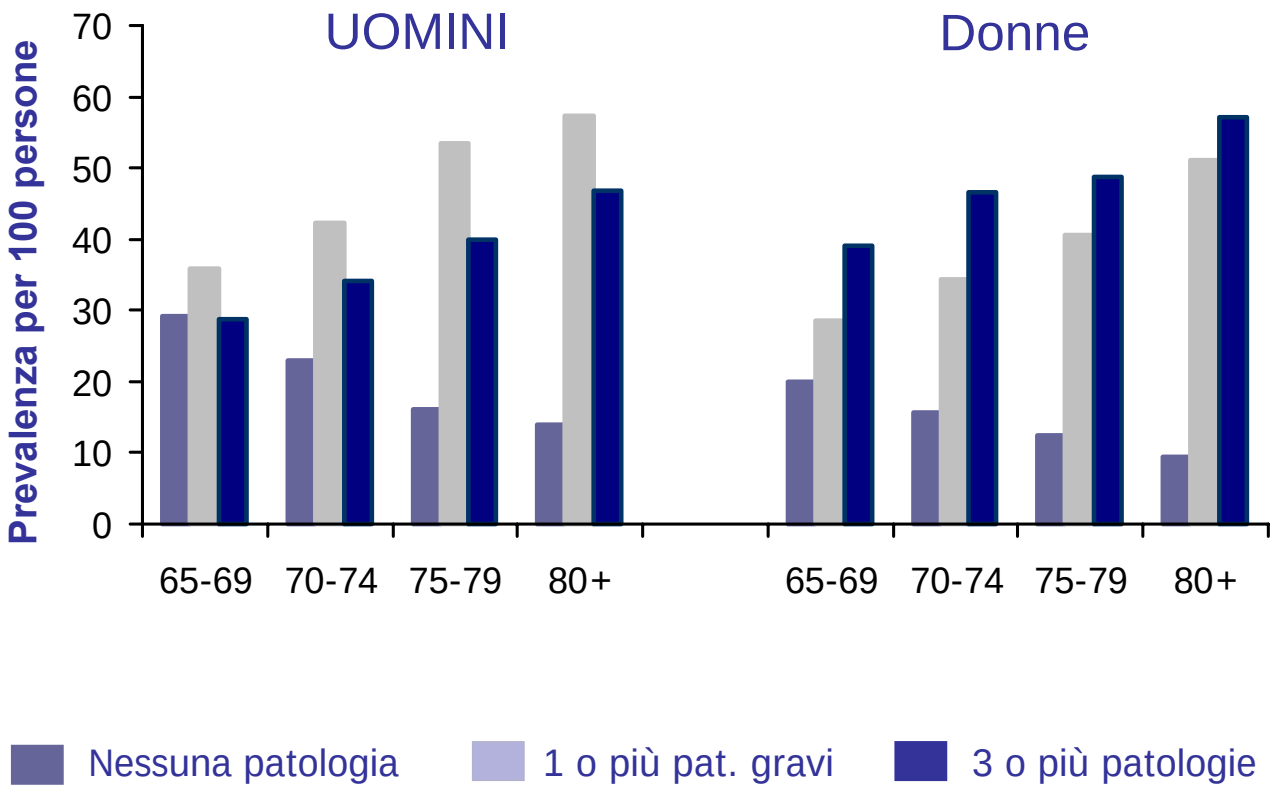
Declino funzionale →

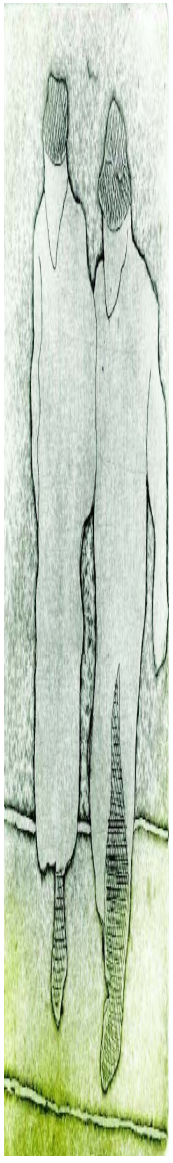
- **Cognitivo**
- **Fisico**
- **Psichico**
- **Socio-economico**

da: Bernabei R, modificata

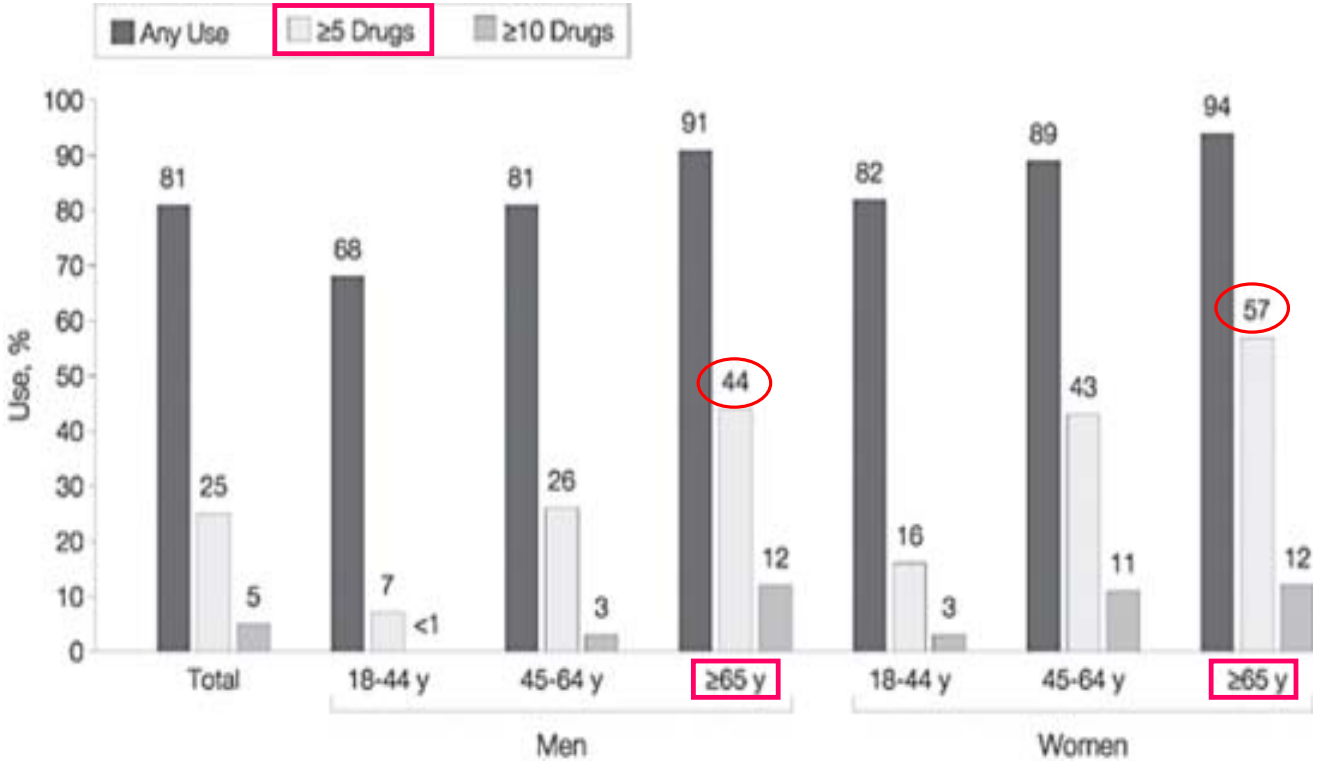


Numero e gravità delle patologie croniche in base al sesso e all'età (ISTAT 2004-2005)

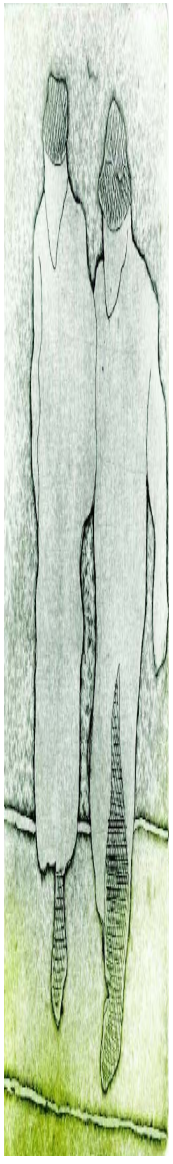




Consumo quotidiano medio di farmaci per età e sesso (USA)



Kaufman, D. W. et al. JAMA 2002



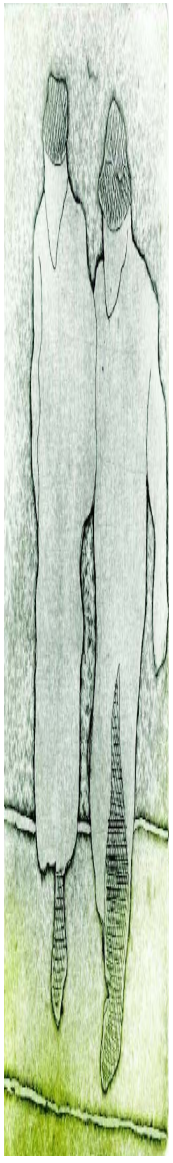
The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Potential Pitfalls of Disease-Specific Guidelines for Patients with Multiple Conditions

Mary E. Tinetti, M.D., Sidney T. Bogardus, Jr., M.D., and Joseph V. Agostini, M.D.

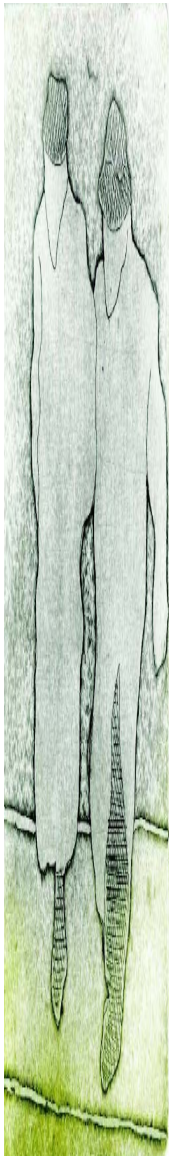
N Engl J Med, 2004; 351: 2870-2874



Principali limitazioni delle attuali Linee-guida

- Orientate su una specifica patologia
- Basate su RCT altamente selezionati raramente dedicati al paziente anziano con comorbilità
- Non sono basate su studi condotti su pazienti complessi e "fragili"
- Le raccomandazioni sono limitate al paziente "ideale"
- Le raccomandazioni non contemplano l'eterogeneità del paziente geriatrico in termini di:
  - Comorbilità
  - Polifarmacoterapia
  - Stato funzionale e cognitivo
  - Stato socio-familiare

Tinetti M. et al. NEJM 2004



Schema terapeutico giornaliero basato sulle linee-guida di pratica clinica

Donna di 79 anni affetta da:

- **artrosi**
- **ipertensione**
- **diabete**
- **osteoporosi**
- **BPCO**

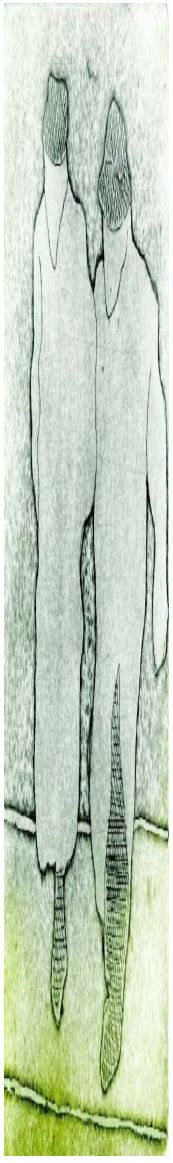
Time	Medications†	Other
7:00 AM	Ipratropium metered dose inhaler 70 mg/wk of alendronate	Check feet Sit upright for 30 min on day when alendronate is taken Check blood sugar
8:00 AM	500 mg of calcium and 200 IU of vitamin D 12.5 mg of hydrochlorothiazide 40 mg of lisinopril 10 mg of glyburide 81 mg of aspirin 850 250 20	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 diabetes‡
12:00 PM		ed fat and m and calcium diabetes‡
1:00 PM	Ipra 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	

13 diverse molecole

18 somministrazioni

+ terapia al bisogno

Boyd, CM et al. JAMA 2005



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12:00 PM		
1:00 PM	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	

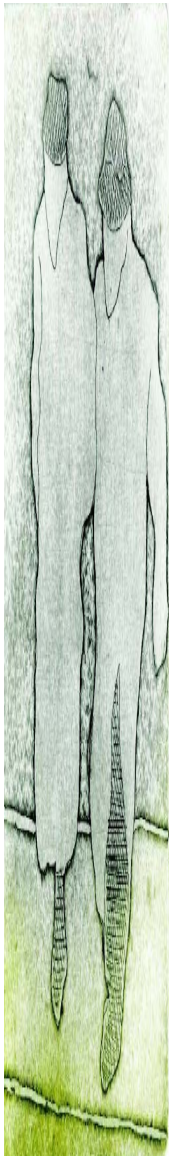
13 diverse molecole

18 somministrazioni

+ terapia al bisogno

- **Alterazione della abitudini quotidiane**
- **↓compliance/aderenza**
- **↑ Interaz. farmacologiche**
- **↑ reazioni avverse**
- **“prescribing cascade”**

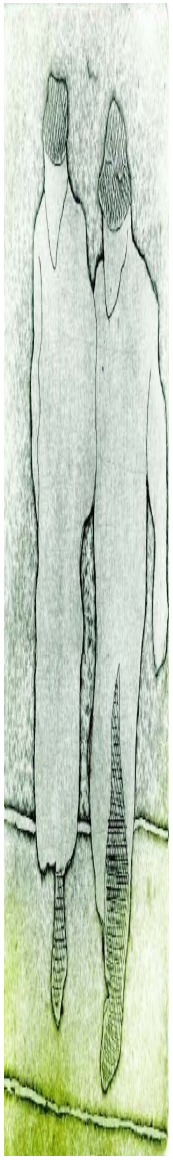
Boyd, CM et al. JAMA 2005



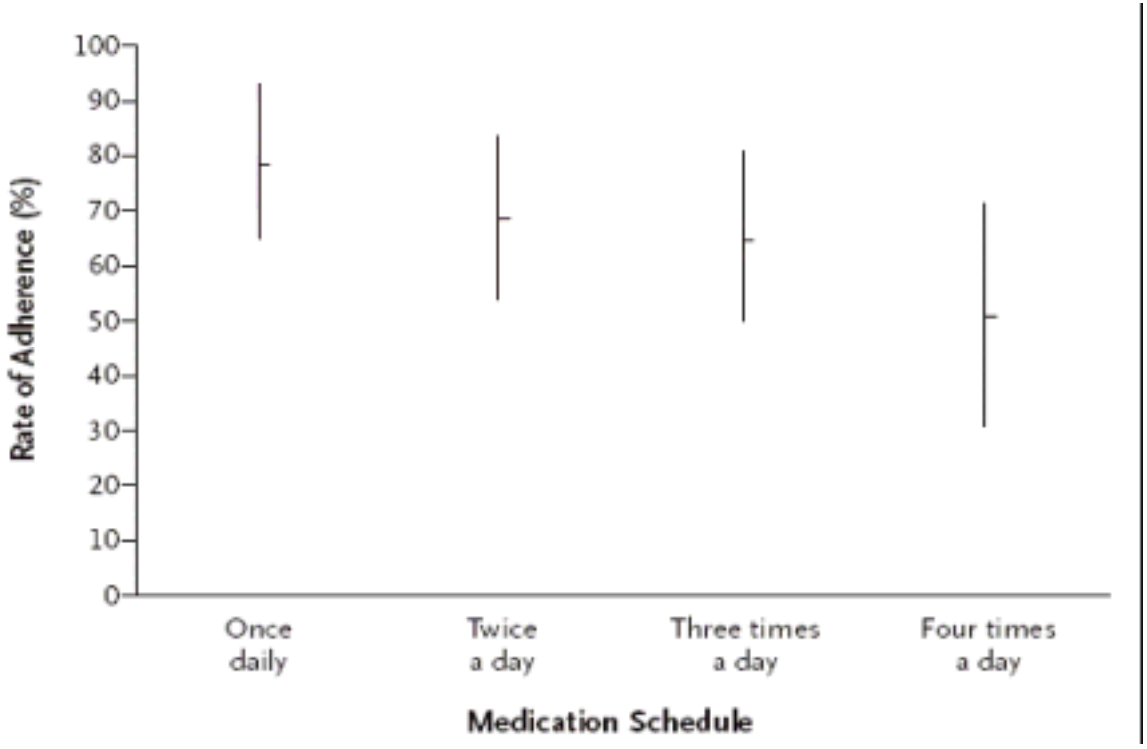
Polifarmacoterapia e aderenza alla terapia a lungo termine

	Univariable	Multivariable
	OR for adherence at 12 m	OR for adherence at 12 m
Age (per 10 y)	0.97 [0.87-1.07]	–
Women†	0.65 [0.52-0.82]	–
Nonwhite race	0.82 [0.61-1.11]	–
Unmarried‡	0.58 [0.46-0.74]	0.65 [0.50-0.85]
Primary insurance, nonprivate§	1.00 [0.81-1.24]	–
Education <high school ‖	0.73 [0.59-0.91]	0.76 [0.60-0.96]
Assisted living—no help	1.17 [0.76-1.81]	–
ALFI-MMSE* score (continuous)	1.00 [0.99-1.01]	–
MCS[F]	1.01 [1.00-1.02]	1.01 [1.00-1.02]
PCS	1.00 [0.98-1.01]	–
Antidepressant use	0.74 [0.53-1.03]	–
Total no. of medications prescribed	0.93 [0.88-0.97]	0.94 [0.90-0.98]

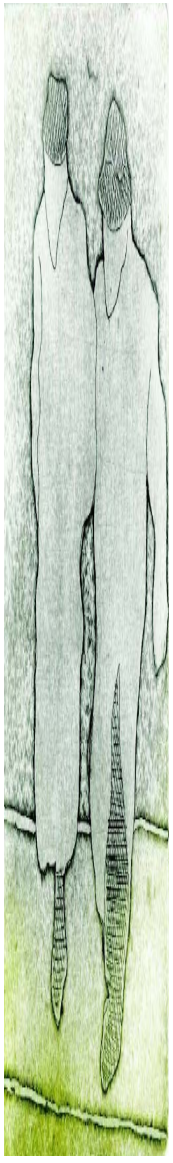
Kulkarni SP et al. Am Heart J 2006



Frequenza di somministrazione della dose e aderenza alla terapia



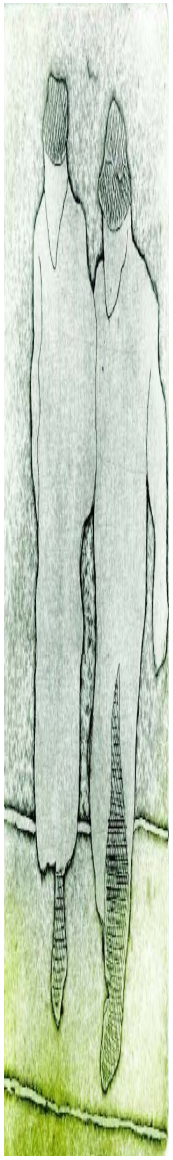
Claxton AJ. et al. Clin Ther 2001



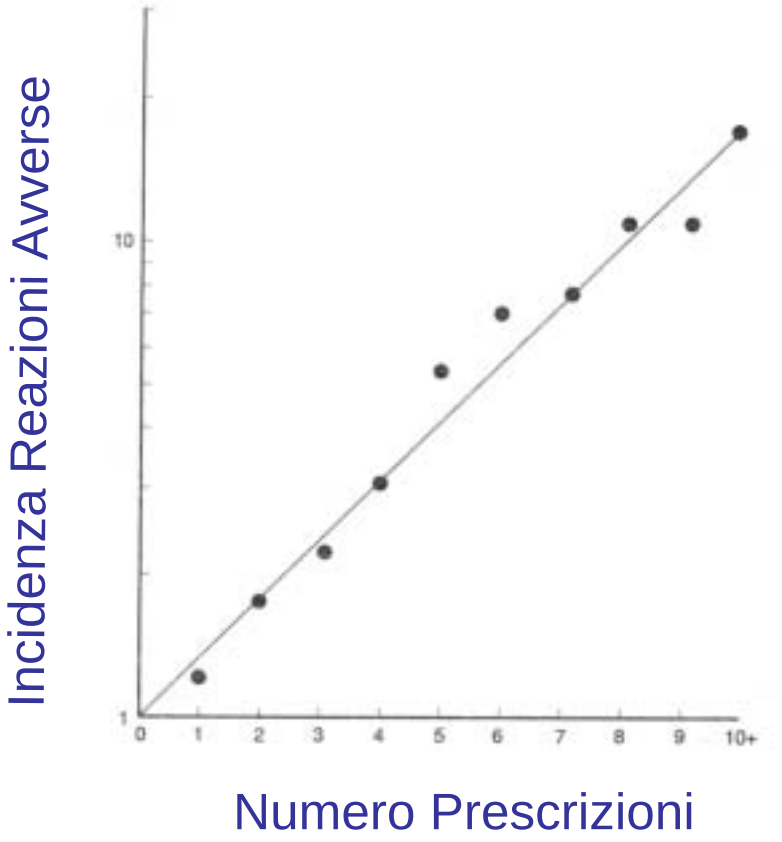
Potential Treatment Interactions for a Hypothetical 79-Year-Old Woman with 5 Chronic Diseases

Type of Disease	Medications With Potential Interactions	Type of Interaction: Medication and Other Disease	Type of Interaction: Medications for Different Diseases	Type of Interaction: 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; asprin 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 β-agonists	NA	NA	NA

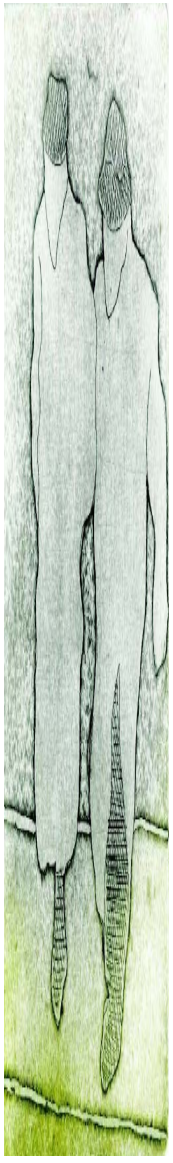
Boyd, CM et al. JAMA 2005



Numero prescrizioni e ADR: studio G.I.F.A.



Carbonin PU et al. JAGS 1991

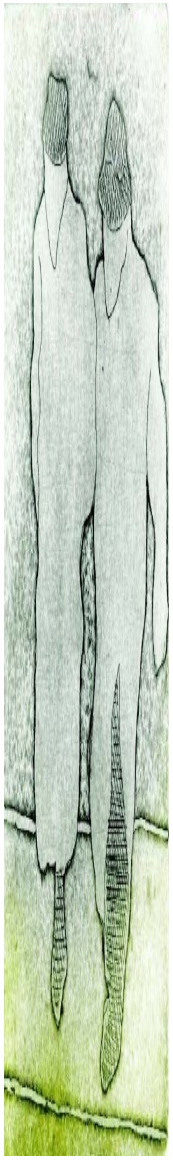


Aderenza alle linee guida di terapia e mortalità a lungo termine dopo infarto del miocardio

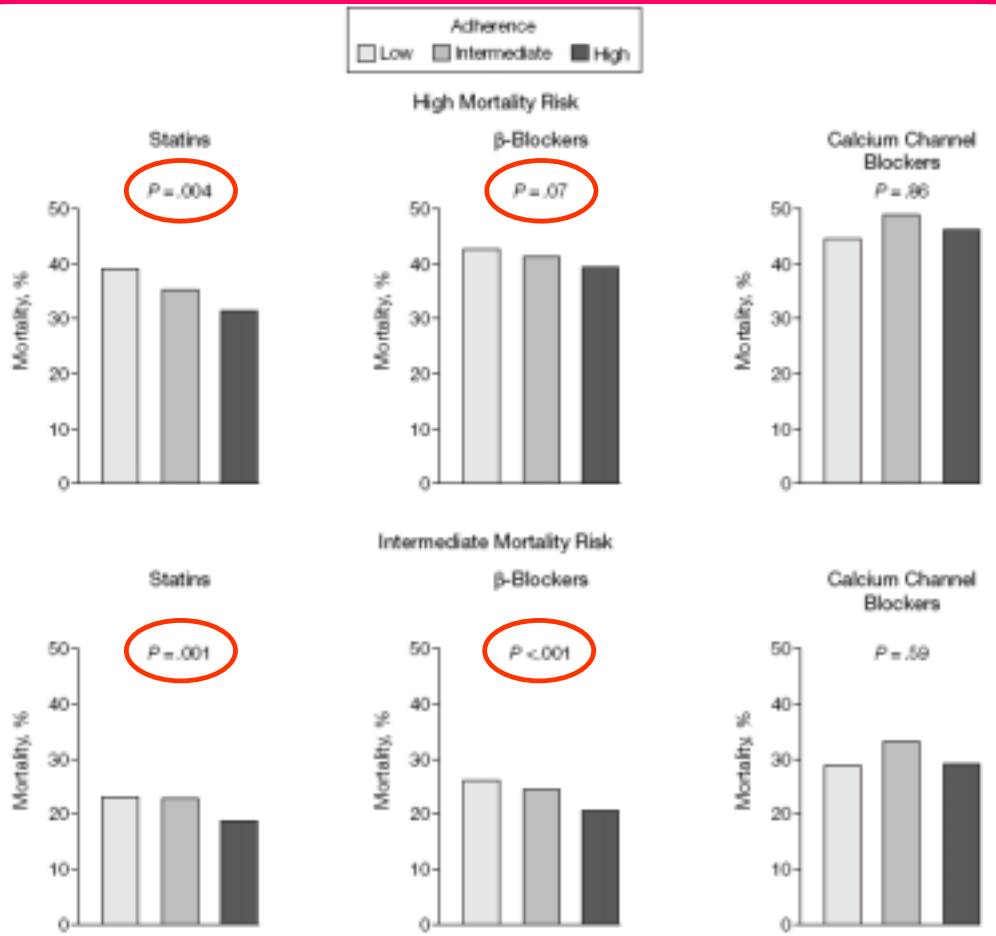
Table 1. Characteristics of Patients According to 1-Year Adherence to Statins, β-Blockers, and Calcium Channel Blockers*

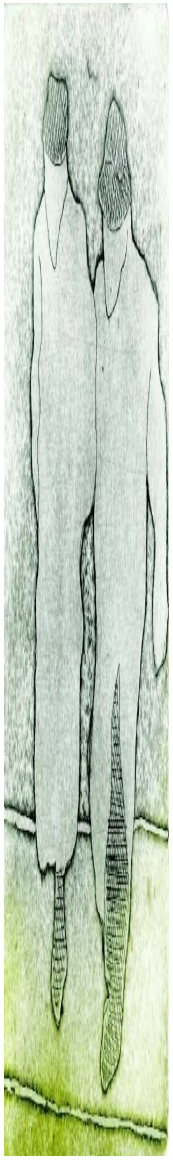
	Adherence Level†											
	Statins				β-Blockers				Calcium Channel Blockers			
Characteristics	High	Intermediate	Low	*P* Value	High	Intermediate	Low	*P* Value	High	Intermediate	Low	*P* Value
Patients	14 345 (80.5)	2407 (13.5)	1071 (6.0)	<.001	17 868 (73.5)	4287 (17.6)	2164 (8.9)	<.001	6243 (68.1)	1506 (16.4)	1419 (15.5)	<.001
Women	5910 (41.2)	1049 (43.6)	515 (48.1)	<.001	8112 (45.5)	1766 (41.2)	894 (41.3)	<.001	3084 (49.4)	684 (45.4)	636 (44.8)	<.001
Low income	4002 (27.9)	676 (28.1)	361 (33.7)	<.001	5378 (30.1)	1196 (27.9)	658 (30.4)	.02	2204 (35.3)	518 (34.4)	490 (34.5)	.74

Rasmusmussen JN et al., JAMA, 2007



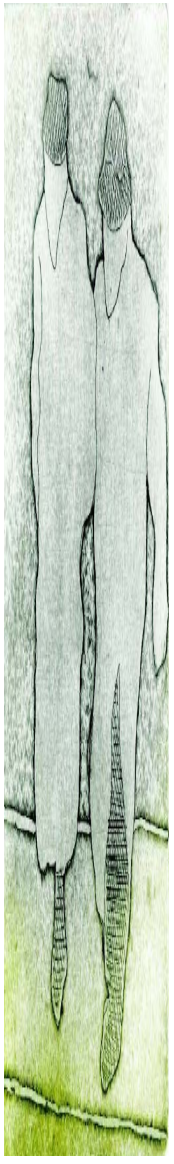
Aderenza alle linee guida di terapia e mortalità a lungo termine dopo infarto del miocardio





Linee guida per pazienti anziani con comorbilità: caratteristiche necessarie

• **Indicazioni di trattamento specifiche:**	➢ Età ➢ Comorbilità ➢ Stato funzionale (fisico/cognitivo)
• **Forza dell'evidenza in rapporto alle caratteristiche del paziente:**	
• **Forza dell'evidenza descritta in termini di effetti positivi ed effetti negativi**	
• **Indicazioni della forza dell'evidenza presentate in termini di rischio assoluto piuttosto che di rischio relativo**	
• **Raccomandazioni più differenziate**	➢ 1 patologia associata ➢ 2 o più patologie associate
• **Prioritarizzazione delle raccomandazioni in relazione al livello e al tipo di comorbilità**	
• **Valutazione del rapporto tra tempo necessario per ottenere il beneficio atteso e la spettanza di vita stimata**	



Multimorbidity is common to family practice

Is it commonly researched?

Martin Fortin, MD, MSC, CCMF Lise Lapointe, MA
Catherine Hudon, MD, CCMF Alain Vanasse, MD, PHD, CCMF

Can Fam Physician 2005;51:244-245.

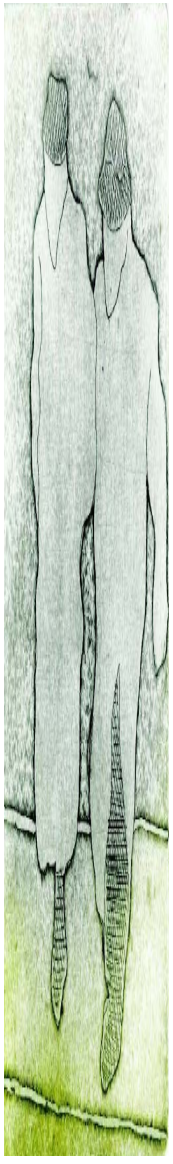
Table 1. Prevalence of certain clinical conditions and number of articles about them published between 1990 and 2002

CONDITIONS	PREVALENCE* (%)	NO. OF PUBLISHED ARTICLES	NO. OF ARTICLES ON PREVALENCE	NO. OF ARTICLES ON OTHER THREE CONDITIONS VS NO. ON MULTIMORBIDITY	NO. OF ARTICLES RELATING TO PRIMARY CARE	% OF ARTICLES RELATING TO PRIMARY CARE† (*P* VALUE)
Multimorbidity	60.02	353	6	1:1	10	2.8
Asthma	6.5‡	26 174	4027	74:1	436	1.7 (*P* = .09)
Hypertension	29.6‡	33 198	1122	94:1	439	1.3 (*P* = .014)
Diabetes	8.7‡	13 575	1560	38:1	302	2.2 (*P* = .4)

*Among people aged 55 to 74 years.

Table 2. Classification of articles on multimorbidity

CATEGORY OF ARTICLE	GENERAL RESEARCH NO. (%)	PRIMARY CARE NO. (%)	OTHER NO. (%)	*P* VALUE*
Unclassifiable	61†	0	0	NA
Unrelated	140†	7†	133†	<.001
Literature reviews	12 (7.9)	2 (4.8)	10 (9.1)	.304
Basic research	1 (0.7)	0	1 (0.9)	.724
Epidemiologic studies	76 (50.0)	25 (59.5)	51 (46.4)	.102
Experimental studies‡	7 (4.6)	0	7 (6.4)	.098
Pharmaco-economic research	4 (2.6)	1 (2.4)	3 (2.7)	.694
Validation studies	34 (22.4)	7 (16.7)	27 (24.5)	.207
Editorials and opinion pieces	18 (11.8)	7 (16.7)	11 (10.0)	.193
TOTAL	152 (100)	42 (100)	110 (100)	NA

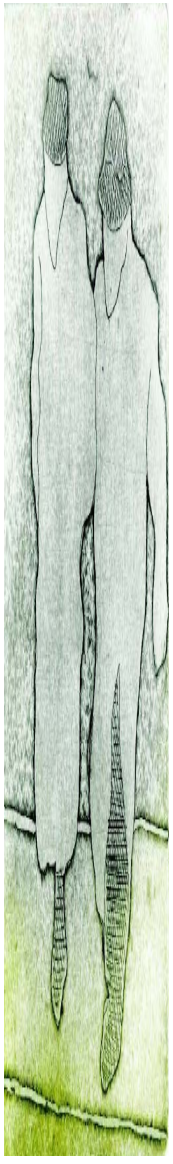


Designing Randomized, Controlled Trials Aimed at Preventing or Delaying Functional Decline and Disability in Frail, Older Persons: A Consensus Report

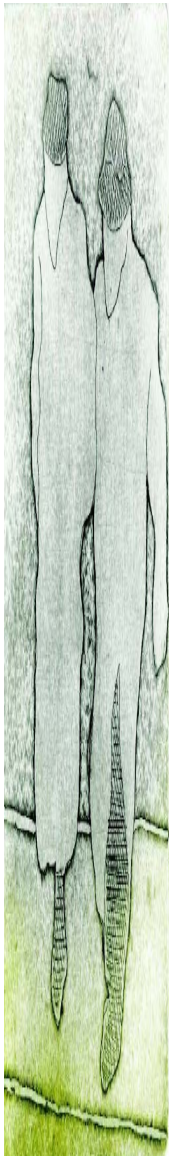
Luigi Ferrucci, MD, PhD, Jack M. Guralnik, MD, PhD,† Stephanie Studenski, MD, MPH,‡ Linda P. Fried, MD, MPH,§‖ Gordon B. Cutler Jr, MD,# and Jeremy D. Walston, MD,§ for The Interventions on Frailty Working Group*

Challenges	Recommendations
Standard criteria for physical frailty are lacking	Operationalize variables in the domains of mobility, nutrition, and body composition. Justify the specific criteria used in the trial
Enrolling the most appropriate study population may be complex and expensive	Use a multistage selection process: 1) Exclude the "robust." 2) Identify those who are frail. 3) Indentify subset according to specific domains of physical frailty
Excessive exclusions may reduce generalizability	Design studies with the idea of enabling participation. The principal exclusion criteria should be factors that prevent participation
	Avoid exclusions for comorbidity
	Ascertain the level of cognitive impairment incompatible with participation in specific interventions
Inclusion and exclusion of frail older persons from trials raise ethical concerns	Make explicit the procedures used for consenting participants. Provide multiple methods to explain the study to the participants and involve a surrogate when needed. Discuss ethical issues when reporting results
Assessing disability through self-report may be problematic	Limit self-report to primary outcomes that are "hard" measures of disability such as activity of daily living disability, mobility disability
	Standardize disability questions and responses and provide continuing, intensive training to interviewers
	Collect objective measures of physical function and proxy information in parallel
	Make the outcome less sensitive to random fluctuations (e.g., defining disability as "lasting more than 3 months" or targeting "multiple falls")
	Include mortality in the primary outcomes
The mechanism by which the intervention prevents disability may be unclear	Use as secondary outcomes physiological or functional measures that are in the theoretical pathway between the intervention target and the disability outcome
Improvements in functional status may not translate into well-being and quality of life	Use secondary outcome measures that assess perceived well-being and factors, such as somatic symptoms, that are important for quality of life in frail older persons
	Consider global impression
Avoid attrition and competing morbidity	The expected mortality and dropout rates should be incorporated into sample size calculations
	Adherence rates can be improved by designing interventions feasible by most, allowing flexible time-frame for follow-up interviews, providing a comfortable environment, prioritizing safety, providing transportation, establishing a good relationship with family or caregivers, preplanning alternatives to full clinic visits (e.g., shorter home visits, telephone calls)

Ferrucci L. et al., JAGS, 2004



Vecchio che soffre "Alle porte dell'Eternità"

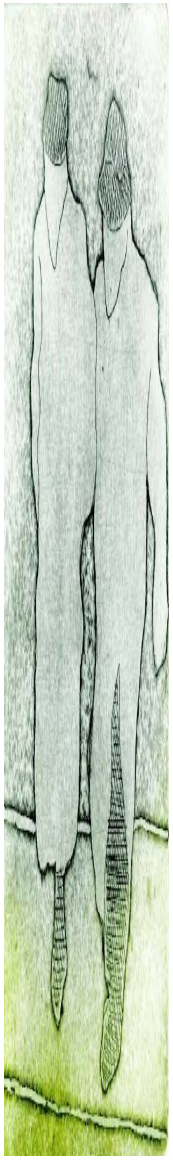


Linee guida e paziente geriatrico

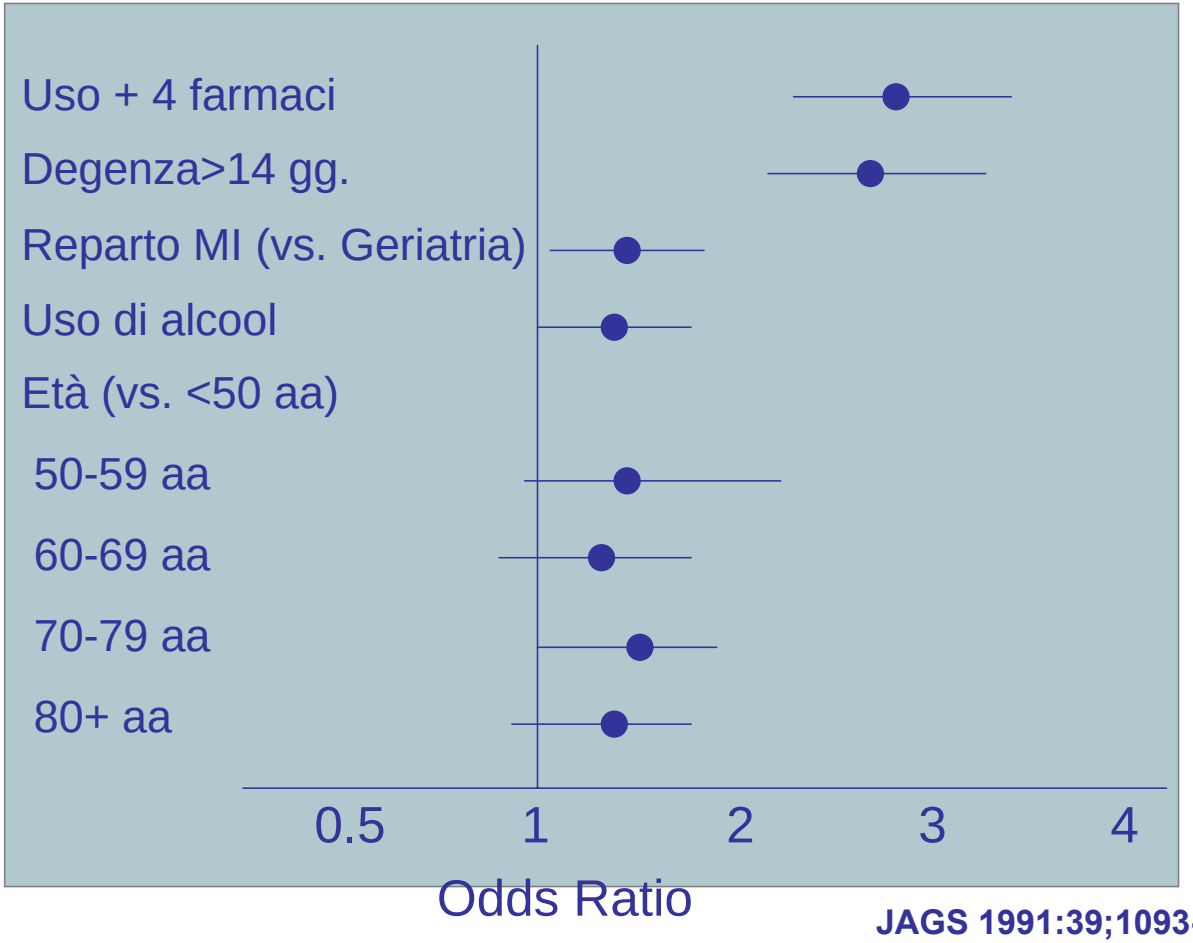
Applicazione sistematica delle linee guida

- Età > 75 aa
- Comorbilità
- Politerapia
  - Incontinenza
  - Cadute
  - Problemi nutrizionali
  - Osteoporosi
  - Anemia
  - Sarcopenia
  - Instabilità clinica
  - Patologia a cascata

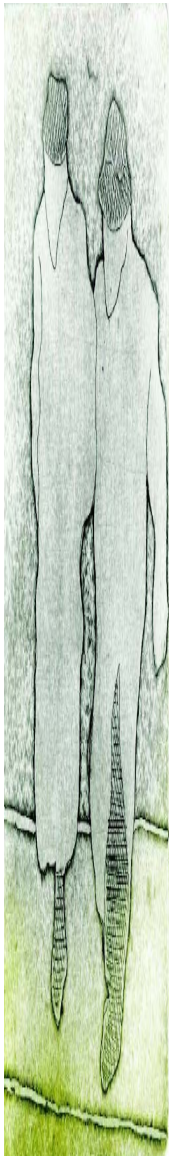
- **Alterazione della abitudini quotidiane**
- **↓ compliance/aderenza**
- **Interazioni farmacologiche**
- **↑ reazioni avverse**
- **“prescribing cascade”**



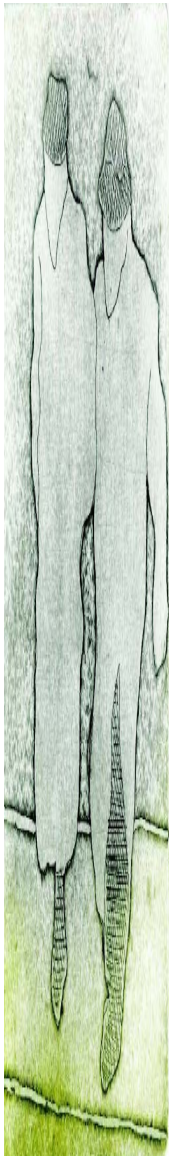
Fattori di rischio per Reazioni Avverse da Farmaci in pazienti ospedalizzati



JAGS 1991:39;1093-99

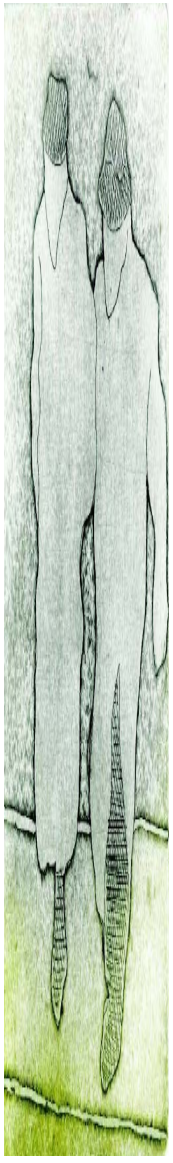


	Chronic Disease Addressed by Guideline				
	Diabetes Mellitus[9-12]	Hypertension[59]	Osteoarthritis[63-66]	Osteoporosis[67]	COPD[27,68]
Guideline addressed treatment for type of patient?	Older: yes Multiple comorbidities: yes Both: yes	Older: yes Multiple comorbidities: no Both: no	Older: yes Multiple comorbidities: yes Both: yes†	Older: no Multiple comorbidities: no Both: no	Older: no Multiple comorbidities: no Both: no
Quality of evidence discussed for type of patient?	Older: yes Multiple comorbidities: yes Quality of evidence poor, requires extrapolation for nutrition recommendations	Older: yes Multiple comorbidities: no Quality of evidence good for treating hypertension in older patients	Older: no Multiple comorbidities: no	Older: no Multiple comorbidities: no	Older: no Multiple comorbidities: no
Specific recommendations for patients with 1 comorbid condition?	Yes Diseases: hypercholesterolemia, hypertension, congestive heart failure, chronic kidney disease, cardiovascular disease, peripheral vascular disease, benign prostatic hypertrophy	Yes Diseases: coronary artery disease, diabetes mellitus, metabolic syndrome, sleep apnea, chronic kidney disease, gout, left ventricular hypertrophy, erectile dysfunction, peripheral vascular disease, congestive heart failure, stroke, dementia,* renal transplantation, renal artery stenosis, urinary outflow obstruction	Yes Diseases/drugs: anticoagulants, glucocorticoids, peptic ulcer disease, chronic kidney disease, hypertension, congestive heart failure	No	No
Specific recommendations for patients with several comorbid conditions?	Yes	No	No	No	No
Time needed to treat to benefit from treatment in the context of life expectancy discussed?	Yes	No	No	No	No



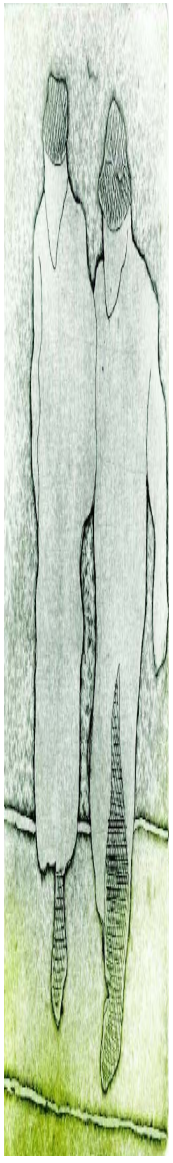
Raccomandazione 12.5 Grado c

- Nell'ictus o TIA cardioembolico associato a cardiopatie e valvulopatie emboligene **è indicata** la terapia anticoagulante orale mantenendo l'INR tra 2 e 3.
- L'età avanzata (>80 anni) è fattore di rischio emorragico, ma coincide con l'epoca di insorgenza di un aumentato rischio tromboembolico legato a malattie cardiovascolari. Laddove la TAO sia indicata si valuterà attentamente il rapporto rischio/beneficio.
- Esiste nell'anziano un maggior rischio di emorragie cerebrali per alterazione del metabolismo dei farmaci e probabilmente per alterazioni degenerative dei piccoli vasi. Questo rende necessaria un'attenta sorveglianza clinica, ma non costituisce di per sé una controindicazione.



Questioni irrisolte

- Qual è l'effetto delle linee-guida sull'aderenza alla prescrizione nei pazienti con comorbilità?
- Che tipo di effetto (positivo/negativo) puo' essere atteso dalla combinazione di più farmaci?
- Come viene modificato il rapporto rischio/beneficio nel contesto di polipatologia e polifarmacoterapia?
- Che tipo di beneficio possiamo aspettarci dall'aggiunta di una ulteriore molecola in pazienti che assumono già 3-4 farmaci?
- In che modo riusciamo a valorizzare le preferenze del paziente durante l'applicazione delle linee-guida?



Utilizzo “non clinico” delle linee guida

- Implementazione come requisito specifico per il processo di accreditamento delle unità operative
- Percentuale di “corretta” applicazione delle linee guida come indicatore di performance di una unità operativa o di un ambulatorio
- Criterio di rimborso per il medico di medicina generale (sistema pay-for-performance) negli USA